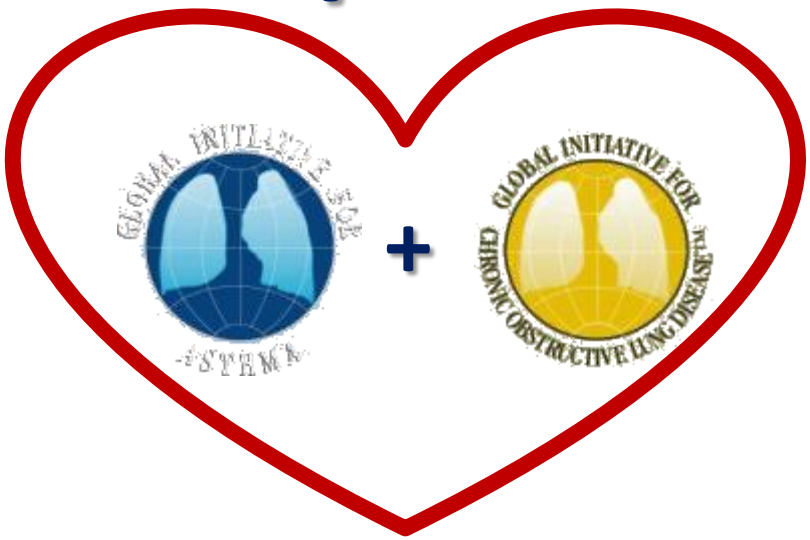
EXISTUJE OVERLAP CHOPN A ASTMATU ?

pro



Vratislav Sedlák

Plicní klinika LF UK a FN Hradec Králové

DUTCH HYPOTHESIS

BRITISH HYPOTHESIS

Existuje „čisté“ AB a COPD ?

- AB a COPD jsou chronická zánětlivá onemocnění, která postihují dýchací cesty a jsou charakteristické obstrukcí DC
- V typických případech mají jednoznačně rozdílné symptomy, rizikové faktory, zánět a odpověď na léčbu

Jsou současné klinické definice dostatečně specifické ?

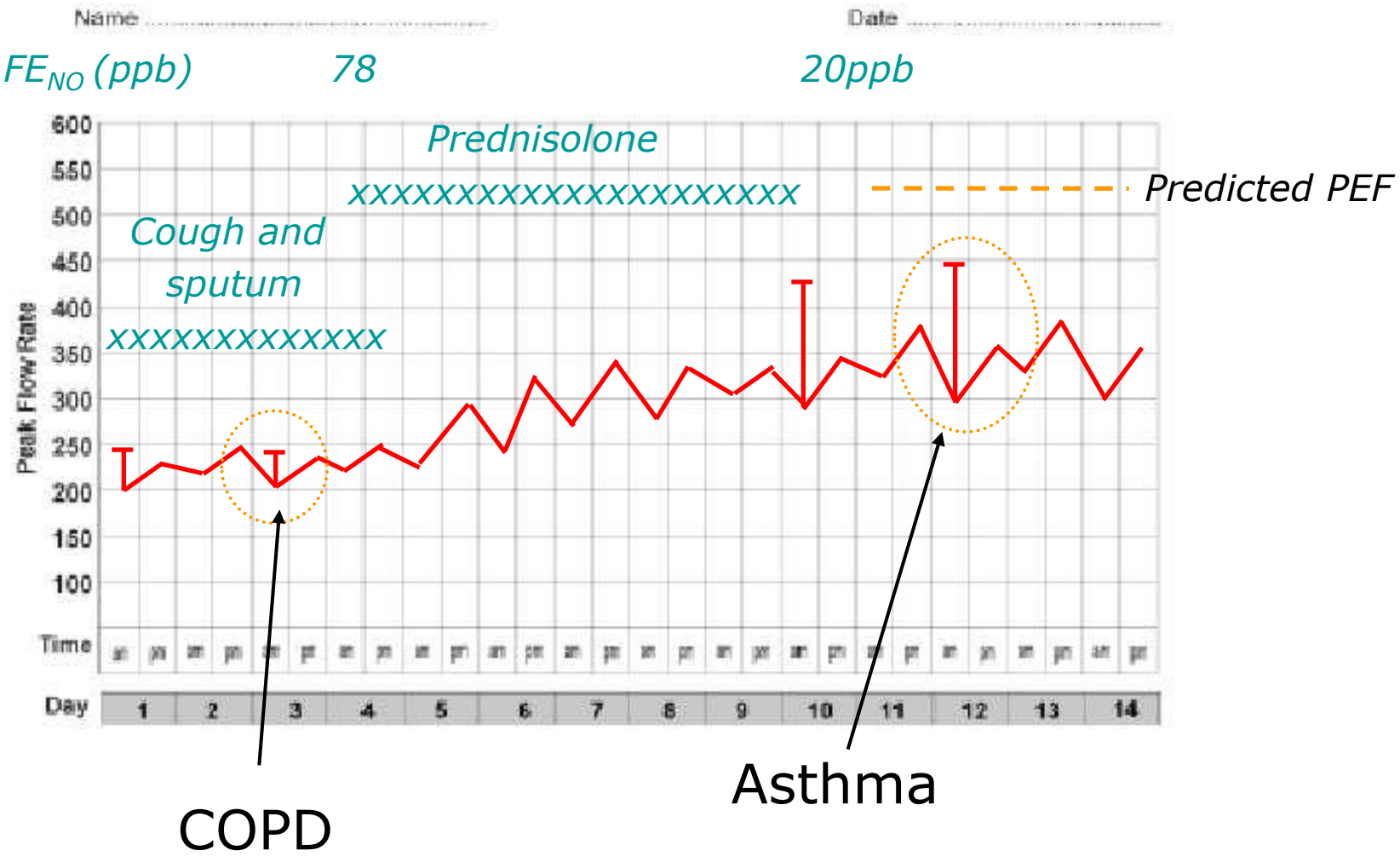
Asthma

- chronické zánětlivé onemocnění
- v patogenezi hraje roli mnoho zánětlivých buněk
- typická je reverzibilní bronchiální obstrukce a bronchiální hyperreaktivita
- opakované epizody pískotů, dušnosti, tísně na hrudi a kašle

COPD

- progresivní bronchiální obstrukce, které není zcela reverzibilní
- důsledek abnormální reakce na vdechované škodliviny (kouření, …)

ASTMA nebo CHOPN



	ASTHMA	COPD
Flow	=/ -	-
BD response (>15%)	+	-/+
Variability	+	-
BHR	++	+
DLCO	+	-
Hyperinflation	0/+	+ (++)
Lung elasticity	0	-

Jsou současné klinické definice dostatečně specifické?

Asthma

- chronické zánětlivé onemocnění
- v patogenezi
- mnoho
- t
- ivita
- ody
- usnosti, tísně na
- a kašle

- ení zcela
- ek abnormální
- eakce na vdechované škodliviny (kouření, …)

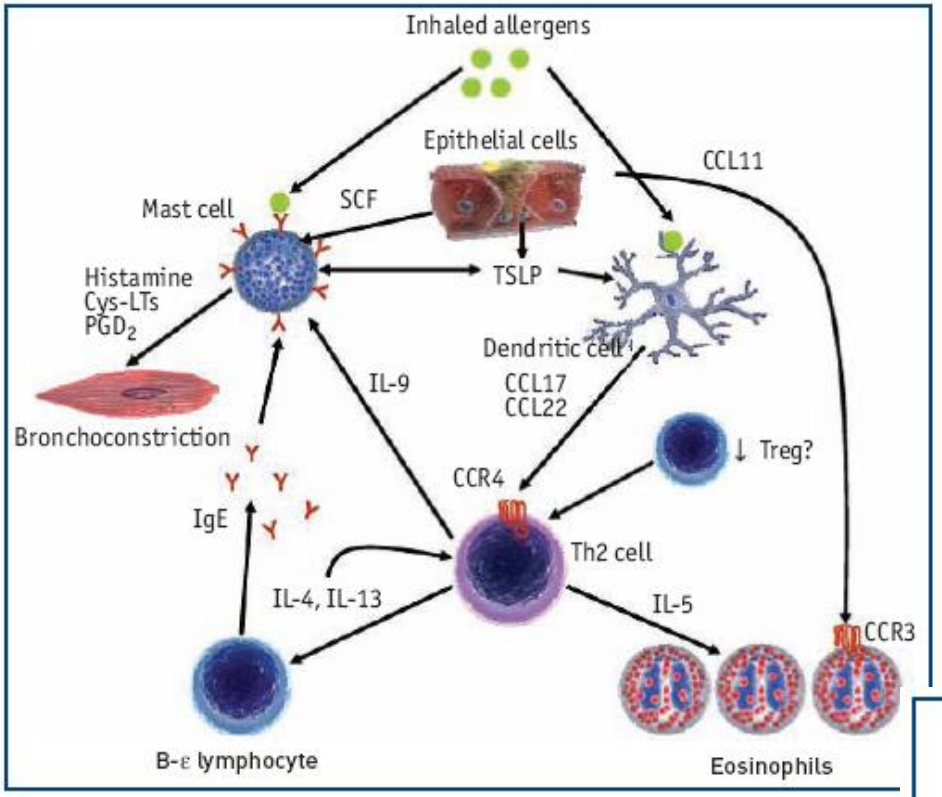
BIOMARKER ?

