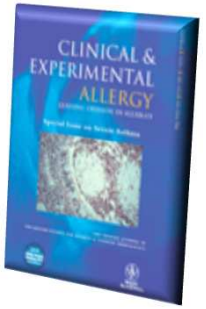
Conoscere l’asma severo per identificarlo

Enrico Heffler, MD, PhD
Assistant Professor in Respiratory Medicine
University of Catania

SEVERE ASTHMA

doi: 10.1111/j.1365-2222.2012.03962.x

Clinical & Experimental Allergy, **42**, 617–624



REVIEW

What is severe asthma?

J. D. Blakey[1] and A. J. Wardlaw[2]

[1]Department of Respiratory Medicine, University of Nottingham, Nottingham, UK and [2]Institute for Lung Health, Department of Infection Immunity and Inflammation, University of Leicester, and University Hospitals of Leicester NHS Trust, Leicester, UK

Box 1
Terms commonly applied in reference to severe asthma and their usual inference

At-risk asthmatics: patients with previous severe exacerbations who continue to be poorly controlled, often because of poor concordance with therapy or persisting risk behaviour.

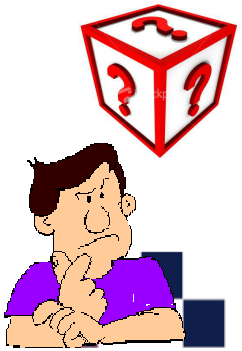
Dicult-to-treat asthma: patients with intrusive symptoms or persistently abnormal investigations despite the prescription of regular asthma therapy, for any reason.

Near-fatal asthma: asthma exacerbation resulting in hypercapnoea that requires intubation and ventilation.

Refractory asthma: persistent asthma symptoms despite good concordance with multiple regular asthma therapies and control of any co-morbid conditions.

Type 1 brittle asthma: unstable asthma characterized by frequent symptoms and high peak flow variability despite asthma treatment.

Type 2 brittle asthma: unstable asthma characterized by infrequent abrupt marked deteriorations against a background of good control.



SEVERE ASTHMA

BOX 1

The definition of severe asthma (according to ERS/ATS 2014) (7)

During treatment with:

- High-dose ICS + at least one additional controller (LABA, montelukast, or theophylline) or
- Oral corticosteroids >6 months/year

...at least one of the following occurs or would occur if treatment would be reduced:

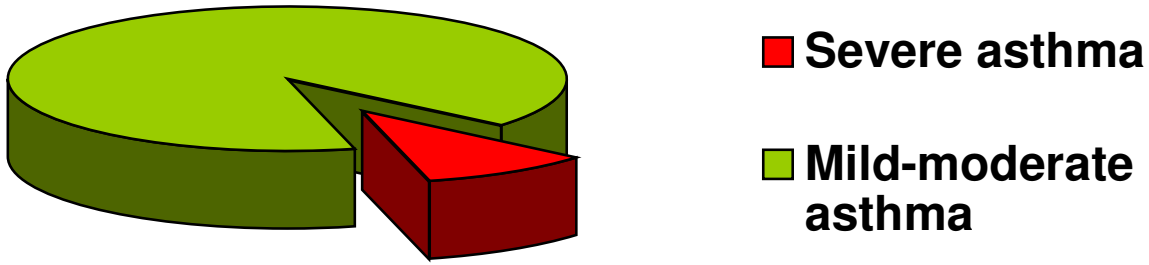
- ACT <20 or ACQ >1.5
- At least 2 exacerbations in the last 12 months
- At least 1 exacerbation treated in hospital or requiring mechanical ventilation in the last 12 months
- FEV_1 <80% (if FEV_1/FVC below the lower limit of normal)

The lower limit of normal (LLN) for FEV_1/FVC can be calculated using appropriate spirometer software (www.lungfunction.org). Current recommendations advocate a FEV_1/FVC <LLN to detect airway obstruction (40). However, if LLN is unknown, in our opinion the formerly universal limit (FEV1/FVC <70% for adults, FEV1/FVC <75% for children) can still be used.

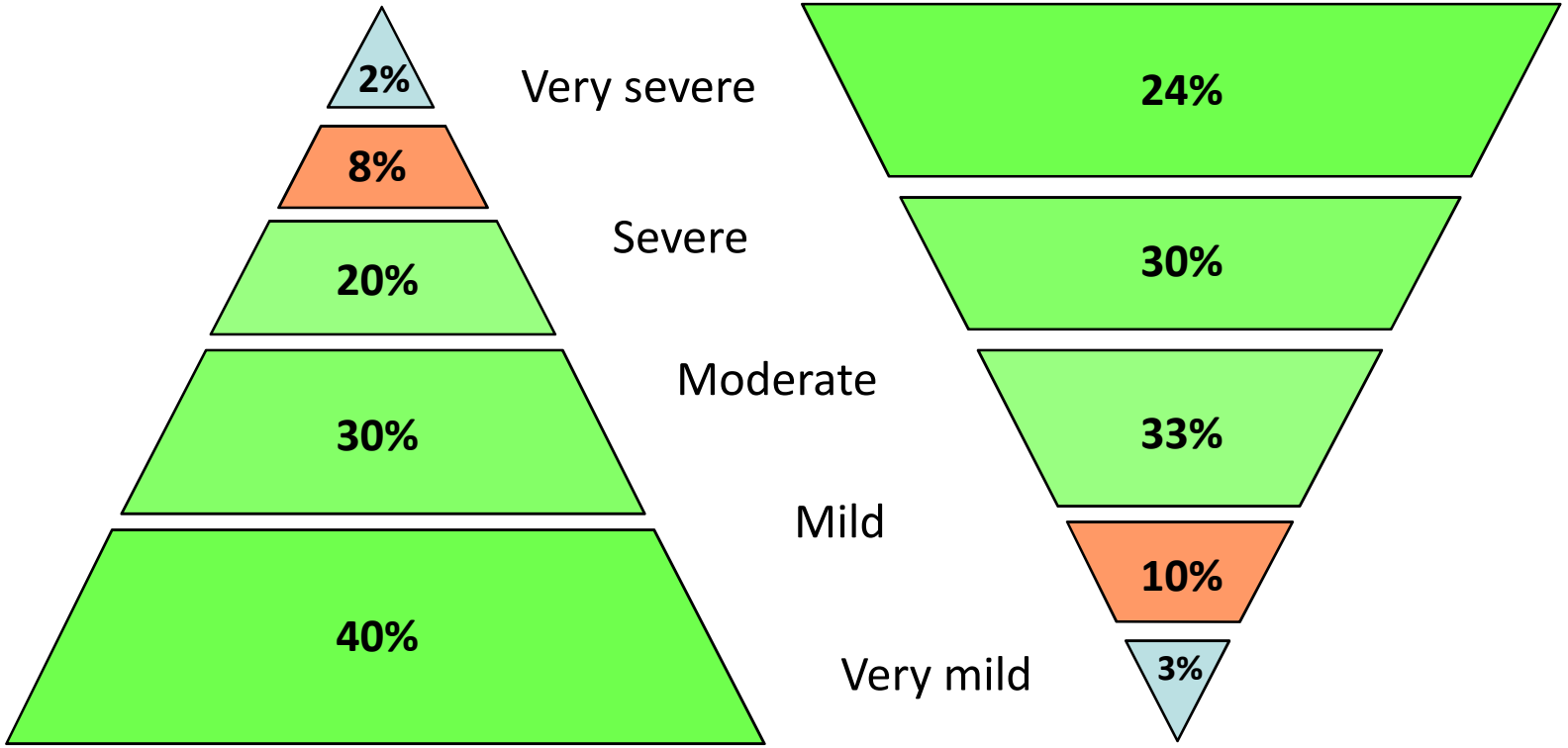
ICS: Inhaled corticosteroid; ACT, Asthma Control Test; ACQ: Asthma Control Questionnaire; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; ERS: European Respiratory Society; ATS: American Thoracic Society; LABA: Long-acting ß2 agonist

SEVERE ASTHMA

- About 5-10 % of patients have a severe form of asthma ("***refractory asthma***", "***difficult to treat asthma***") …



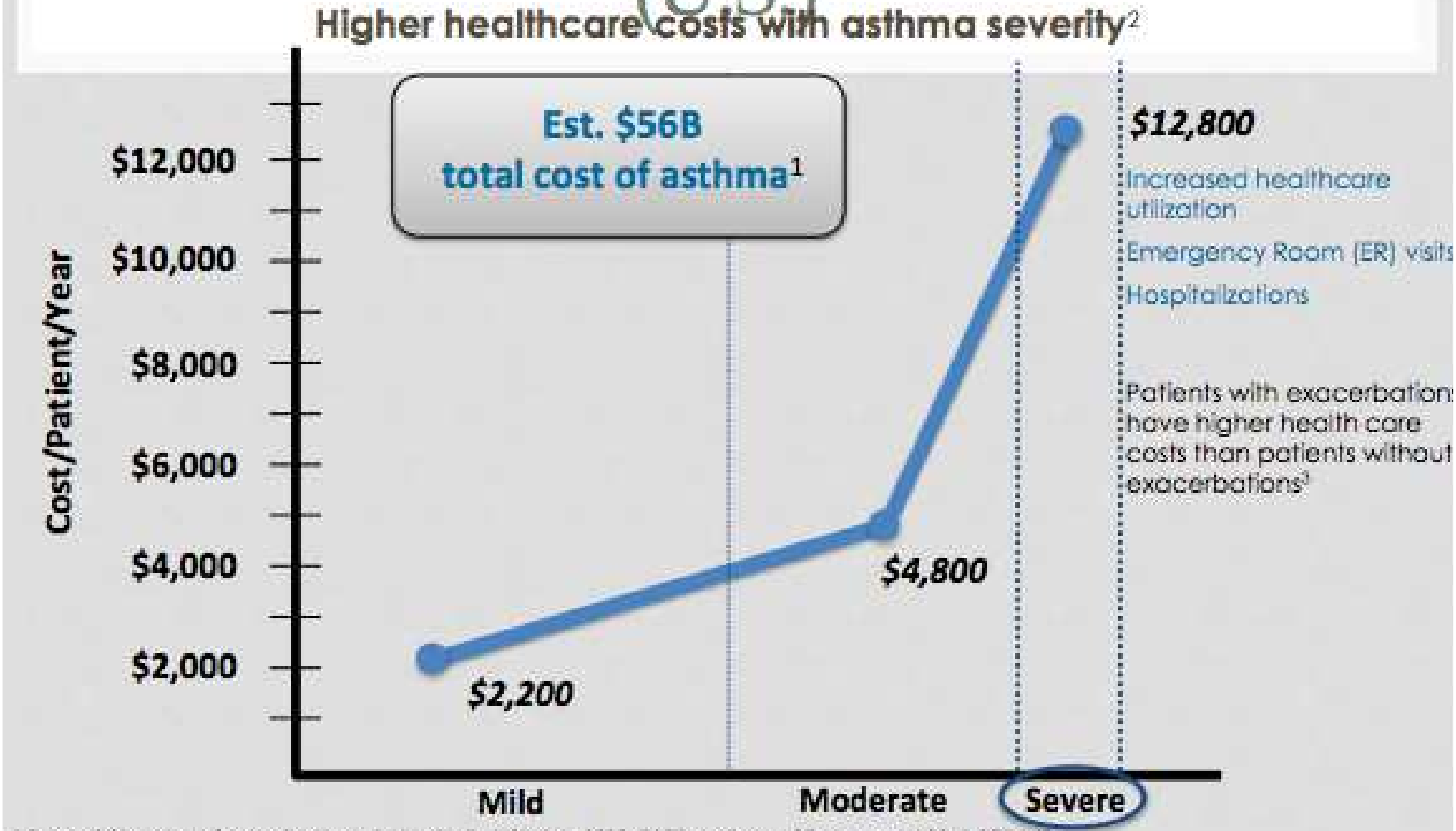
SEVERE ASTHMA



Boston Consulting Group 1995T

he subset of severe asthma patients has greater morbidity and a disproportionate need for health care support compared with less severe subsets

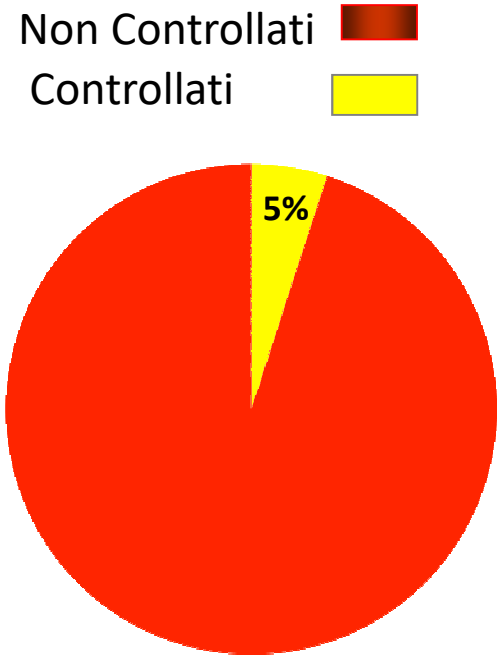
HIGHER COST OF SEVERE ASTHMA (U.S.)



