
7
APRILE
8
OTTICA
RESPIRO
VERONA 2017
CROWNE PLAZA

Verso una terapia personalizzata delle malattie ostruttive

Fabio Ricciardolo
Dipartimento di Scienze Cliniche e Biologiche
Malattie dell'Apparato Respiratorio
Università di Torino

COI
Rapporti di natura lavorativa con industrie negli ultimi 2 anni

- Finanziamenti di ricerca: Boehringer; Chiesi; Mundipharma; AstraZeneca; GSK
- Advisory Board: AstraZeneca; Mundipharma; Novartis
- Speaker: Chiesi; Guidotti/Malesci; Boehringer; Mundipharma; Novartis; Teva; Merck; AstraZeneca

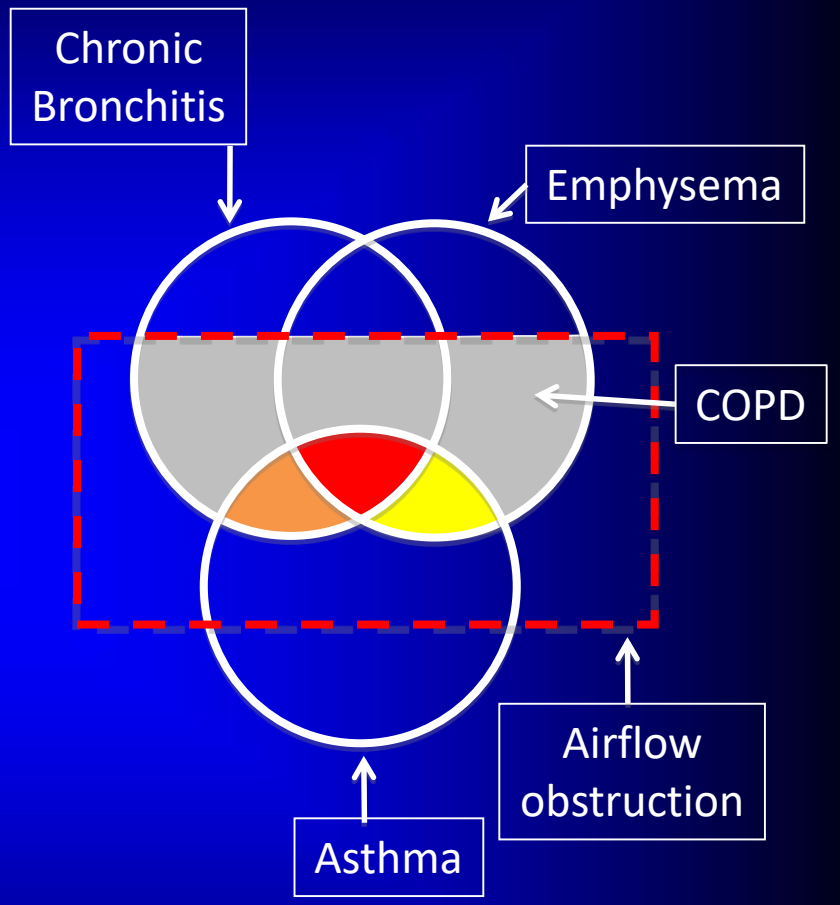
Asthma-COPD overlap syndrome

- Asthma with fixed airflow limitation:
  Asthma phenotype

- Asthma + Smoking ➤ Fixed airflow limitation:
  COPD

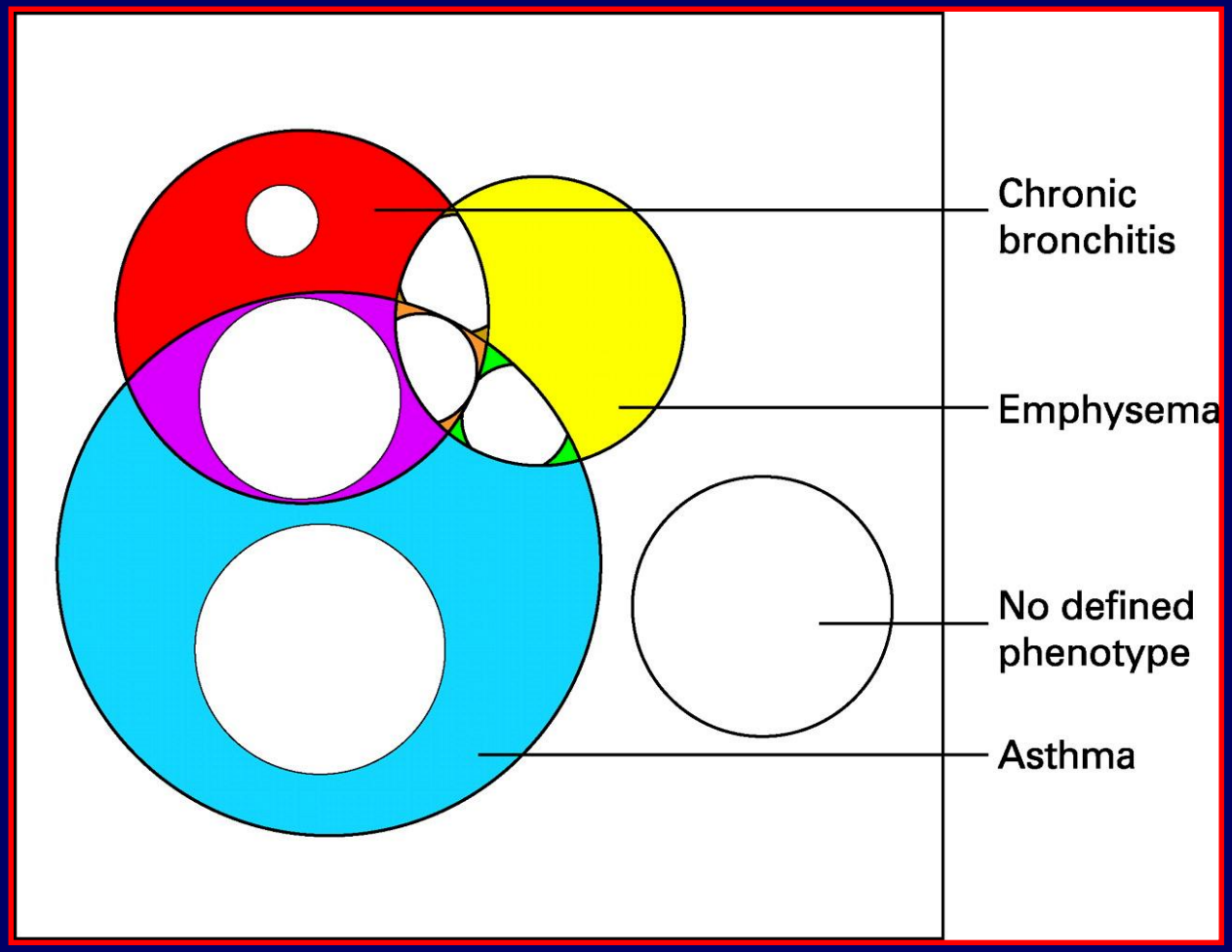
- Coexistence of asthma and COPD in older people: *Overlap syndrome*

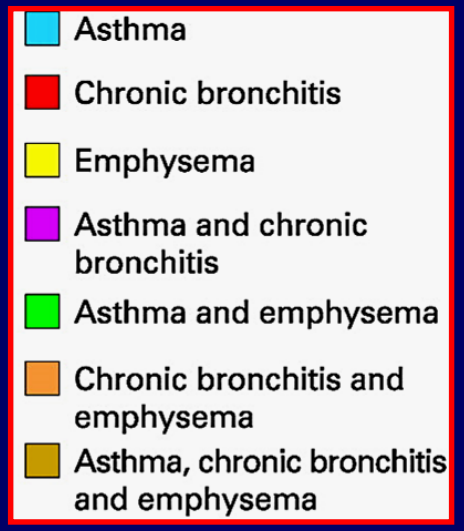
- Severe Asthma:
  Overlap?



Wellington Respiratory Survey (NZ)

Diagram di Venn Proporzionale





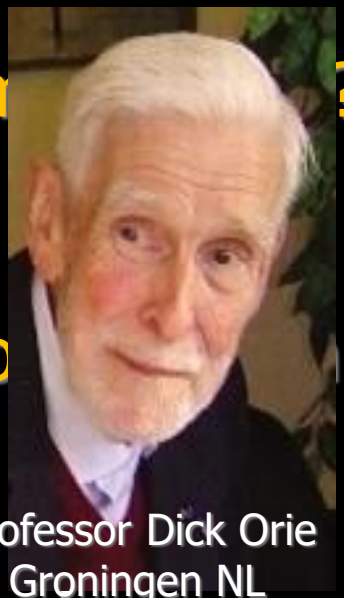
- 469 soggetti
- diagnosi medica
- spirometria
- TC

Marsh, S E et al. Thorax 2008;63:761-767

"Dutch hypothesis"

Comm ?

Commo isms



Professor Dick Orie
Groningen NL

Asthma **COPD**

"British hypothesis"

ses

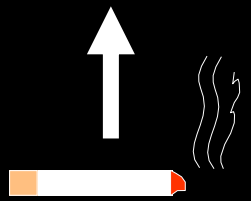
Dif nisms

Prof Charles Fletcher
London UK

Asthma

Allergy

COPD



Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

GINA 2014

KEY POINTS

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
- Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'; however, these do not correlate strongly with specific pathological processes or treatment responses.
- The diagnosis of asthma should be based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.
- If possible, the evidence for the diagnosis of asthma should be documented before starting controller treatment, as it is often more difficult to confirm the diagnosis afterwards.
- Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.

DEFINITION OF ASTHMA

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma and that distinguish it from other respiratory conditions.

Definition of COPD

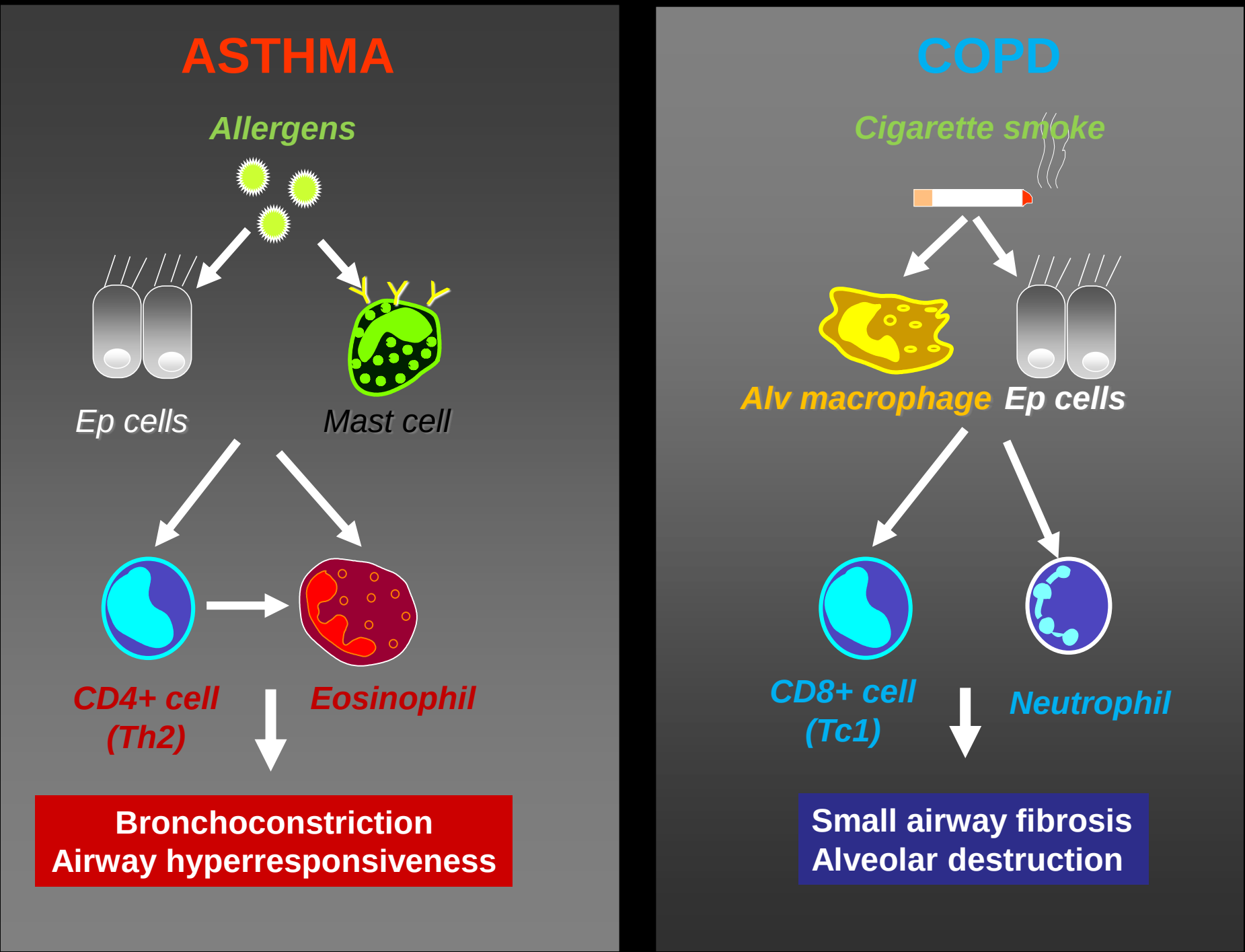
- COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.
- Exacerbations and comorbidities contribute to the overall severity in individual patients.

COPD Definition

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

ASTHMA vs COPD: CLINICAL DIFFERENCES

	ASTHMA	COPD
Main symptoms	Variable Wheeze	Persistent SOB on exertion
Productive cough	Rare	Frequent
Nocturnal sympt.	Usually	Rare
Onset	Usually childhood	Usually >45yr
Course	Variable, remissions, rarely progressive	Progressive
Smoking	Sometimes	Usually
Atopy	Frequent	Rare
Resp to b/d	Good	Poor - partial
Resp to steroids	Good	Poor


ASTHMA
Allergens
Ep cells
Mast cell
CD4+ cell
(Th2)
Eosinophil
Bronchoconstriction
Airway hyperresponsiveness
COPD
Cigarette smoke
Alv macrophage
Ep cells
CD8+ cell
(Tc1)
Neutrophil
Small airway fibrosis
Alveolar destruction

AIRWAY OBSTRUCTION IN ASTHMA AND COPD

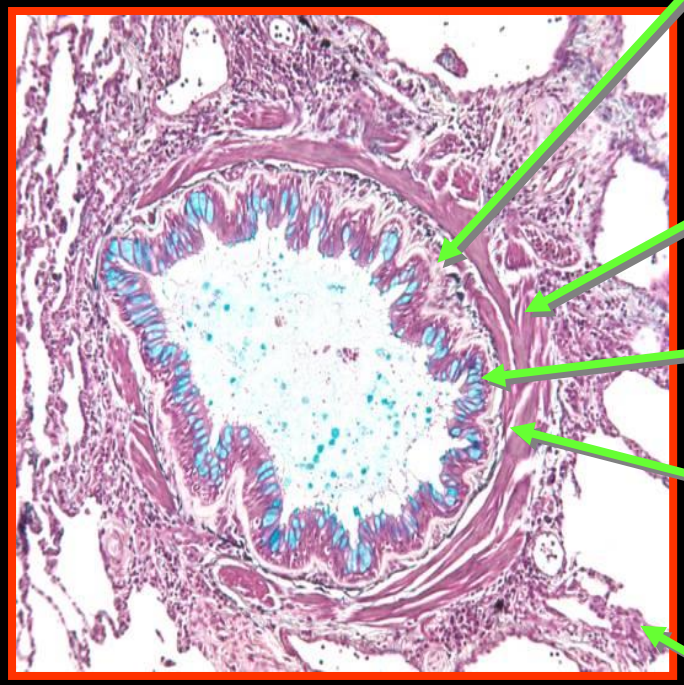
ASTHMA

- **Bronchoconstriction**
  (multiple b/c mediators)
  Mast cell activation
- **Edema**
  (acute exacerbations)
- **Mucus plugging**
  (fatal asthma)
- **Structural changes**
  (irreversible)

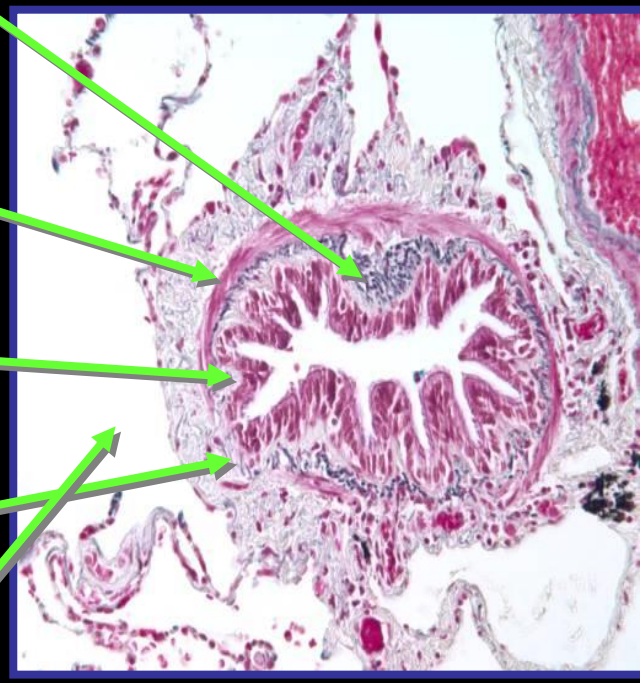
COPD

- **Small airway fibrosis**
  (2^0 to inflammation)
- **Emphysema**
  (loss of alveolar attachments)
- **Mucous exudate**
- **Edema**
  (acute exacerbations)

ASTHMA AND COPD PATHOLOGY



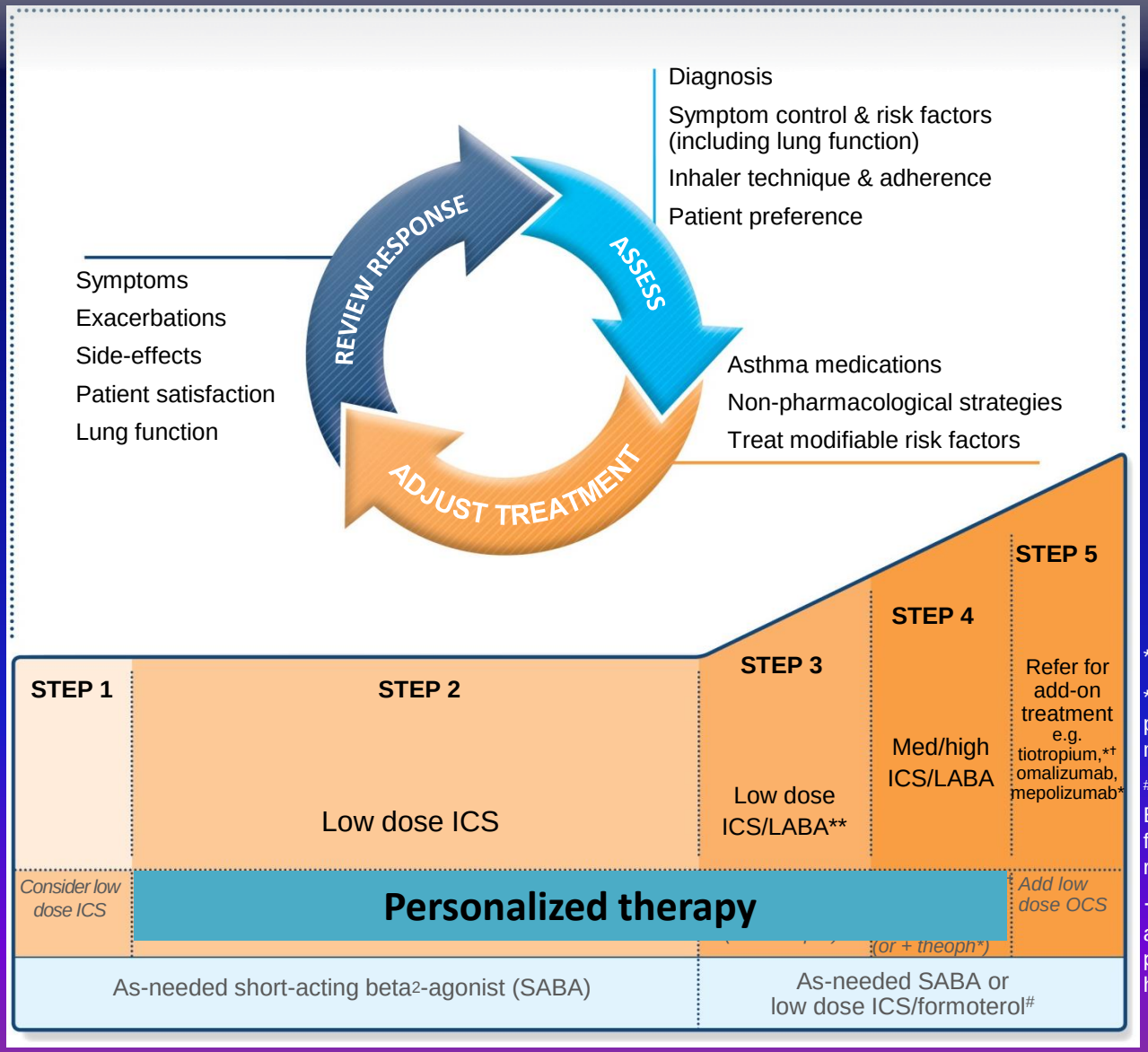
Asthma death		Severe COPD
+++	Inflammation	+++
+++	ASM	+
+++	BM	-
+	Fibrosis	+++
-	Alveolar disruption	+++



Courtesy of Jim Hogg

Stepwise management - pharmacotherapy

UPDATED!



*Not for children <12 years

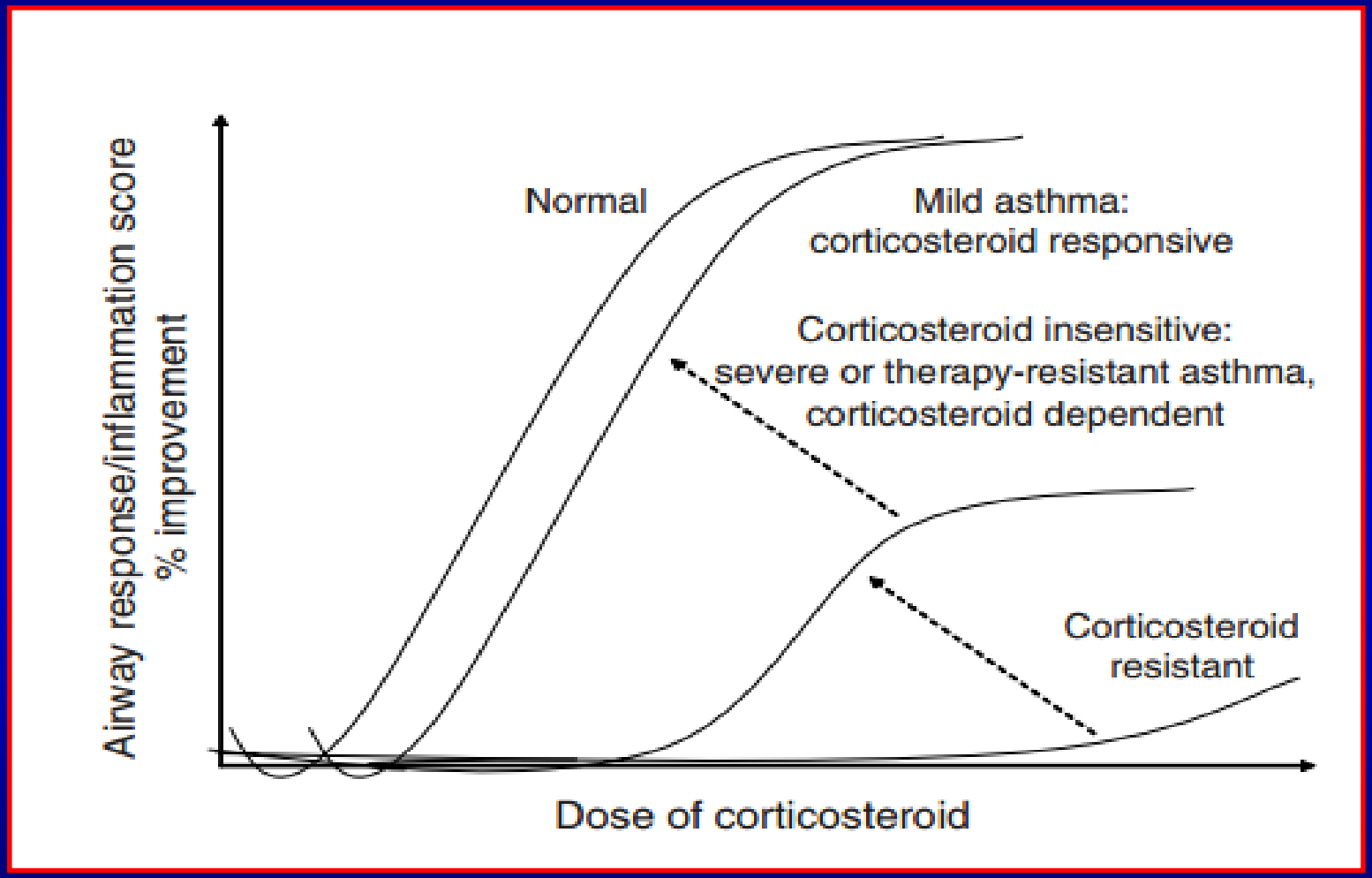
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

GINA 2016, Box 3-5 (2/8) (upper part)

CS insensitivity



Chung et al. Eur Respir Mon 2011;51:236-252.