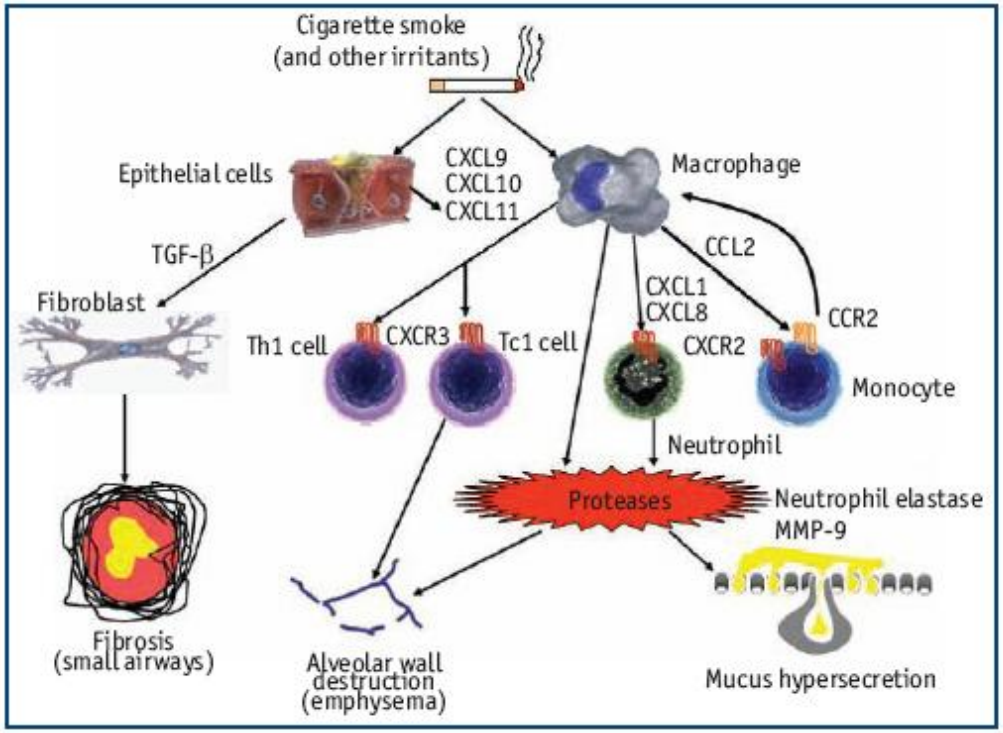
Co už víme dnes ?

ASTHMA *vs* COPD

INFLAMMATION	ASTHMA	COPD
Cells	Mast cells Eosinophils $CD4^+$ T cells Macrophages +	 Neutrophils $CD8^+$ T cells Macrophages +++
Mediators	LTD_4, histamine IL-4, IL-5 ROS +	LTB_4 IL-8, TNF-α ROS +++
Effects	All airways Little fibrosis Ep shedding	Periph airways Lung destruction Fibrosis + Sq metaplasia
Response to steroids	+++	-

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


Inhaled allergens
Epithelial cells
CCL11
Mast cell
SCF
Histamine
Cys-LTs
PGD_2
TSLP
Dendritic cell
CCL17
CCL22
IL-9
Bronchoconstriction
↓ Treg?
CCR4
IgE
Th2 cell
IL-4, IL-13
IL-5
CCR3
B-ε lymphocyte
Eosinophils


Cigarette smoke
(and other irritants)
Epithelial cells
CXCL9
CXCL10
CXCL11
Macrophage
TGF-β
CCL2
Fibroblast
CXCL1
CXCL8
CCR2
Th1 cell
CXCR3
Tc1 cell
CXCR2
Monocyte
Neutrophil
Proteases
Neutrophil elastase
MMP-9
Fibrosis
(small airways)
Alveolar wall
destruction
(emphysema)
Mucus hypersecretion

	COPD	ASTHMA	SEVERE ASTHMA
Cells	Neutrophils ++ Macrophages +++ CD8+T cells (Tc1) CD4+Tcells (Th2) Th17	Eosinophils ++ Macrophages + Mastocites CD4+Tcells (Th2)	Neutrophils + Macrophages CD4+Tcells (Th2) CD8+T cells(Tc1) Th17
Key mediators	IL- 8 TNFα,IL-1β.IL-6 NO+	Eotaxin IL-4,IL-5,IL-13, NO+++	IL-8 IL-5,IL-13 NO++
Oxidative stress	+++	+	+++
Site of disease	Peripheral airways Lung parenchyma Pulmonary vessels	Proximal airways	Proximal airways Peripheral airways
Consequences	Squamous metaplasia Mucous metaplasia, Small airway fibrosis Parenchymal destruction, Pulmonary vascular remodeling	Fragile epithelium Mucous metaplasia, ↑ Basement membrane, Bronchoconstriction	
Response to therapy	Small b/d response Poor response to steroids	Large b/d response Good response to steroids	Smaller b/d response Reduced response to steroids

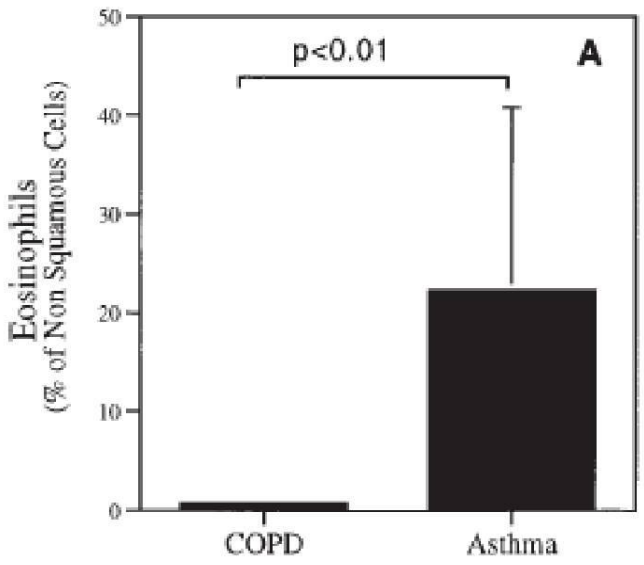
Máme skvělé biomarkery ?

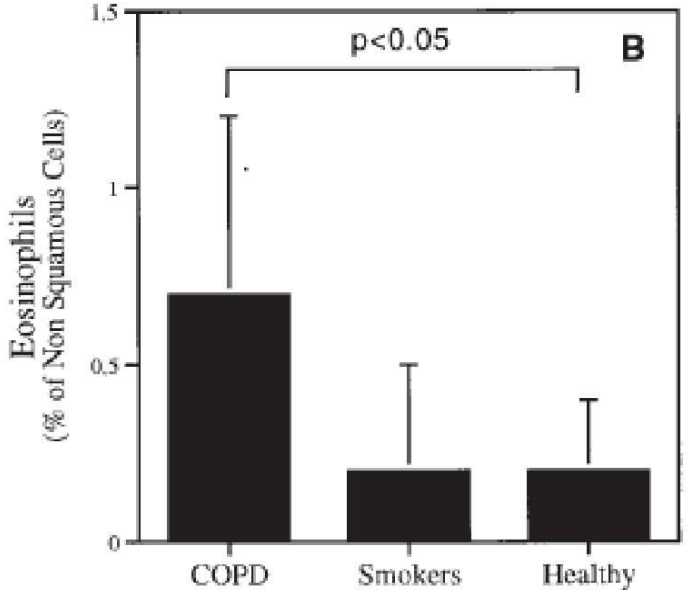
- **Astma:**
  - Eozinofilie sputa: riziko exacerbace
  - Neutrofílie sputa: těžké astma
  - eNO: safe ICS dose reduction
  - IgE >80IU predicts response to Xolair

- **COPD:**
  - α1 anti-trypsin - emphysema
  - CRP: correlates with decline in FEV_1
  - High resolution CT

Eosinophilic Inflammation in Stable Chronic Obstructive Pulmonary Disease

Relationship with Neutrophils and Airway Function





EOS jsou u některých pacientů se COPD také zvýšené

(méně než u AB, více než u kuřáků bez CHOPN a u zdravých kontrol)