1.Barnett SBL, et al. Costs of asthma in the United States: 2002–2007. J Allergy Clin Immunol 2011;127:145–52.
2.Cisternas M, et al., A comprehensive study of the direct and indirect costs of an adult with asthma. J Allergy Clin Immunol 2003;111(6):1212-1218.

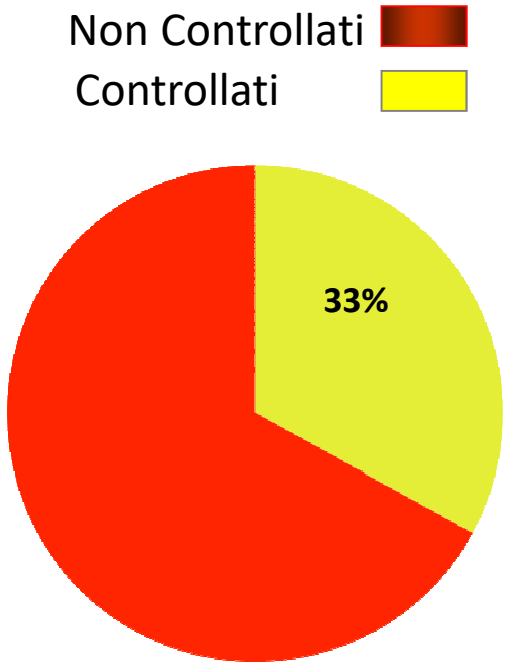
Nonostante la diffusione delle Linee Guida, il controllo dell'asma è ancora insoddisfacente

Studio AIRE (fine anni '90)

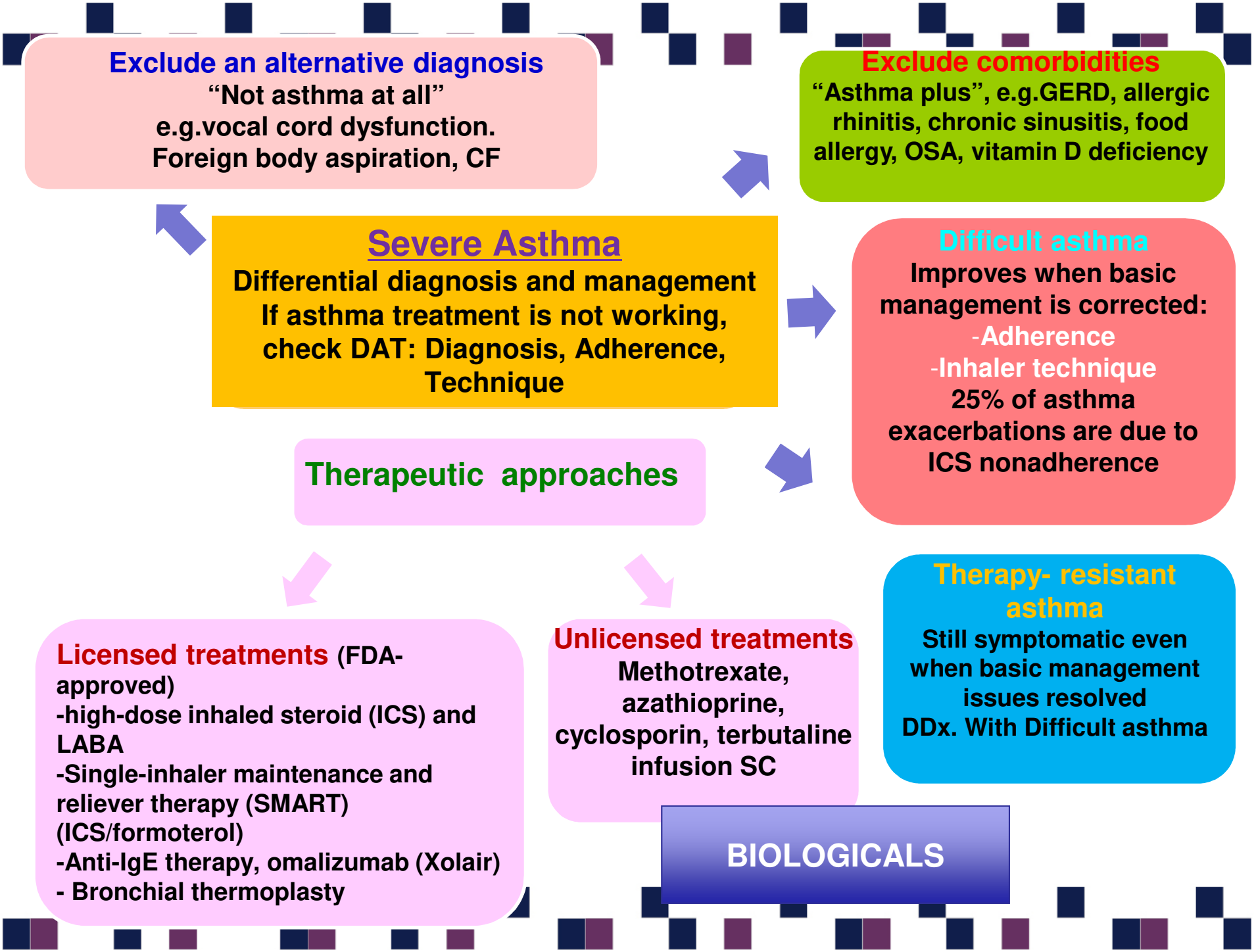


Rabe KF et al., Eur Respir J 2000;16:802-807

Studio NHWS 2008



Demoly P et al., Eur Respir Rev 2010; 19: 150–157


Exclude an alternative diagnosis
"Not asthma at all"
e.g.vocal cord dysfunction.
Foreign body aspiration, CF
Exclude comorbidities
"Asthma plus", e.g.GERD, allergic rhinitis, chronic sinusitis, food allergy, OSA, vitamin D deficiency
Severe Asthma
Differential diagnosis and management
If asthma treatment is not working, check DAT: Diagnosis, Adherence, Technique
Difficult asthma
Improves when basic management is corrected:
-Adherence
-Inhaler technique
25% of asthma exacerbations are due to ICS nonadherence
Therapeutic approaches
Licensed treatments (FDA-approved)
-high-dose inhaled steroid (ICS) and LABA
-Single-inhaler maintenance and reliever therapy (SMART) (ICS/formoterol)
-Anti-IgE therapy, omalizumab (Xolair)
- Bronchial thermoplasty
Unlicensed treatments
Methotrexate, azathioprine, cyclosporin, terbutaline infusion SC
Therapy- resistant asthma
Still symptomatic even when basic management issues resolved
DDx. With Difficult asthma
BIOLOGICALS

ADHERENCE TO ASTHMA THERAPY

Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults

Angelo G. Corsico[a,*], Lucia Cazzoletti[b], Roberto de Marco[b], Christer Janson[c], Deborah Jarvis[d], Maria C. Zoia[a], Massimiliano Bugiani[e], Simone Accordini[b], Simona Villani[f], Alessandra Marinoni[f], David Gislason[g], Amund Gulsvik[h], Isabelle Pin[i], Paul Vermeire[j], Isa Cerveri[a]

Among the 428 non-adherent subjects in ECRHS-I,

the only predictors of increased adherence among the variables considered were having:

- **regular appointments for asthma**
- **not thinking that it is bad to take medicine all the time**

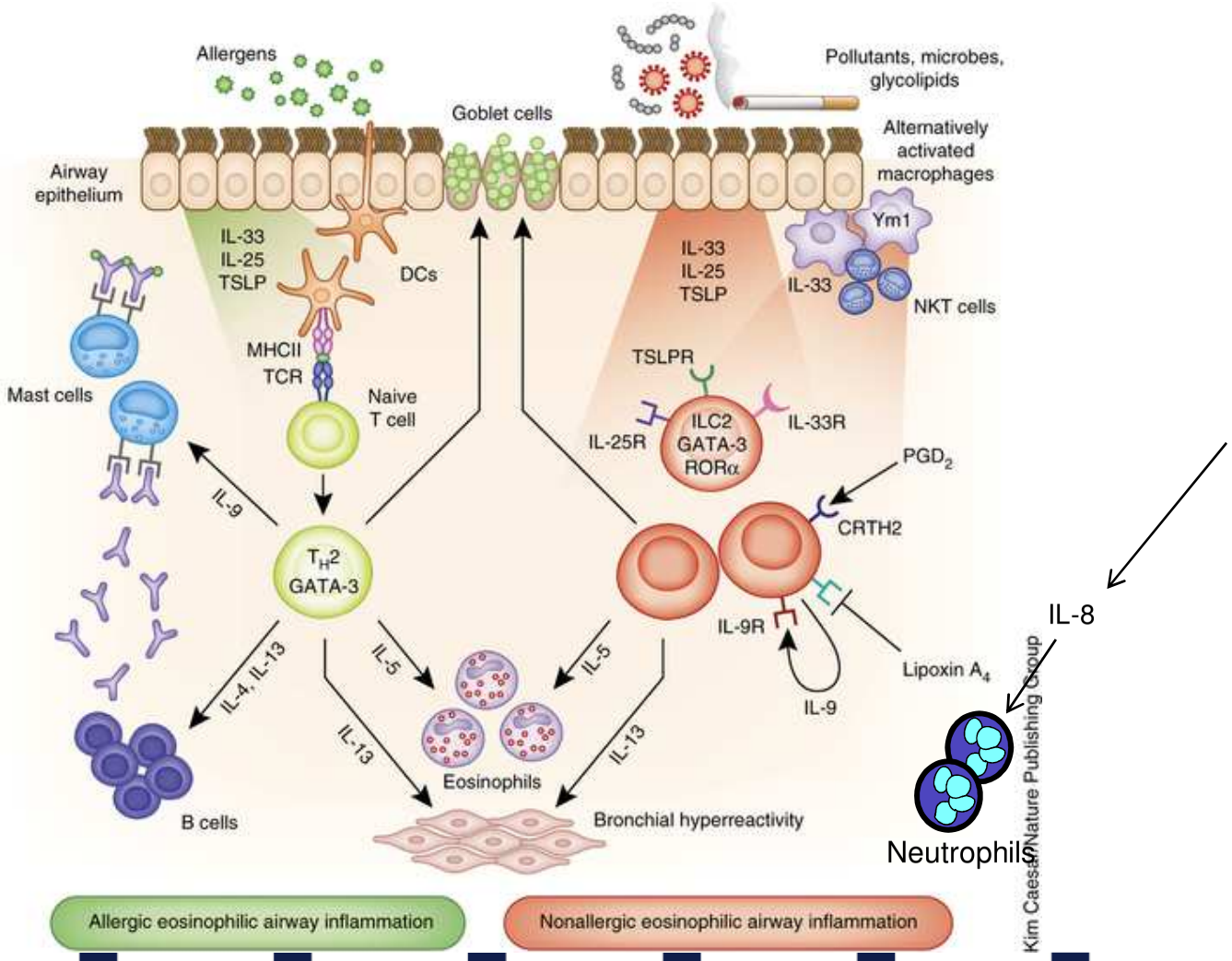
ADHERENCE TO ASTHMA THERAPY

Educazione del paziente

Corretto utilizzo dei devices

ADHERENCE TO ASTHMA THERAPY

SEVERE ASTHMA



modified from:

Lambrecht BN & Hammad H – Nature 2015

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

Three phenotypes of adult-onset asthma

M. Amelink[1], S. B. de Nijs[1], J. C. de Groot[2], P. M. B. van Tilburg[3], P. I. van Spiegel[4], F. H. Krouwels[5], R. Lutter[6], A. H. Zwinderman[7], E. J. M. Weersink[1], A. ten Brinke[2], P. J. Sterk[1] & E. H. Bel[1]

Cluster 1: severe eosinophilic inflammation-predominant

The first group we identified consisted of 69 (34.5%) patients and described a severe eosinophilic inflammation-predominant group with persistent airflow limitation. This group was characterized by predominantly women (71%) with a postbronchodilator FEV_1/FVC percentage predicted of 85.6% (±15.5), increased exhaled FeNO levels and increased sputum eosinophil percentages (6.3% (0.3–24.7)) These patients were treated with medium-to-high doses of ICS and in 26% of the cases combined with maintenance OCS. Twenty-nine per cent had at least three exacerbations and 13% had at least one hospitalization or emergency department visit in the past 12 months.