La definizione di asma grave

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

Eur Respir J 2014; 43: 343–373 | DOI: 10.1183/09031936.00202013

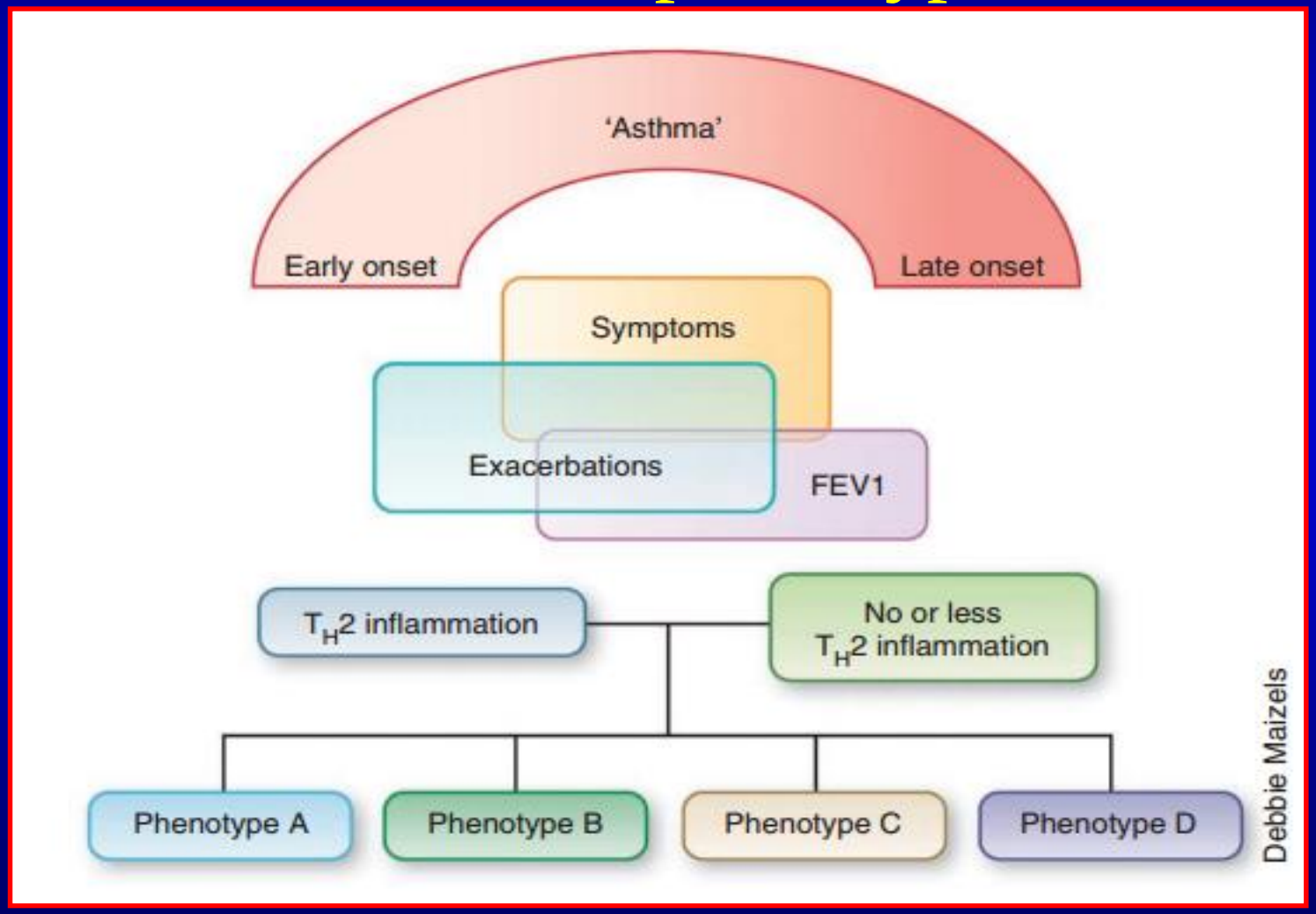
What is a phenotype?

The composite of *observable* characteristics of an organism…

resulting from interaction between its *genetic* make-up and *environmental* influences…

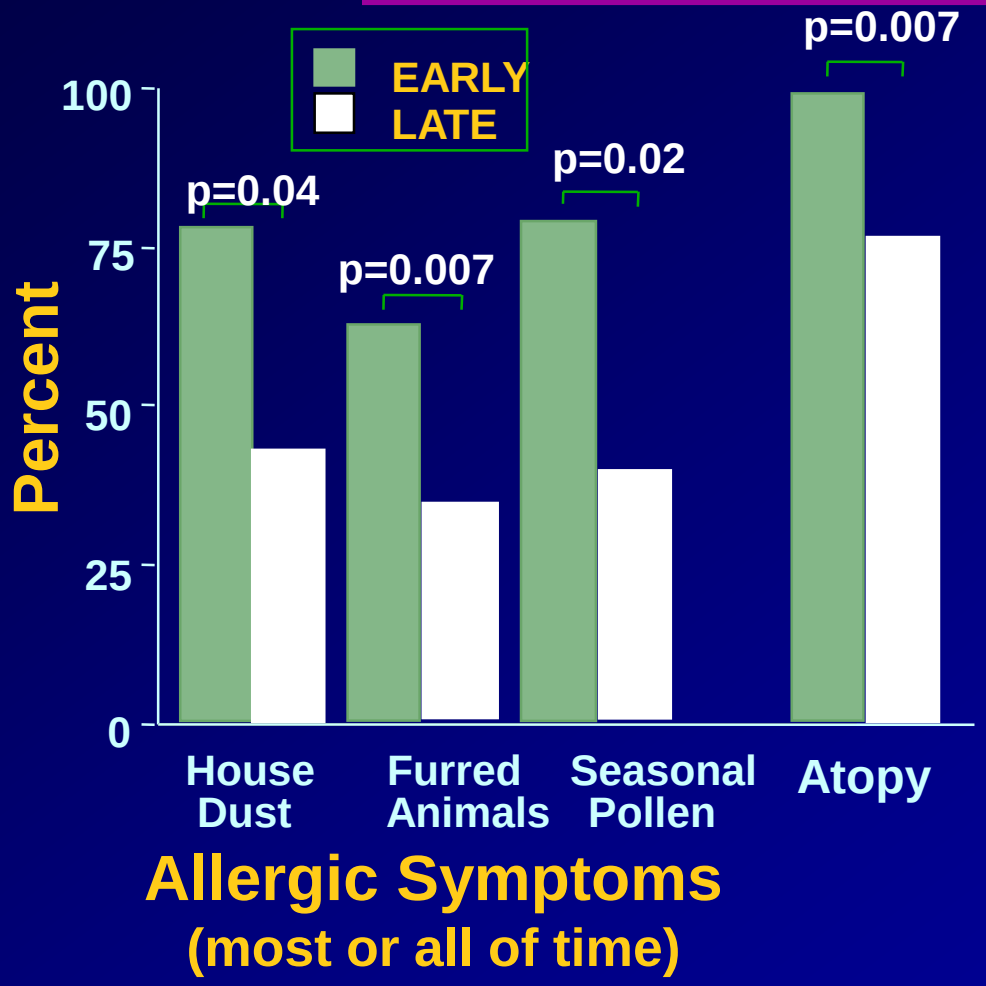
that is relatively stable, but not invariable with *time.*

The umbrella term asthma: from clinical/inflammatory features to associated phenotypes



Wenzel S. Nat Med 2012;18:716-725.

Early onset asthma: Identifies an "allergic"/Th2 phenotype



Hx eczema (p=0.0007)

Early 40% Late 4%

Serum IgE (p=0.12)

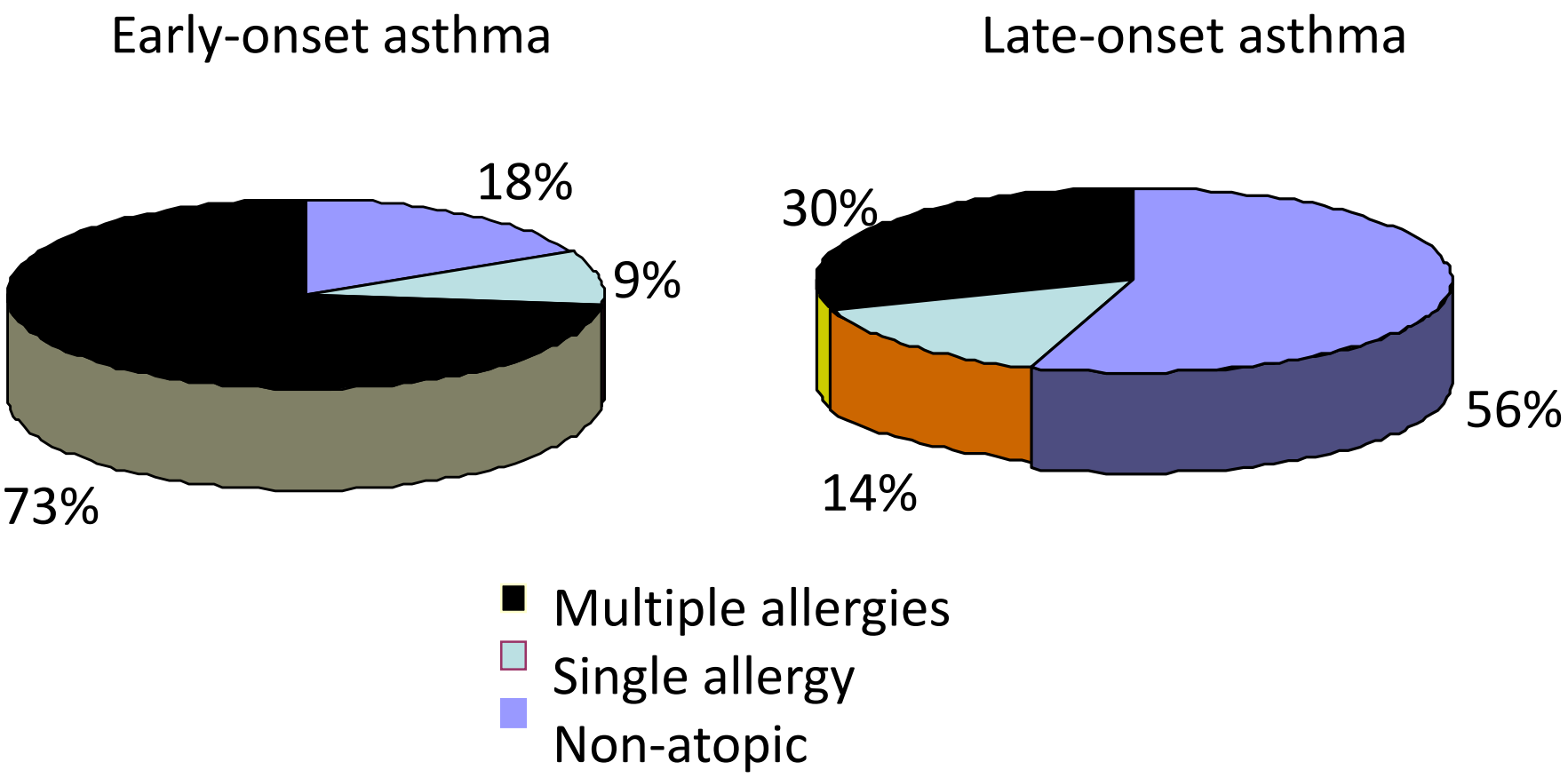
Early 108 Late 56

Family hx of asthma

Early>late

Miranda, JACI 2004

Phenotypes: Allergic Sensitization
Patients with Severe Asthma



Grootendorst DC et al., Am J Respir Crit Care Med 2000;161:A918

The Transition to Endotype

Phenotypes

Overlapping clinical physiologic hereditary characteristics

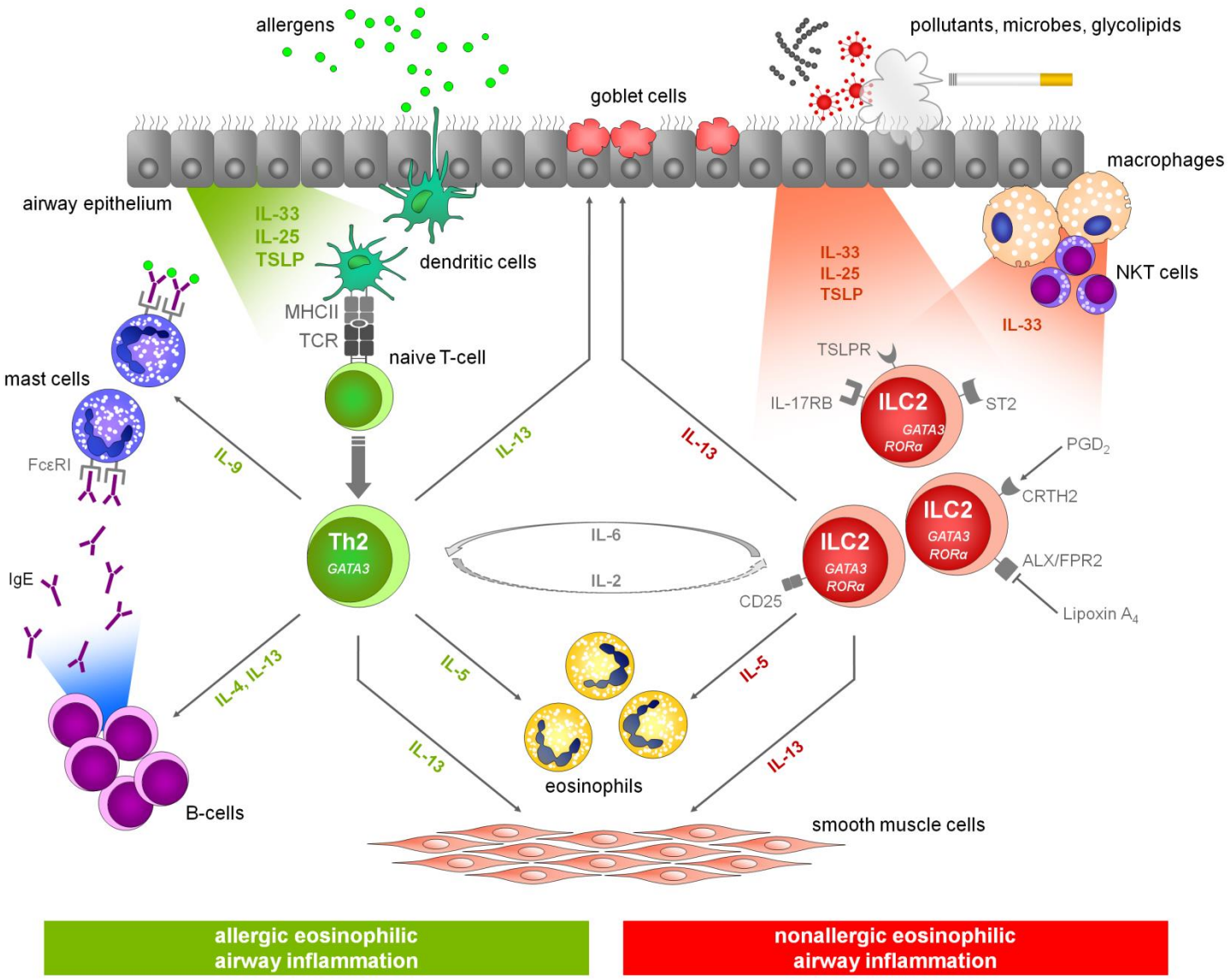
Molecular phenotypes

Incorporation of associated pathobiologic processes, ideally at molecular level, to clinical phenotype

Endotypes

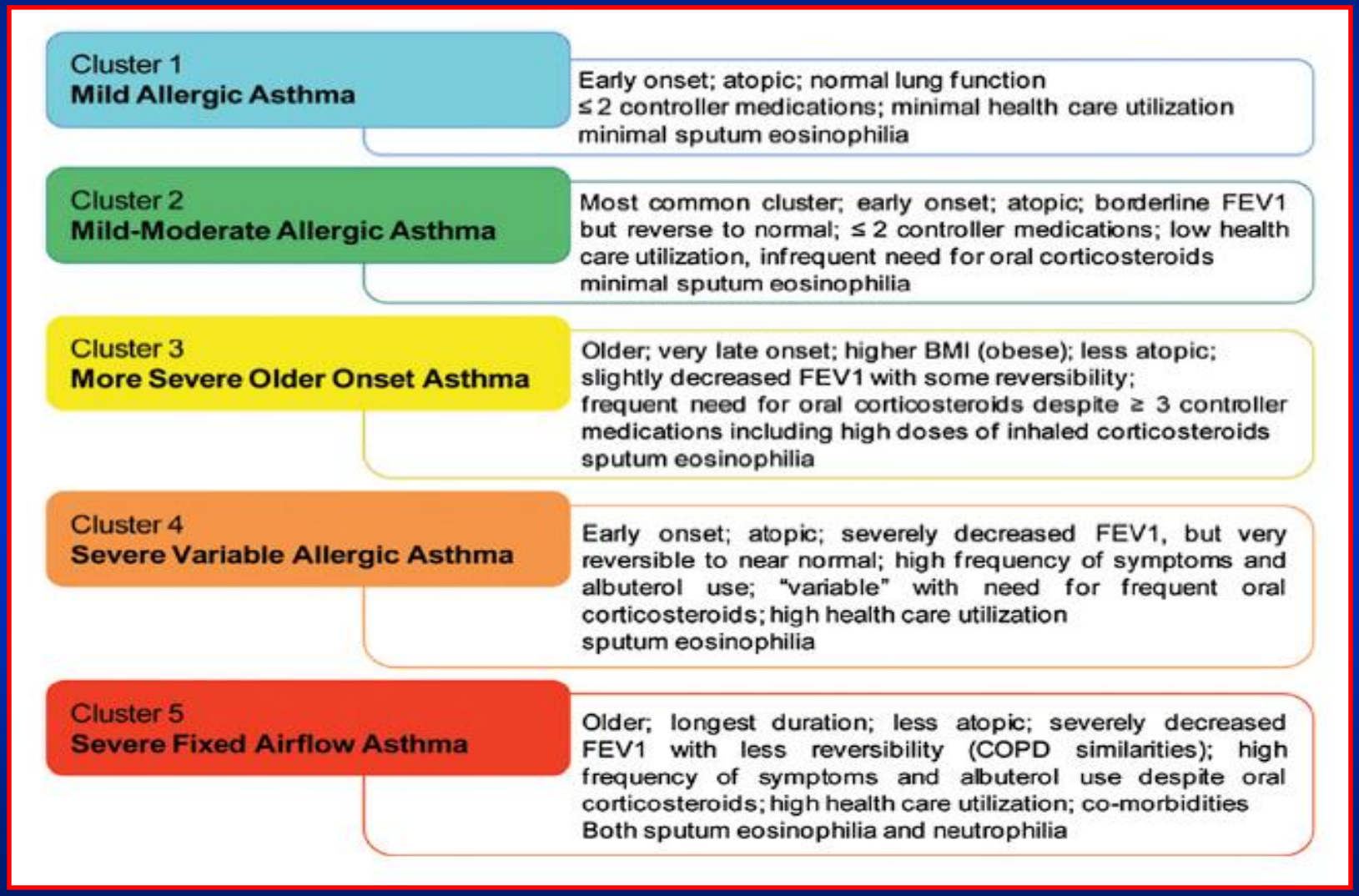
Confirmation through molecular targeting that identifiable molecular pathway contributes to clinical characteristics associated with molecular phenotypes

Heterogeneity of eosinophilic asthma



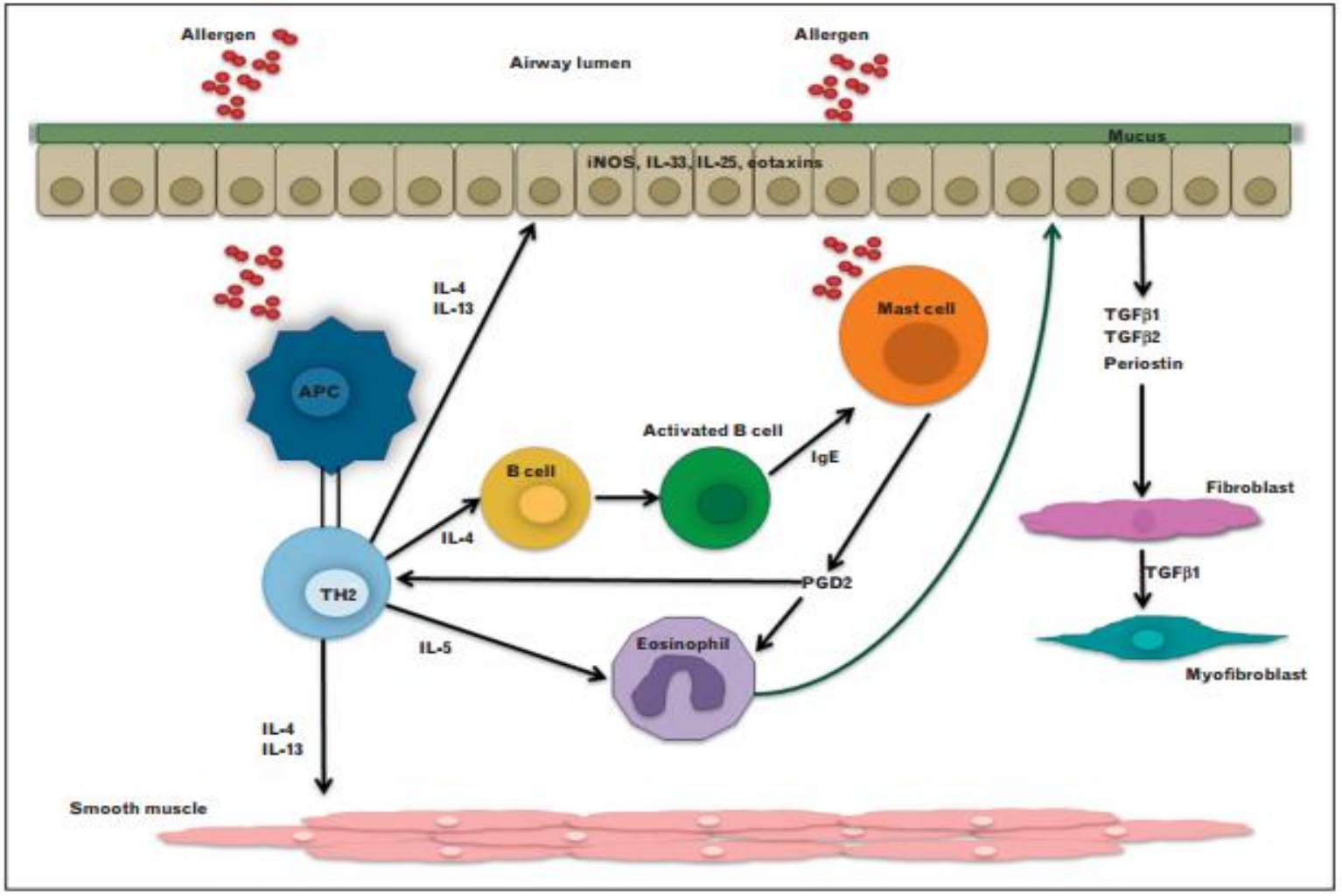
Brusselle G. et al, Nature Medicine 2013.

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program



Moore et al. AJRCCM 2010;181:315-323.

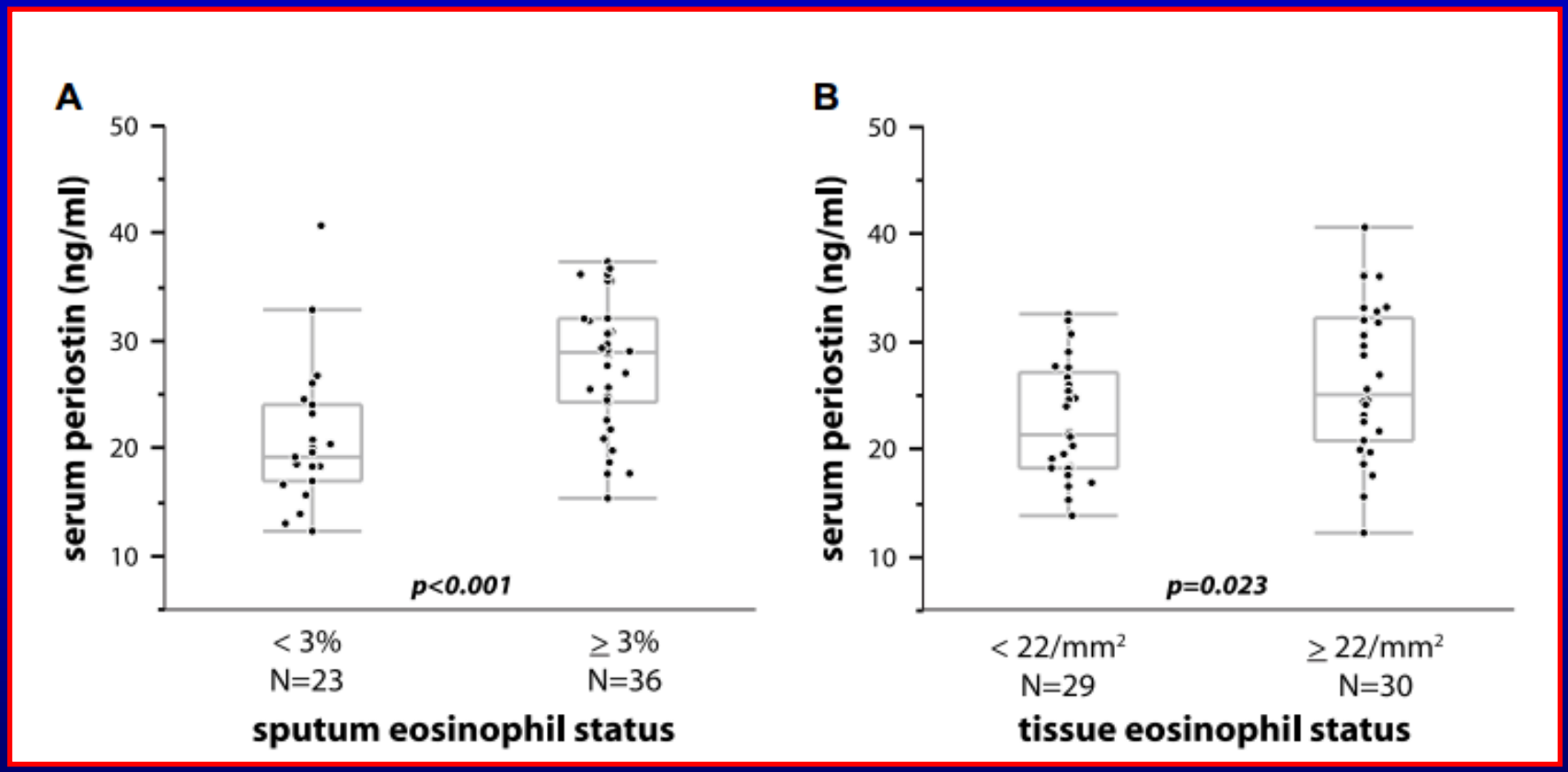
Periostin and asthma



Parulekar et al. Curr Opin Pulm Med 2014;20:60-65.