EOS ve sputu u CHOPN = prediktor dobré odpovědi na IKS/GKS

G. Balzano et al. AJRCCM 1999; 160: 1486-1492

Airway Eosinophilia in Chronic Bronchitis during Exacerbations

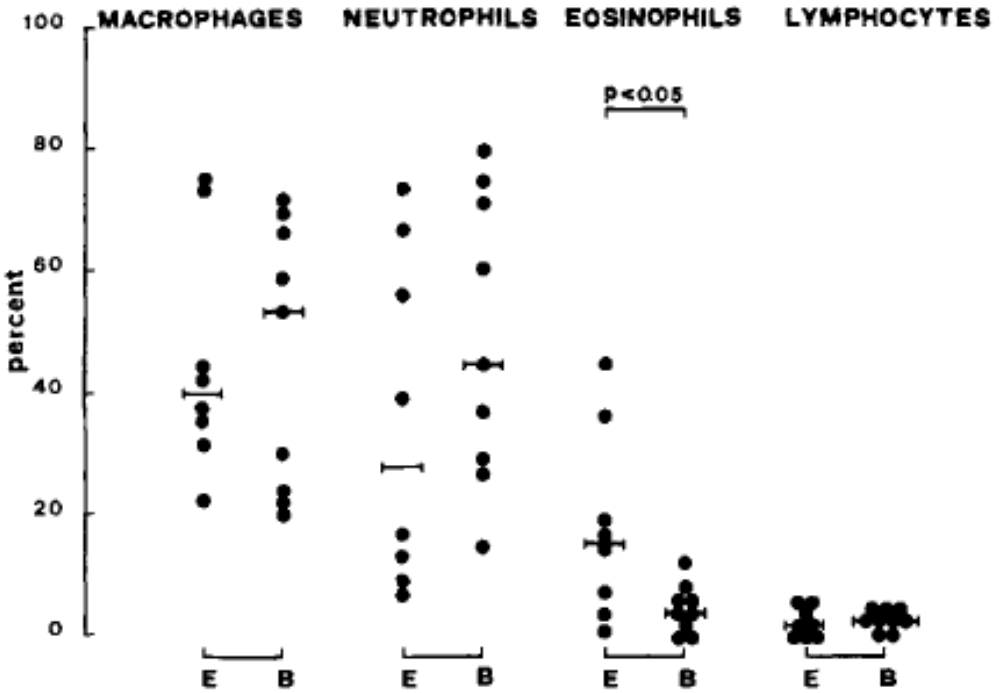
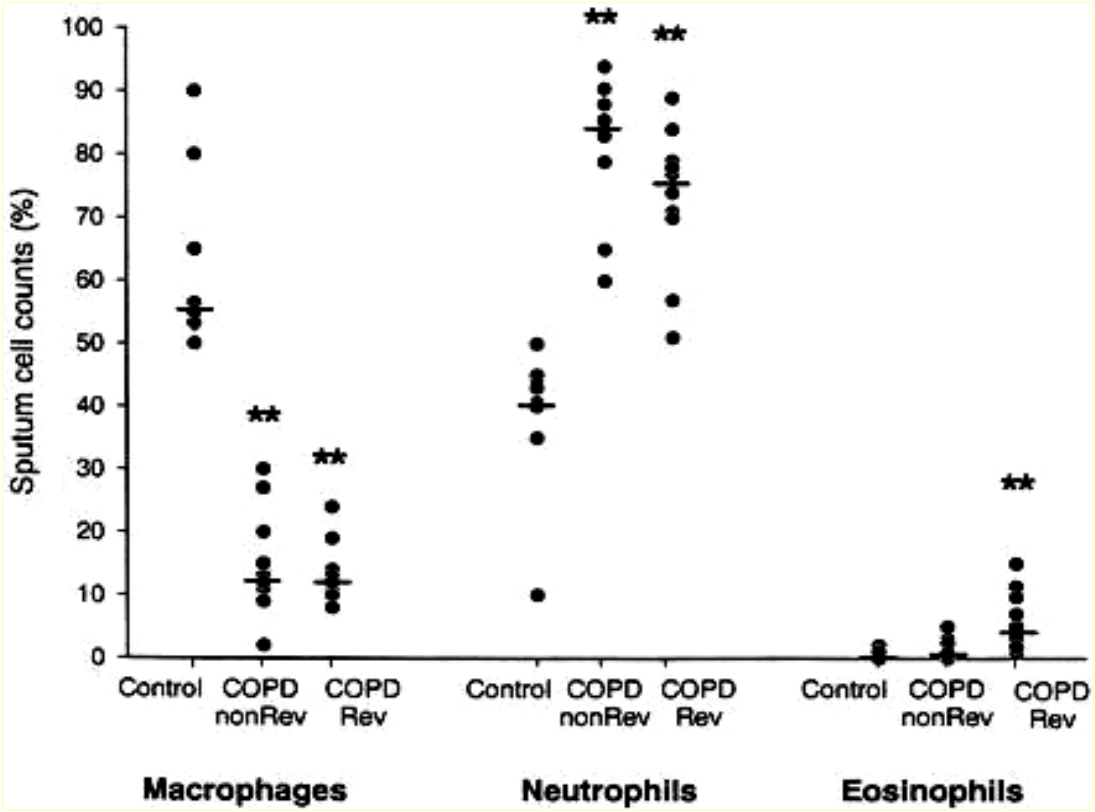


Figure 1. Individual differential cell counts in the sputum of subjects with chronic bronchitis during exacerbations (E) and under baseline conditions (B). The results are expressed as the percent of nucleated cells. Horizontal bars represent median values.

Eozinofilie sputa u exacerbací astmatu roste

M Saetta et al. AJRCCM 1994; 150: 1646-1652

Partial Reversibility of Airflow Limitation and Increased Exhaled NO and Sputum Eosinophilia in Chronic Obstructive Pulmonary Disease

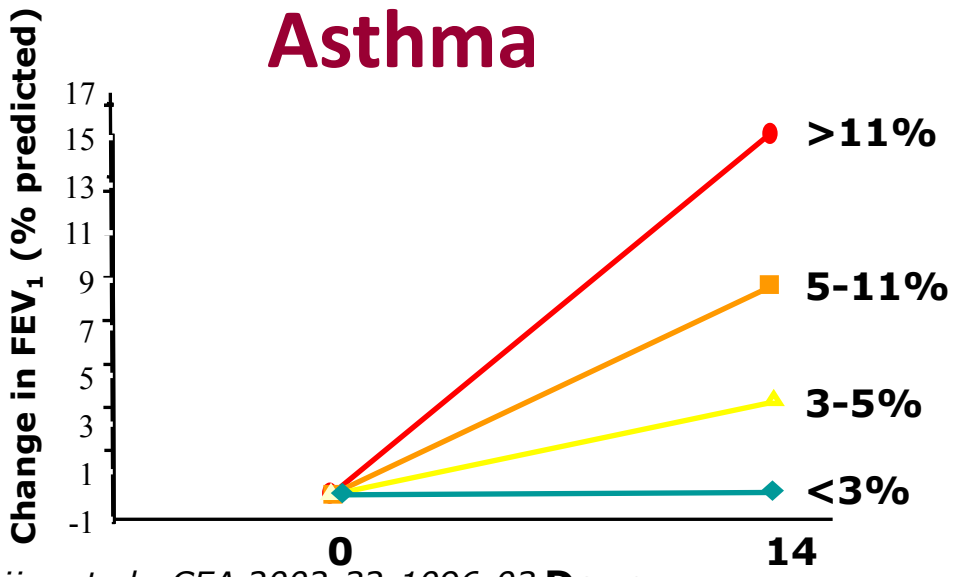


• ** = $p < 0,01$

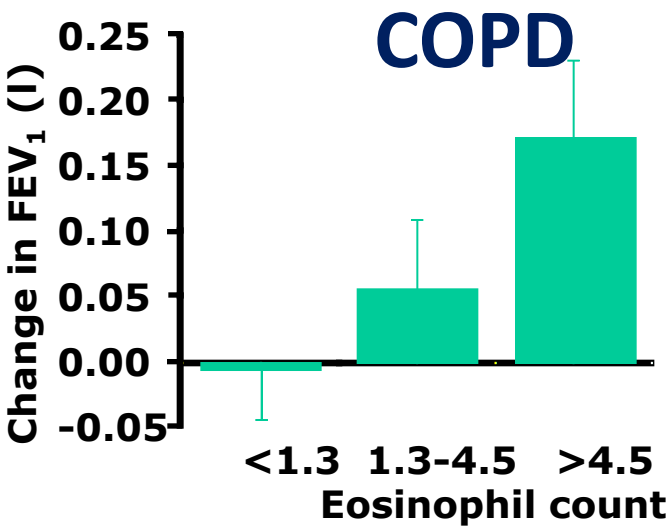
Eozinofilie sputa koreluje s mírou reverzibility bronchiální obstrukce

Papi A. et al Am J Respir Crit Care Med 2000; 162: 1773-1777

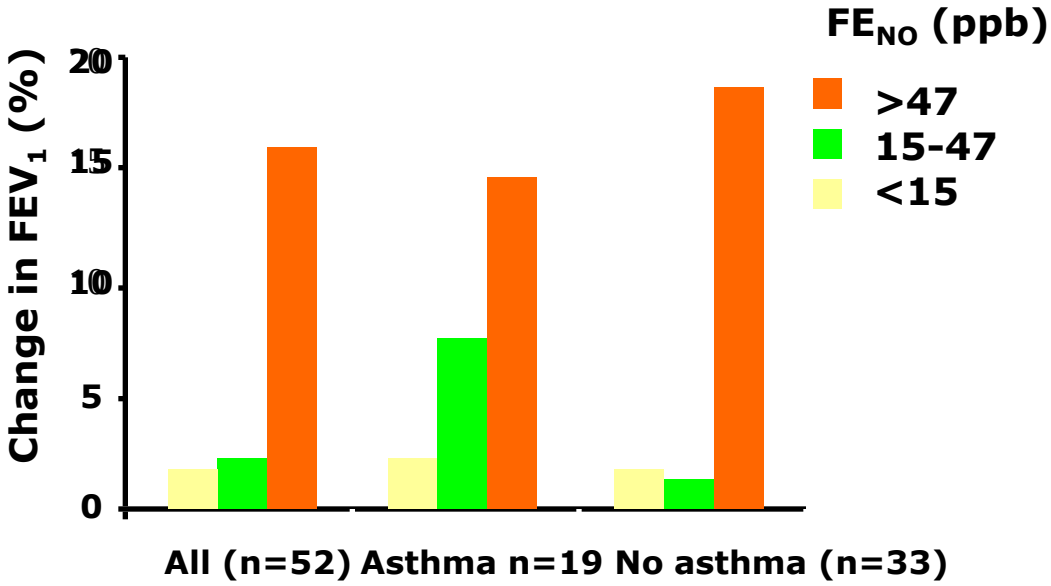
Sputum eosinophils, FE_{NO} and steroid response