Cluster 2: frequent symptoms, high healthcare utilization and low sputum eosinophils

The second subphenotype ($n = 41$, 20.5%) had a higher prevalence of patients of non-Caucasian descent and was characterized by obese women with frequent symptoms, high healthcare utilization and low sputum eosinophils. Patients in this cluster had the highest symptom scores and were most often treated for gastroesophageal reflux disease (GERD) or had complaints of GERD. Their postbronchodilator FEV_1 was reduced, but their FEV_1/VC ratio was normal. They were treated with high-dose ICS often combined with OCS or anti-IgE treatment. Despite these high treatment regimens, they had the most frequent doctors' visits (70.7%), exacerbations (53.7%) and hospitalizations or emergency department visits (31.8%). These symptoms and high healthcare utilization seemed to be out of proportion with their clinical and inflammatory markers as they showed no airways obstruction, low FeNO levels and low sputum eosinophils counts.

Cluster 3: mild-to-moderate, well-controlled asthma

The third cluster was the largest and consisted of 90 patients (45%) with a mild-to-moderate, well-controlled asthma. This group has a male preponderance of Caucasian descent and more often a history of aspirin sensitivity. Symptom scores, lung function measurements and airway inflammation were often within the normal range, and these patients were mostly treated with an intermediate dose of ICS. In addition, patients in this cluster had the lowest number of exacerbations (29%) and hospitalizations or emergency department visits (5.6%) in the past 12 months.

SEVERE ASTHMA

FENOTIPO: Asma grave **ALLERGICO**

Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study

Bradley E. Chipps, MD,[a] Robert S. Zeiger, MD, PhD,[b] Larry Borish, MD,[c] Sally E. Wenzel, MD,[d] Ashley Yegin, MD,[e*] Mary Lou Hayden, MS, FNP-C, AE-C,[f] Dave P. Miller, MS,[g] Eugene R. Bleecker, MD,[h] F. Estelle R. Simons, MD,[i] Stanley J. Szefler, MD,[j] Scott T. Weiss, MD, MS,[k] and Tmirah Haselkorn, PhD,[e] for the TENOR Study Group‡ *Sacramento, San Diego, South San Francisco, and San Francisco, Calif, Charlottesville, Va, Pittsburgh, Pa, Winston-Salem, NC, Winnipeg, Manitoba, Canada, Denver, Colo, and Boston, Mass*

(TENOR) study was a large, 3-year, multicenter, observational cohort study of 4756 patients (n = 3489 adults ≥18 years of age, n = 497 adolescents 13-17 years of age, and n = 770 children 6-12 years of age) with severe or difficult-to-treat asthma. identify high-risk patients. IgE and allergen sensitization played a role in the majority of severe or difficult-to-treat asthmatic patients. (J Allergy Clin Immunol 2012;130:332-42.)

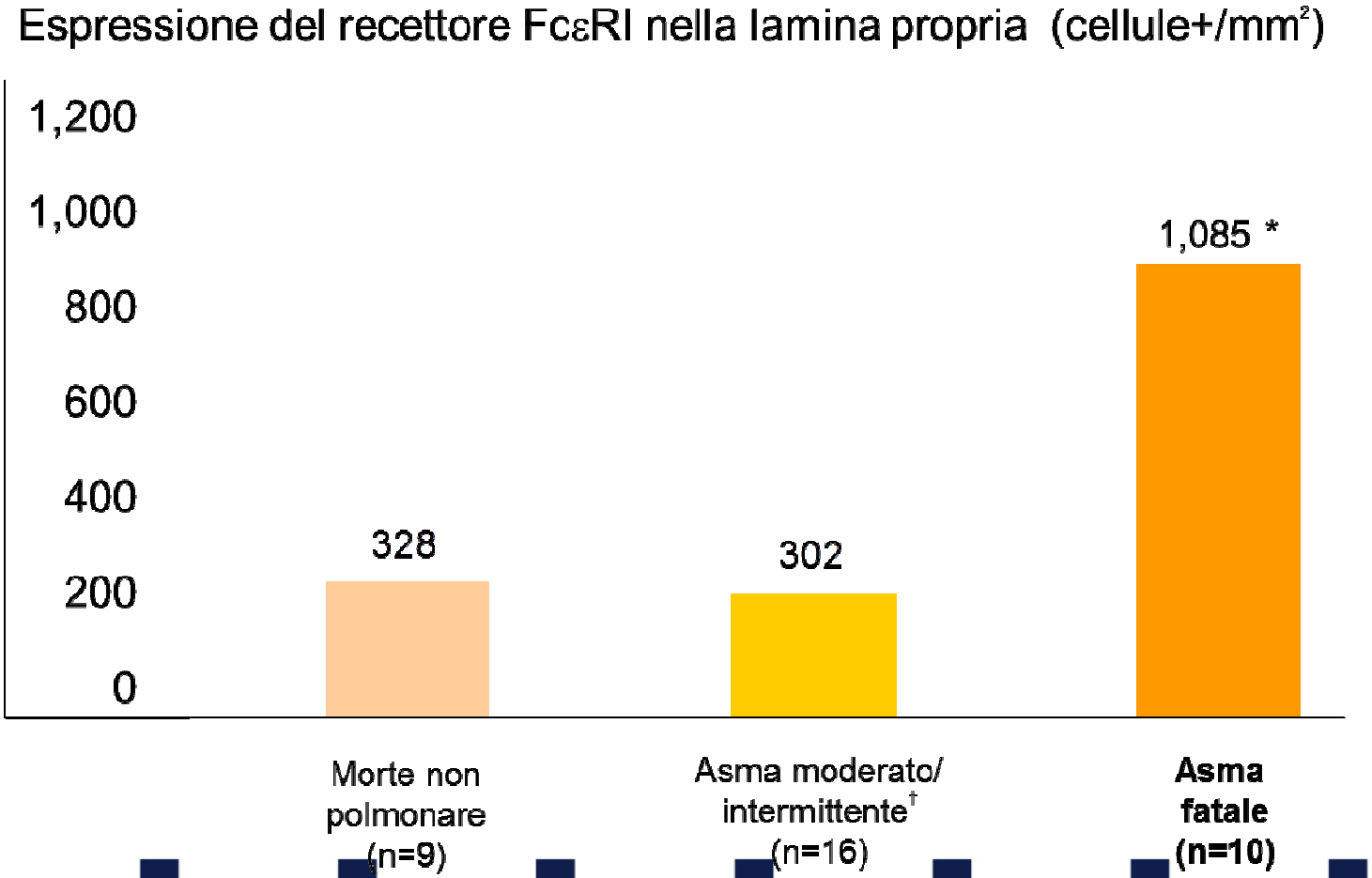
SEVERE ASTHMA

FENOTIPO: Asma grave **ALLERGICO**

- Solitamente **EARLY ONSET**
- **POLISENSIBILIZZATI**…
- ...oppure sensibilizzati ad allergeni **PERENNI**
- Minore prevalenza di poliposi nasale
- Frequenti **ESACERBAZIONI** di asma e **RICOVERI OSPEDALIERI**
- Particolarmente **SINTOMATICI** anche al di fuori delle esacerbazioni

SEVERE ASTHMA

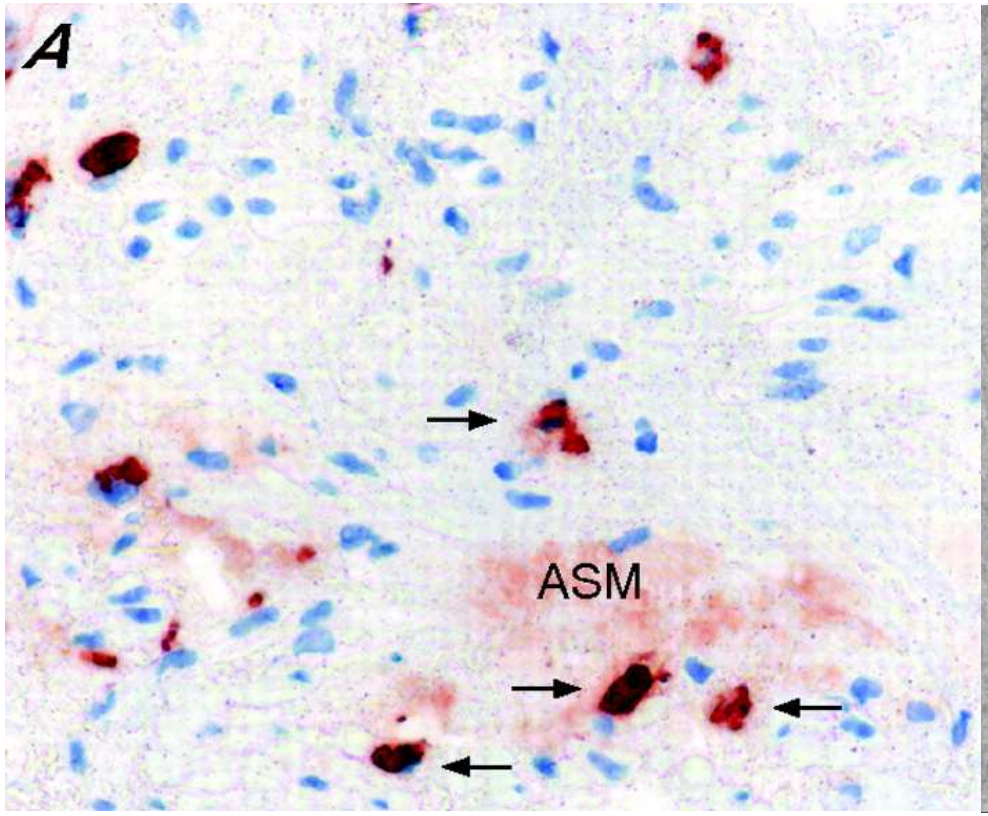
FENOTIPO: Asma grave **ALLERGICO**

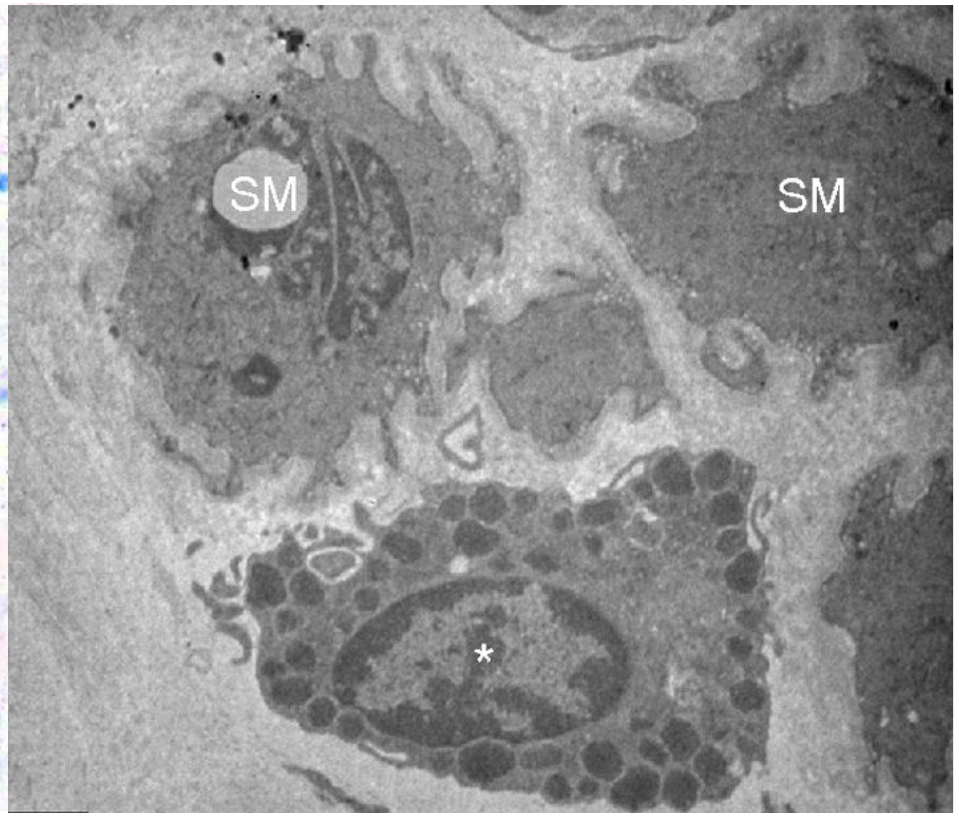


Fregonese L, et al. Am J Respir Crit Care Med 2004

SEVERE ASTHMA

Direct interaction between EOSINOPHILS, MAST CELLS and SMOOTH MUSCLE CELLS





Begueret H et al - Thorax 2007

ERS/ATS guidelines on severe asthma

TABLE 9 Potential phenotype-targeted therapies in severe asthma[#]

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High F_{ENO}	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High F_{ENO}	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

F_{ENO}: exhaled nitric oxide fraction; IL: interleukin; LTB4: leukotriene B4; ICS: inhaled corticosteroid; OCS: oral corticosteroid; MAPK: mitogen-activated protein kinase. #: Unless otherwise stated, these potential treatments apply to adults; ¶: neutrophilic asthma is rare in children.