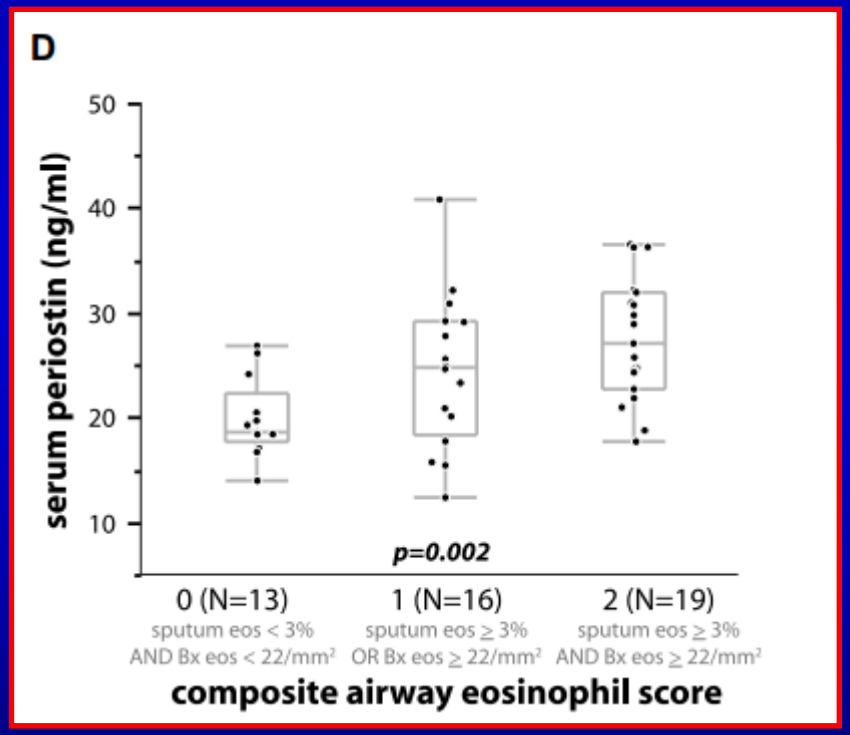
Serum Periostin and EOS in uncontrolled severe asthma (BOBCAT Study)

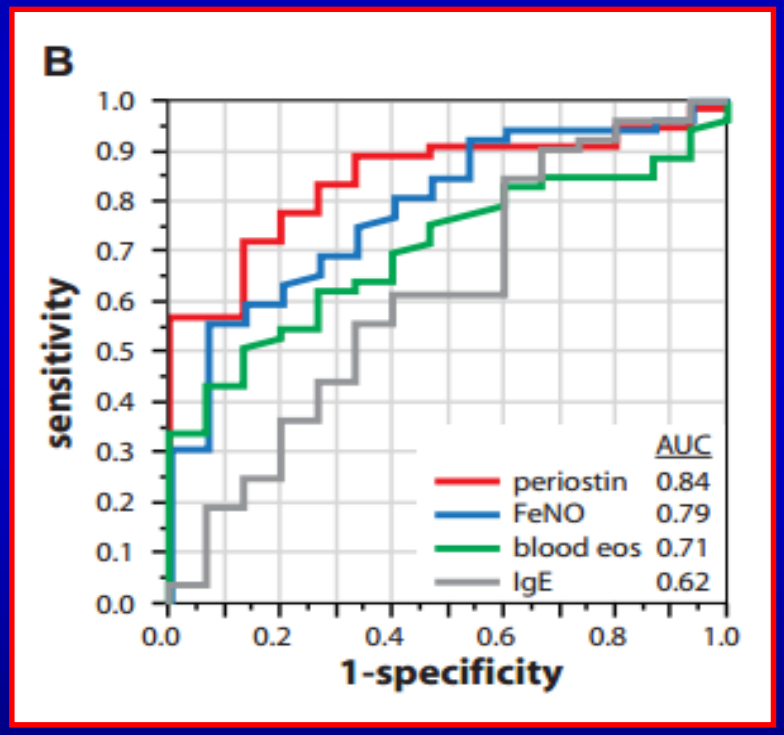
High dose ICS ≥ 1000 mcg Fluticasone



Jia et al. JACI 2002; 130:647-654.

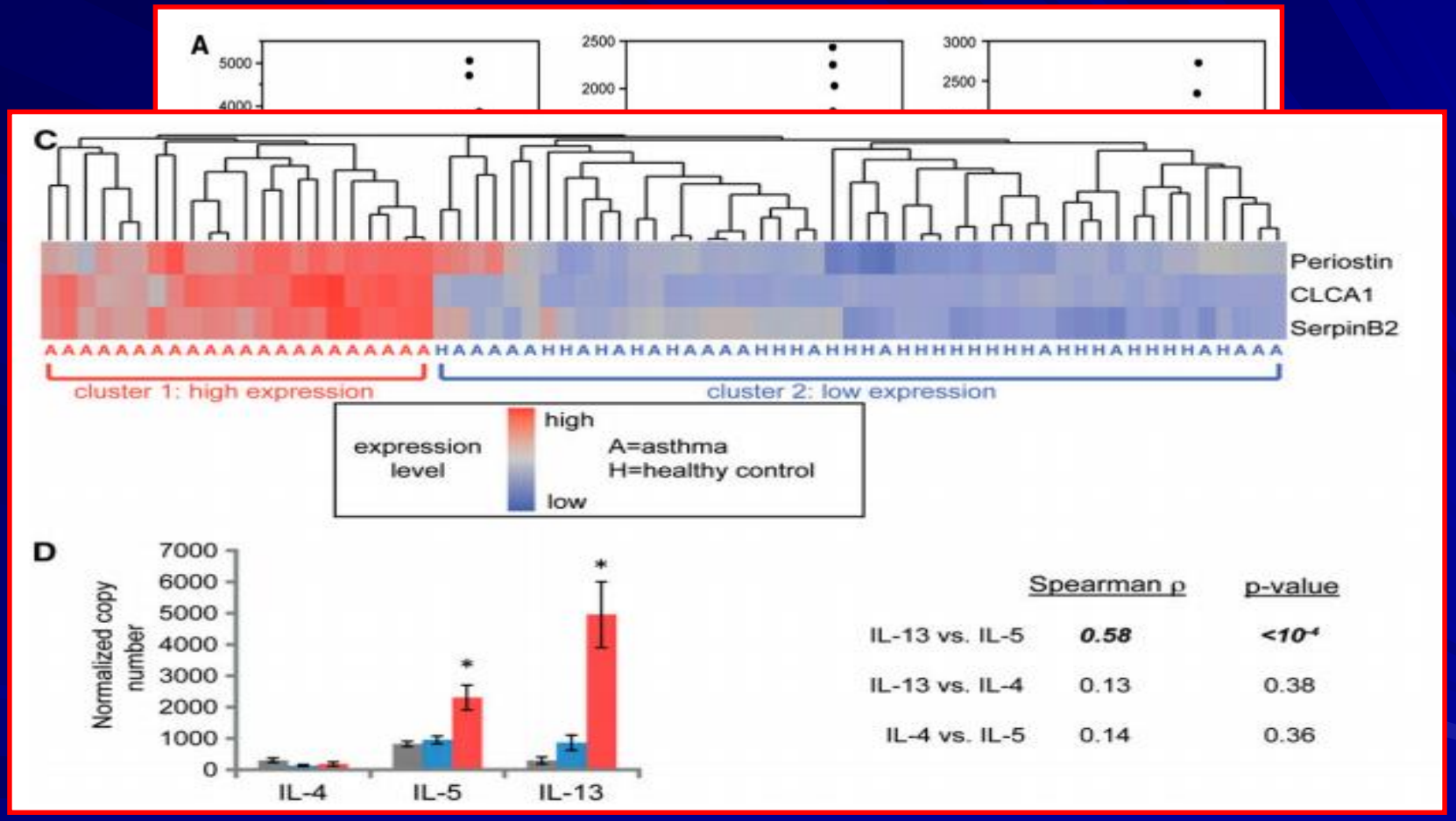
Serum periostin in uncontrolled SA





Jia et al. JACI 2002; 130:647-654.

Th2 gene expression in asthma

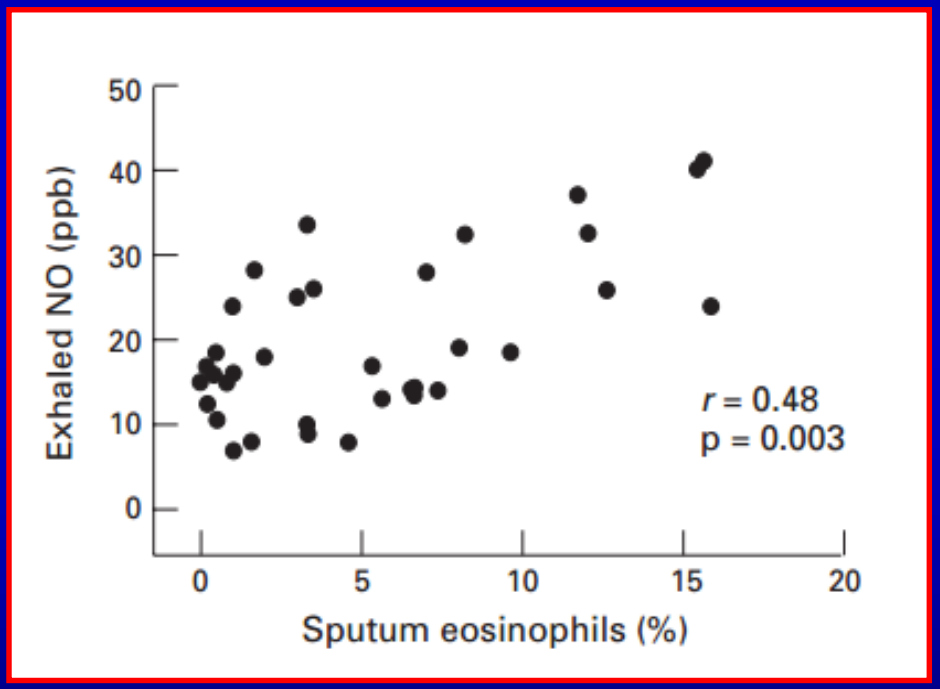


	Spearman ρ	p-value
IL-13 vs. IL-5	***0.58***	***<10⁻⁴***
IL-13 vs. IL-4	0.13	0.38
IL-4 vs. IL-5	0.14	0.36

Woodruff et al. AJRCCM 2009; 180:388-395.

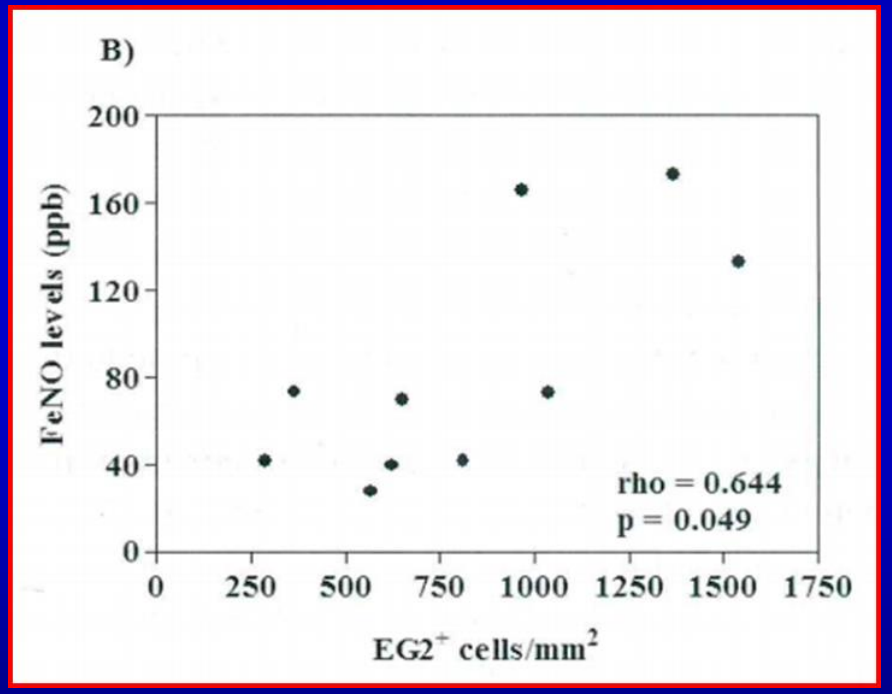
FeNO and sputum/bronchial EOS in atopic asthma

35 stable atopic asthmatics
not on ICS



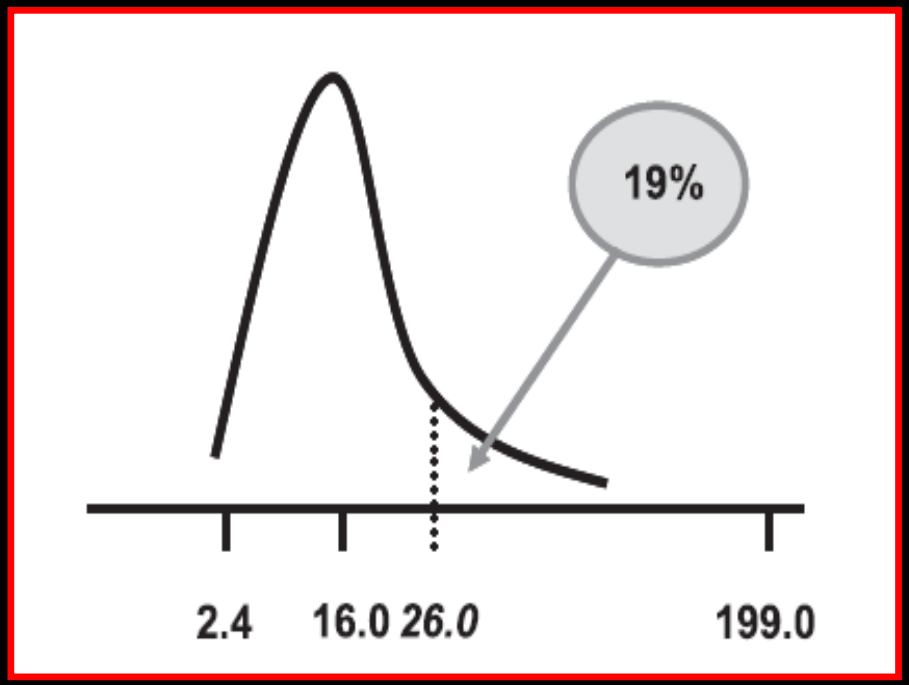
Jatakanon et al. Thorax 1998; 53:91-95.

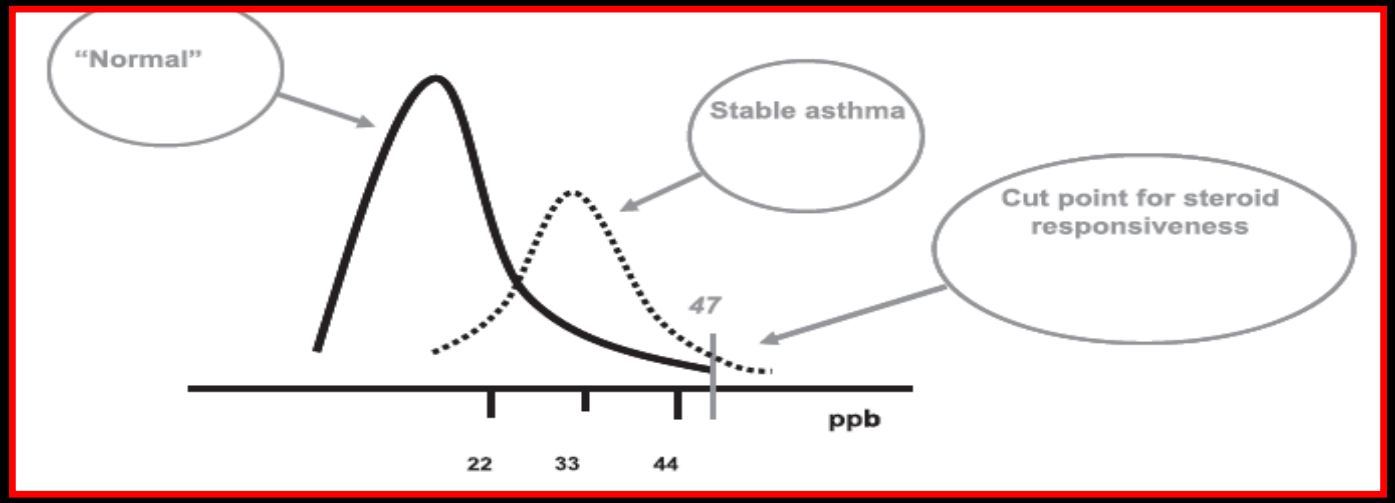
10 atopic mild asthmatics 48 hrs
after allergen challenge



Ricciardolo et al. Int J Imm Pharm 2012;25:175-182.

F_ENO: cut points

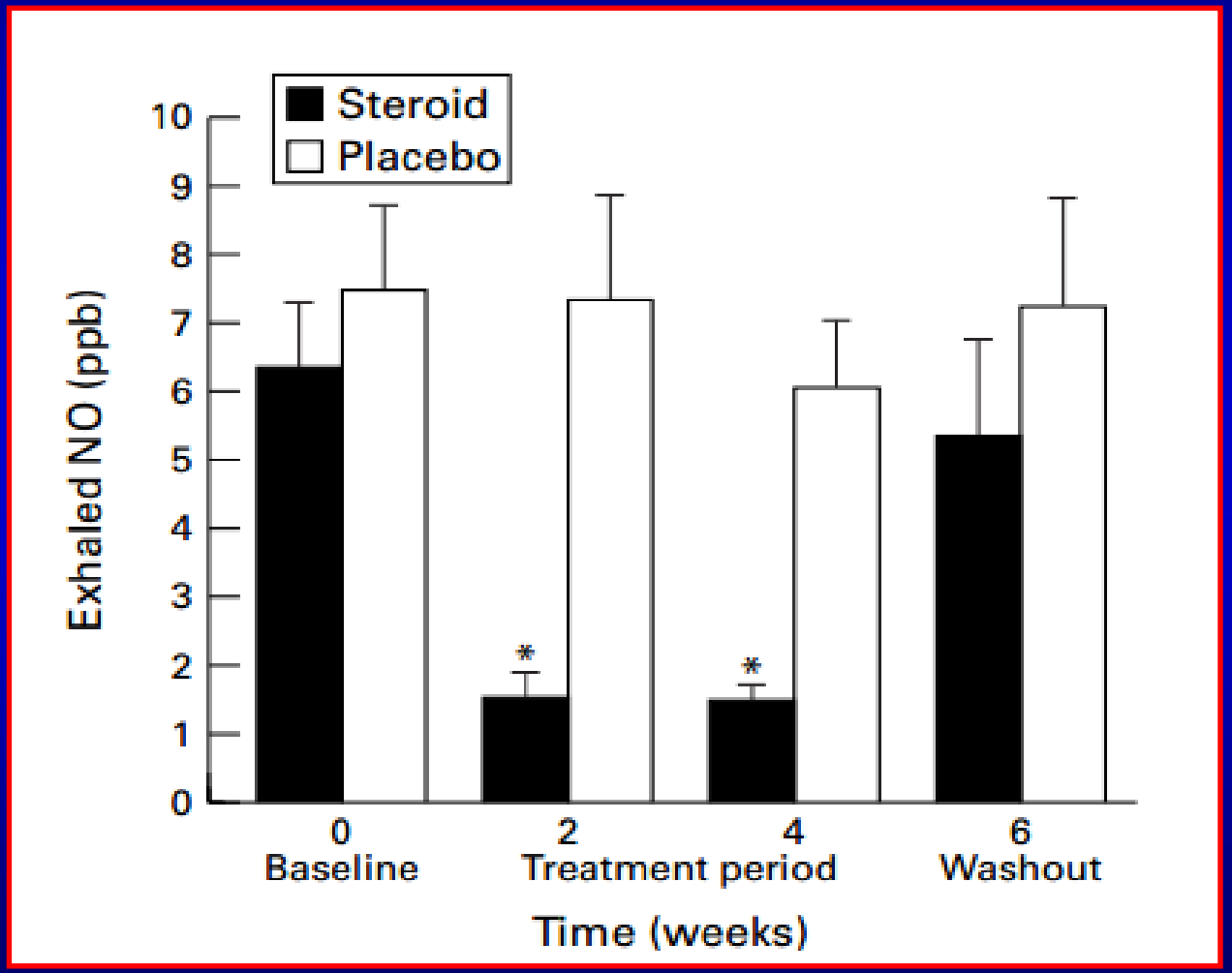




Dweik et al: AJRCCM 2011;184:602-615.

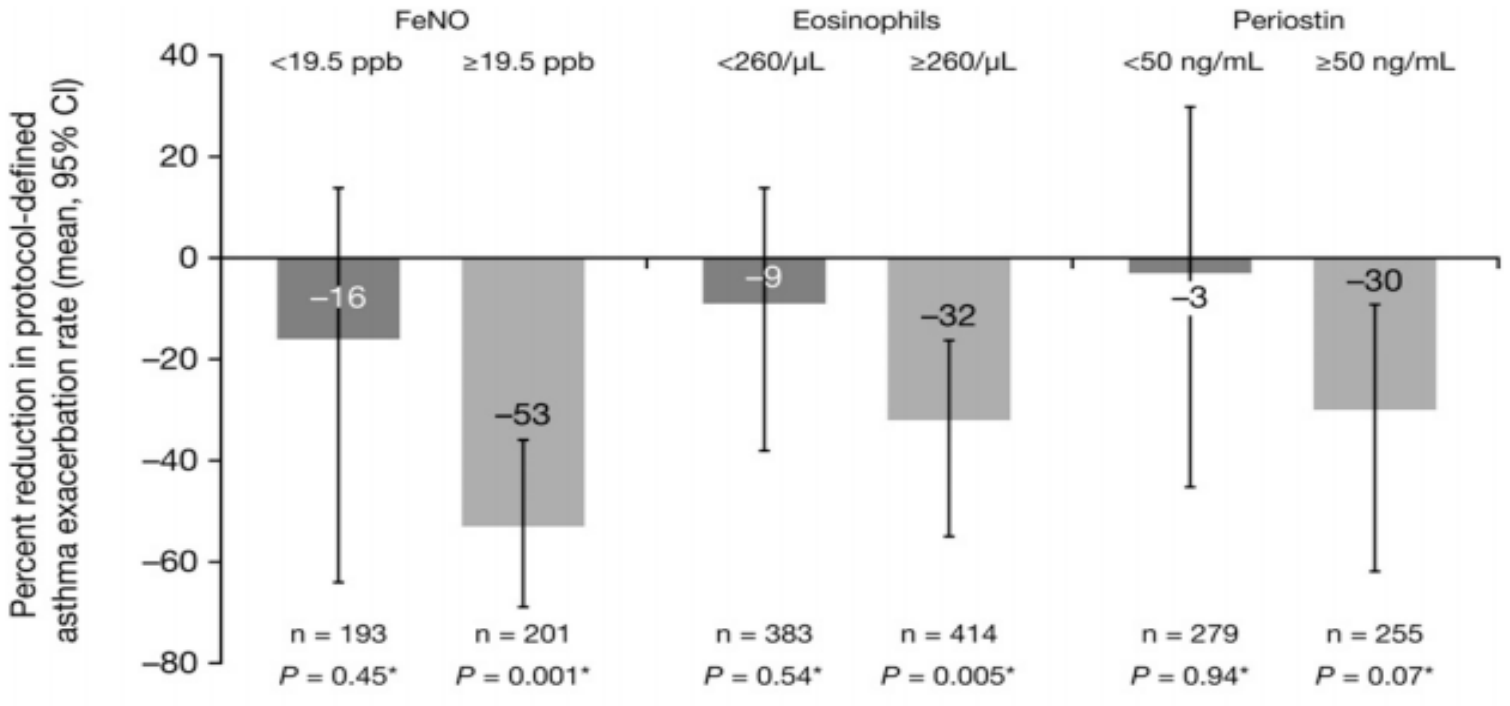
Effects of ICS on FeNO in asthma

Fluticasone proprionate 1000 mcg/day for 4 weeks



Van Rensen et al. Thorax 1999; 54:403-408.

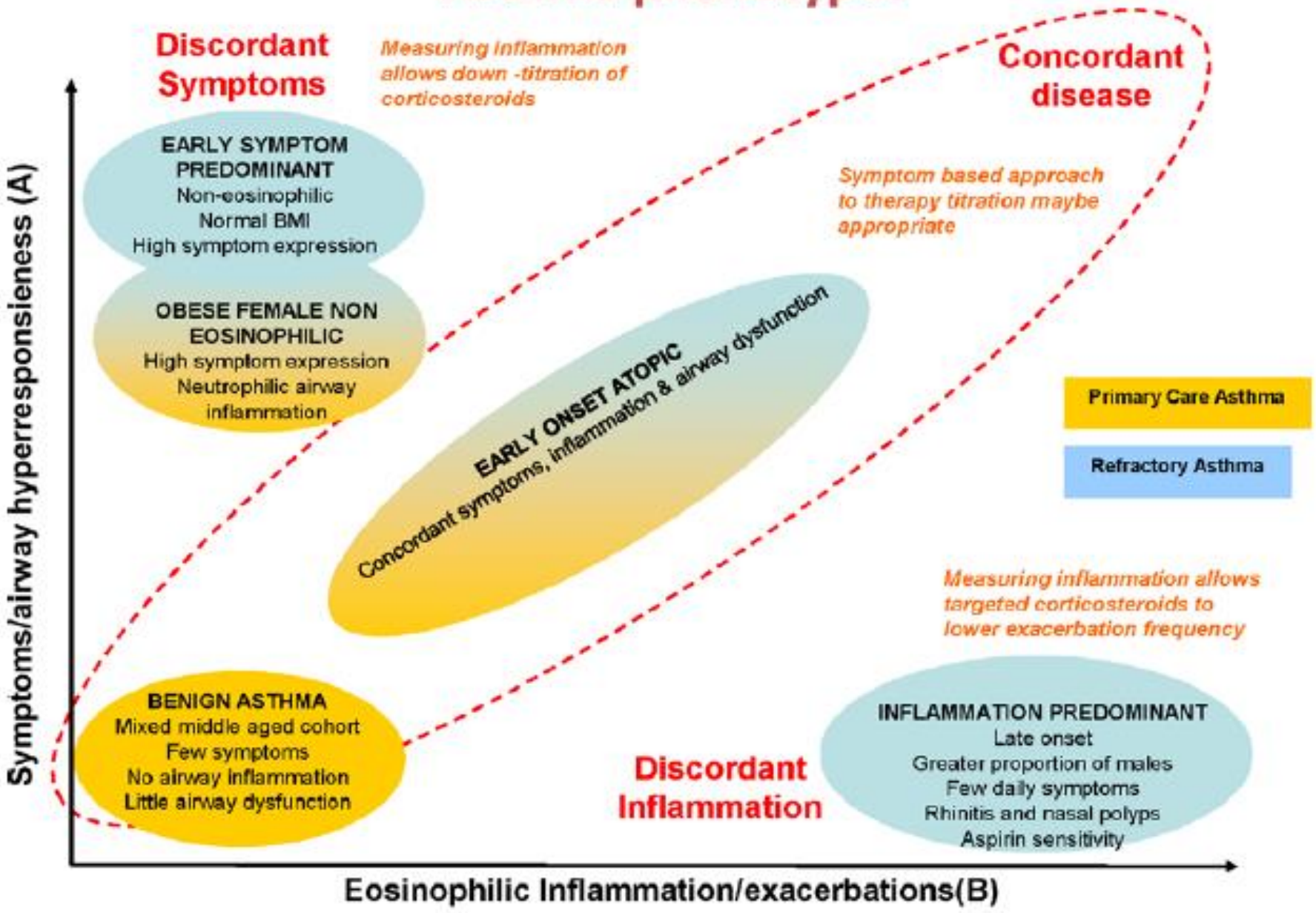
Biomarkers as predictors for omalizumab



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania et al. AJRCCM 2013;187:804-811.