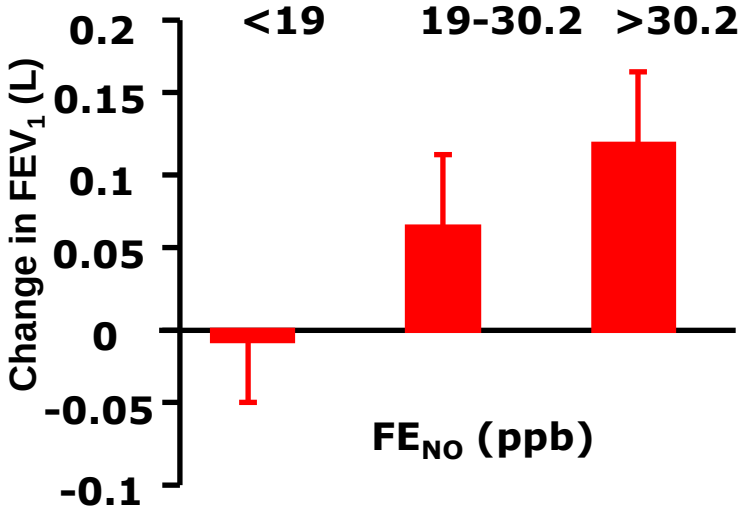
Meijer et al . CEA 2002;32:1096-03



Brightling et al. Lancet 2000;356:1480-85

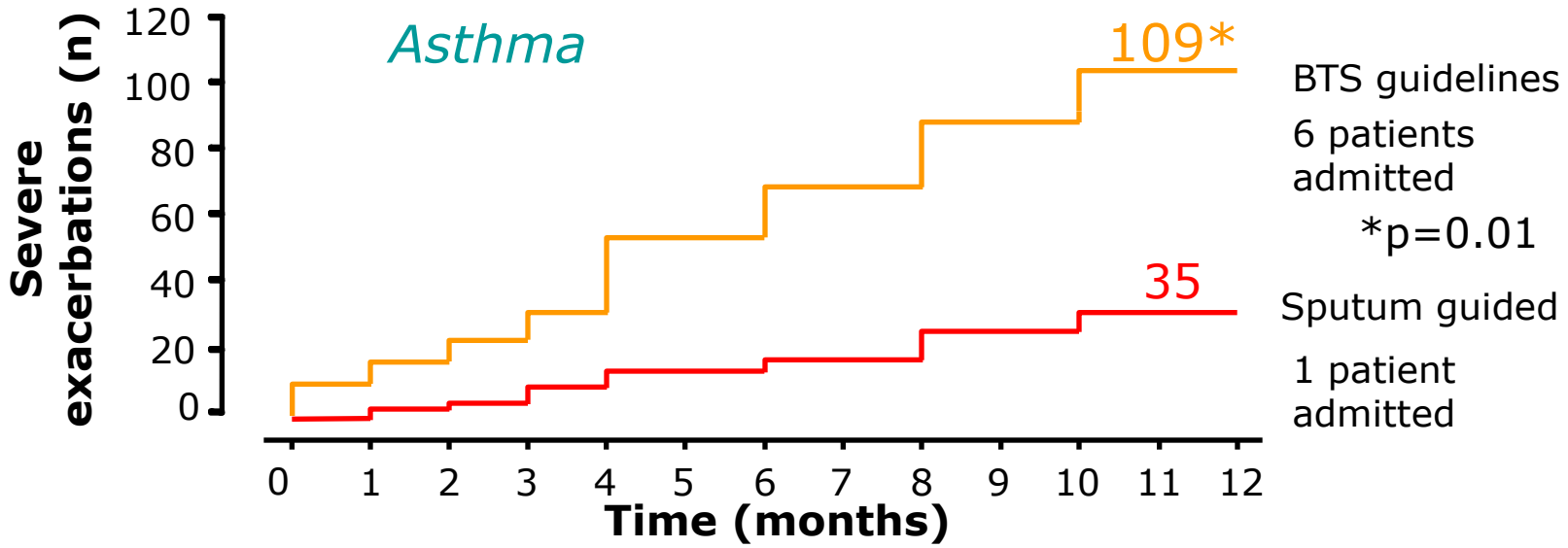


Smith et al. AJRCCM 2005;172:453-50

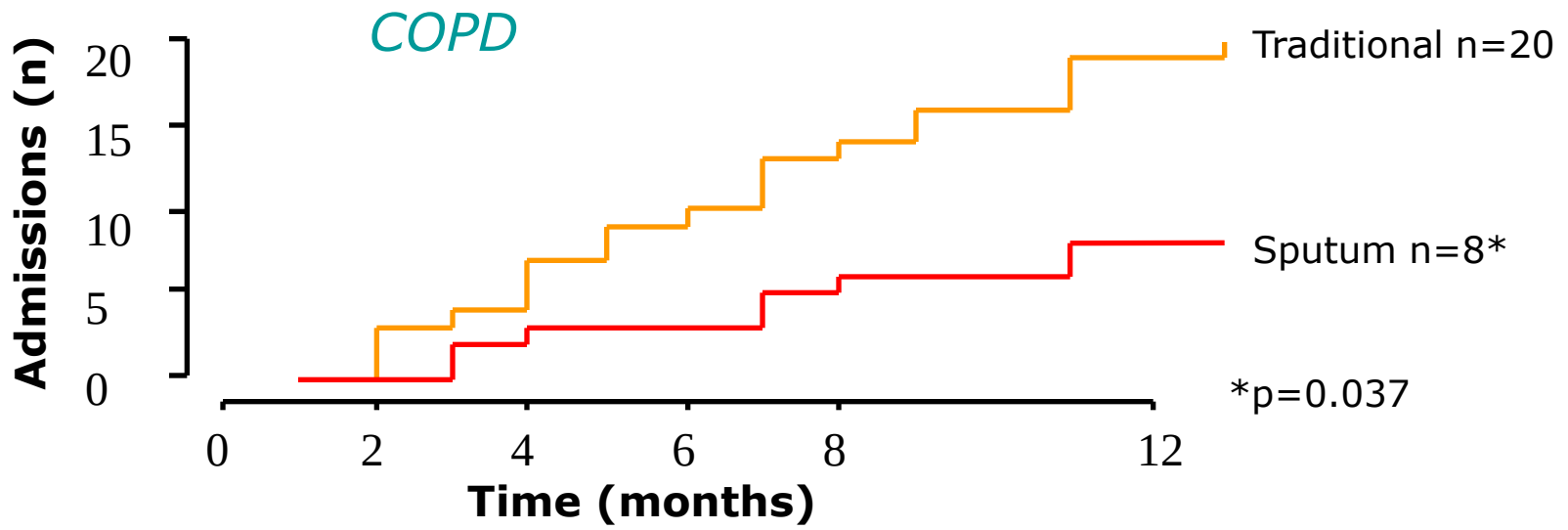


Drummer et al. AJRCCM 2009;180:846-52

Targeting sputum eosinophilia and severe exacerbations of asthma and COPD



Green et al, Lancet 2002; 360: 1715-21



Siva et al. Eur Respir J 2007; 29:906-913

Máme skvělé biomarkery ?

- **Astma:**
  - **Eozinofilie sputa: rizik**
  - **Neutrofílie sputa**
  - **eNO: safe**
  - **IgE >**

NIC MOC !

Xolair

sin - emphysema

orrelates with decline in FEV_1

High resolution CT

Potenciální zdroje pro studium BIOMARKERŮ

- Periferní krev
- Sputum
- Kondenzát VV (EBC)
- Sliny
- Nosní výplach

- BAL
- Biopsie bronchu

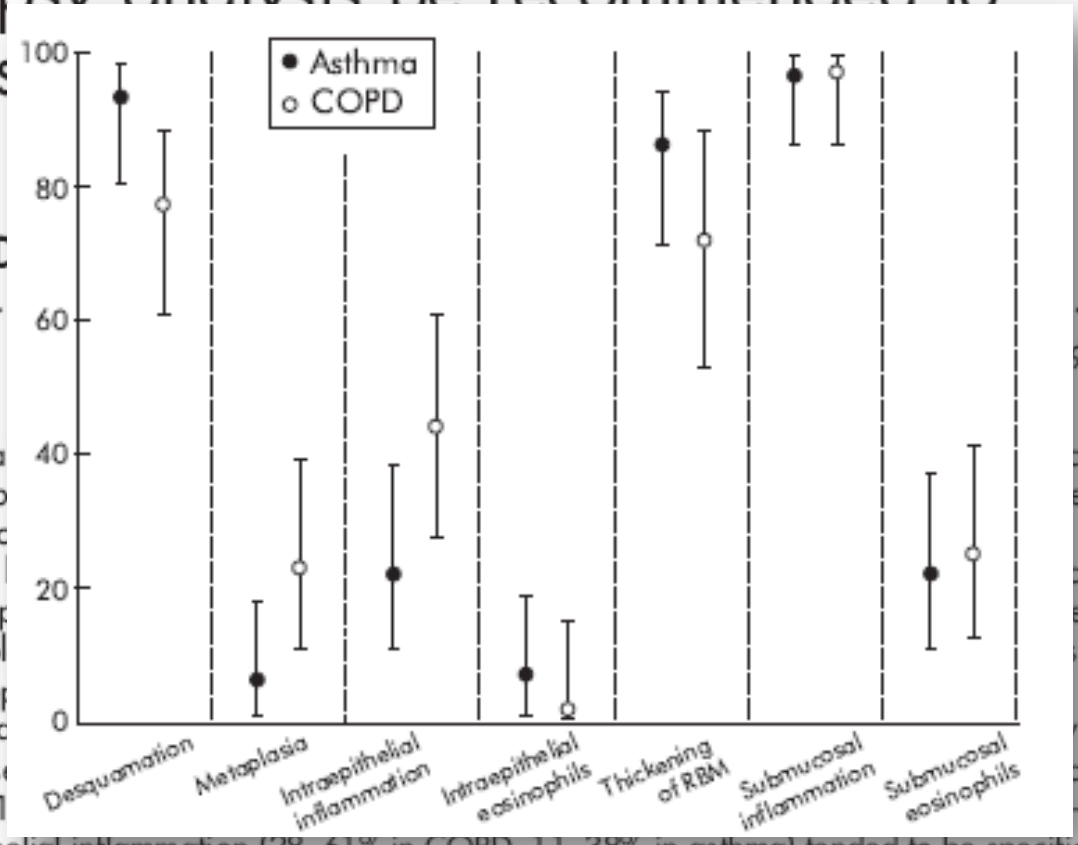
Can endobronchial biopsy analysis be recommended to discriminate between as practice?

A Bourdin, I Serre, H Flamme, P Vic, D

See end of article for authors' affiliations

Correspondence to: Dr P Chanez, Hôpital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France; chanez@montp.inserm.fr

Received 2 October 2003
Accepted
25 February 2004



Background: Internationa
and chronic obstructive p
been described for both c
Methods: Endobronchial
and COPD (50 per group
asked to propose a pathol
frequent abnormalities rep
Results: The sensitivity and
Eosinophils strongly biase
prevalence was similar (1
18% in asthma) and epithelial inflammation (28–61% in COPD, 11–38% in asthma) tended to be specific to COPD, whereas epithelial desquamation (80–98% in asthma, 61–88% in COPD) and basement membrane thickening (71–94% in asthma, 53–88% in COPD) tended to be associated with asthma. There was acceptable intra- and inter-observer agreement only for metaplasia and epithelial eosinophils.
Conclusions: Specific histopathological features of asthma and COPD probably exist, but current routine analysis procedures to assess EBB specimens are not sufficiently discriminatory. This might be rectified by improving pathological definitions.