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

Three phenotypes of adult-onset asthma

M. Amelink[1], S. B. de Nijs[1], J. C. de Groot[2], P. M. B. van Tilburg[3], P. I. van Spiegel[4], F. H. Krouwels[5], R. Lutter[6], A. H. Zwinderman[7], E. J. M. Weersink[1], A. ten Brinke[2], P. J. Sterk[1] & E. H. Bel[1]

Cluster 1: severe eosinophilic inflammation-predominant

The first group we identified consisted of 69 (34.5%) patients and described a severe eosinophilic inflammation-predominant group with persistent airflow limitation. This group was characterized by predominantly women (71%) with a postbronchodilator FEV_1/FVC percentage predicted of 85.6% (±15.5), increased exhaled FeNO levels and increased sputum eosinophil percentages (6.3% (0.3–24.7)) These patients were treated with medium-to-high doses of ICS and in 26% of the cases combined with maintenance OCS. Twenty-nine per cent had at least three exacerbations and 13% had at least one hospitalization or emergency department visit in the past 12 months.

Cluster 2: frequent symptoms, high healthcare utilization and low sputum eosinophils

The second subphenotype (n = 41, 20.5%) had a higher prevalence of patients of non-Caucasian descent and was characterized by obese women with frequent symptoms, high healthcare utilization and low sputum eosinophils. Patients in this cluster had the highest symptom scores and were most often treated for gastroesophageal reflux disease (GERD) or had complaints of GERD. Their postbronchodilator FEV_1 was reduced, but their FEV_1/VC ratio was normal. They were treated with high-dose ICS often combined with OCS or anti-IgE treatment. Despite these high treatment regimens, they had the most frequent doctors' visits (70.7%), exacerbations (53.7%) and hospitalizations or emergency department visits (31.8%). These symptoms and high healthcare utilization seemed to be out of proportion with their clinical and inflammatory markers as they showed no airways obstruction, low FeNO levels and low sputum eosinophils counts.

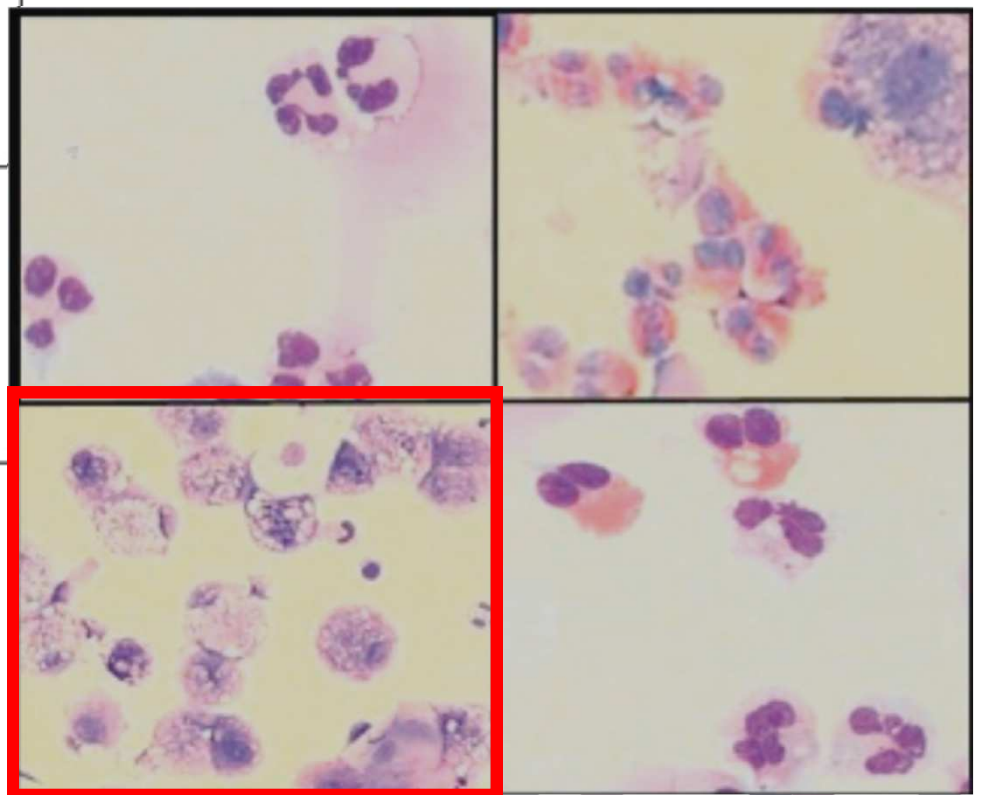
Cluster 3: mild-to-moderate, well-controlled asthma

The third cluster was the largest and consisted of 90 patients (45%) with a mild-to-moderate, well-controlled asthma. This group has a male preponderance of Caucasian descent and more often a history of aspirin sensitivity. Symptom scores, lung function measurements and airway inflammation were often within the normal range, and these patients were mostly treated with an intermediate dose of ICS. In addition, patients in this cluster had the lowest number of exacerbations (29%) and hospitalizations or emergency department visits (5.6%) in the past 12 months.

SEVERE ASTHMA

FENOTIPO: Asma grave **NEUTROFILICO**

	Noneosinophilic asthma	Eosinophilic asthma
	Normal eosinophil count (<1.9%)	**Raised eosinophil count**
Normal neutrophil count (< 61%)	**Paucigranulocytic** - Well controlled or intermittent asthma - Consider alternative diagnosis	**Eosinophilic** - Typical asthma, frequently associated with atopic disease - May indicate inadequate corticosteroid therapy
Raised neutrophil count	**Neutrophilic** - Acute infection (viral or bacterial) - Chronic infection (chlamydia, adenovirus) - Smoking - Environmental pollutants (ozone, NO_2) - Occupational antigens - Endotoxin exposure - Obesity	**Mixed granulocytic** - (Severe) asthma exacerbations - Refractory asthma



NON EOSINOPHILIC SEVERE ASTHMA

Acceleration of lung function decline

↑ Airway oxidative stress

↑ IgE production

↑ Neutrophilic airway inflammation

↓ Histone deacetylase activity at macrophage level

↑ GR-β / GR-α at PBMC level

Corticosteroid resistance

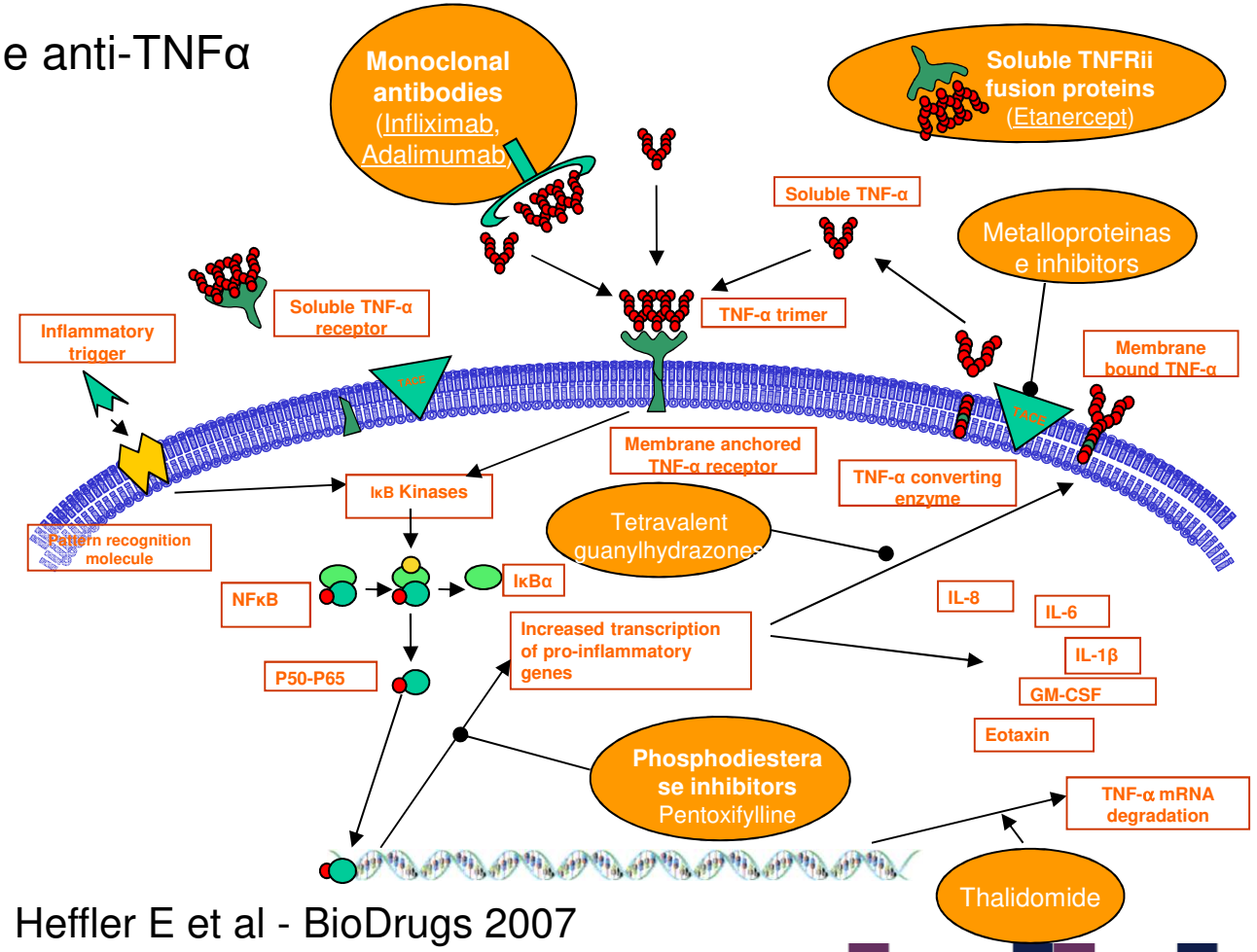
More severe asthma

Del Giacco SR et al. Is there a role for Allergy in severe Asthma? – Allergy 2017

SEVERE ASTHMA

FENOTIPO: Asma grave **NEUTROFILICO**

Strategie anti-TNFα



Heffler E et al - BioDrugs 2007

ANTI-TNF-ALFA

Studi su un maggior numero di pazienti si sono associati ad un inaspettato incremento di neoplasie nei pazienti trattati

Studi interrotti e farmaci non più attualmente studiati nell'asma grave

ERS/ATS guidelines on severe asthma

TABLE 9 Potential phenotype-targeted therapies in severe asthma[#]

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High F_{ENO}	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High F_{ENO}	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

F_{ENO}: exhaled nitric oxide fraction; IL: interleukin; LTB4: leukotriene B4; ICS: inhaled corticosteroid; OCS: oral corticosteroid; MAPK: mitogen-activated protein kinase. #: Unless otherwise stated, these potential treatments apply to adults; ¶: neutrophilic asthma is rare in children.

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

Three phenotypes of adult-onset asthma

M. Amelink[1], S. B. de Nijs[1], J. C. de Groot[2], P. M. B. van Tilburg[3], P. I. van Spiegel[4], F. H. Krouwels[5], R. Lutter[6], A. H. Zwinderman[7], E. J. M. Weersink[1], A. ten Brinke[2], P. J. Sterk[1] & E. H. Bel[1]

Cluster 1: severe eosinophilic inflammation-predominant

The first group we identified consisted of 69 (34.5%) patients and described a severe eosinophilic inflammation-predominant group with persistent airflow limitation. This group was characterized by predominantly women (71%) with a postbronchodilator FEV_1/FVC percentage predicted of 85.6% (±15.5), increased exhaled FeNO levels and increased sputum eosinophil percentages (6.3% (0.3–24.7)) These patients were treated with medium-to-high doses of ICS and in 26% of the cases combined with maintenance OCS. Twenty-nine per cent had at least three exacerbations and 13% had at least one hospitalization or emergency department visit in the past 12 months.