Asthma phenotypes



Haldar et al AJRCCM 2008;178:218-24

Aspirin-induced asthma

- 20% of adult onset asthma; 40% of adult onset severe eosinophilic asthma.
- Rhinosinusitis and nasal polyposis common (Samter's triad) and usually precede asthma
- Local and systemic reactions to aspirin and other cyclooxygenase (COX)-1 inhibitors
- Marked eosinophilic airway inflammation. Blood eosinophilia usually present
- Airway inflammation is typically unresponsive to topical steroids. Systemic treatment is more successful.

DREAM study: inclusion criteria

- Age 12-74 years
- Clinical diagnosis of asthma (refractory)
- History of two or more exacerbations / year
- **Evidence of eosinophilic inflammation**:

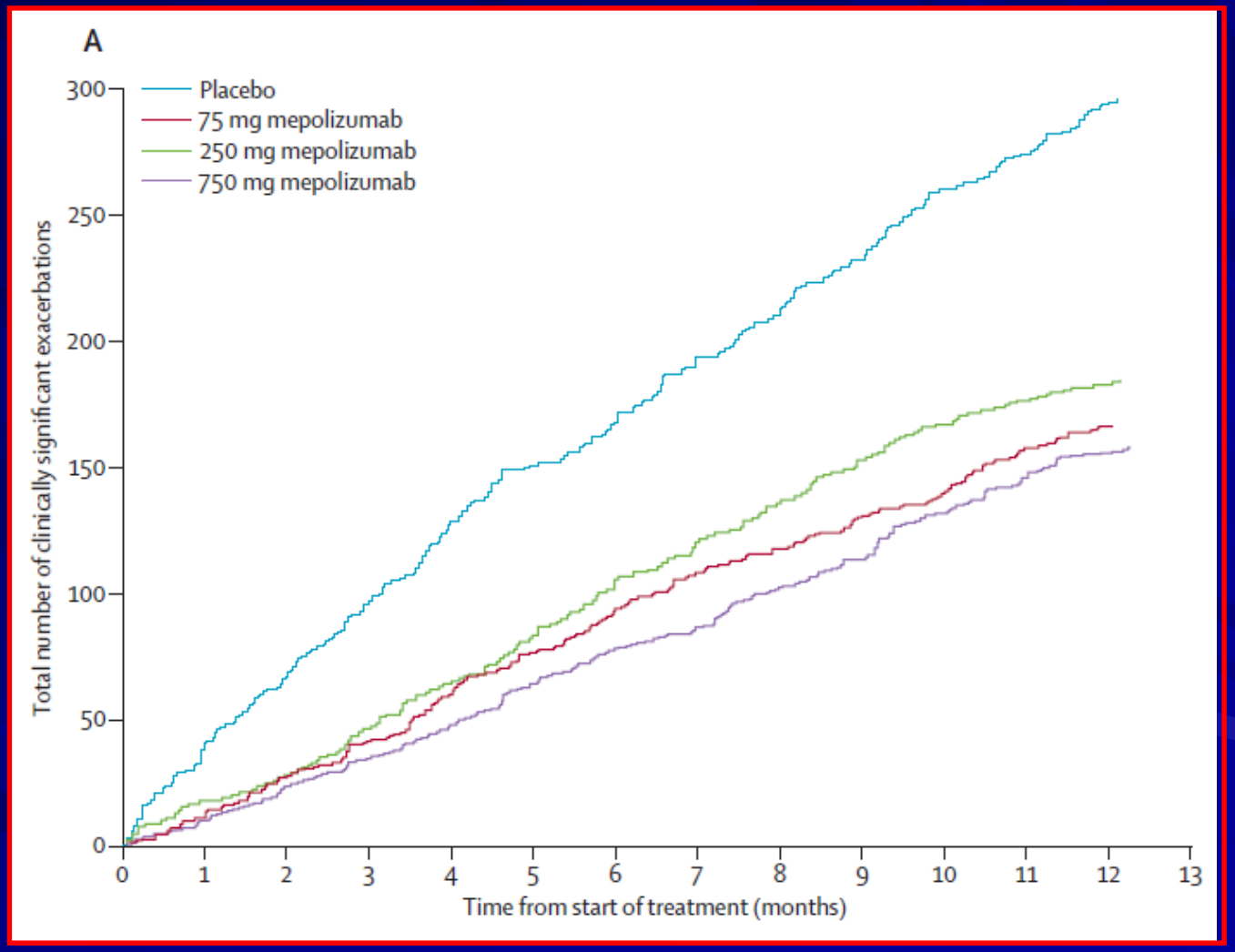
1) sputum eosinophil count ≥ 3%, *or*

2) blood eosinophil count ≥ 300/µL, *or*

3) FE_{NO} ≥ 50 ppb.

Pavord I. et al, Lancet 2012; 380: 651-659.

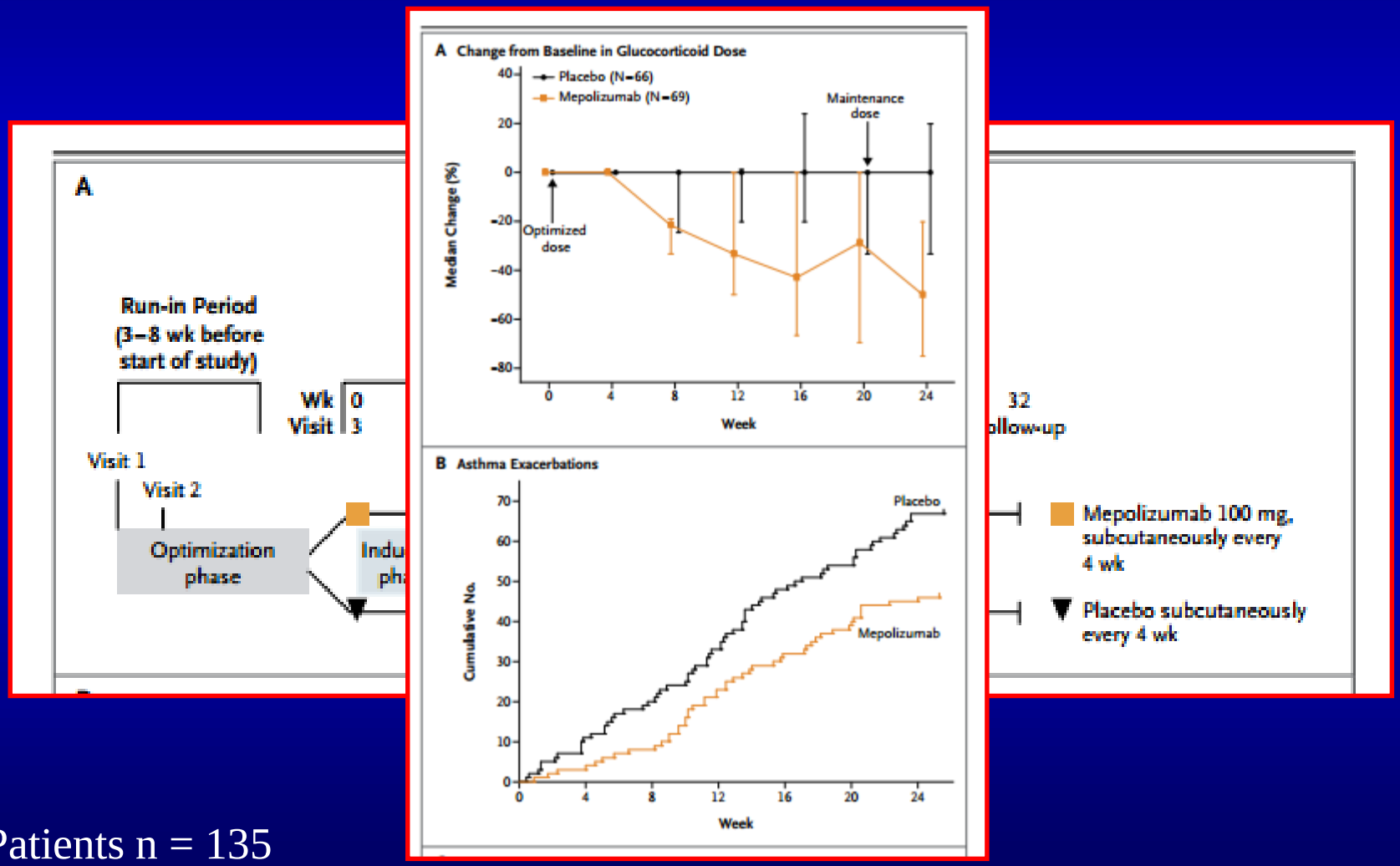
Mepolizumab in severe eosinophilic asthma: impact on exacerbations



Pavord I. et al, Lancet 2012; 380: 651-659.

UNIVERSITEIT GENT

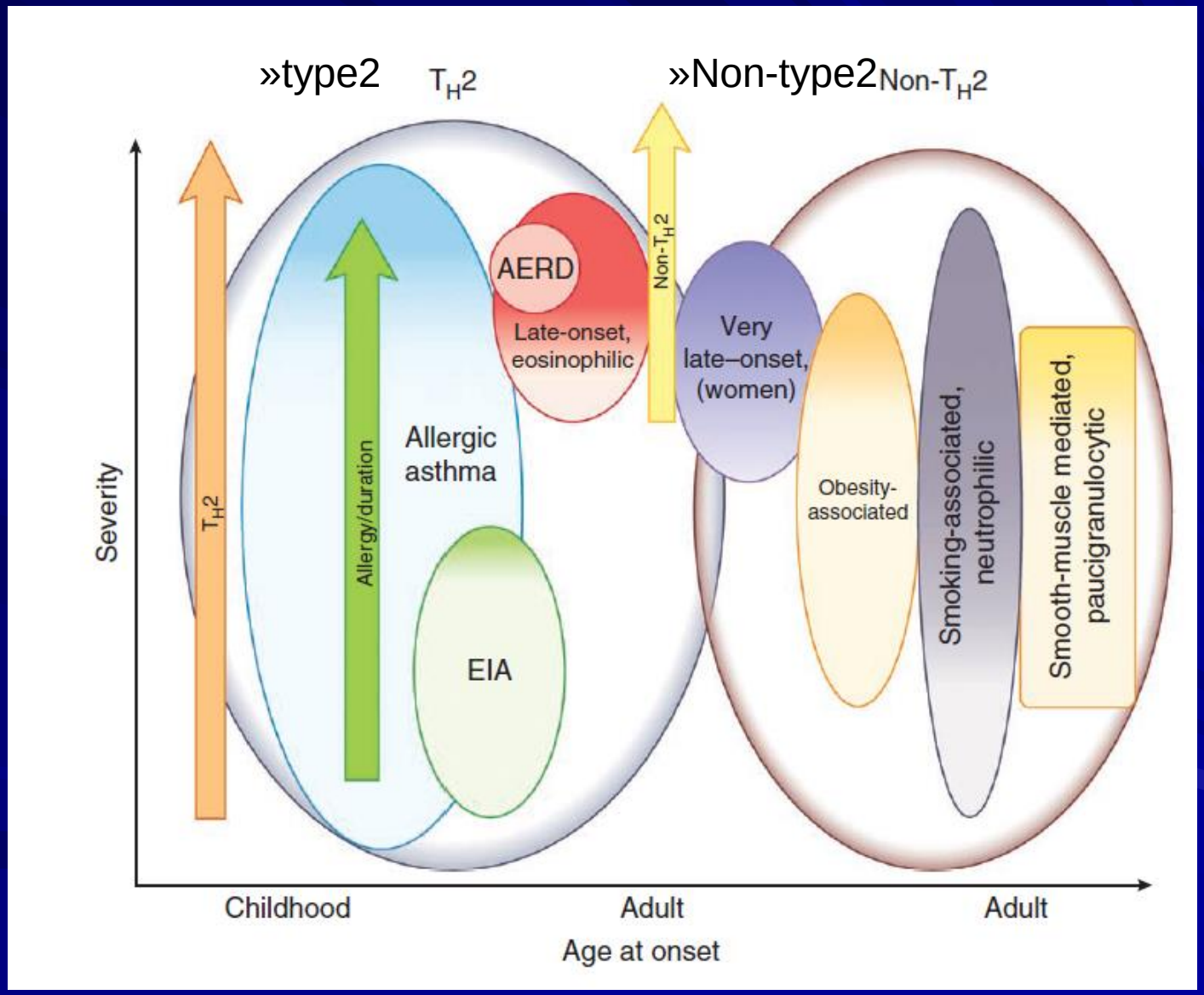
Oral GC-sparing effect of mepolizumab in eosinophilic asthma



Patients n = 135

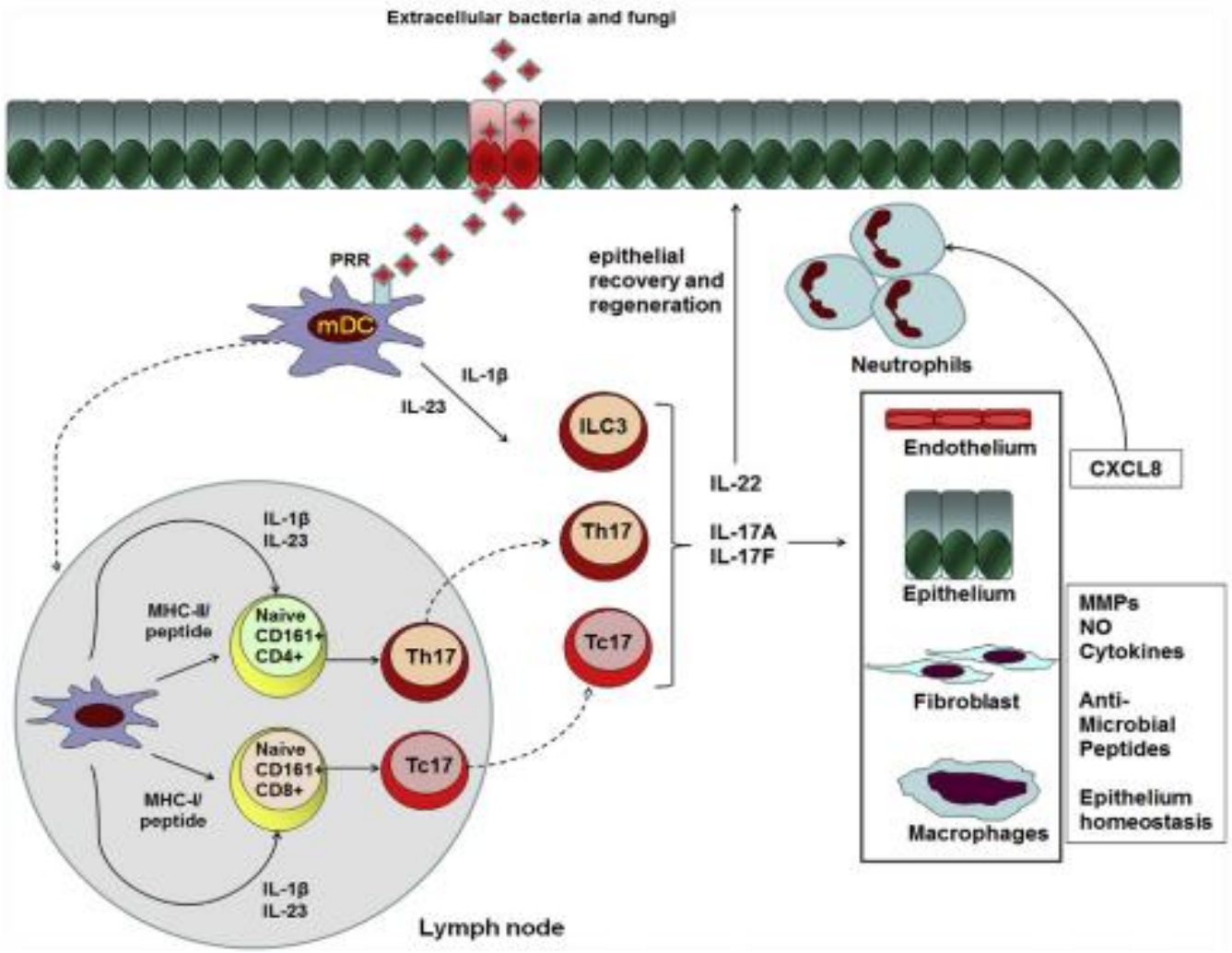
Bel et al. NEJM 2014;371:1189-97.

Asthma phenotypes



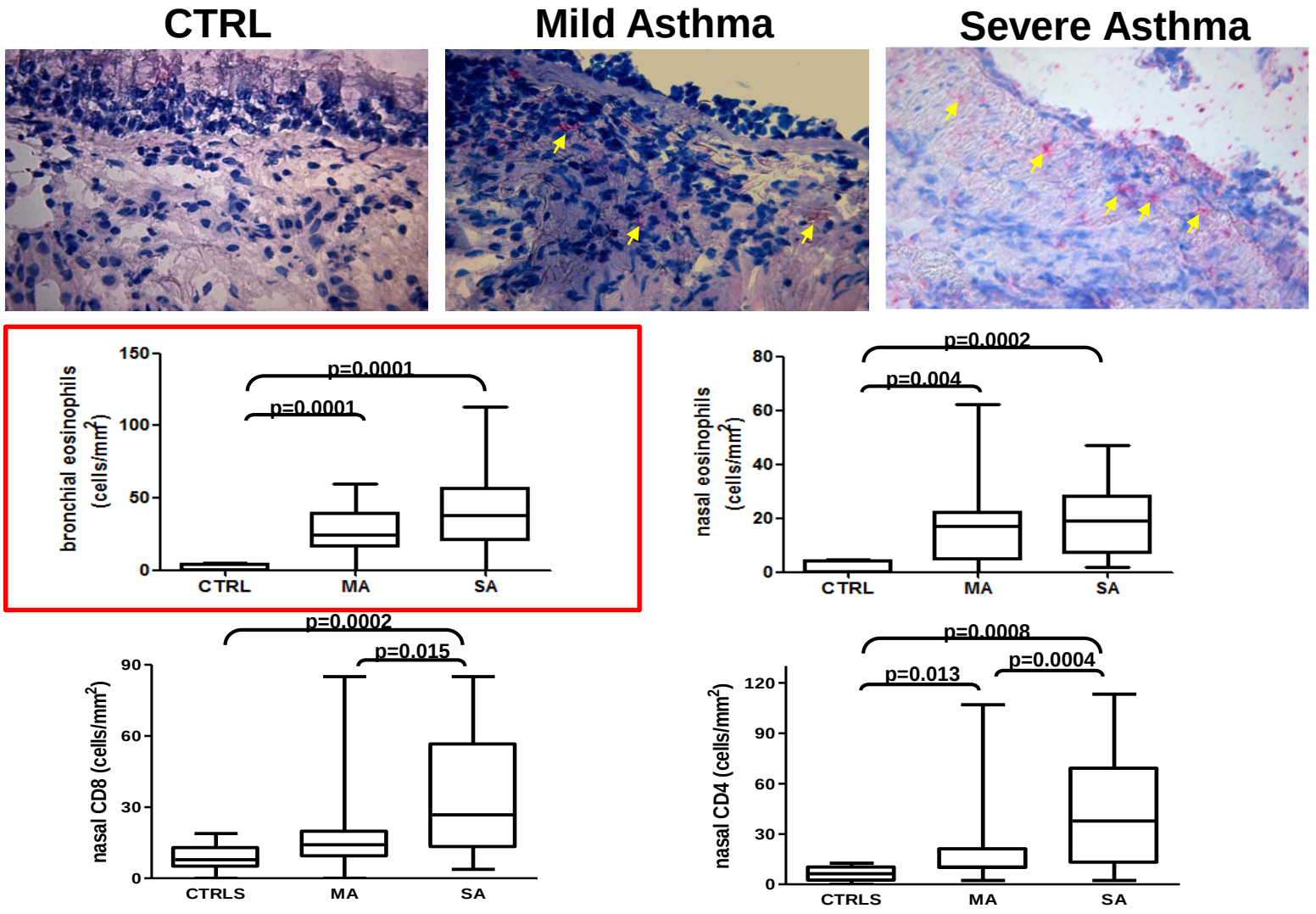
Wenzel S., Nature Medicine 2012.

Type 3 immunity



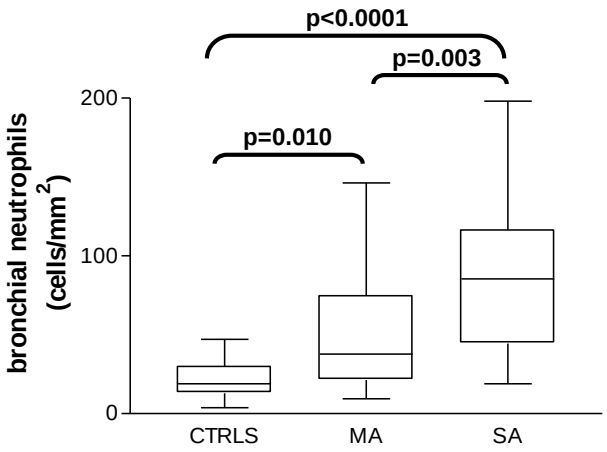
Annunziato et al. JACI 2015;135:626-35.

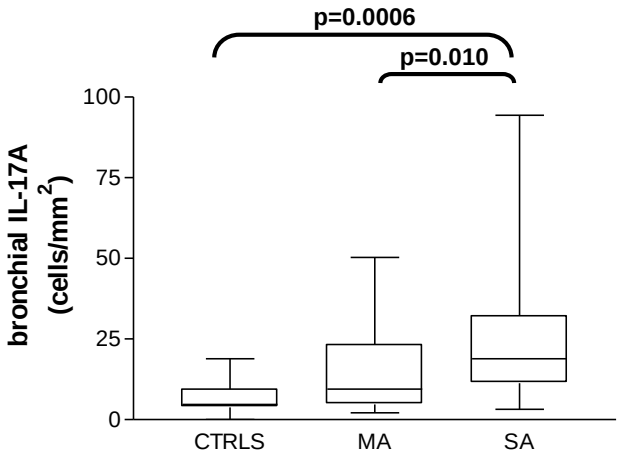
IL-17 related cytokines expression in bronchial mucosa of Severe Asthma

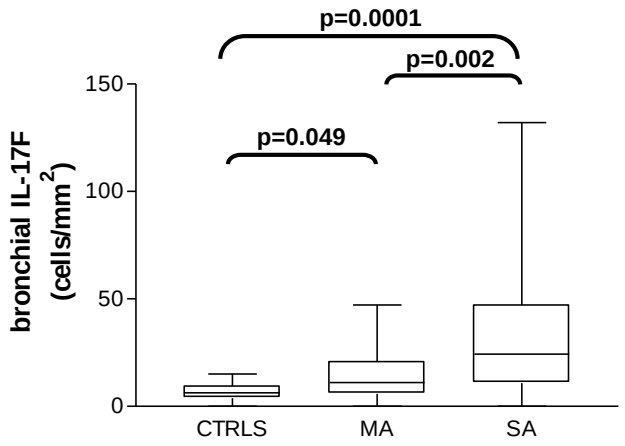


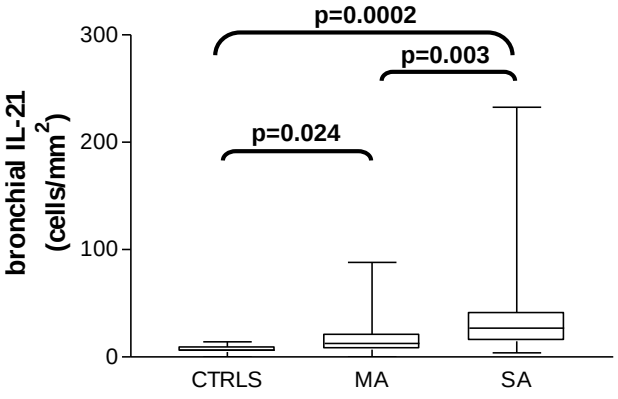
Ricciardolo et al. Journal of Allergy Clinical Immunology 2017

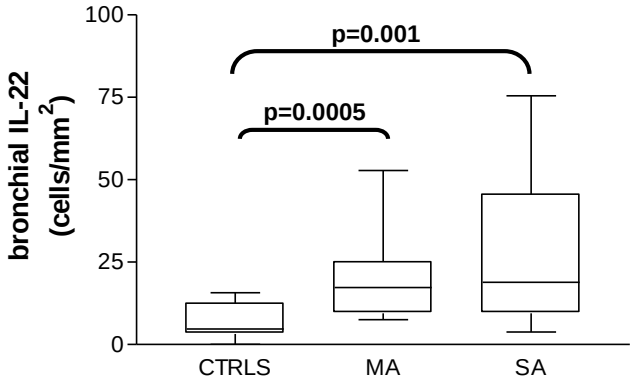
IL-17 related cytokines expression in bronchial mucosa of Severe Asthma