Histopathology

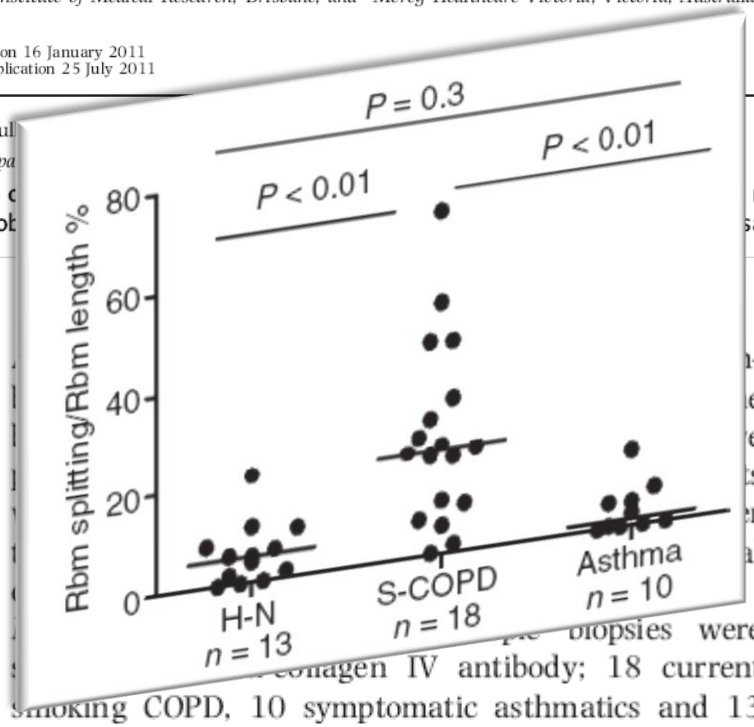
Histopathology 2012, **60**, 964–970. DOI: 10.1111/j.1365-2559.2011.04147.x

Distinctive characteristics of bronchial reticular basement membrane and vessel remodelling in chronic obstructive pulmonary disease (COPD) and in asthma: they are not the same disease

Amir Soltani,[1] Hans Konrad Muller,[2] Sukhwinder S Sohal,[1] David W Reid,[3] Steve Weston,[1] Richard Wood-Baker[1] & Eugene Haydn Walters[1,4]

[1]*Respiratory Research Group and* [2]*Descipline of Pathology, Menzies Research Institute, University of Tasmania, Hobart,* [3]*Queensland Institute of Medical Research, Brisbane, and* [4]*Mercy Healthcare Victoria, Victoria, Australia*

Date of submission 16 January 2011
Accepted for publication 25 July 2011



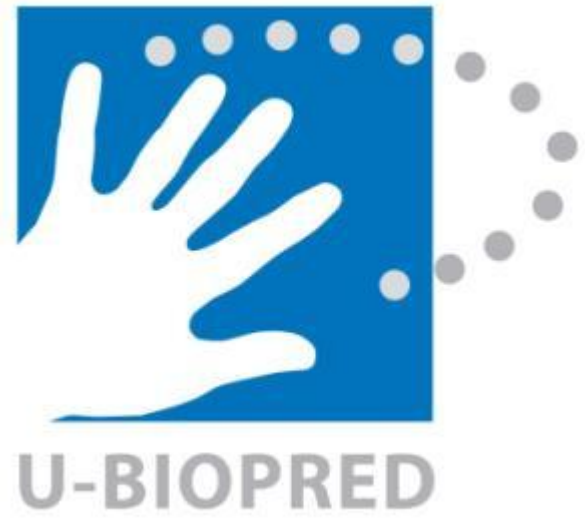
biopsies were
collagen IV antibody; 18 current smoking COPD, 10 symptomatic asthmatics and 13 healthy non-smoking controls were studied. The Rbm in COPD was fragmented, non-homogeneous, variable in thickness and hypervascular, whereas in asthma the Rbm was compact and homogeneous with no evidence of increased vascularity compared to controls. Length of Rbm splitting presented as percentage of Rbm length was used to measure fragmentation; it was greater in COPD than in controls and asthmatics [median (range) 20.7% (0.4–68.5) versus 5.3% (0.0–21.7) versus 1.5% (0.0–15.1), $P < 0.001$]. The number of Rbm vessels/mm Rbm [median (range) 10.1 (1.6–23.0) versus 4.5 (0.0–26.4) versus 4.4 (0.4–8.1), $P < 0.01$] and area of Rbm vessels, μm^2/mm Rbm [median (range) 953 (115–2456) versus 462 (0–3263) versus 426 (32–2216), $P < 0.05$] was also increased in COPD compared to normal subjects and asthmatics.

Conclusions: The characteristics of Rbm remodelling are quite different in asthma and COPD.

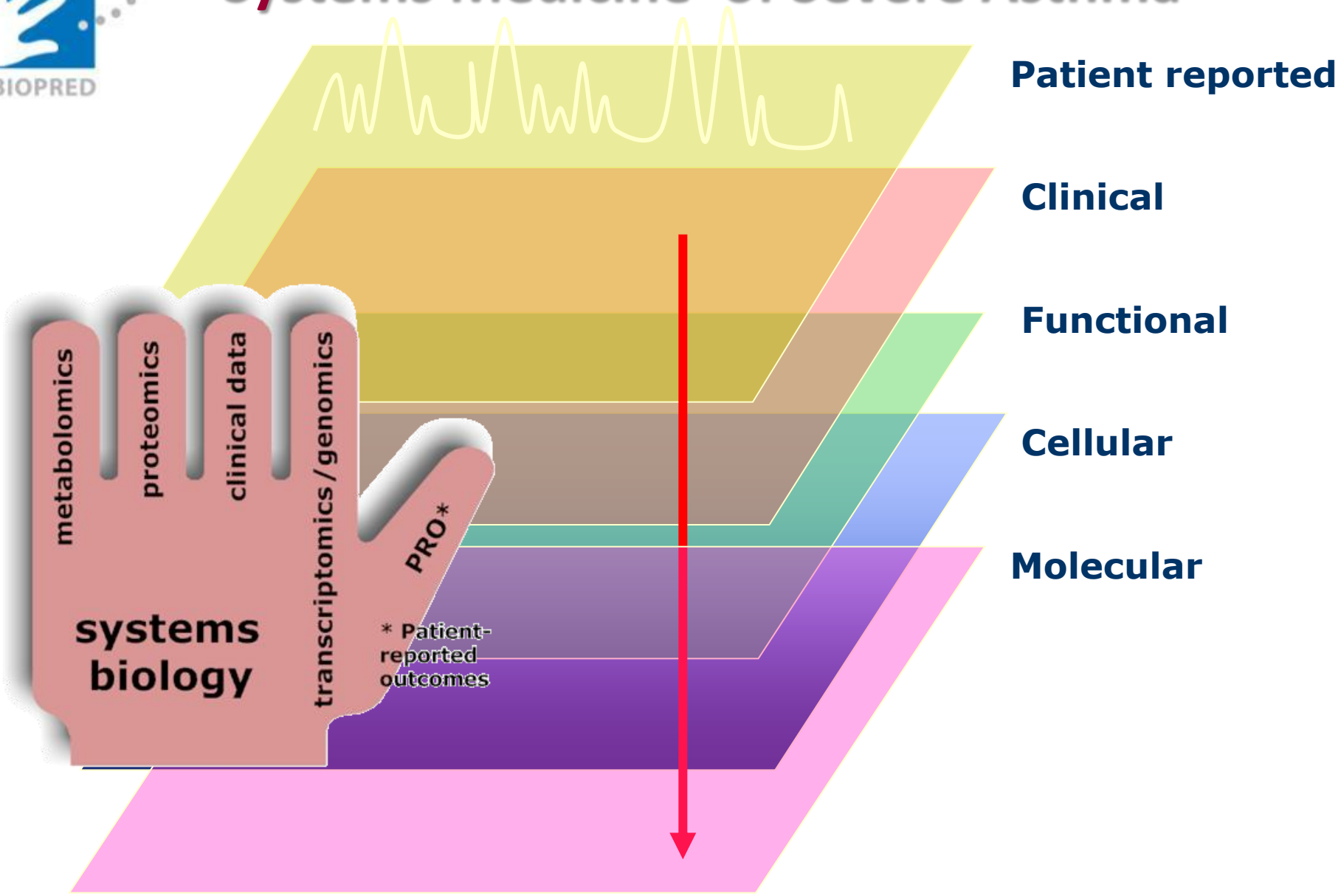
Biomarkery budoucnosti ?

- **Biased: selected biomarkers**

- **Unbiased ‘omics platforms**
  - **Transcriptomics**
  - **Proteomics**
  - **Lipidomics**
  - **Breathomics / metabolomics**
  - **Metagenomics**