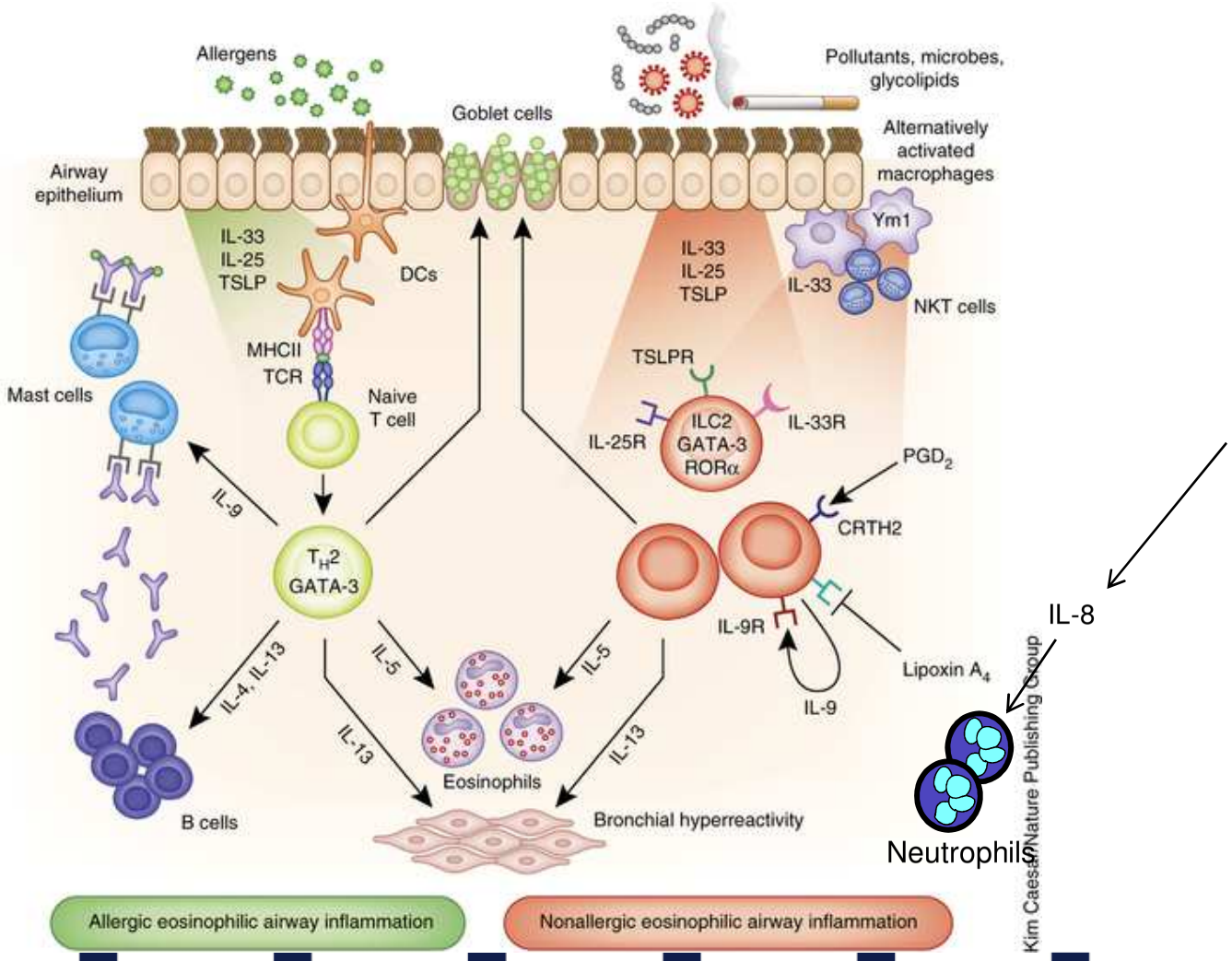
Cluster 2: frequent symptoms, high healthcare utilization and low sputum eosinophils

The second subphenotype (n = 41, 20.5%) had a higher prevalence of patients of non-Caucasian descent and was characterized by obese women with frequent symptoms, high healthcare utilization and low sputum eosinophils. Patients in this cluster had the highest symptom scores and were most often treated for gastroesophageal reflux disease (GERD) or had complaints of GERD. Their postbronchodilator FEV_1 was reduced, but their FEV_1/VC ratio was normal. They were treated with high-dose ICS often combined with OCS or anti-IgE treatment. Despite these high treatment regimens, they had the most frequent doctors' visits (70.7%), exacerbations (53.7%) and hospitalizations or emergency department visits (31.8%). These symptoms and high healthcare utilization seemed to be out of proportion with their clinical and inflammatory markers as they showed no airways obstruction, low FeNO levels and low sputum eosinophils counts.

Cluster 3: mild-to-moderate, well-controlled asthma

The third cluster was the largest and consisted of 90 patients (45%) with a mild-to-moderate, well-controlled asthma. This group has a male preponderance of Caucasian descent and more often a history of aspirin sensitivity. Symptom scores, lung function measurements and airway inflammation were often within the normal range, and these patients were mostly treated with an intermediate dose of ICS. In addition, patients in this cluster had the lowest number of exacerbations (29%) and hospitalizations or emergency department visits (5.6%) in the past 12 months.

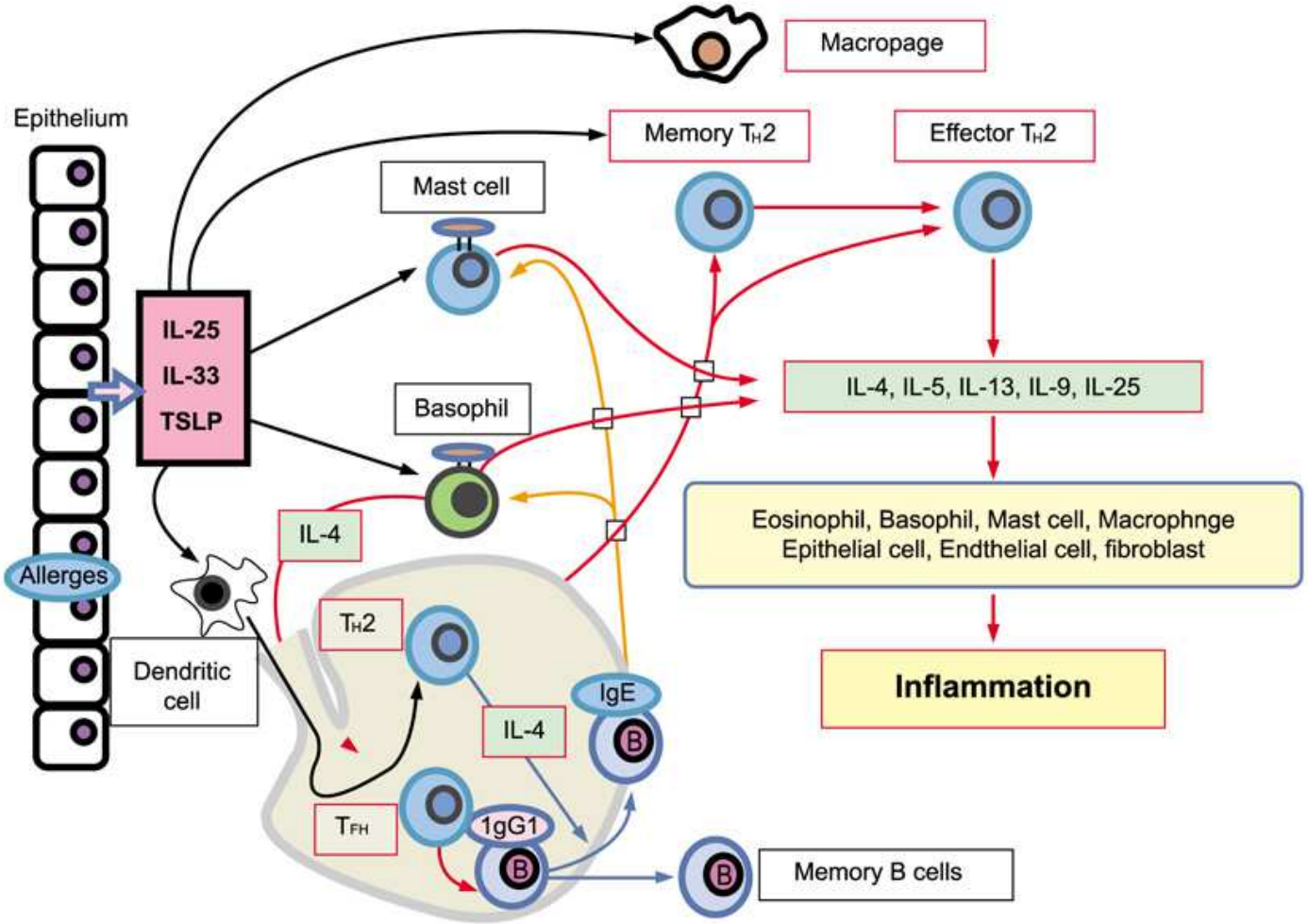
SEVERE ASTHMA



modified from:

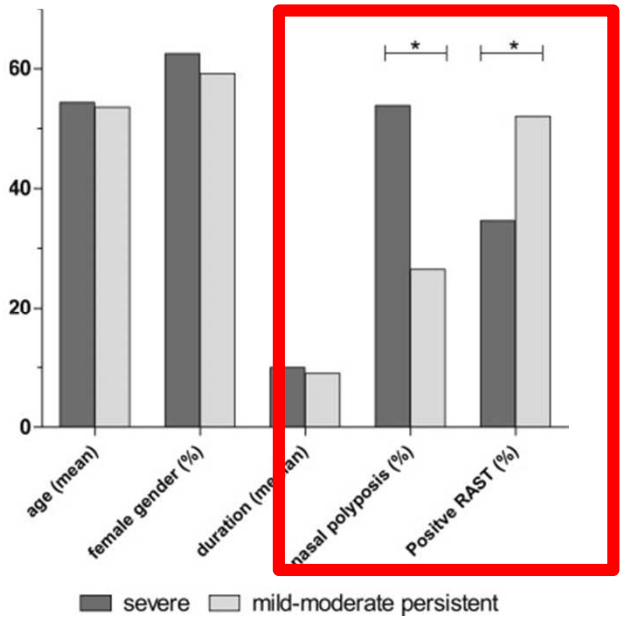
Lambrecht BN & Hammad H – Nature 2015

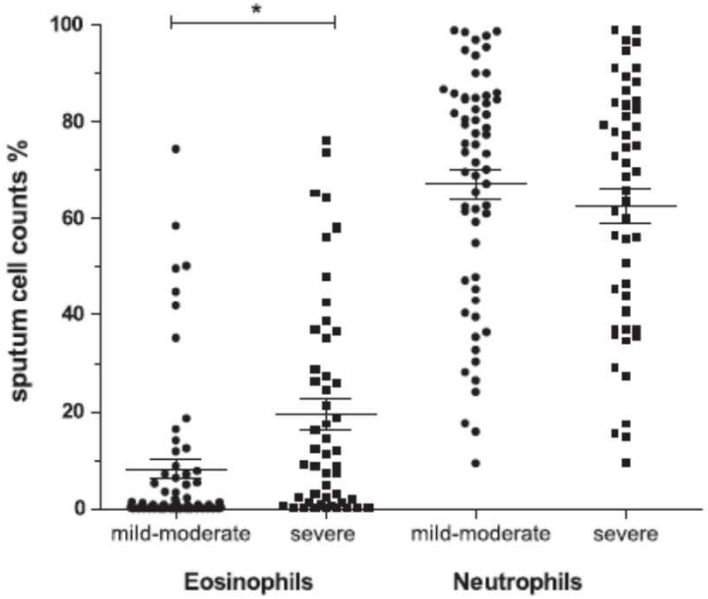
SEVERE ASTHMA



Severe adult-onset asthma: A distinct phenotype

Marijke Amelink, MD,[a] Jantina C. de Groot, MD,[b] Selma B. de Nijs, MSc,[a] Rene Lutter, PhD,[a] Aeilko H. Zwinderman, PhD,[c] Peter J. Sterk, MD, PhD,[a] Anneke ten Brinke, MD, PhD,[b] and Elisabeth H. Bel, MD, PhD[a] *Amsterdam and Leeuwarden, The Netherlands*