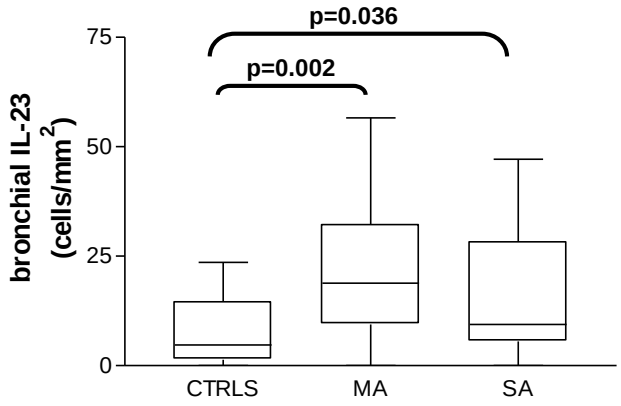






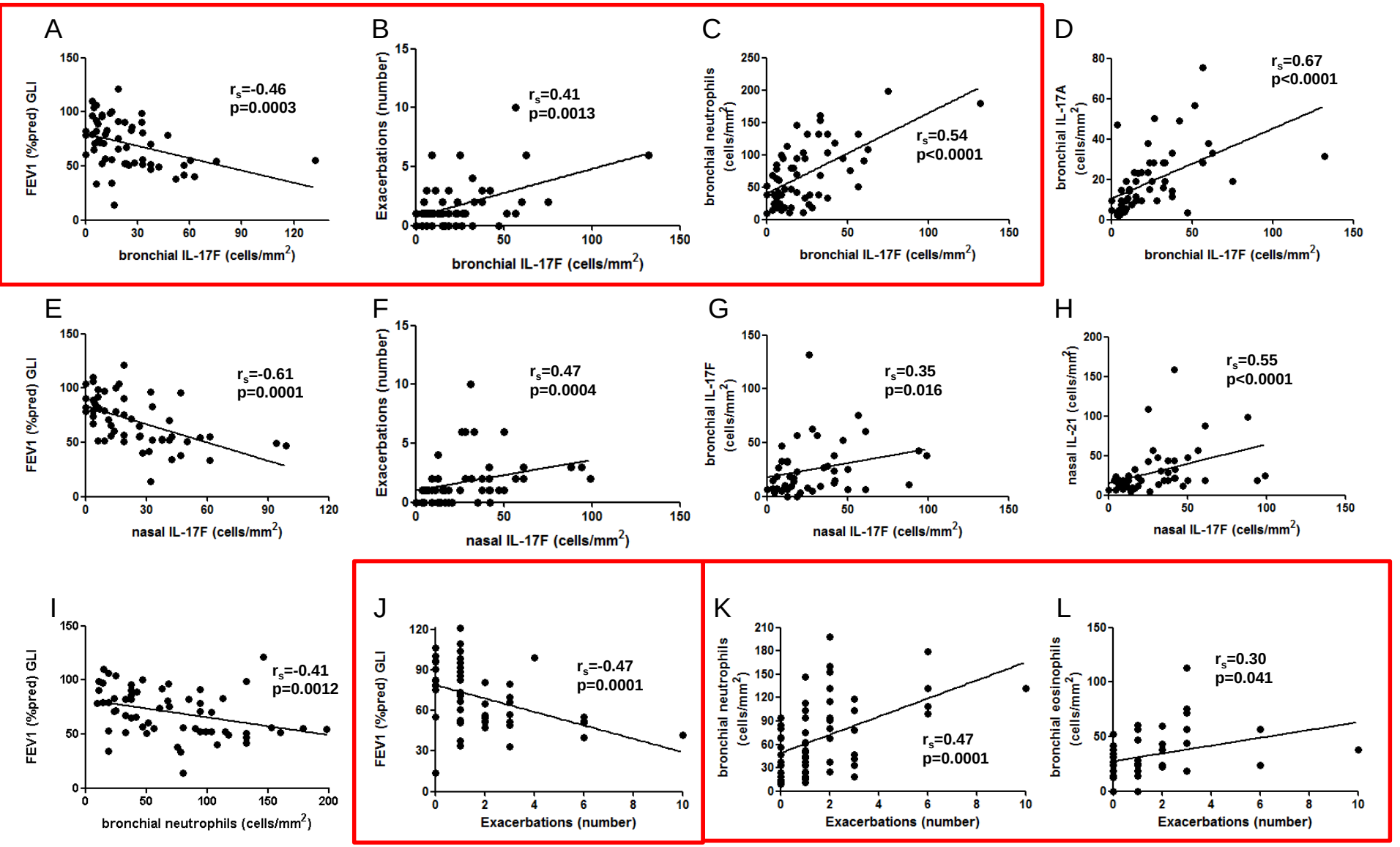






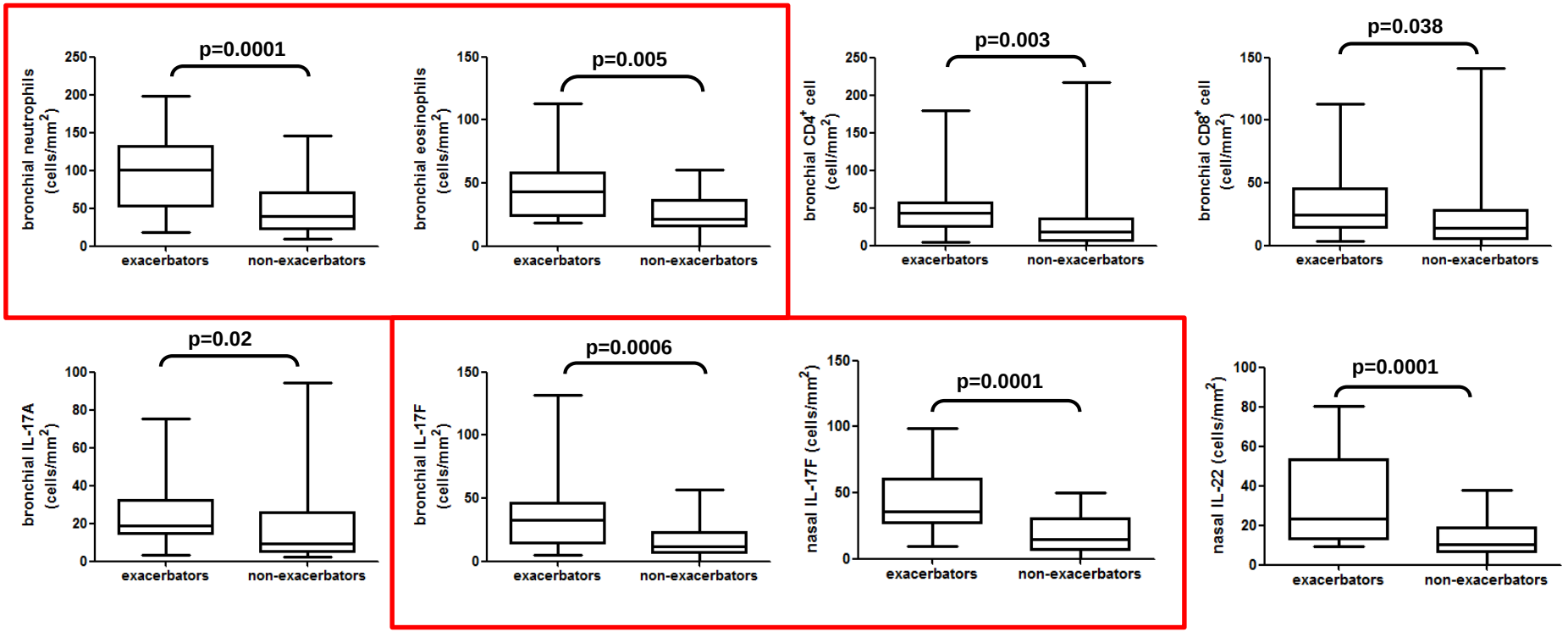
Ricciardolo et al. Journal of Allergy Clinical Immunology 2017

IL-17 related cytokines expression in bronchial mucosa of Severe Asthma



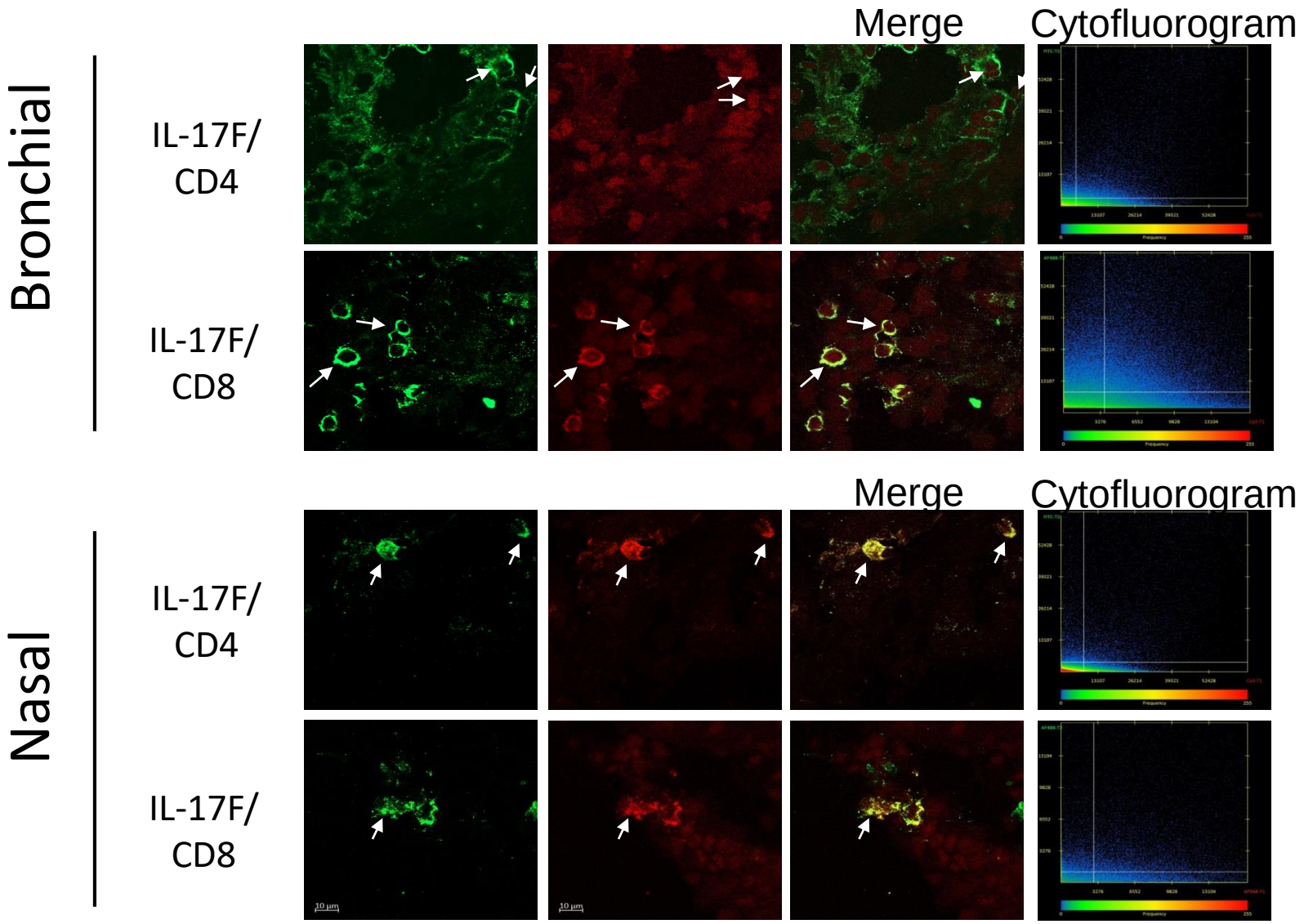
Ricciardolo et al. Journal of Allergy Clinical Immunology 2017

Identification of IL-17F/Frequent Exacerbator endotype in Asthma



Ricciardolo et al. Journal of Allergy Clinical Immunology 2017

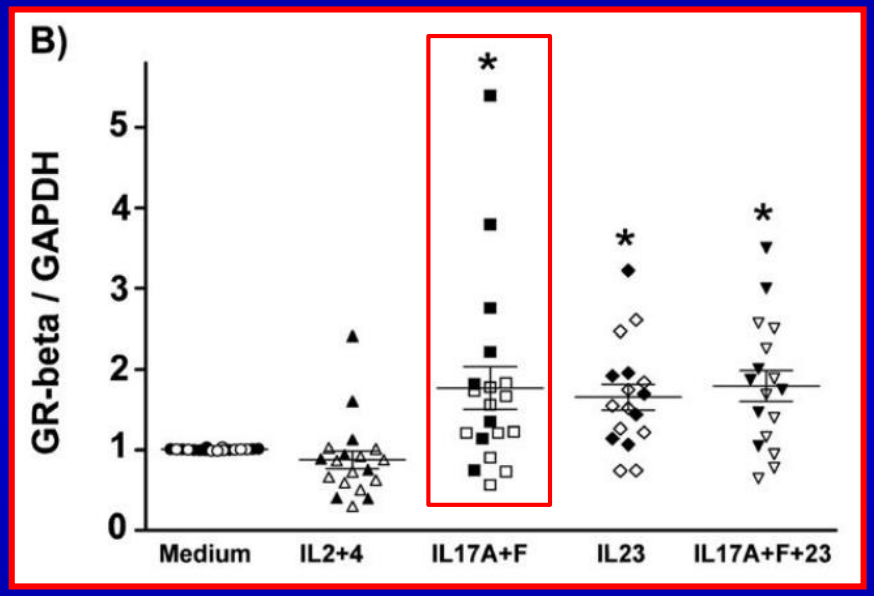
Identification of IL-17F/Frequent Exacerbator endotype in Asthma



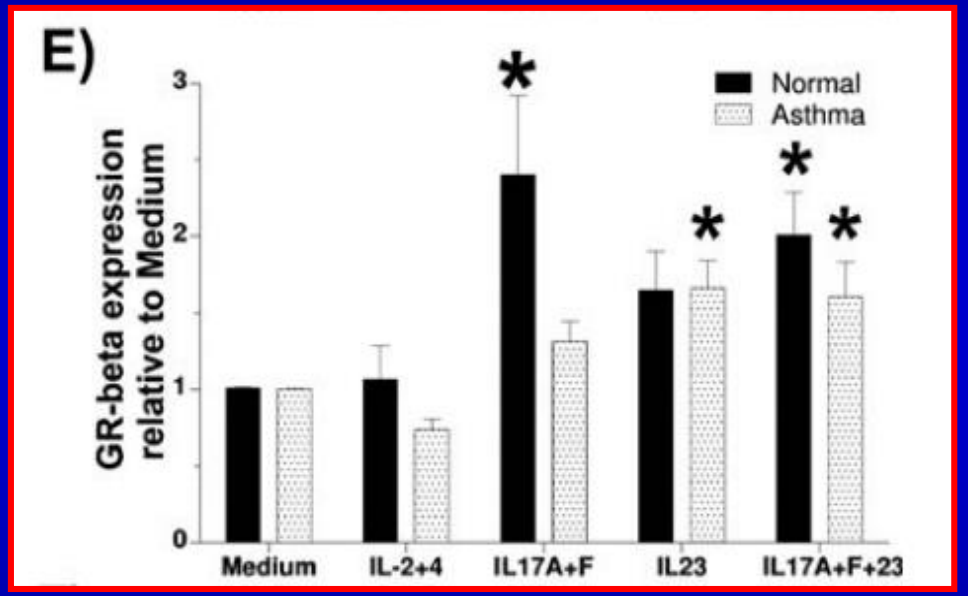
Ricciardolo et al. Journal of Allergy Clinical Immunology 2017

GR-beta up-regulation and steroid resistance induction by IL-17 and IL-23 in PBMC

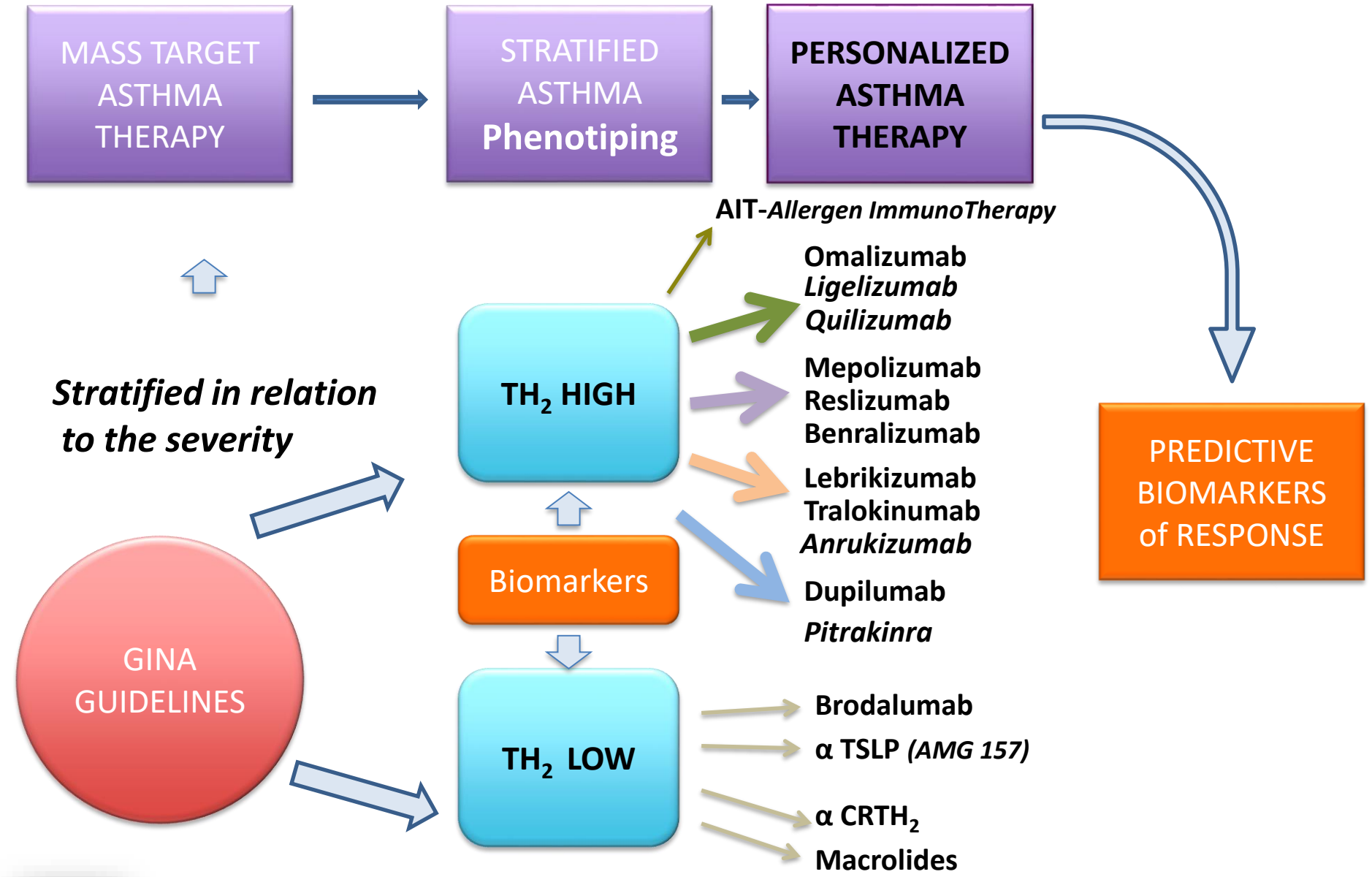
mRNA



protein

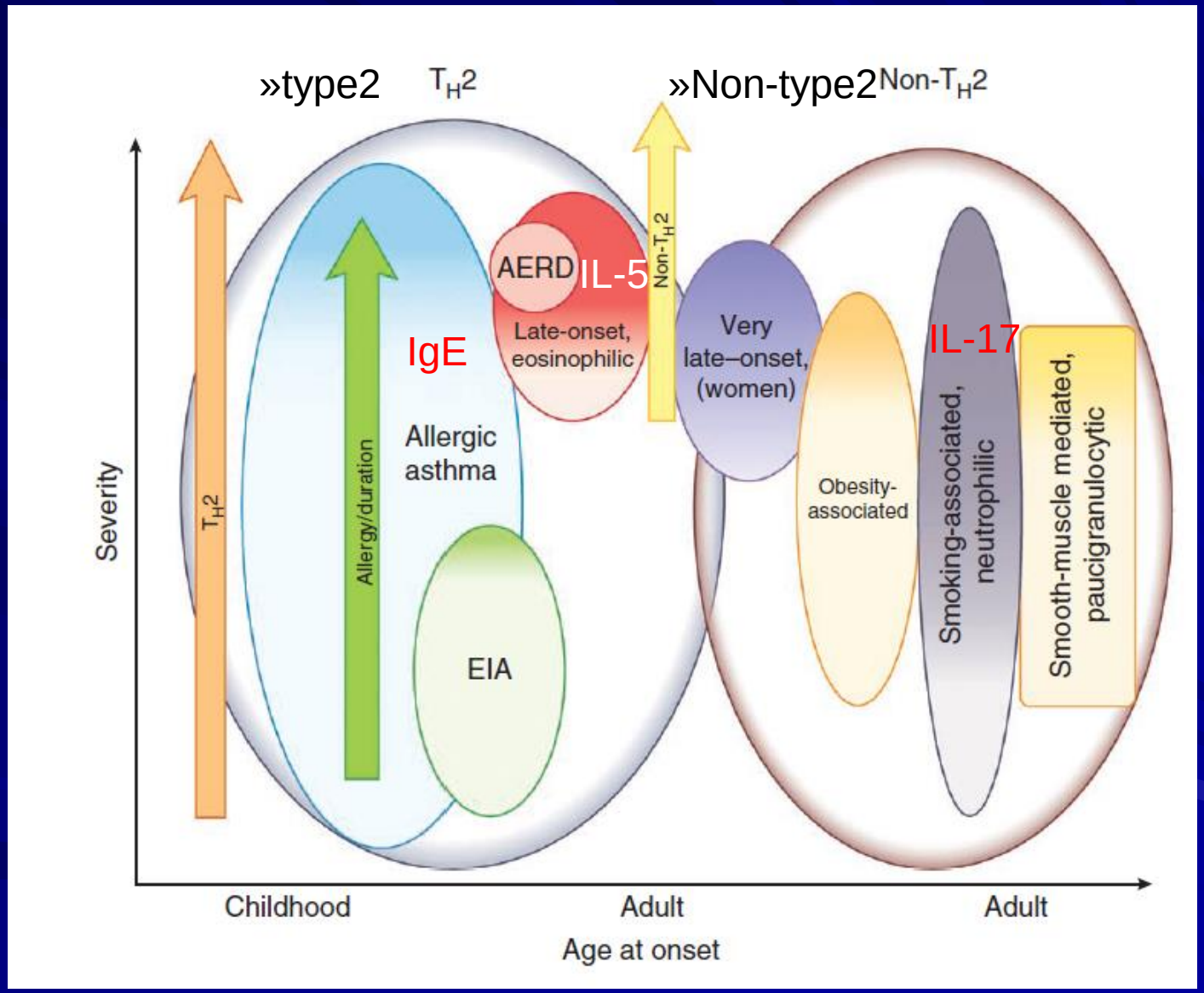


Vazquez-Tello A et al. J Clin Immunol 2013; 33:466-78.



Bagnasco et al. Exp.Rev.Resp.Med. *2016*

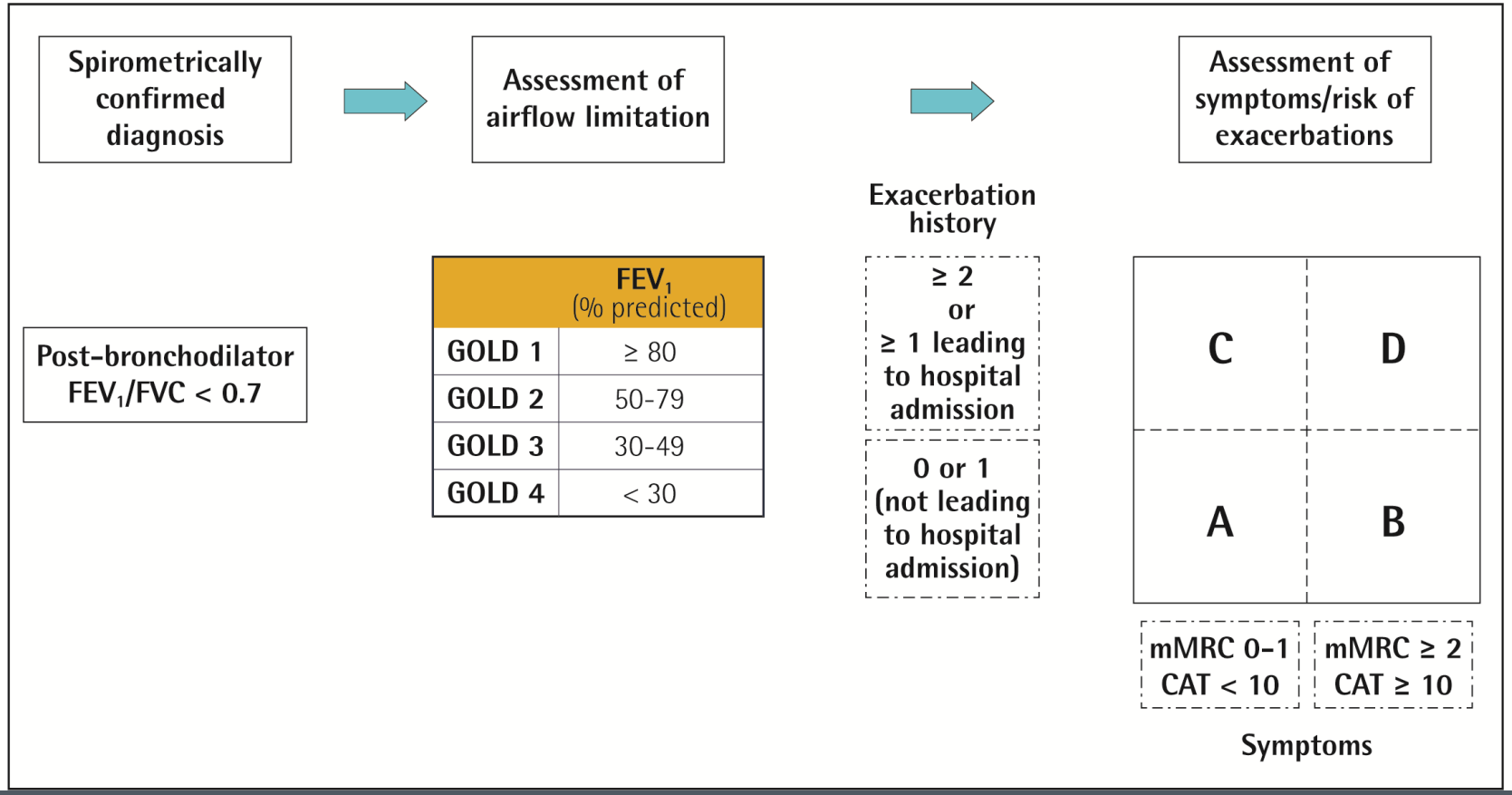
Asthma phenotypes/endotypes



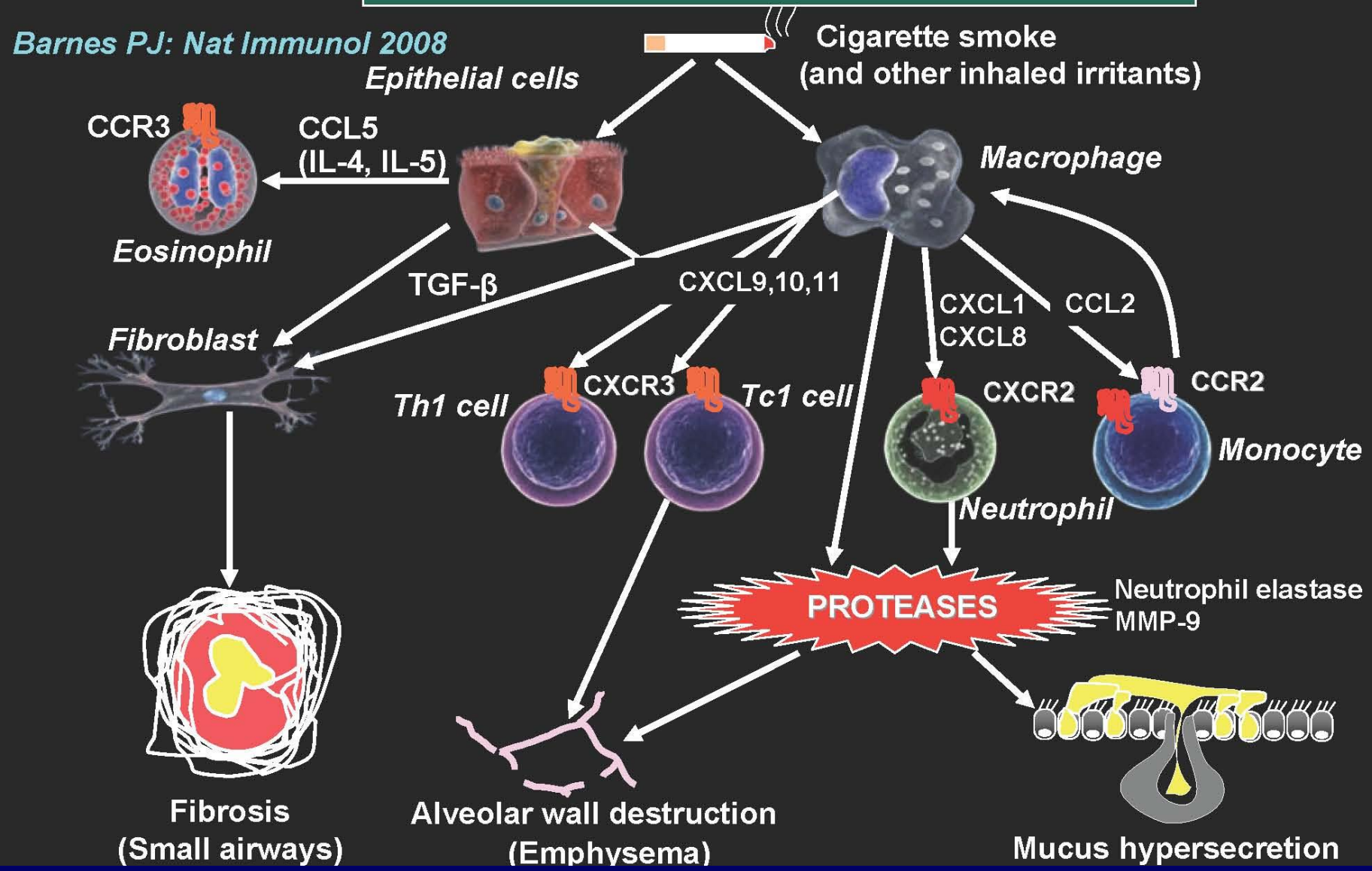
Wenzel S., Nature Medicine 2012.

ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool



CELLULAR MECHANISMS OF COPD



Professor Peter J. Barnes, MD
National Heart and Lung Institute, London UK

Large versus Small airways in moderate COPD: inflammatory cells

Table 2. The number of NF-κBp65-positive, HDAC2-positive and inflammatory cells in large and small airways

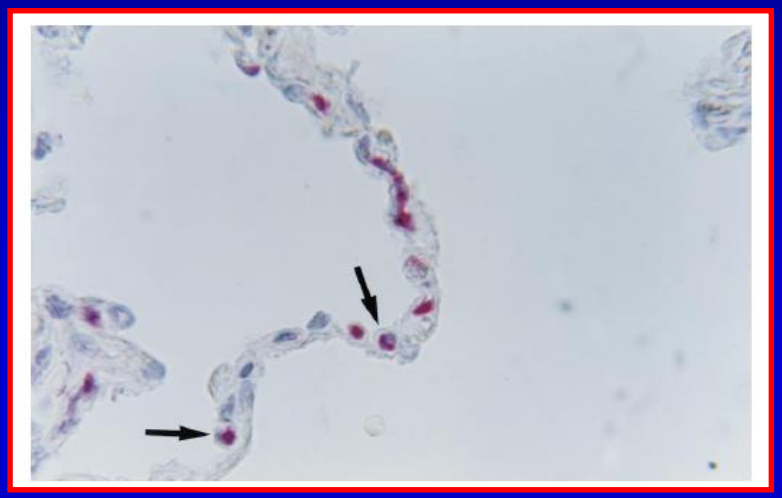
Patients	NF-κBp65-positive cells, cells/mm^2	HDAC-2-positive cells, cells/mm^2	CD8+ T lympho-cytes, cells/mm^2	Neutrophils cells/mm^2	Macrophages cells/mm^2
In large airways					
Nonsmokers	245 (198–310)	58 (54–168)	71 (8–141)	87 (23–518)	90 (21–269)
Asymptomatic smokers	319 (290–367)[b, c]	61 (2–128)	154 (12–398)[b, c]	234 (72–456)[c]	234 (23–564)[b, c]
COPD patients	490 (399–510)[a]	29 (12–144)[a, b]	321 (77–543)[a]	290 (90–457)[a]	590 (211–678)[a]
In small airways					
Nonsmokers	161 (145–197)	68 (41–102)	56 (18–196)	56 (23–104)	90 (43–234)
Asymptomatic smokers	245 (199–309)[b, c]	35 (8–80)[b, c]	254 (86–432)[b, c]	268 (34–904)[b, c]	350 (21–534)[b, c]
COPD patients	521 (478–579)[a]	16 (2–72)[a]	432 (245–678)[a]	433 (234–754)[a]	274 (98–430)[a]

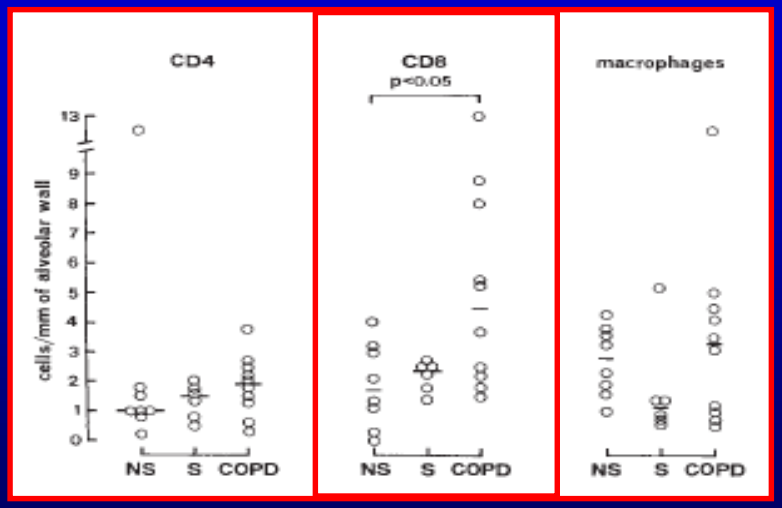
Data are presented as medians (range). [a] $p < 0.05$ compared to nonsmokers; [b] $p < 0.05$ compared to COPD patients; [c] $p < 0.05$ compared to nonsmokers.

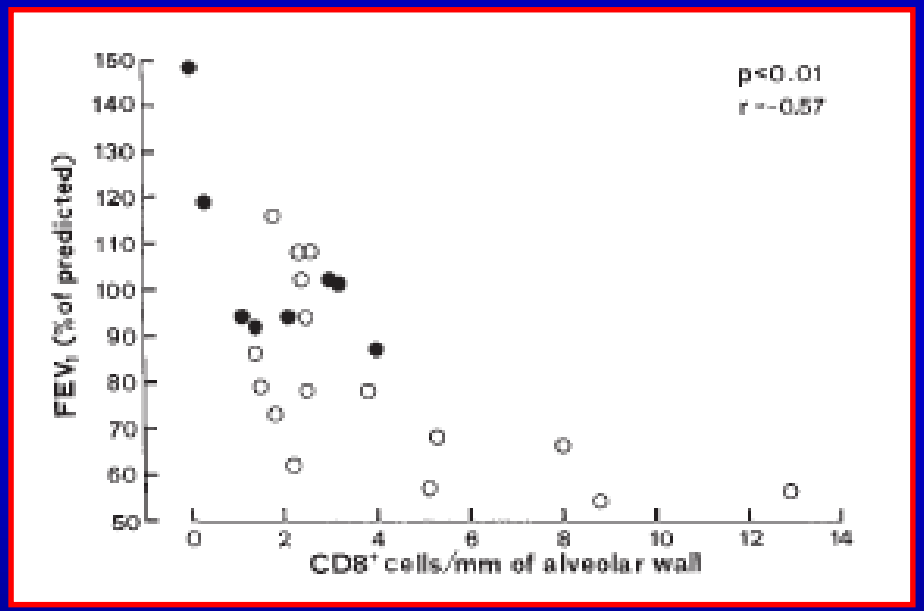
Isajevs et al. Respiration 2011;81:362.

COPD: CD8 in alveolar wall

COPD: $CD8^+$ cells







Saetta et al. AJRCCM 1999;160:711-7.

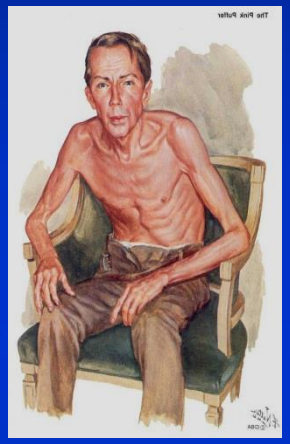
Clinical features of COPD

Burrows et al. *Lancet* 1966

Pink Puffer

SYMPTOMS:

- Dyspnoea on exertion



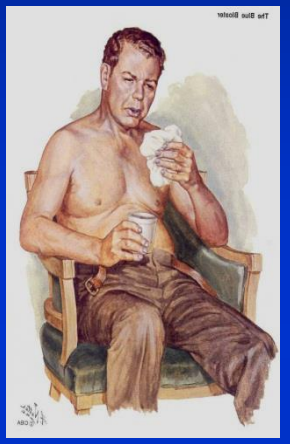
PHYSICAL SIGNS:

- Anorexia and weight loss
- Tachypnoea
- Barrel-chest deformity
- Hoover's sign
- Percussion: increased resonance
- Decreased vescicular breath sounds
- Prolonged expiration
- Pursed-lips breathing

Blue Bloater

SYMPTOMS:

- Productive cough
- Dyspnoea, at rest
- Fatigue/daytime somnolence

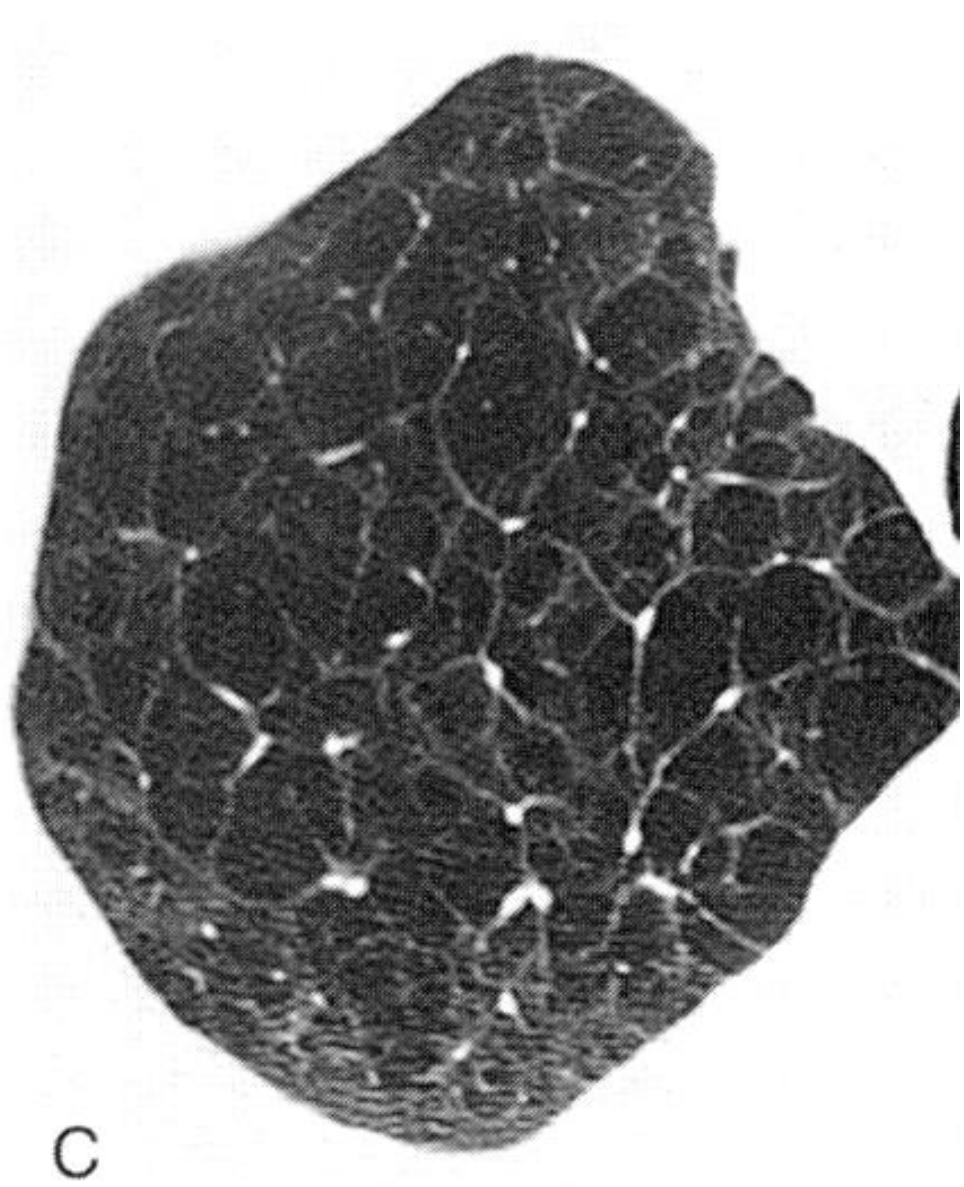


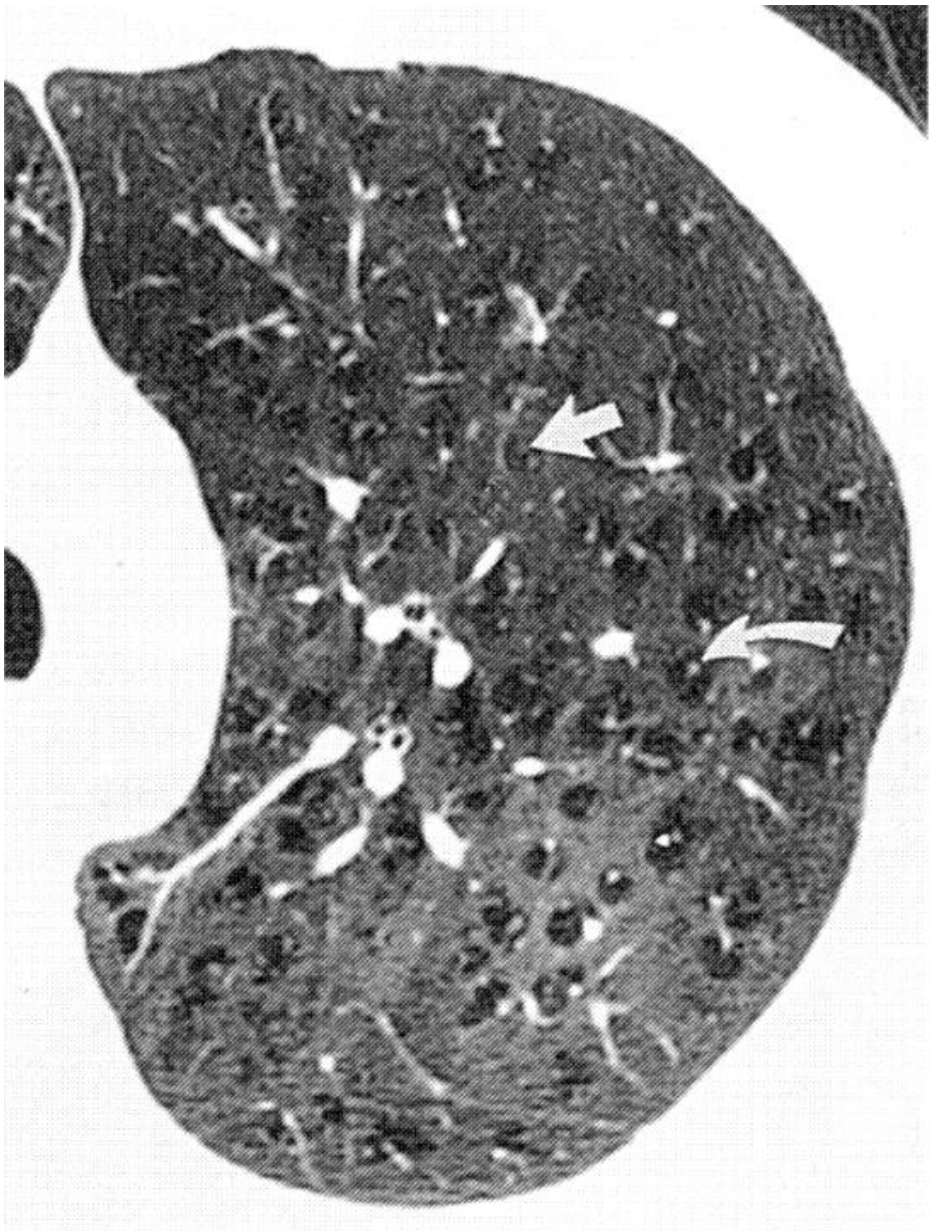
PHYSICAL SIGNS:

- Overweight
- Peripheral oedema
- Cyanosis
- Right heart failure
- Crackles on inspiration; wheezing

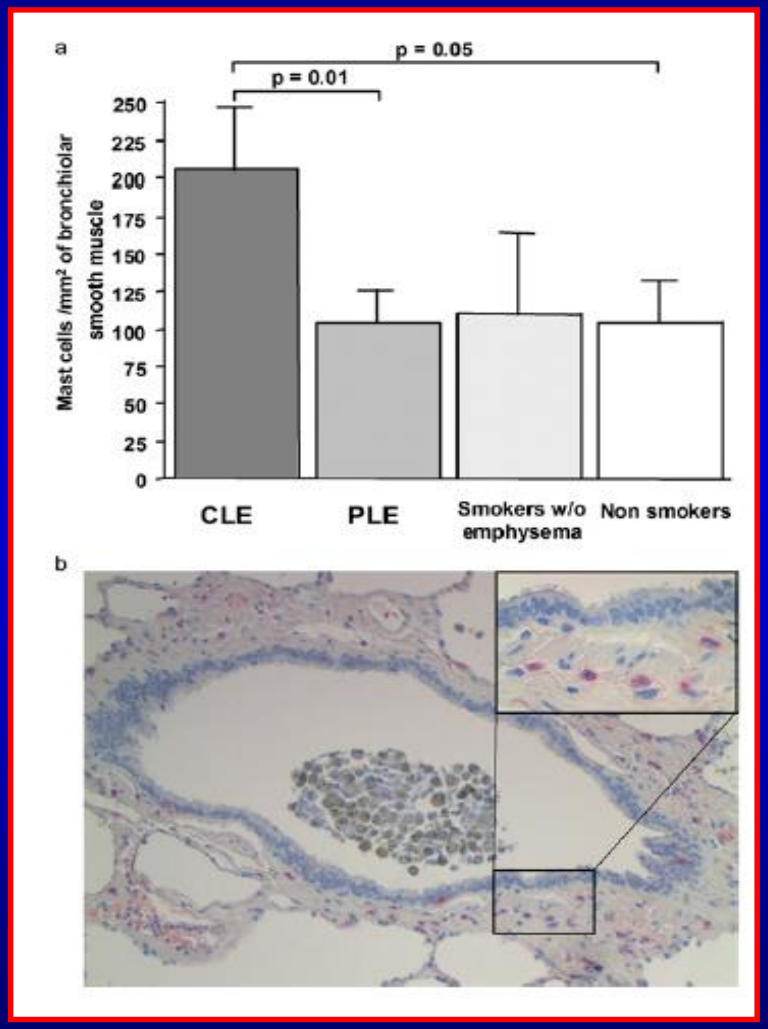
“Pink Puffer”

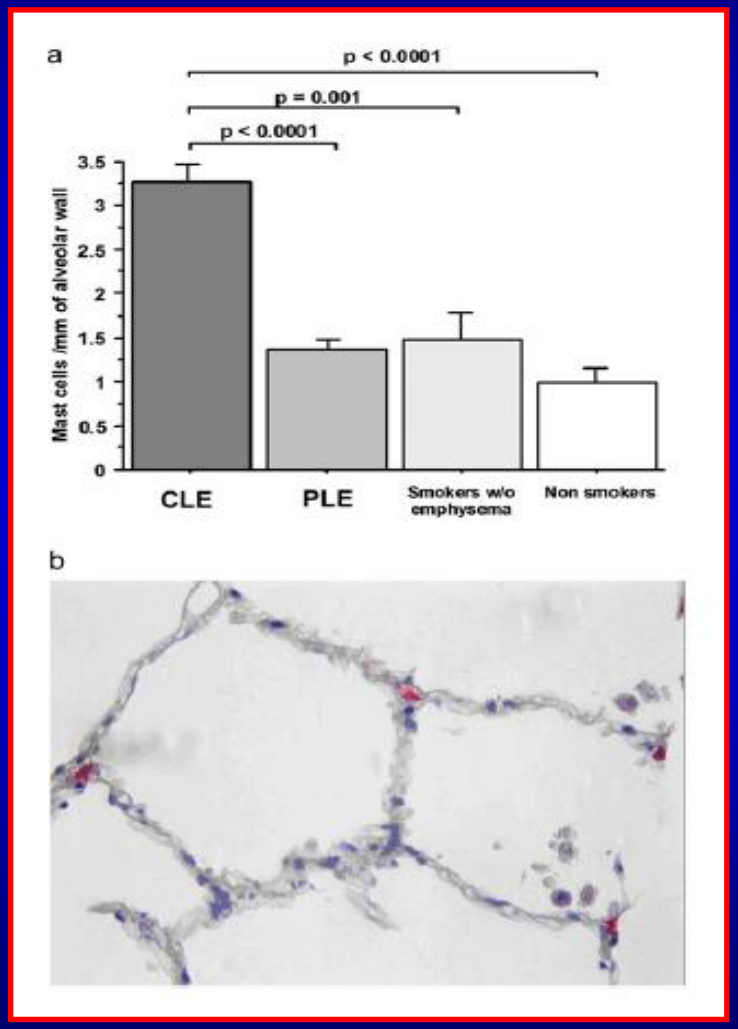
“Blue Bloater”





Mast cells in small airways and alveolar walls in CL and PL emphysema



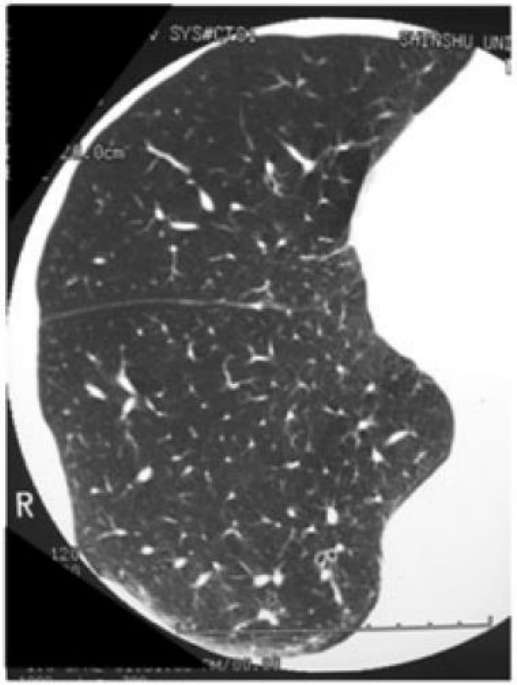


CL: centrilobular; PL: panlobular

Ballarin et al. AJRCCM 2012;186:233-9.

Phenotypes of COPD

Phenotype A

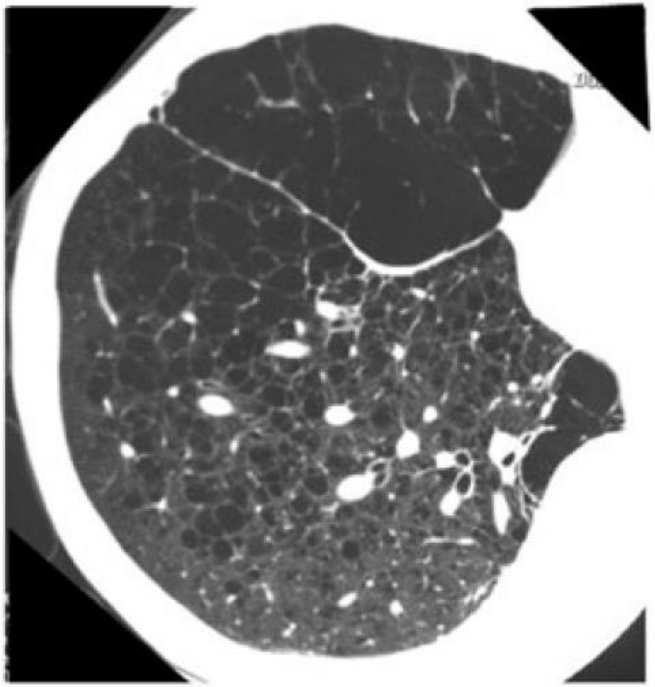


FEV_1 = 47.5%

DI_{co} = 78.2%

Ex/yr = 0.70

Phenotype E

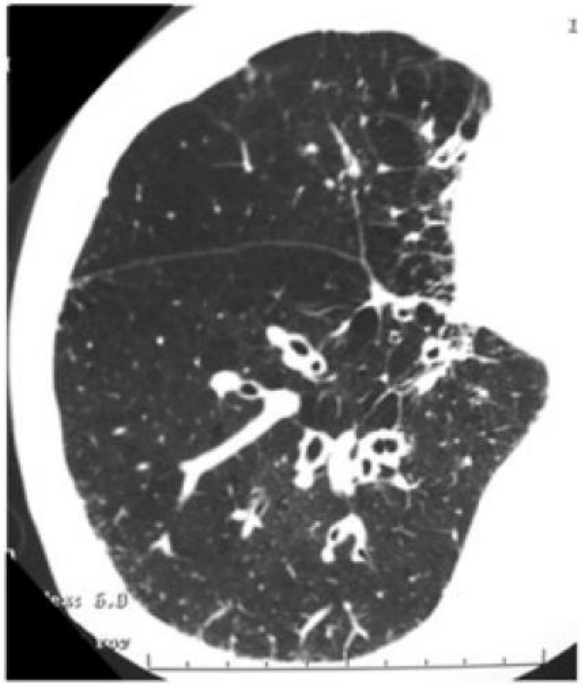


FEV_1 = 46.4%

DI_{co} = 49.3%

Ex/yr = 0.59

Phenotype M



FEV_1 = 42.0%

DI_{co} = 61.6%

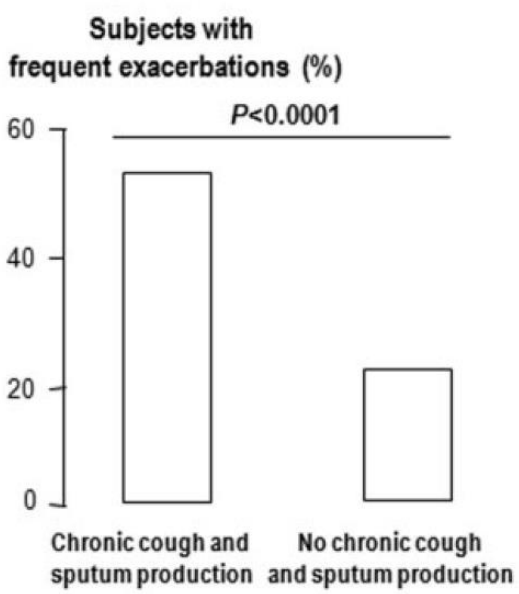
Ex/yr = 1.36

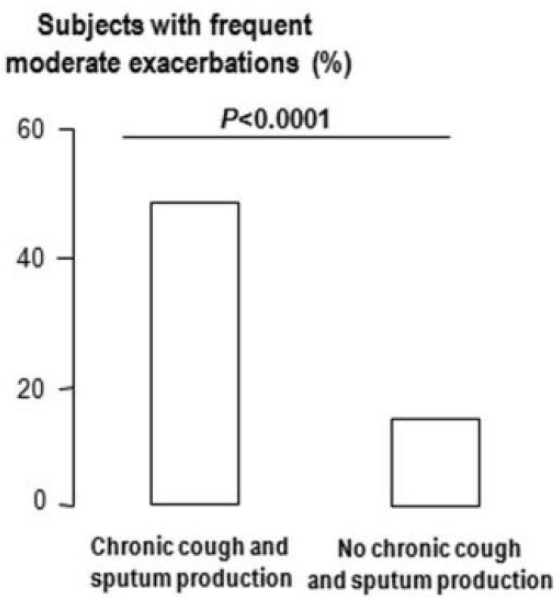
DI_{co} = diffusing capacity for carbon mononide
Ex/yr = exacerbations per year

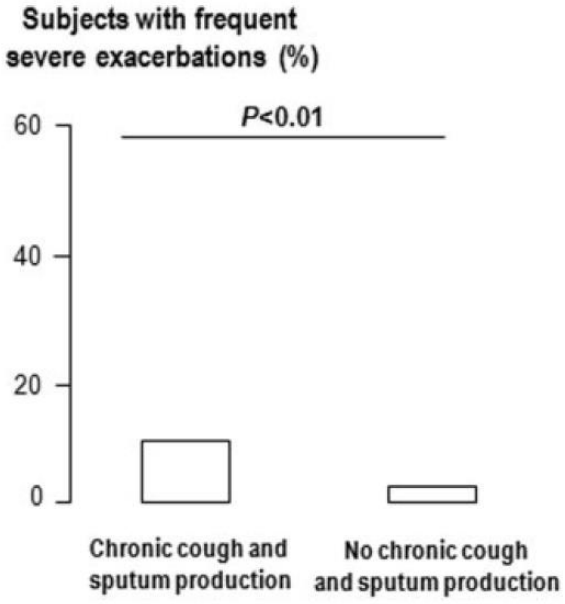
Fujimoto K, et al. Respirology 2006;11:731–740

Cough and Sputum Production Are Associated With Frequent Exacerbations and Hospitalizations in COPD Subjects*

Pierre-Régis Burgel, MD, PhD; Pascale Nesme-Meyer, MD; Pascal Chanez, MD, PhD; Denis Caillaud, MD; Philippe Carré, MD; Thierry Perez, MD; and Nicolas Roche, MD, PhD; on behalf of the Initiatives Bronchopneumopathie Chronique Obstructive (BPCO) Scientific Committee†







(CHEST 2009; 135:975–982)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

John R. Hurst, M.B., Ch.B., Ph.D., Jørgen Vestbo, M.D., Antonio Anzueto, M.D., Nicholas Locantore, Ph.D., Hana Müllerova, Ph.D., Ruth Tal-Singer, Ph.D., Bruce Miller, Ph.D., David A. Lomas, Ph.D., Alvar Agusti, M.D., Ph.D., William MacNee, M.B., Ch.B., M.D., Peter Calverley, M.D., Stephen Rennard, M.D., Emiel F.M. Wouters, M.D., Ph.D., and Jadwiga A. Wedzicha, M.D., for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators*

Frequent Exacerbations of Chronic Obstructive Pulmonary Disease — A Distinct Phenotype?