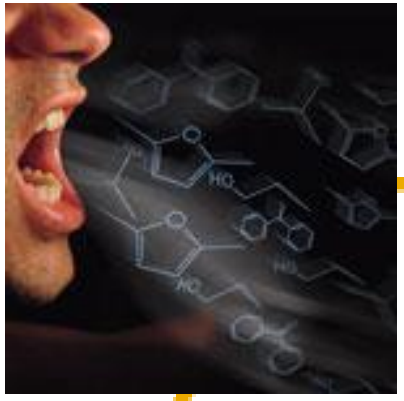
•'Systems Medicine' of Severe Asthma



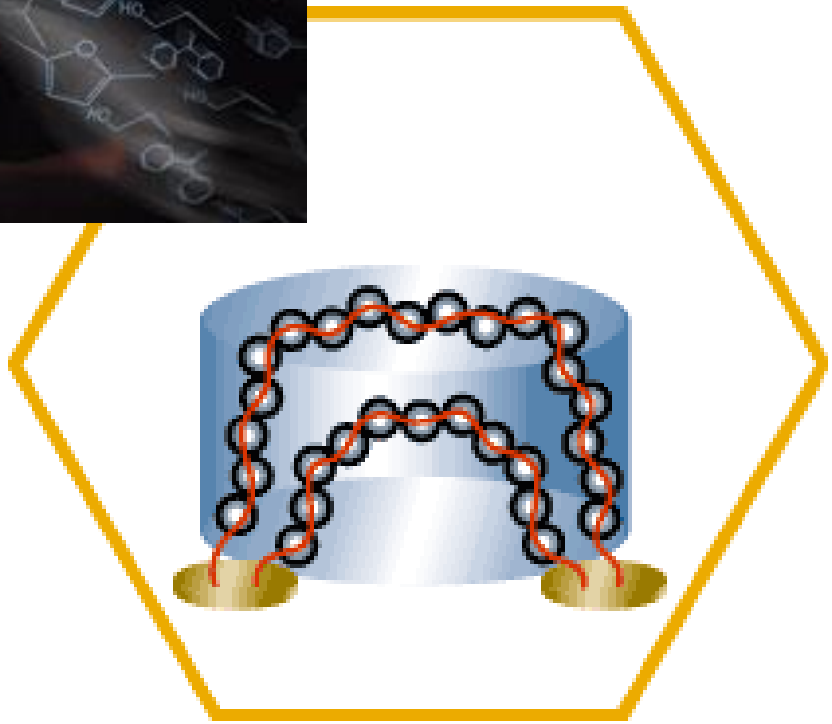
Auffray et al. Genome Med 2009;1:2

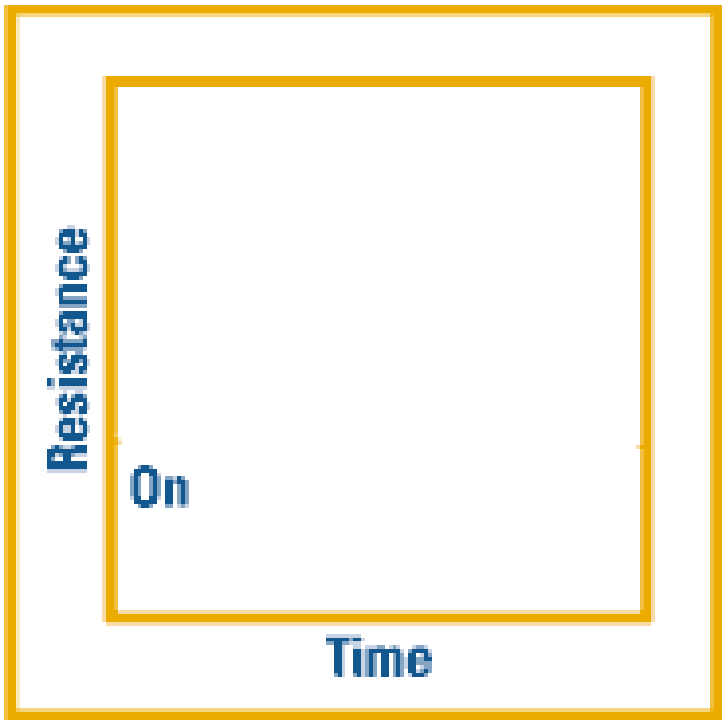

•fibroblast
•ICAM-1
•IL-11
•collagenase
•SCF
•PDGF
•VCAM-1
•GM-CSF
•TGF-β
•IL-8
•MCP-1
•RANTES
COLLAGEN I, II, V
•dendritic cell
•IL-12
•IL-1
•macrophage
•monocyte
•G-CSF
•ICAM-1
•LTC-4
•LTB-4
•IL-3
•IL-2
•epitheli
ce
•Th-1
•IFN-γ
•Th-0
•basophil
•histamine
•protease
•IL-4
•IL-13
•PGS
•GM-CSF
•IL-6
•IL-5
•IgE
•MCP-1
•PGE2
•RANTES
•smooth
•muscle cell
•GM-CSF
•C-kit
•IL-6
•myofibroblast
•neurokinins
http://qq.funpic.hu

Elektronický NOS



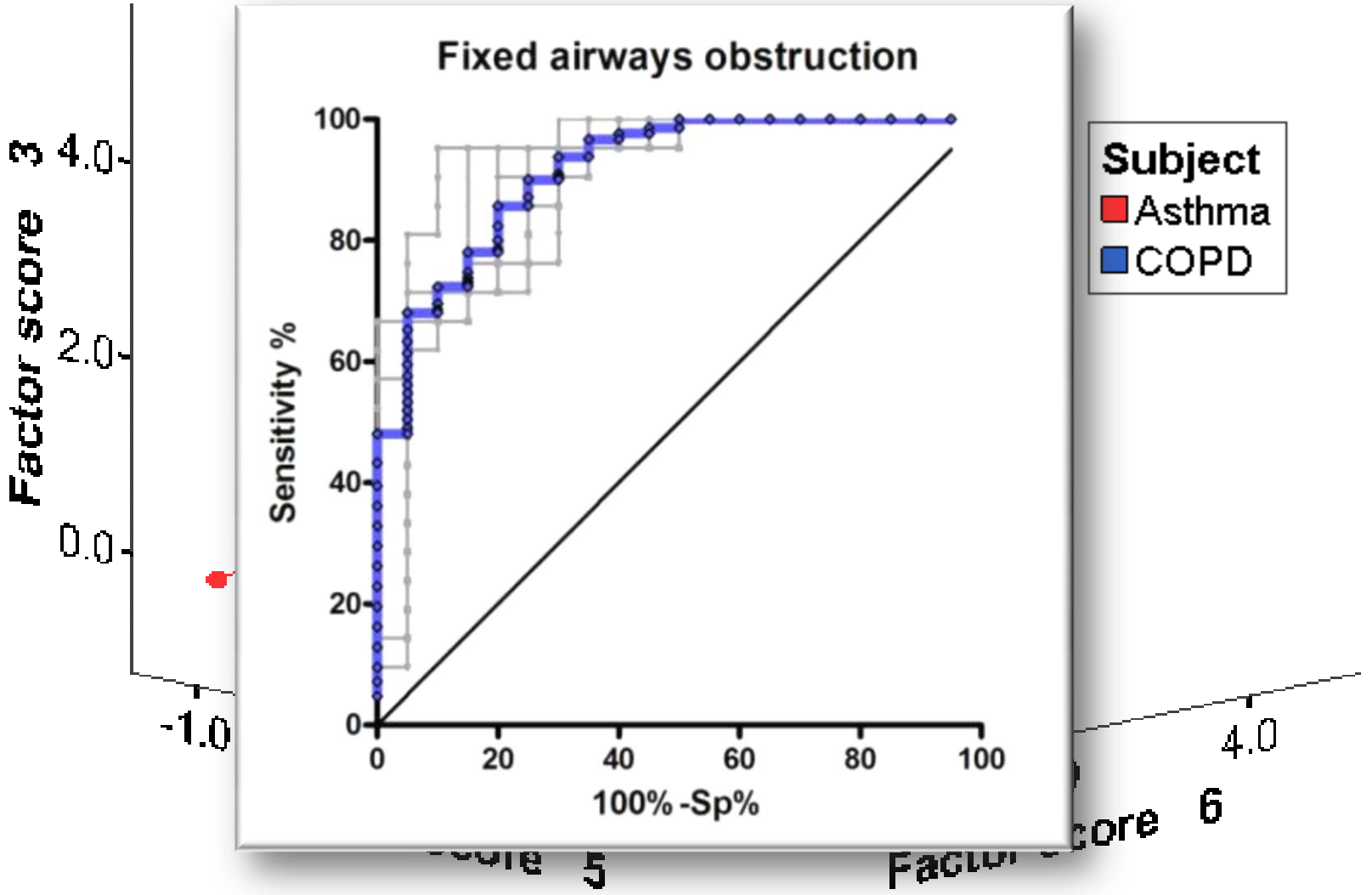
- *Smelling by swelling*





VOCs bind to polymer sensor causing swelling

This changes the electrical resistance



Sensitivity	Specificity	Precision	Accuracy	AUROC
0.82	0.86	0.91	0.84	0.89

OK, ale

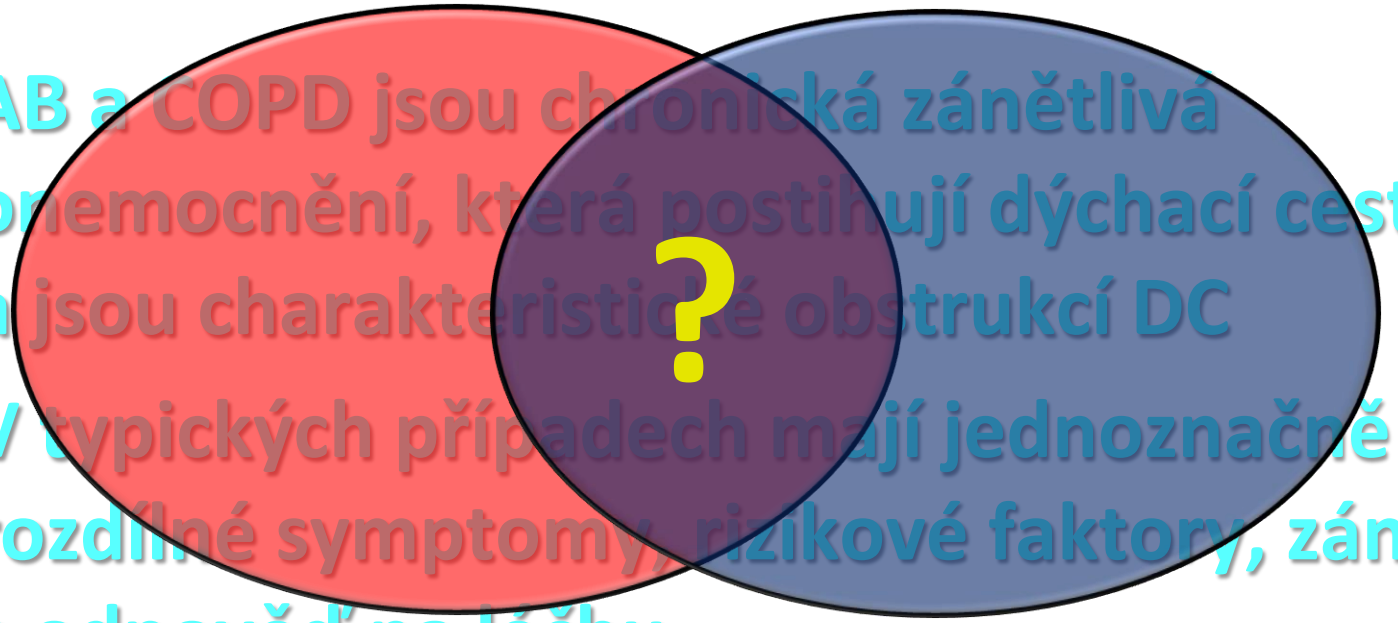
JE TO DŮLEŽITÉ

???