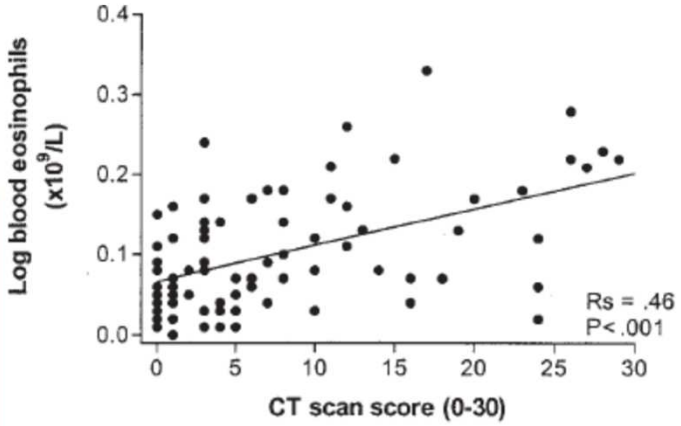


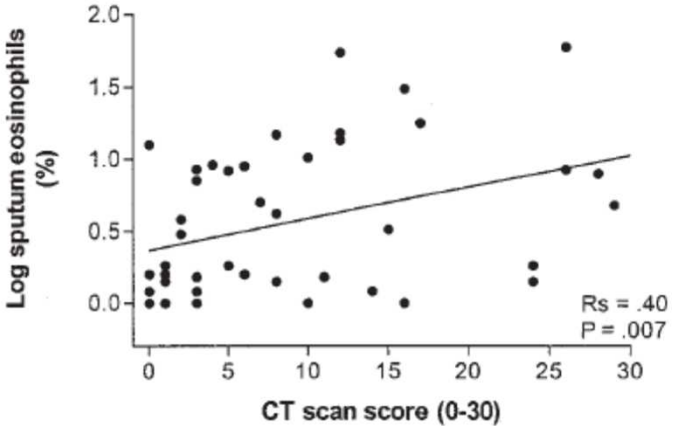
	Mild-to-moderate persistent asthma (n = 98)	Severe asthma (n = 78)	*P* value
Blood eosinophils (10^9/L)	0.18 (0.09-0.31)	0.25 (0.14-0.5)	.05
Blood neutrophils (10^9/L)	4 (3.1-4.9)	5.3 (3.9-6.8)	<.001
FENO (ppb)	27 (16-50)	38 (19-73)	.02
Sputum eosinophils (% [n = 110])	0.8 (0.1-7.1)	11.6 (1.5-33.4)	<.001
Sputum neutrophils (% [n = 110])	73.5 (46.7-84.9)	67.2 (37.9-83.2)	.9

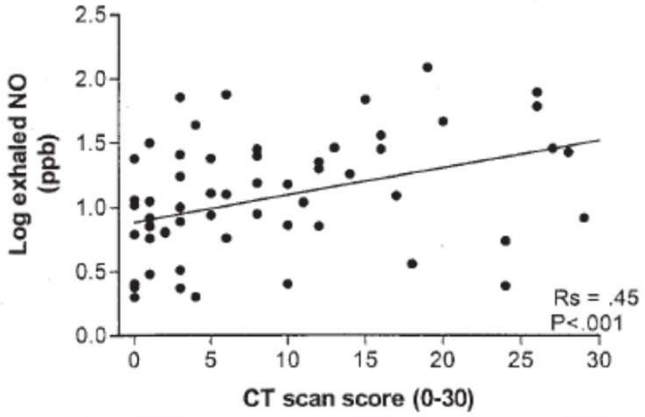
Values are presented as medians (first and third interquartiles).

Chronic sinusitis in severe asthma is related to sputum eosinophilia

Anneke ten Brinke, MD,[a,d] Diana C. Grootendorst, MSc,[a]
Judith Th. Schmidt, MD, PhD,[b] Francisca T. de Bruïne, MD, PhD,[c]
Mark A. van Buchem, MD, PhD,[c] Peter J. Sterk, MD, PhD,[a] Klaus F. Rabe, MD, PhD,[a]
and Elisabeth H. Bel, MD, PhD[a] *Leiden and Leeuwarden, The Netherlands*

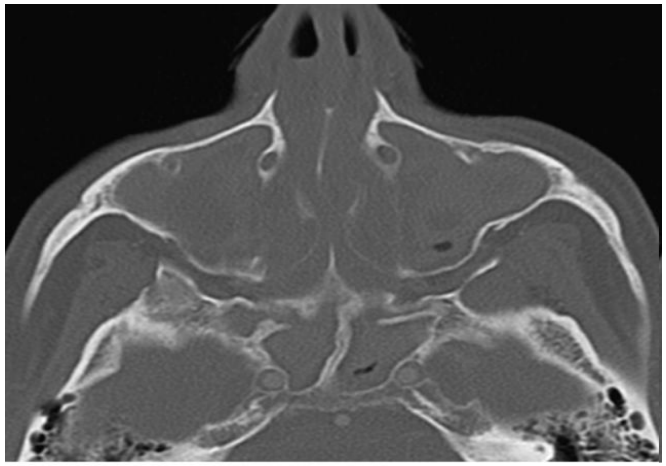


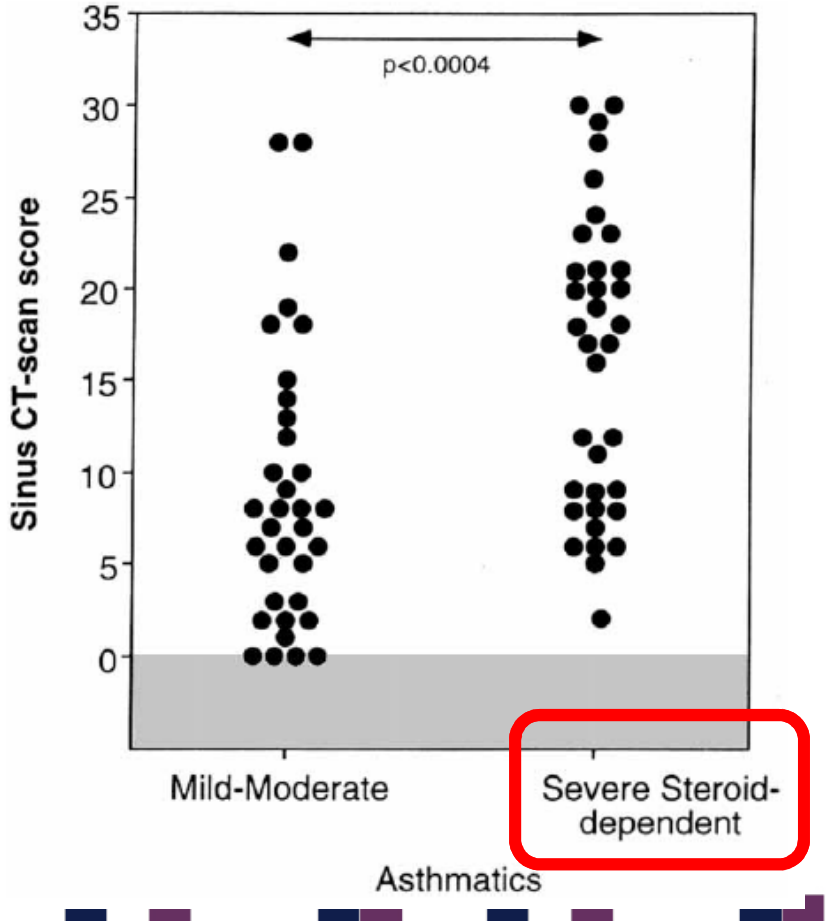




EOSINOPHILIC REFRACTORY ASTHMA

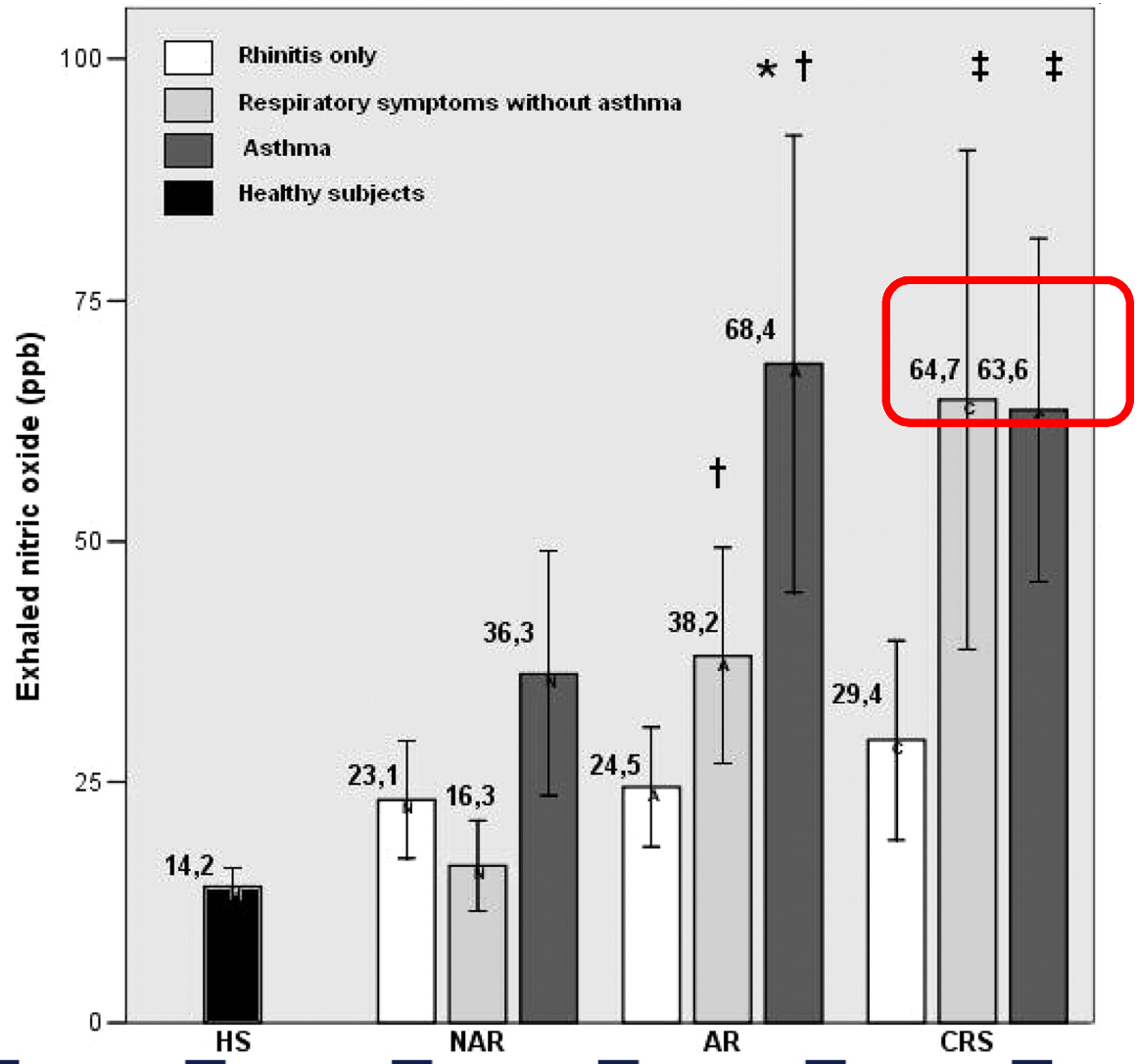
Chronic rhinosinusitis as risk factor for asthma