Donald P. Tashkin, M.D.

COPD: Frequent Exacerbators

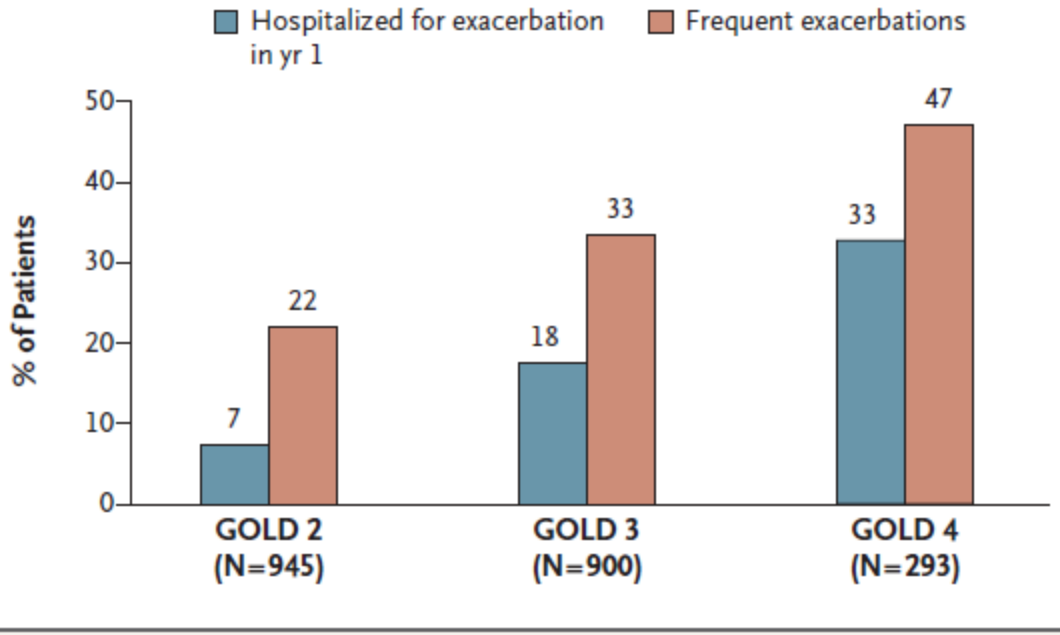


Figure 1. Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease.

Patients with two or more exacerbations during the year were considered to have frequent exacerbations. An exacerbation requiring hospitalization was classified as severe. Disease severity was classified according to the stages of disease defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). P<0.001 for both comparisons.

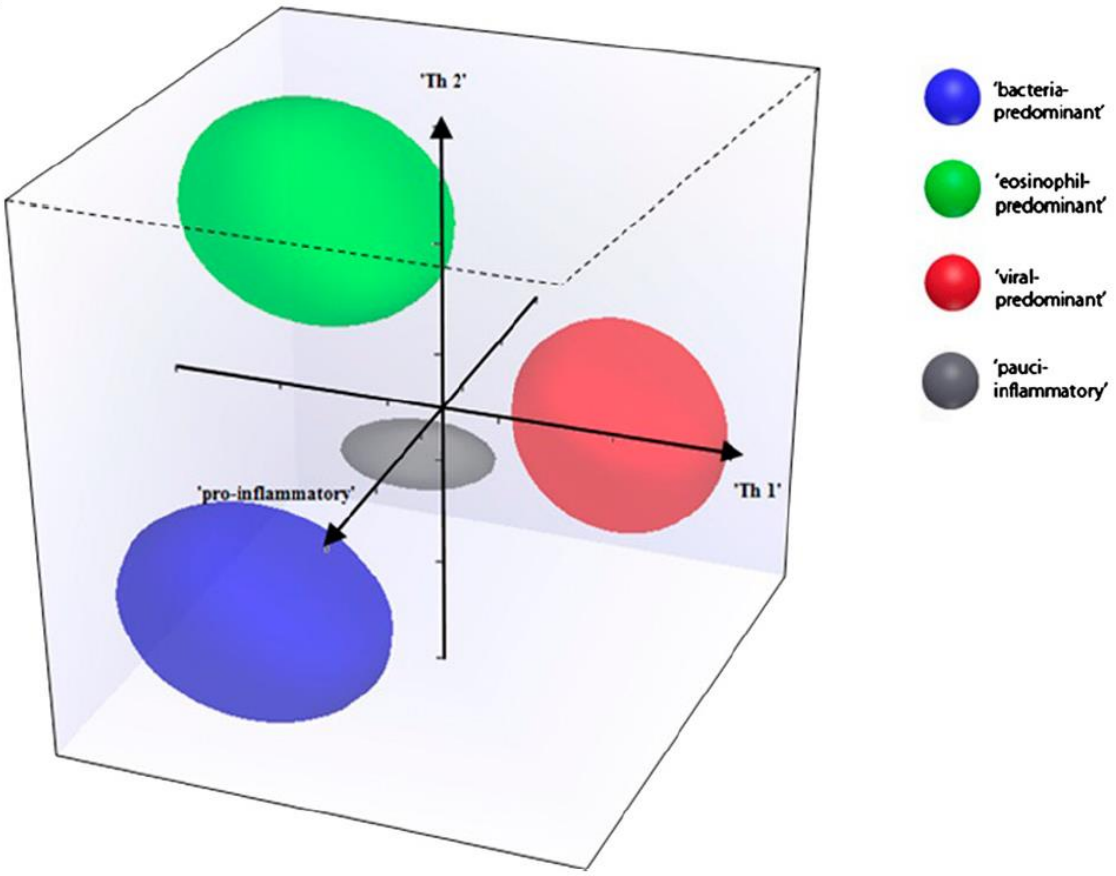
Hurst et al. N Engl J Med 2010;363:1128-1138.

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Identification of Biologic Clusters and Their Biomarkers

Mona Bafadhel[1,2], Susan McKenna[1], Sarah Terry[1], Vijay Mistry[1,2], Carlene Reid[1], Pranabashis Haldar[2], Margaret McCormick[3], Koirobi Haldar[2], Tatiana Kebadze[4], Annelyse Duvoix[5], Kerstin Lindblad[6], Hemu Patel[7], Paul Rugman[3], Paul Dodson[3], Martin Jenkins[3], Michael Saunders[3], Paul Newbold[3], Ruth H. Green[1], Per Venge[6], David A. Lomas[5], Michael R. Barer[2,7], Sebastian L. Johnston[4], Ian D. Pavord[1], and Christopher E. Brightling[1,2]

B



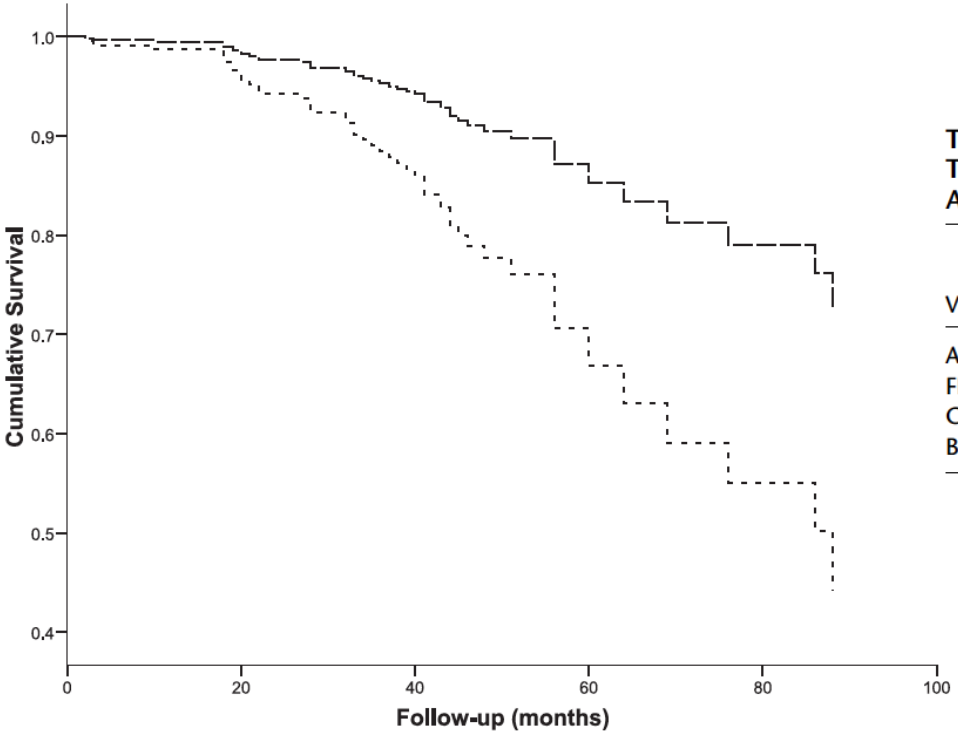
AJRCCM 2011; 184: 662-671

Frequent exacerbators

71 year-old man	74 year-old man
Ex smoker 52 pack-year	Ex smoker 40 pack-year
Admitted for ECOPD	Admitted for ECOPD
2 ECOPD past year	2 ECOPD past year
FEV1(%) = 39%	FEV1(%) = 47%
White sputum	Dark sputum
Diagnosed with asthma at 16 yrs.	Cylindrical brochiectasis
No bacteria isolation	Pseudomonas aeruginosa

Prognostic Value of Bronchiectasis in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

Miguel-Angel Martínez-García[1,2], David de la Rosa Carrillo[3], Juan-Jose Soler-Cataluña[4], Yolanda Donat-Sanz[4], Pablo Catalán Serra[4], Marco Agramunt Lerma[5], Javier Ballestín[5], Irene Valero Sánchez[1], Maria Jose Selma Ferrer[1], Anna Roma Dalfo[6], and Montserrat Bertomeu Valdecillos[6]



------ COPD without bronchiectasis (n=86; 8 deaths)

- - - - COPD with bronchiectasis (n=115; 43 deaths)

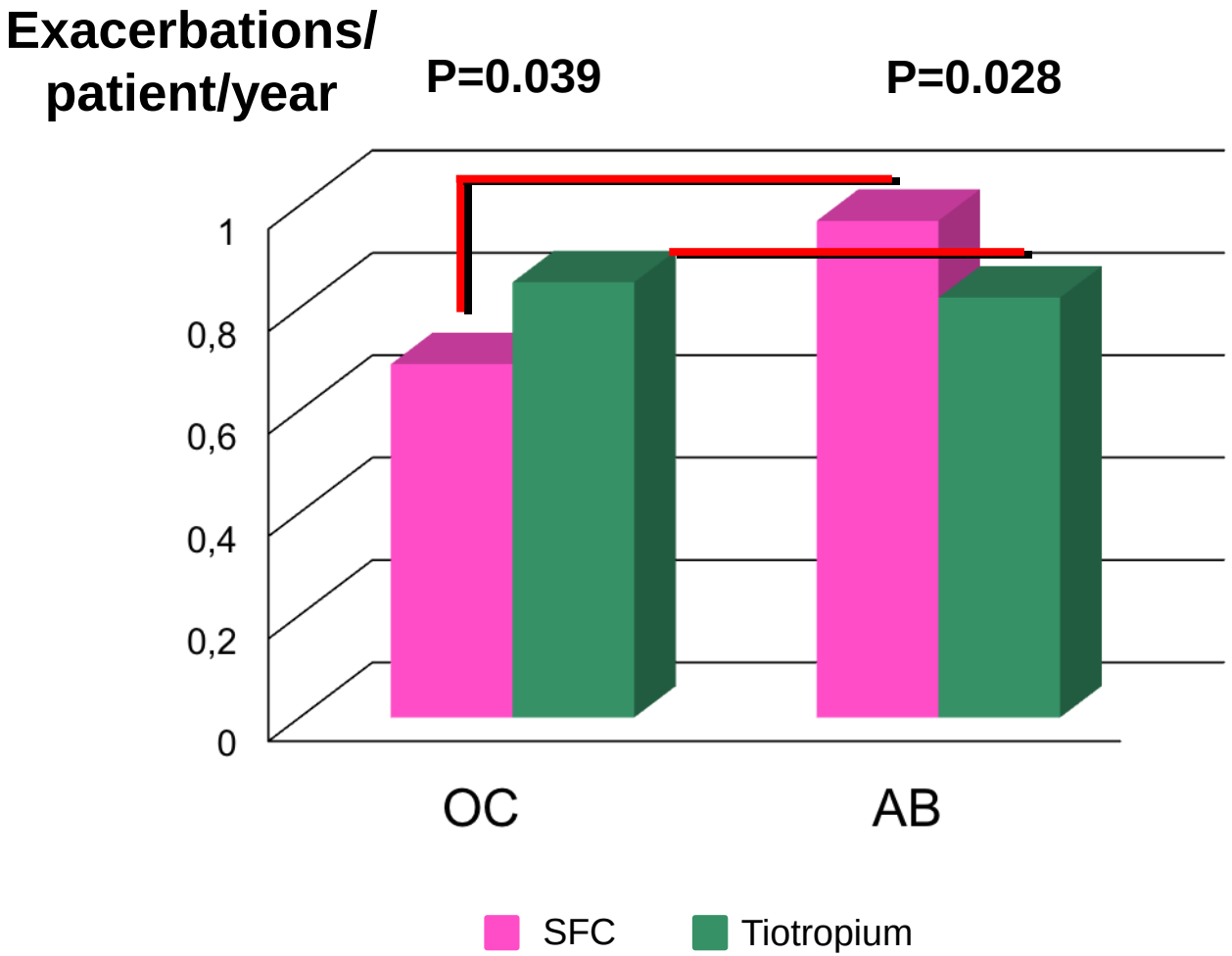
TABLE 5. VARIABLES ASSOCIATED WITH DEATH IN MODERATE-TO-SEVERE COPD, USING THE PRESENCE OF BRONCHIECTASIS AS A DICHOTOMIC VARIABLE

	Unadjusted		Fully Adjusted	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.13 (1.08–1.18)	0.0001	1.10 (1.05–1.15)	0.0001
FEV_1 ppb %	0.97 (0.95–0.99)	0.002	0.97 (0.95–0.99)	0.023
Charlson Index	1.31 (1.11–1.56)	0.002	1.22 (1.02–1.46)	0.033
Bronchiectasis	4.07 (1.91–8.67)	0.0001	2.54 (1.16–5.56)	0.02

Am J Respir Crit Care Med Vol 187, Iss. 8, pp 823–831, Apr 15, 2013

Prevention of exacerbations

Prevention of exacerbations with SFC or tiotropium

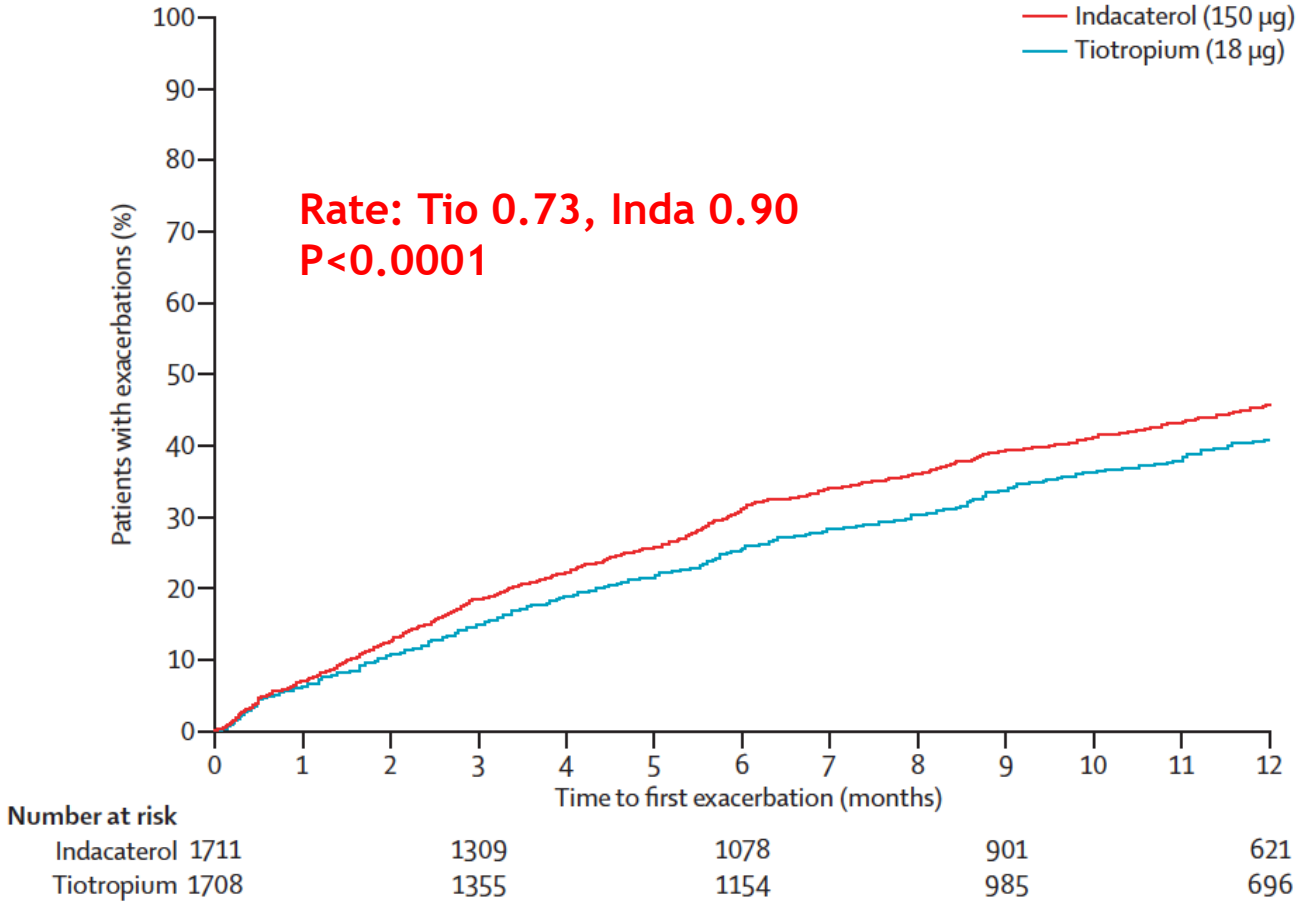


AB = requiring antibiotics
OC = exacerbations requiring oral cortocosteroids
SFC = salmeterol/fluticasone propionate

Wedzicha JA, et al. Am J Respir Crit Care Med 2008;177:19–26

Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study

Marc L Decramer, Kenneth R Chapman, Ronald Dahl, Peter Frith, Gilles Devouassoux, Carlos Fritscher, Ray Cameron, Muhammad Shoaib, David Lawrence, David Young, Danny McBryan, on behalf of the INVIGORATE investigators

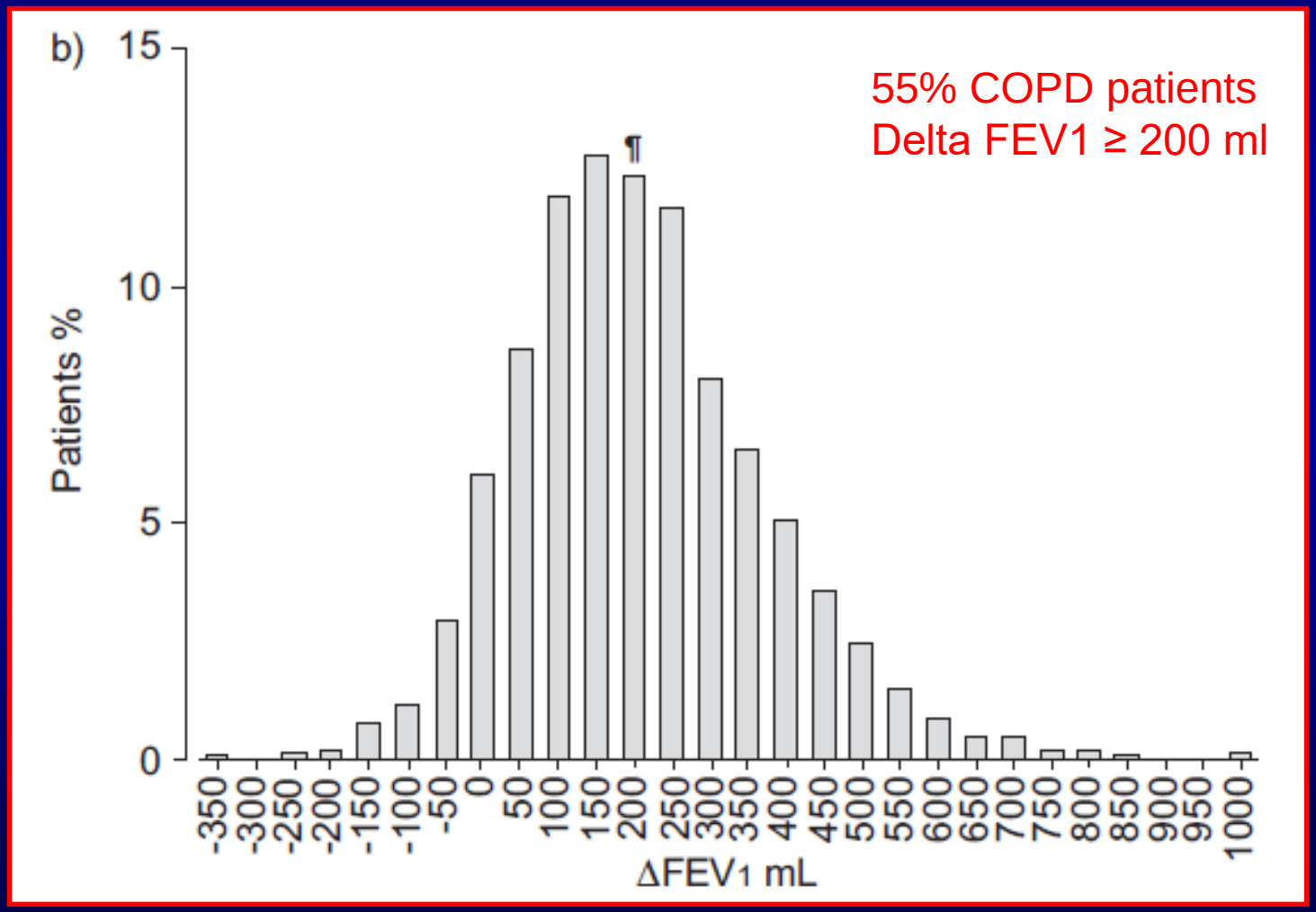


Lancet Respir Med 2013; 1: 524-533

Eur Respir J 2008; 31: 742–750
DOI: 10.1183/09031936.00129607

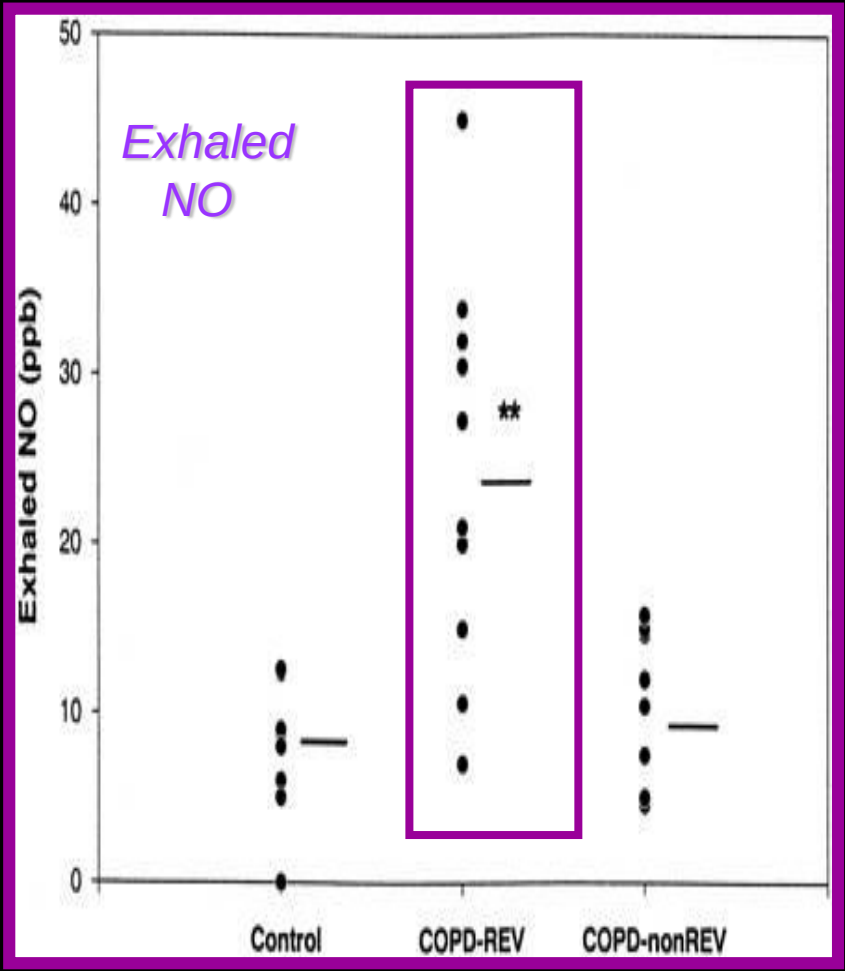
Bronchodilator responsiveness in patients with COPD