- **IKS – lék 1. volby**
- **Nejasná data na RHB**
- **Režimová opatření**

- **IKS fenotypově specifický lék**
  - **Fenotyp exacerbační**
  - **Fenotyp AB a COPD**
- **RHB !!!**

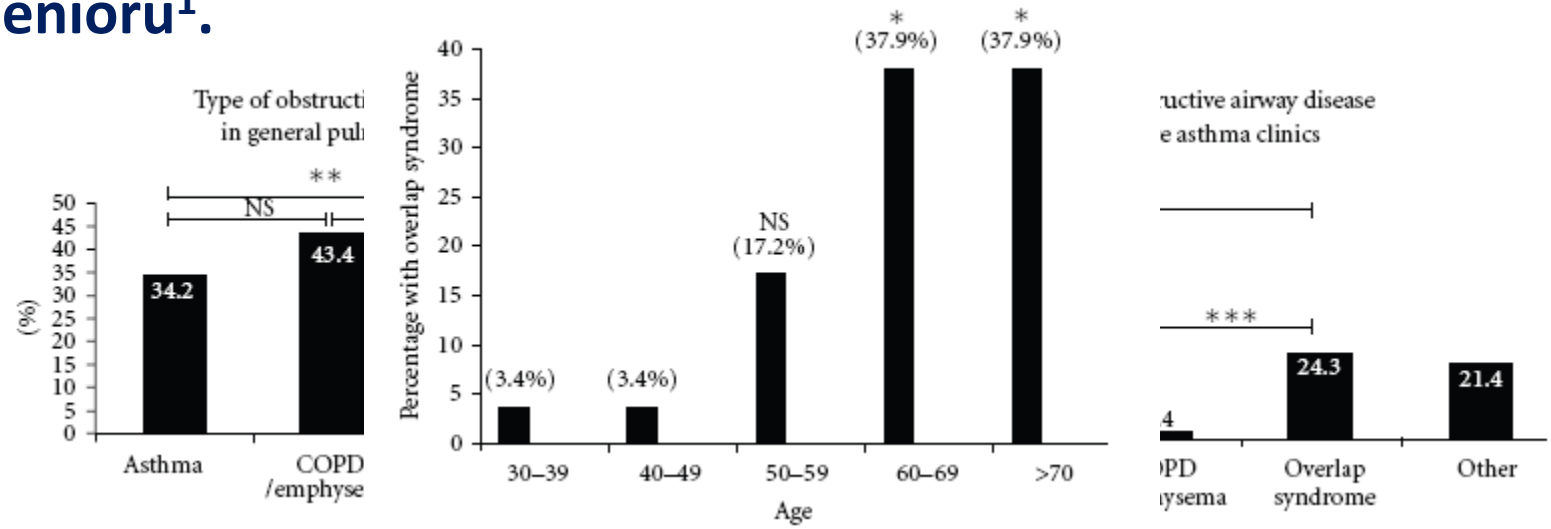
Existuje „čisté“ AB a COPD ?



- AB a COPD jsou chronická zánětlivá onemocnění, která postihují dýchací cesty a jsou charakteristické obstrukcí DC
- V typických případech mají jednoznačně rozdílné symptomy, rizikové faktory, zánět a odpověď na léčbu
- **Avšak u významné části pacientů probíhá jejich onemocnění s pod klinickým obrazem podobným COPD i AB**

Klinické charakteristiky COPD-asthma overlap

- **Koexistence astmatu a CHOPN je v populaci častá, zejména u seniorů[1].**



- **Syndrom AB-COPD může sdílet vlastní klinické charakteristiky např. nižší kvalitu života nebo zvýšenou četnost exacerbací oproti pacientů s pouze astmatem či pouze CHOPN[2,3,4]**

•1 Soriano JB et al. Chest 2003, 124(2):474-481.
•2 Kauppi P et al. J Asthma 2011, 48:279-285.
•3 Hardin M et al. Respir Res 2011, 12:127.
•4 Miravitlles M et al. Respir Med 2013

Arch Bronconeumol. 2012;48(7):247–257

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www.archbronconeumol.org

Recommendations of SEPAR

Spanish COPD Guidelines (GesEPOC): Pharmacological Treatment of Stable COPD☆,☆☆,★

Marc Miravitlles,[a,b,*] Juan José Soler-Cataluña,[c] Myriam Calle,[d] Jesús Molina,[e] Pere Almagro,[f]

Definition of Mixed COPD Asthma

The mixed COPD phenotype is defined as an airflow obstruction that is not completely reversible acc
or signs of an increased reversibility of the
guidelines, these patients are described as
prominent asthmatic component"[18] or as
COPD.[19]

For the diagnosis of the mixed phenot
have agreed on some criteria that are pres
diagnosis, 2 major criteria or 1 major and 2
met.[20] This classification is restrictive due
evidence between the relationship of the different criteria and the response to treatment in COPD. Prospective studies are required to validate these criteria.

Major criteria
- Very positive bronchodilator test (increase in FEV_1 >15% and >400 mL)
- Eosinophilia in sputum
- Personal history of asthma

Minor criteria
- High levels of total IgE
- Personal history of atopy
- Positive bronchodilator test on at least two occasions (increase of FEV_1 >12% and >200 mL)

Table 1 Inclusion and exclusion criteria.

Inclusion criteria

- Patients aged 40 or older.
- Patients with smoking background whose pack-year index (PYI) is greater than 10.
- Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) according to GOLD 2007 criteria (post-bronchodilator FEV_1/FVC (after inhaling 400 μg salbutamol) < 0.70).
- Patients receiving treatment and follow-up through pulmonology visits, both in hospitals and in other specialized health centers.
- Clinical stability in the last month.
- Patients who have given their written informed consent.

Exclusion criteria

- Patients with current asthma diagnosis.
- Patients with a primary pulmonary vascular disease.
- Patients presenting, at the time of performing the study, any serious physical and/or mental impediment that would not make the fulfillment of the respiratory function tests possible.

Table 2 Definition of phenotypes.

Phenotype 1: EMPHYSEMA (at least one of the criteria)

1. Pulmonary emphysema proved by CT.
2. Diffusion test with TLCO/VA values inferior to 80% and thorax radiography suggesting emphysema, according to the criteria described by Miniati et al.[36–38]

Phenotype 2: Chronic bronchitis.

1. Habitual coughing and expectoration (chronic bronchitis criteria).[4]
2. Diffusion test with TLCO/VA values superior to 80%.
3. Absence of pulmonary emphysema demonstrated through imaging techniques, CT, or thorax radiography, according to the previous criteria.
4. Absence of asthma antecedents.

Phenotype 3: "COPD-asthma"

1. Diffusion test with TLCO/VA values superior to 80%.
2. Absence of pulmonary emphysema demonstrated through imaging techniques, CT, or thorax radiography, according to the previous criteria.
3. Personal history of asthma before the age of 40.[6]

admittances. Type 2 patients showed a greater prevalence of cardiovascular comorbidities and of sleep apnea syndrome (4.9%, 23.6% and 12.5%, respectively, $p < 0.001$).

Fenotyp bronchitický

- přítomnost produktivního kašle (>3 měsíce/rok, v posledních nejméně 2 letech)

Fenotyp emfyzematický

- celoživotní nepřítomnost produktivního kašle (suchý kašel může být přítomen), současně (dle HRCT a TLCO) známky plicního emfyzému

Fenotyp CHOPN a bronchiektázií

- akcentovaná každodenní, expektorace, mladší věk, nekuřáci, prolongované infekce plic a DDC, hemoptýzy, HRCT známky bronchiektázií

Fenotyp overlapu CHOPN s bronchiálním astmatem
(2 hlavní a 1 hlavní + 2 vedlejší kritéria)

- hlavní kritéria: (a) výrazně pozitivní BDT (vzestup FEV_1 >15 % a >400 ml) (b) pozitivní BKT, (c) ↑FENO (≥45-50 ppb) a/nebo ↑eo ve sputu (≥3 %) (d) AB v anamnéze
- vedlejší kritéria: (a) pozitivní BDT (vzestup FEV_1 >12 % a >200 ml) (b) ↑celkové IgE (c) atopická anamnéza

Fenotyp frekventní exacerbace

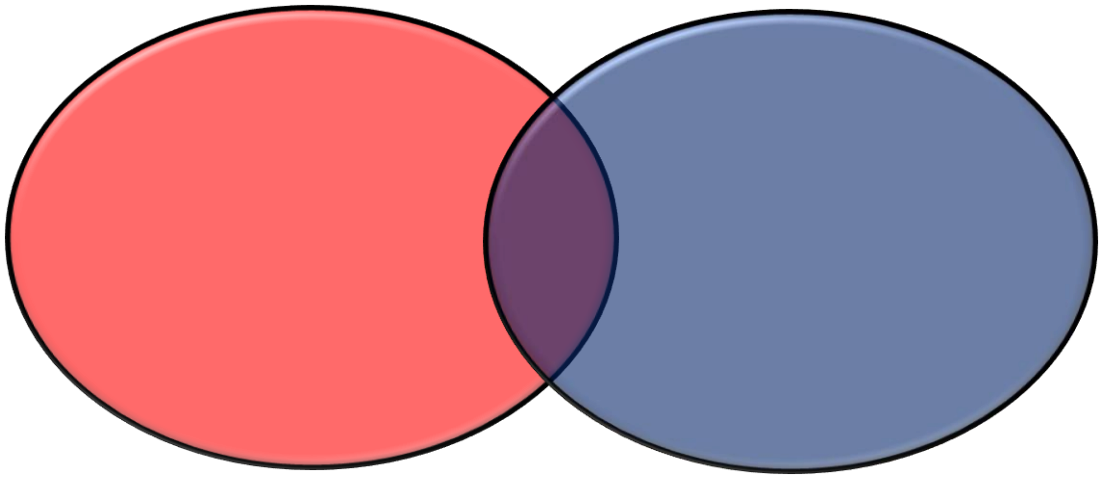
- přítomnost častých akutních exacerbací (≥2/rok) léčených ATB a/nebo systémovými kortikosteroidy