Bresciani M et al. – JACI 2001

EXHALED NITRIC OXIDE IN CHRONIC RHINOSINUSITIS



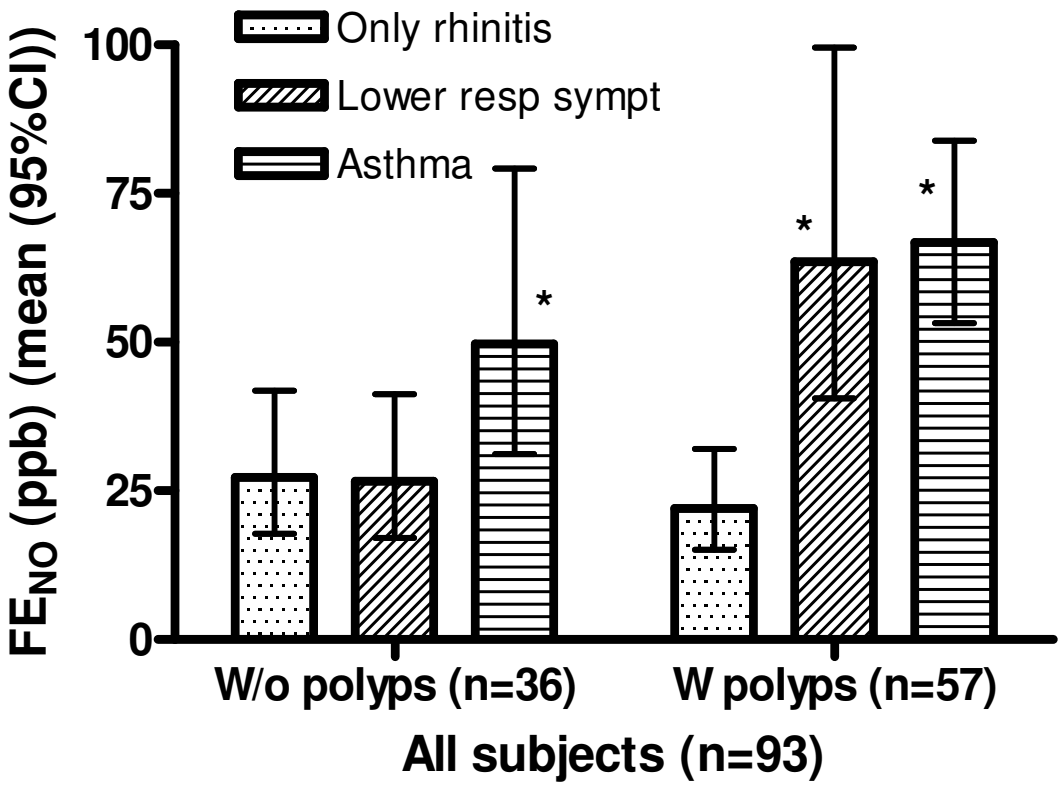
Rolla G et al. Chest 2007

EXHALED NITRIC OXIDE IN CHRONIC RHINOSINUSITIS

Parametro	B	I.C. 95%	Significatività (p)
Costante	1.181	0.886-1.476	<0.001
	0.003	-0.001 – 0.008	
Sesso		0.080	0.477
	-0.068	-0.197 – 0.061	
Asma	0.372	0.219 – 0.526	**<0.001**
Asthma-like	0.232	0.056 – 0.407	**0.01**
Poliposi nasali	0.179	0.043 – 0.315	**0.01**
Asthma-like + Poliposi	0.546	0.208 – 0.885	**0.002**

Guida G et al. Chest 2010

EXHALED NITRIC OXIDE IN CHRONIC RHINOSINUSITIS



Guida G et al. Chest 2010

DETERMINANTS OF POOR ASTHMA CONTROL

Table 3. Determinants of asthma control according to ACQ (dependent variable).

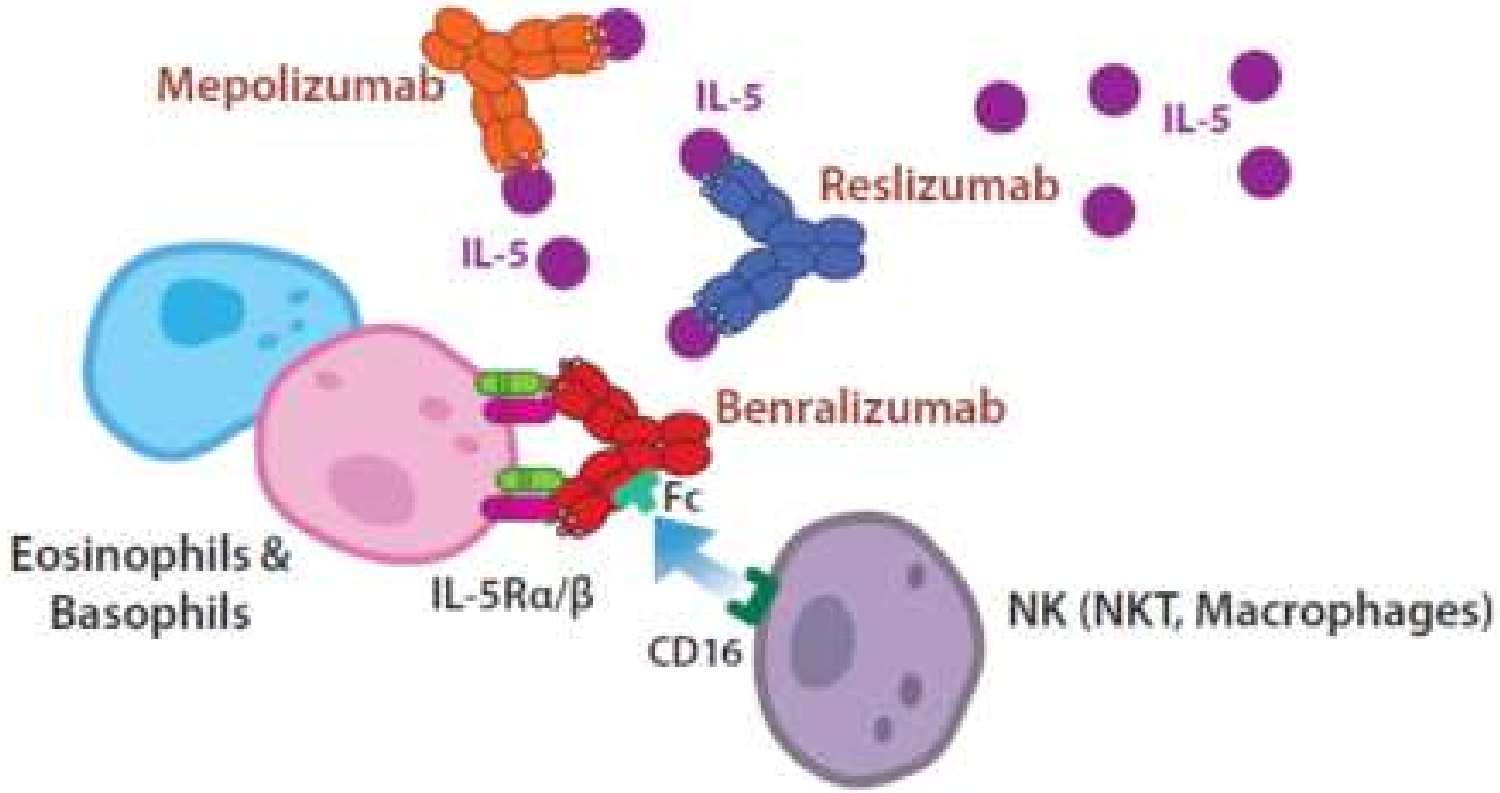
PARAMETER	Mean square	*F*	*p*-value
Corrected model	1.207	1.656	0.144
Intercept	1.735	2.380	0.133
Gender	1.283	1.760	0.195
Age	0.407	0.559	0.461
Atopy	0.368	0.506	0.483
BMI	0.483	0.662	0.422
BUD equivalents	0.003	0.004	0.948
FE_{NO}	0.000	0.000	0.989
Jaw_{NO}	2.513	3.448	0.073
$Calv_{NO}$	0.256	0.351	0.558
nNO	5.856	8.035	**0.008**

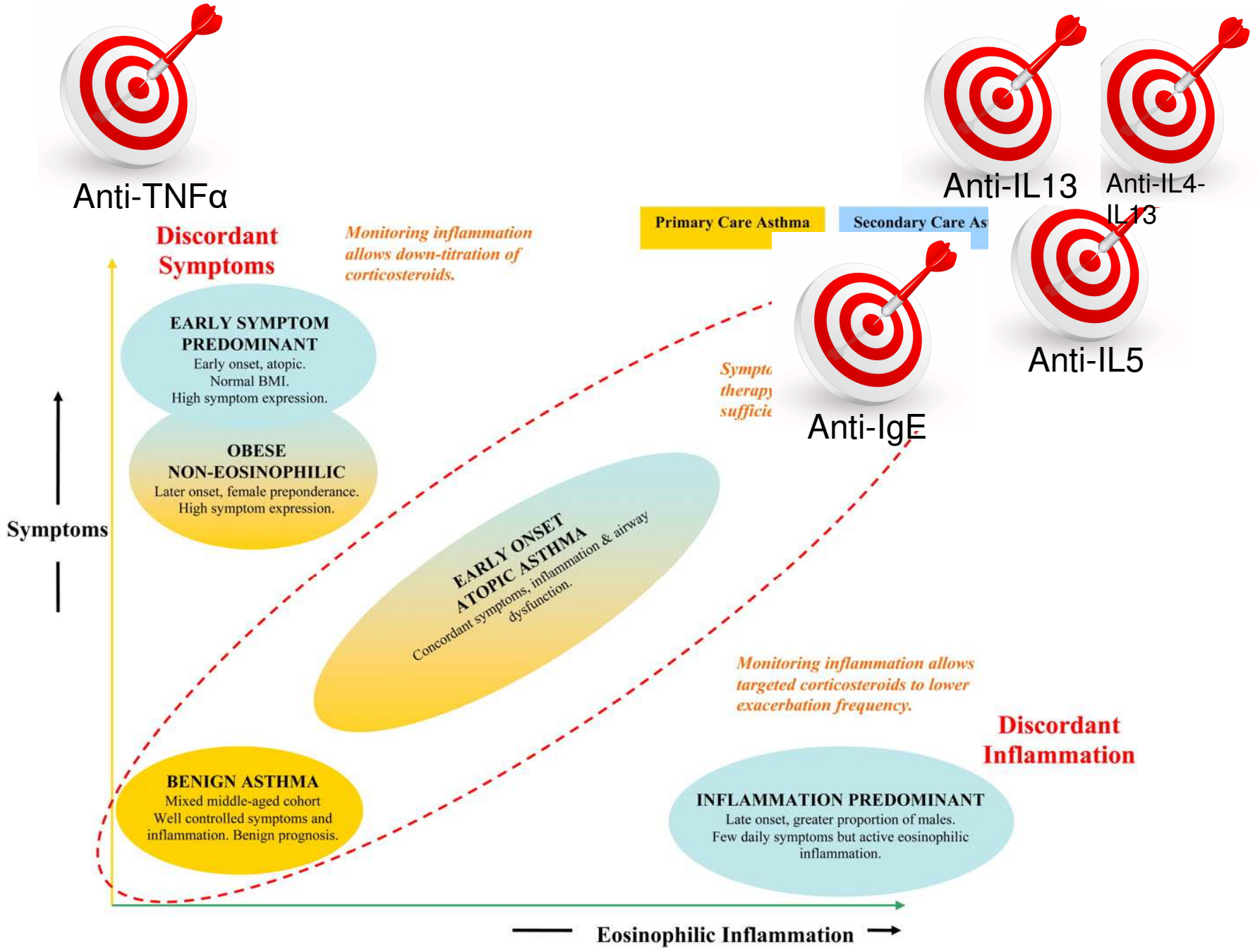
BUD = Budesonide.
Significant *p*-values have been marked in **bold font**.

	Patients with controlled asthma (ACQ ⩽ 1.5) ($n = 54$)	Patients with uncontrolled asthma (ACQ > 1.5) ($n = 28$)	*p*-value
Age (median age, range)	47.5, 21–80	50.1, 32–59	0.707
Gender (M/F)	32/22	8/20	0.138
Atopy (*n*,%)	43 (79.6%)	19 (67.8%)	0.342
BMI (mean ± DS)	24.1 ± 2.7	24.0 ± 3.7	0.758
Patients with CRS (*n*,%)	23 (42.6%)	18 (64.3%)	0.097
Patients with CRSwNP (*n*,%)	18 (33.3%)	16 (57.1%)	**0.038**
FEV_1% pr. (mean% ± DS)	91.5 ± 15.5	79.1 ± 19.2	0.06
FEV_1/VC (mean% ± DS)	70.6 ± 9.4	69.5 ± 7.8	0.763
FEF_{25-75}% pr. (mean% ± DS)	59.8 ± 26.5	44.9 ± 30.4	0.198
FE_{NO} (mean ppb, IC95%)	40.6 (28.8–52.4)	57.0 (26.1–87.9)	0.107
nNO (mean ppb ± DS)	705.1 ± 405.2	481.6 ± 390.6	**0.018**
Jaw_{NO} (mean nl/s, IC95%)	2.03 (1.46–2.59)	3.34 (0.63–6.05)	0.104
$Calv_{NO}$ (mean ppb, IC95%)	5.24 (2.82–7.65)	4.72 (1.43–8.01)	0.836
Inhaled Budesonide equivalent (mcg, IC95%)	658.7 (461.5–856.0)	950.0 (550.0–1350.0)	0.163