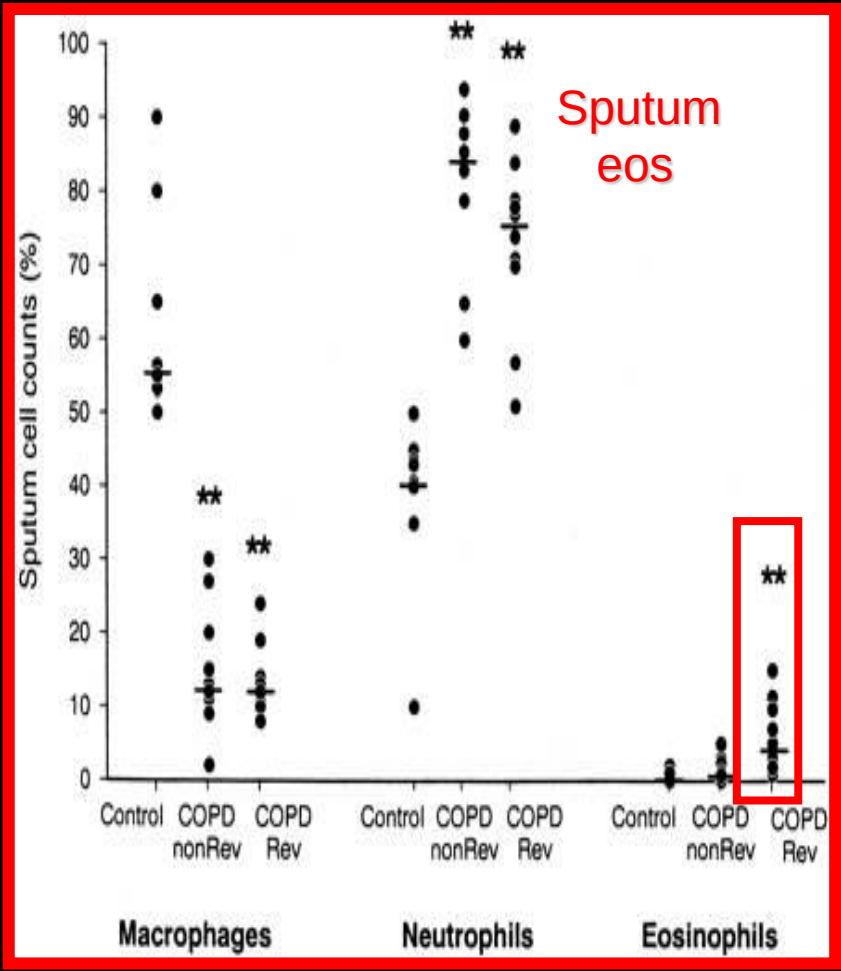
D.P. Tashkin*, B. Celli#, M. Decramer¶, D. Liu+, D. Burkhart+, C. Cassino+ and S. Kesten§



↑ FeNO & SPUTUM EOS IN "REVERSIBLE" COPD

Reversible: >15%↑ in FEV_1 after b/d





Papi A et al: AJRCCM 2000

Blood eosinophils as a marker of response to inhaled corticosteroids in COPD

Neil C. Barnes[1,2], Raj Sharma[1], Sally Lettis[3] and Peter M.A. Calverley[4]

ISOLDE STUDY

TABLE 2 Rate of decline in post-bronchodilator forced expiratory volume in 1 s (FEV_1) in patients receiving fluticasone propionate 500 µg twice daily (FP) or placebo twice daily according to blood eosinophil level[#]

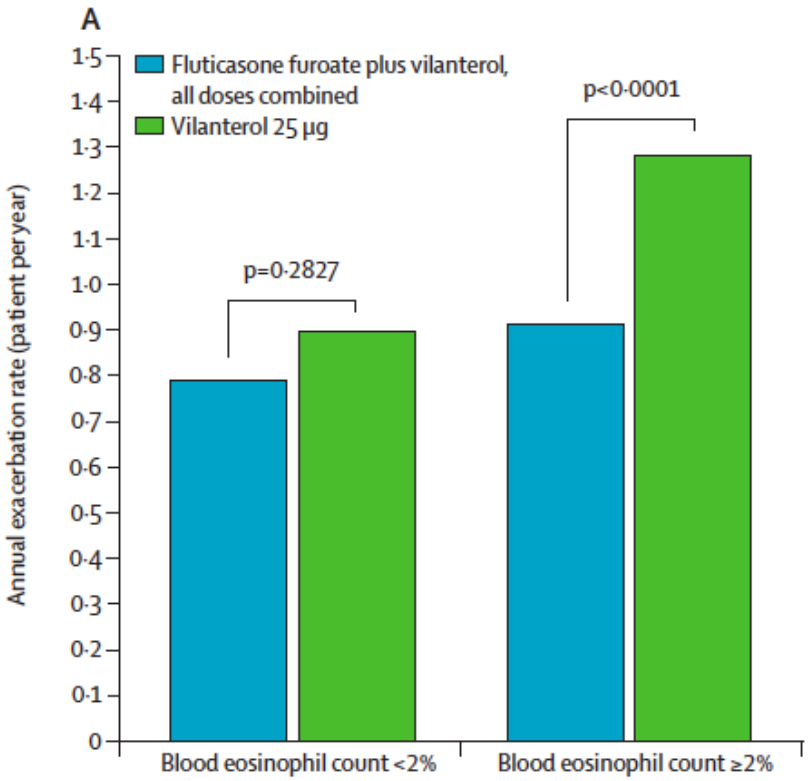
	Eosinophils <2%		Eosinophils ≥2%	
	FP	Placebo	FP	Placebo
Patients n	240	216	97	107
Baseline FEV_1 (mean±SD) L	1.46±0.487	1.39±0.469	1.32±0.440	1.45±0.525
Adjusted rate of decline in FEV_1 (mean±SE) $mL \cdot year^{-1}$	−54.2±4.8	−51.3±5.3	−40.6±8.0	−74.5±8.0
Slope: FP *versus* placebo (mean±SE) (95% CI)	−2.9±7.2 (−17.0–11.3), p=0.688		33.9±11.3 (11.5–56.2),	p=0.003

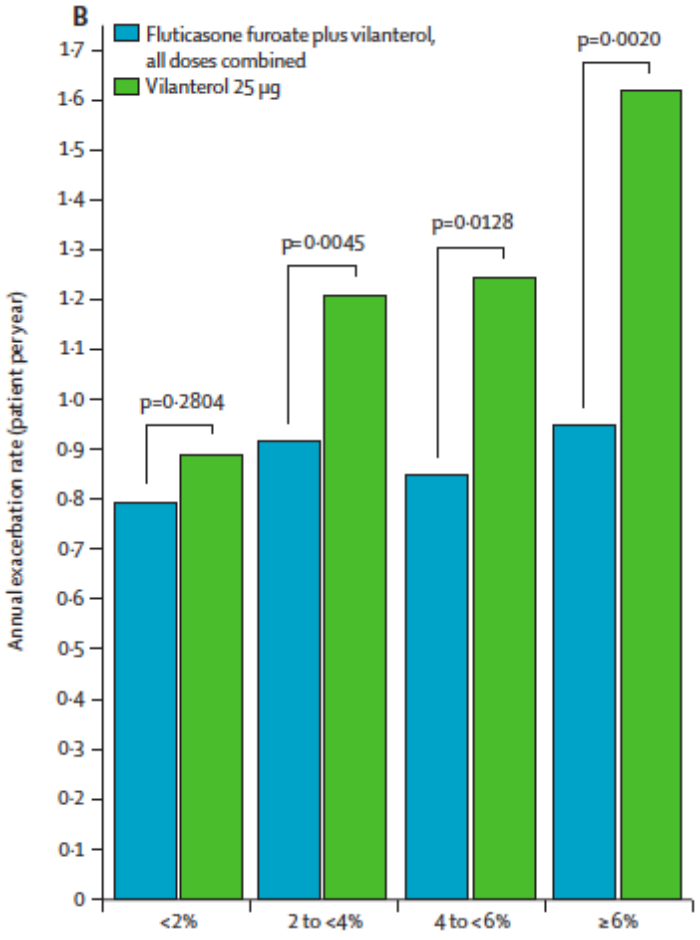
Random coefficients model for each eosinophil subgroup separately, with fixed effects of age, sex, baseline post-bronchodilator FEV_1, treatment group and time, and random subject effects. [#]: using baseline post-bronchodilator FEV_1 as a covariate.

ERJ 2016

Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials

Steven Pascoe, Nicholas Locantore, Mark T Dransfield, Neil C Barnes, Ian D Pavord



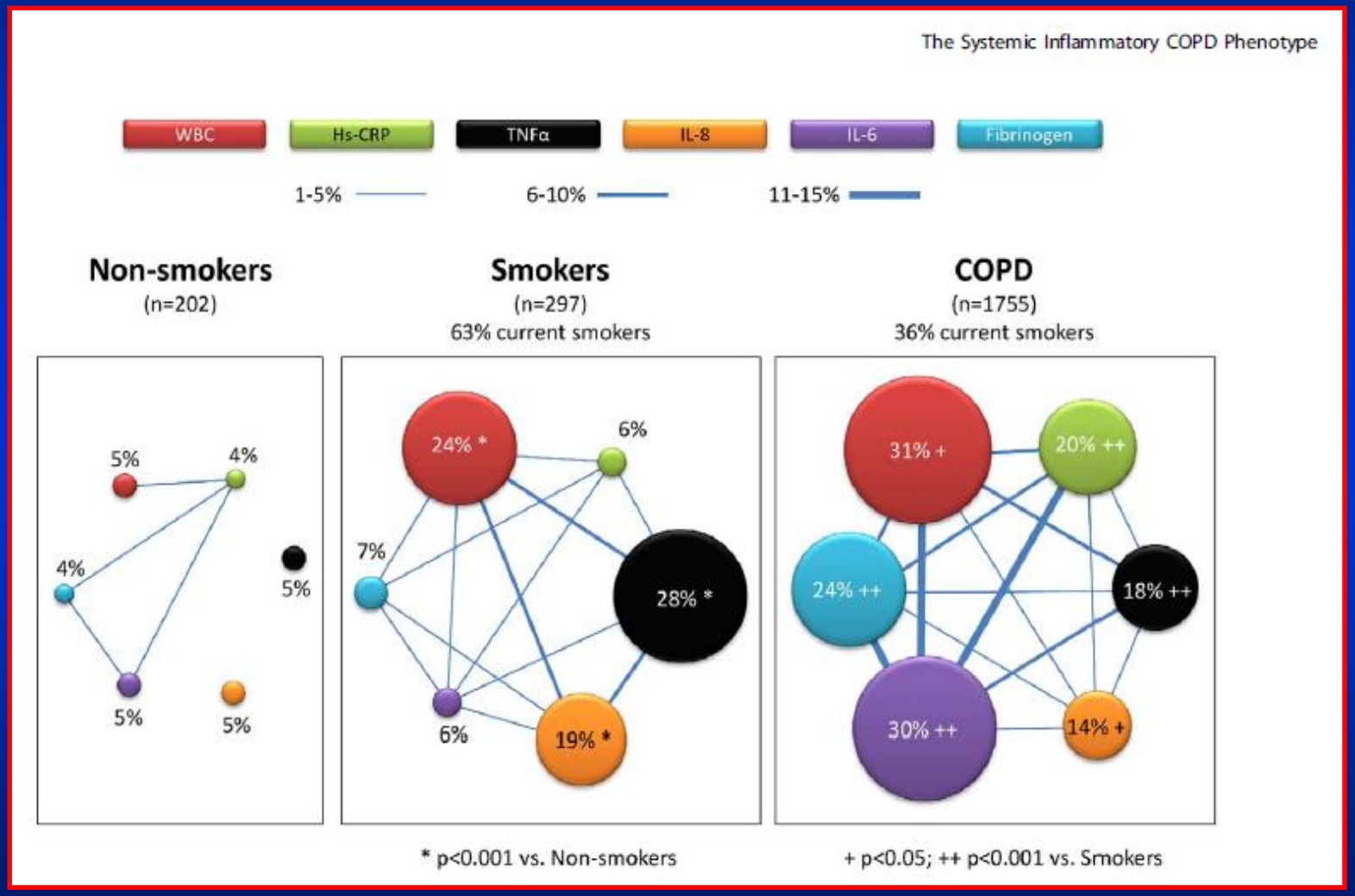


Pascoe S, et al. Lancet Respir Med 2015; 3:435–442.

OPEN ACCESS Freely available online

PLOS one

Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype

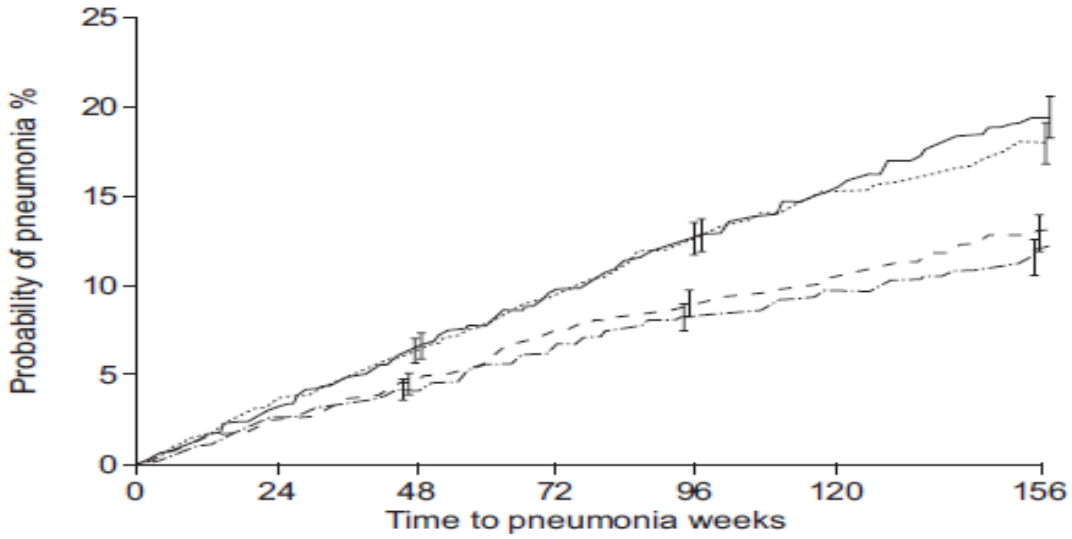


Agusti et al. ECLIPSE Study. Plos One 2012; e37483.

Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results

C. Crim*, P.M.A. Calverley#, J.A. Anderson¶, B. Celli+, G.T. Ferguson§, C. Jenkinsƒ, P.W. Jones**, L.R. Willits¶, J.C. Yates* and J. Vestbo##,¶¶

Time to first Pneumonia in COPD



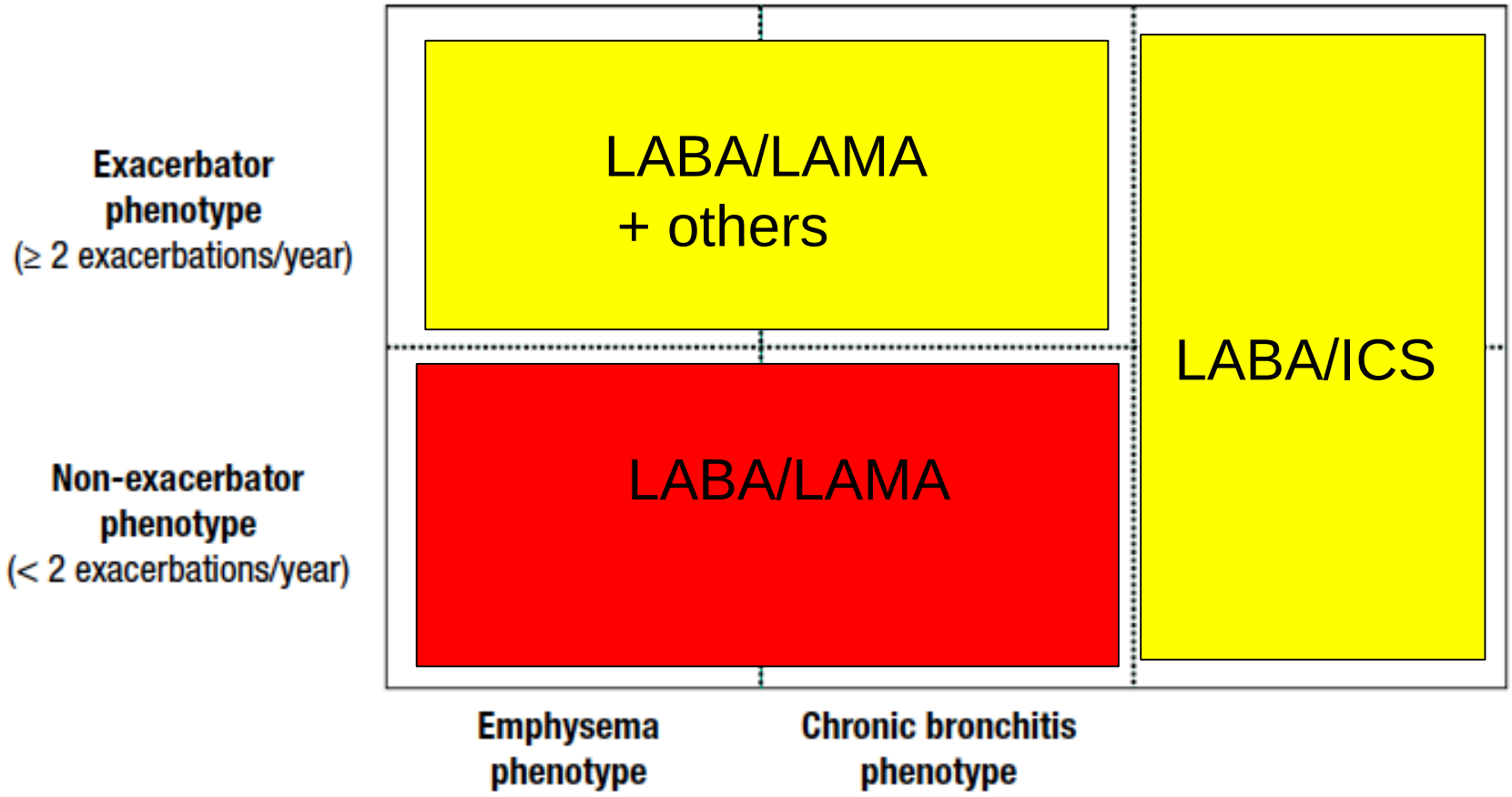
Patients n				
SFC	1546	1231	1034	631
FP	1552	1189	992	574
SAL	1542	1214	1024	645
P	1544	1117	947	587

FIGURE 1. Kaplan–Meier estimate of time to first pneumonia for patients taking placebo (P; – · – · –), salmeterol (SAL; – – – –), fluticasone propionate (FP; ·····), and FP-SAL combination (SFC; ——). Values given below the figure are the numbers of patients at risk at randomisation and following 48, 96 and 156 weeks of treatment. Vertical bars represent SE.

ERJ 2009;34:641-7

Spanish Guideline for COPD (GesEPOC). Update 2014

Marc Miravitlles[a,b,*], Juan José Soler-Cataluña[b,c], Myriam Calle[d], Jesús Molina[e], Pere Almagro[f], José Antonio Quintano[g], Juan Antonio Riesco[h], Juan Antonio Trigueros[i], Pascual Piñera[j], Adolfo Simón[k], Juan Luis Rodríguez-Hermosa[d], Esther Marco[l], Daniel López[m], Ramon Coll[n], Roser Coll-Fernández[ñ], Miguel Ángel Lobo[o], Jesús Díez[p], Joan B. Soriano[q] and Julio Ancochea[r]



Arch Bronconeumol. 2014;**50(Suppl 1)**:1-16

A new algorithm for the management of COPD

*Christopher B Cooper, Igor Barjaktarevic

Clinical stage	GOLD stage (approximate)
At risk	0
Intermittent symptoms	1
Persistent symptoms	2
Frequent exacerbations	3
Respiratory failure	4

Inhaled therapy

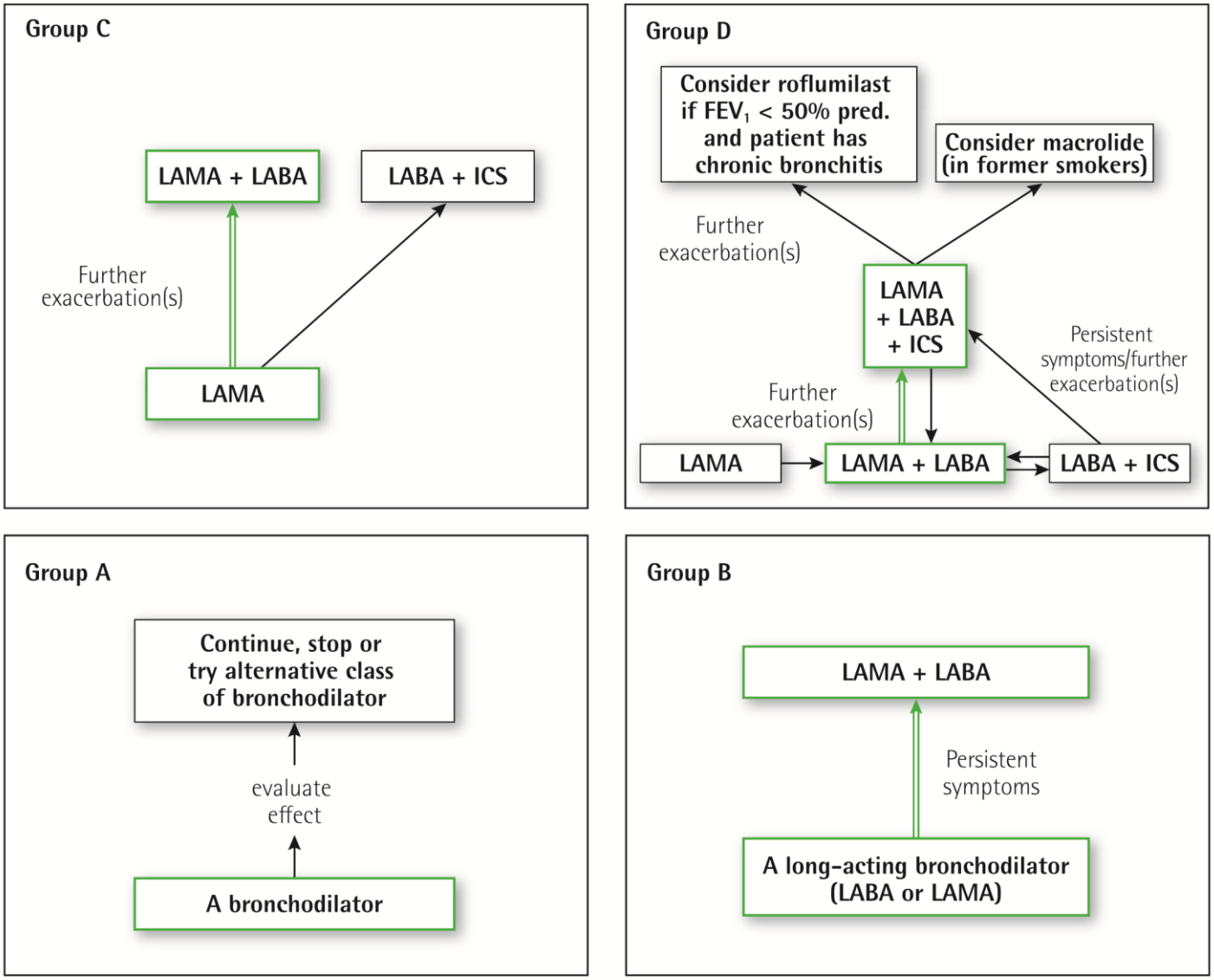
- SAMA, SABA, or SAMA + SABA
- LAMA + SABA
- LABA + SAMA
- LAMA + LABA
- Clinical phenotyping

Non-pharmacological therapy

- Smoking cessation
  Avoidance of exposure
- Vaccination
  (influenza, pneumococcal)
- Pulmonary rehabilitation
  (exercise prescription)
- Supplemental oxygen
  Lung volume reduction surgery
  Lung transplantation

Lancet Respir Med 2015;3:266–268

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

Phenotypes and Disease Characterization in Chronic Obstructive Pulmonary Disease

Toward the Extinction of Phenotypes?

Alvar Agustí[1]

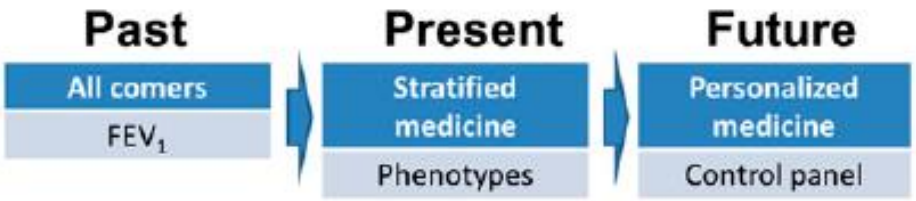


Figure 2. Phenotypes are a necessary but intermediate step from the classical approach ("one size [FEV_1] fits all") to the future personalized treatment of chronic obstructive pulmonary disease. It is likely that the concept of "phenotypes" will be abandoned.

Annals ATS 2013;10:S125