Heffler E et al. J Breath Res 2013

ANTI-IL5 STRATEGIES

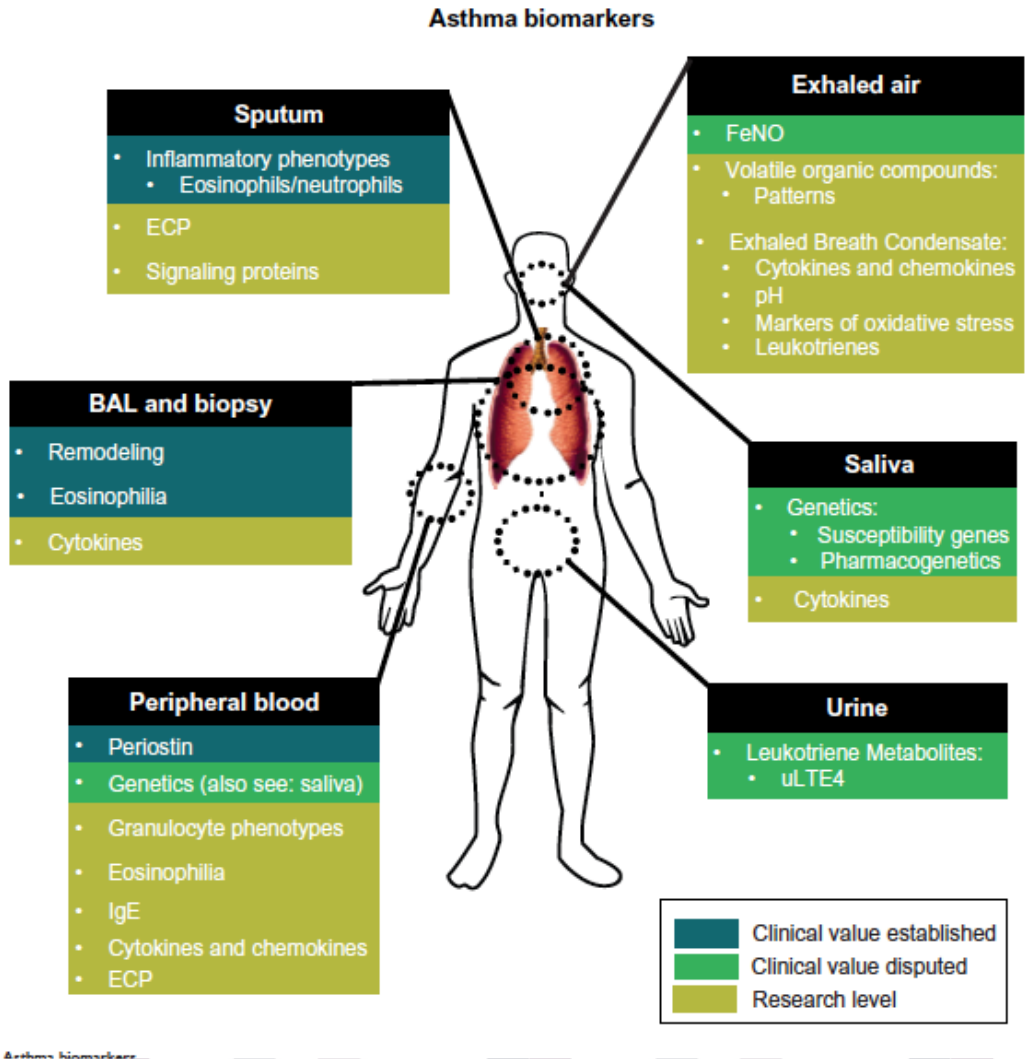




Haldar P, Pavord ID et al. – Am J Respir Crit Care Med 2008

EOS vs NON EOS SEVERE ASTHMA

WHICH BIOMARKERS?

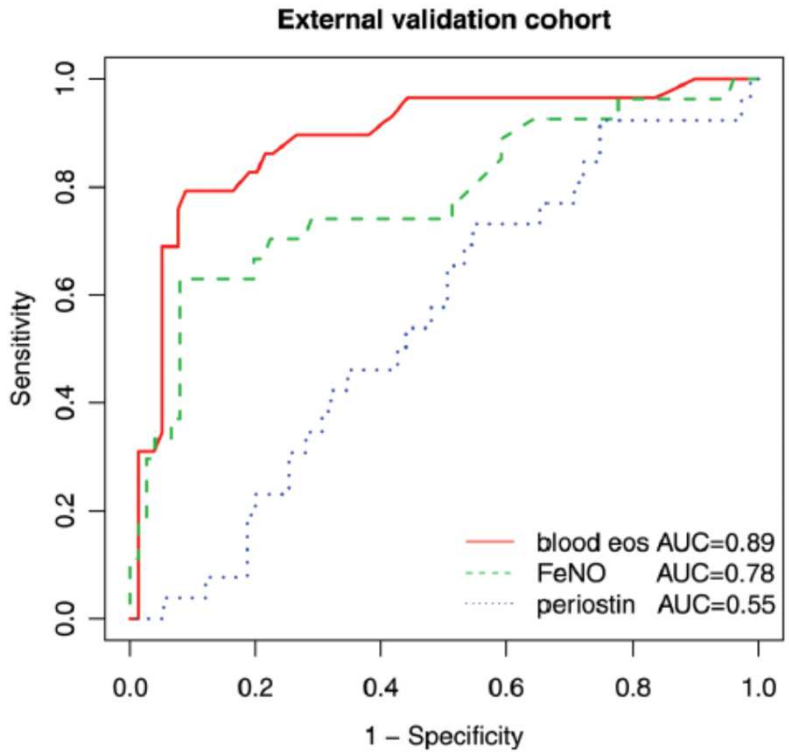


Vijverberg S et al. Biologics 2013

External validation of blood eosinophils, FE_{NO} and serum periostin as surrogates for sputum eosinophils in asthma

A H Wagener,[1] S B de Nijs,[1] R Lutter,[1,2] A R Sousa,[3] E J M Weersink,[1] E H Bel,[1] P J Sterk[1]

Thorax 2015;**70**:115–120.



Discriminating sputum-eosinophilic asthma: Accuracy of cutoffs in blood eosinophil measurements versus a composite index, ELEN

Score 1 (score for sputum eosinophils <2·0%):

$-9{\cdot}5243 + [70{\cdot}0975 \times \text{blood eosinophils/blood lymphocytes}] - [3{\cdot}7790 \times \text{natural log(blood eosinophils/blood neutrophils)}]$ (equation 1)

Score 2 (score for sputum eosinophils ≥2·0%):

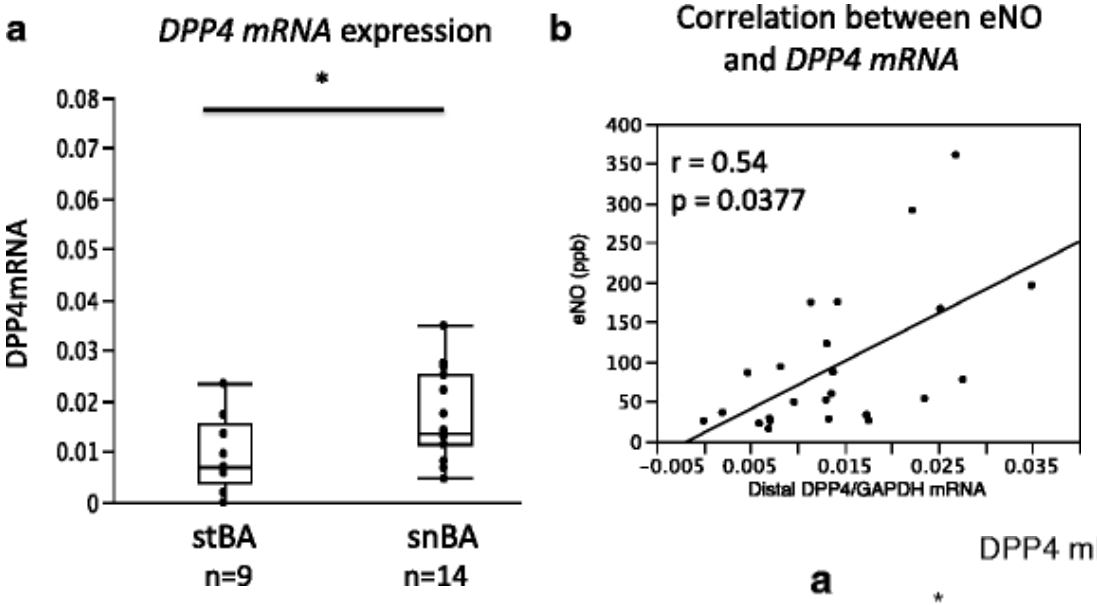
$-14{\cdot}5853 + [101{\cdot}2198 \times \text{blood eosinophils/blood lymphocytes}] - [3{\cdot}9567 \text{ x natural log(blood eosinophils/blood neutrophils)}]$ (equation 2)

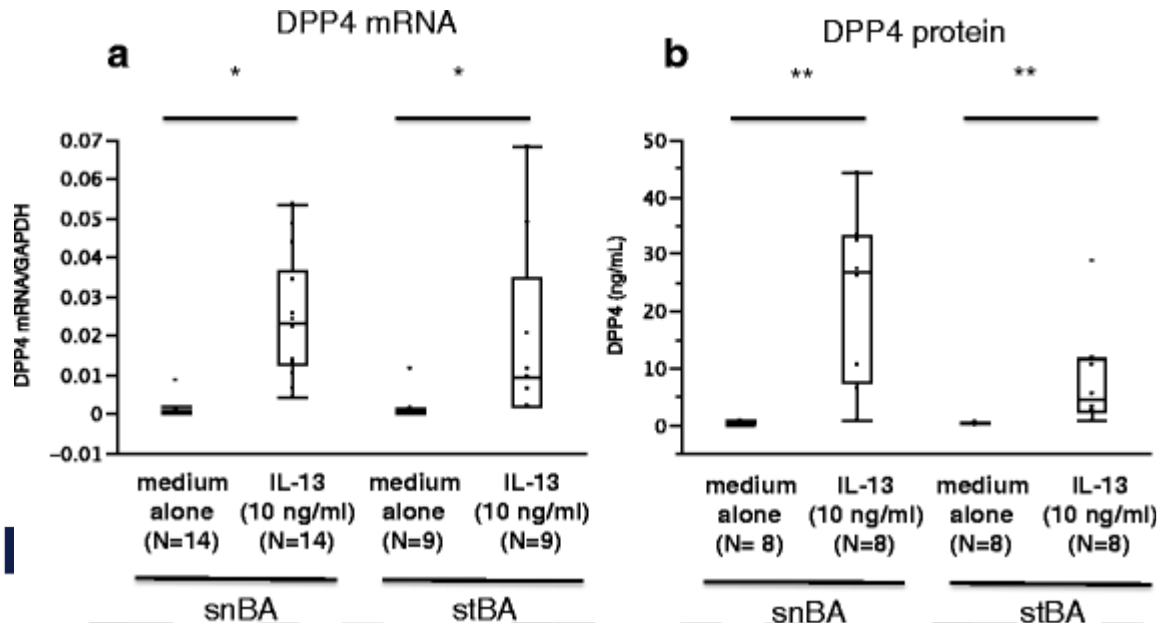
Decision rule

The decision rule for case assignment to groups is as follows: if score 1 > score 2, assign the subject to the non-sputum eosinophilic group; otherwise, assign the subject to the sputum eosinophilic group.

Khartry DB et al – JACI 2015

ARE THE CURRENT AVAILABLE BIOMARKERS ENOUGH?





Shiobara T et al – Resp Res 2016

CONCLUSIONS

- Severe asthma is an heterogeneous disease
- It comprises different phenotypes (and endotypes)
- ***Allergic severe asthma*** is a frequent phenotype
- ***Eosinophilic refractory asthma*** is the most frequent phenotype of severe asthma → nasal polyposis as hallmark
- ***Non eosinophilic severe asthma*** → still a "orphan" disease
- Novel emerging biological treatments will be soon available → problem of choosing the right therapy for each sub-phenotype


thank you
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
dziękuję
bedankt
спасибо
Баярлалаа
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
хвала
asante
manana
obrigada
murakoze
tenki
chokrane
mauruuru
hvala
kiitos
dankie
nandri
nanni
dhanyavad
bayarlalaa
gràcie
köszönöm
enkosi
akun
dankon
ačiū
djiere dieuf
tau
mochchakkeram
mamnun
дякую
go raibh maith agat
sukriya
kop khun krap
chnorakaloutioun
gralias ago
gràcies
sulpáy
tạiku
takk
arigatô
dakujem
trugarez
grazie
terima kasih
ありがとう
najis tuke
tanemirt
rahmet
dhanyavadagalu
shukriya
merce
мерси
ευχαριστώ
diolch
xièxie
감사합니다
তোমাকে ধন্যবাদ
rahmat
kam sah hamnida
didi madloba
mësi
sagolun
sobodi
dēkuji
barka
mersi
kia ora
spas
welalin
tack