Fenotyp plicní kachexie

- FFMI < 16 kg/m² (muži), FFMI < 15 kg/m² (ženy), případně BMI < 21 kg/m² (nezávisle na pohlaví) - bez jiné zjevné příčiny

Fenotyp overlapu CHOPN s bronchiálním astmatem
(2 hlavní a 1 hlavní + 2 vedlejší kritéria)

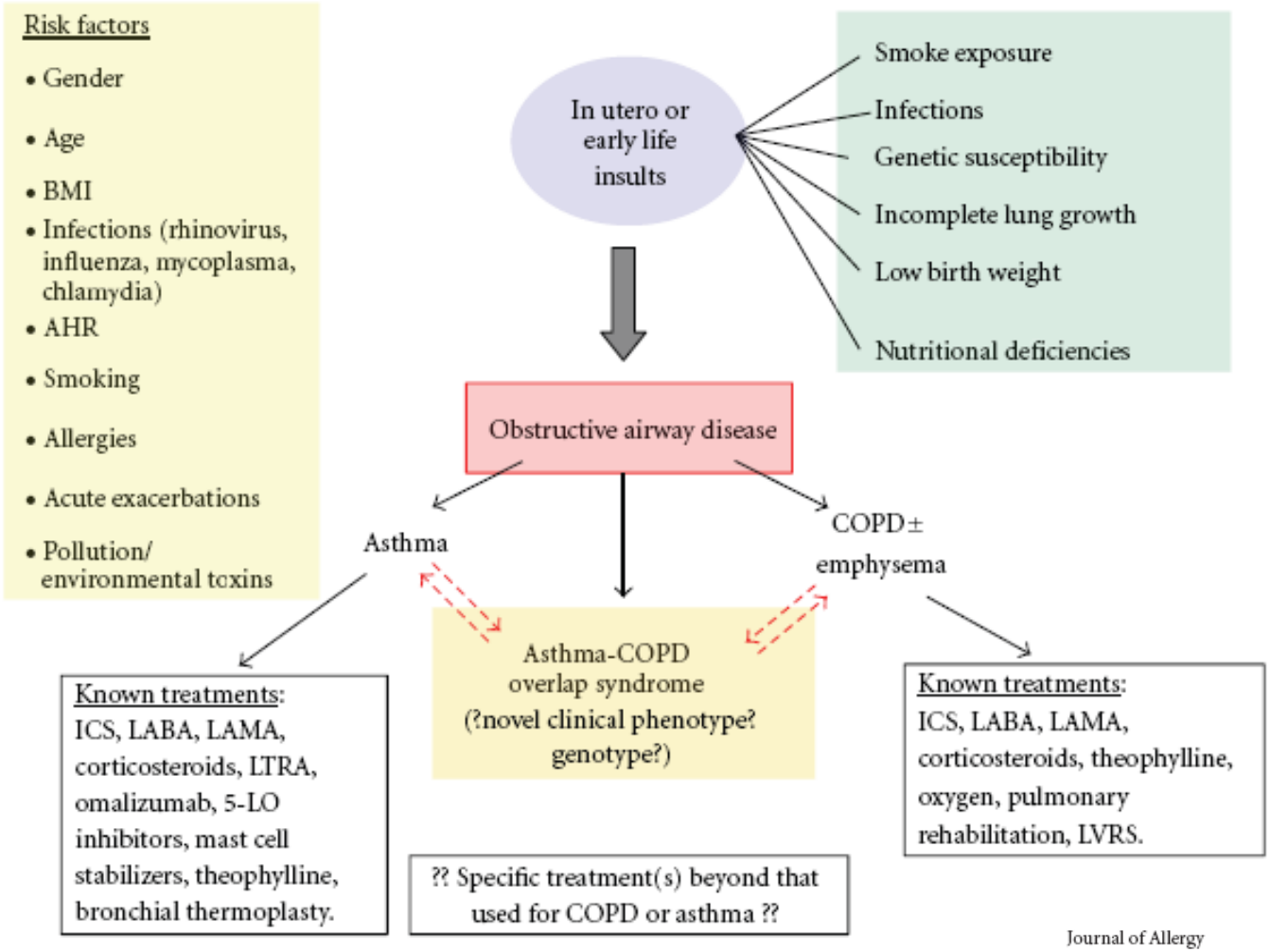
- hlavní kritéria: (a) výrazně pozitivní BDT (vzestup FEV_1 >15 % a >400 ml) (b) pozitivní BKT, (c) ↑FENO (≥45-50 ppb) a/nebo ↑eo ve sputu (≥3 %) (d) AB v anamnéze
- vedlejší kritéria: (a) pozitivní BDT (vzestup FEV_1 >12 % a >200 ml) (b) ↑celkové IgE (c) atopická anamnéza



Review Article

The Asthma-COPD Overlap Syndrome: A Common Clinical Problem in the Elderly

Amir A. Zeki,[1,2] Michael Schivo,[1,2] Andrew Chan,[1,3] Timothy E. Albertson,[1,3] and Samuel Louie[1]



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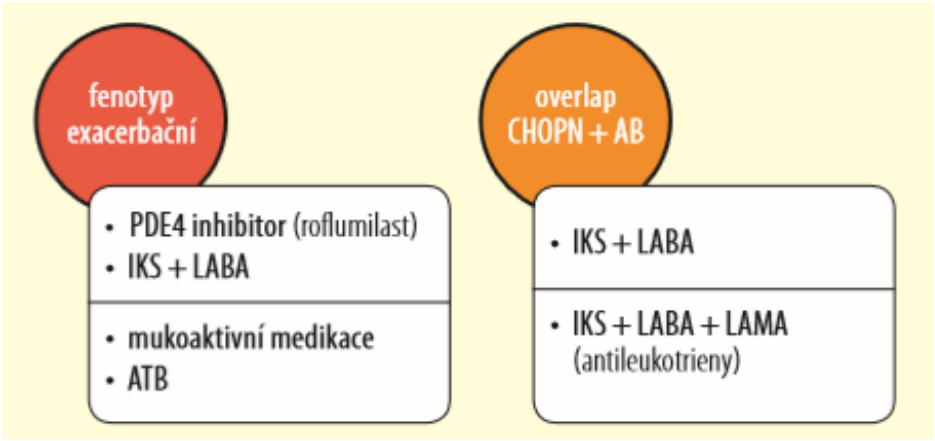
doi:10.1155/2011/861926


fenotyp exacerbační
• PDE4 inhibitor (roflumilast)
• IKS + LABA
• mukoaktivní medikace
• ATB
overlap CHOPN + AB
• IKS + LABA
• IKS + LABA + LAMA (antileukotrieny)

Respiratory Medicine (2008) 102, 50–56

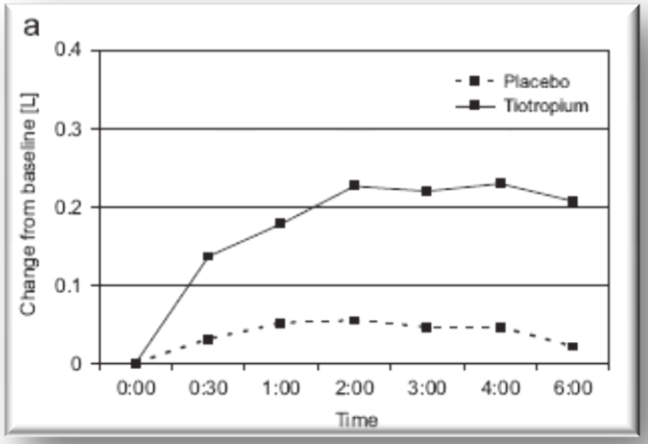
ELSEVIER

Table 1 Baseline characteristics of patients in the tiotropium and placebo groups.

	Placebo, $n = 244$	Tiotropium, $n = 228$	Total, $n = 472$
Age (years)	60.2 (9.4)	59.1 (9.8)	59.6 (9.6)
Male (%)	149 (61.1)	141 (61.8)	290 (61.4)
Duration of COPD (years)	9.1 (6.8)	9.2 (7.2)	9.2 (7.0)
Duration of asthma (years)	43.9 (13.9)	42.5 (14.3)	43.2 (14.1)
Current smoker (%)	99 (40.6)	103 (45.2)	202 (42.8)
Smoking history (pack-years)	33.6 (16.8)	33.9 (17.3)	33.7 (17.0)

Improvements with tiotropium in COPD patients with concomitant asthma

H. Magnussen[a,*], B. Bugnas[b], J. van Noord[c], P. Schmidt[d], F. Gerken[d], S. Kesten[d]



Summary

Background: Chronic obstructive pulmonary disease (COPD) and asthma have different diagnostic criteria and treatment paradigms. Both are common and can occur in the same patient. We sought to determine the spirometric effects of tiotropium in COPD patients with concomitant asthma.

Methods: A 12-week randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg daily was performed. Patients continued usual respiratory medications except for inhaled anticholinergics. *Inclusion criteria*: Physician diagnosis of COPD and asthma, age $\geqslant$40 years, smoking $>$10 pack years, post-bronchodilator forced expiratory volume in 1s (FEV_1)$<$80% predicted, FEV_1/forced vital capacity (FVC)$<$70%, $\geqslant$12%, and $\geqslant$200 ml increase in FEV_1 following inhaled bronchodilator, treatment with inhaled steroids $\geqslant$1 year. Spirometry was measured serially for 6 h on days 1, 29 and 85.

Results: Four hundred and seventy-two patients were randomized. Baseline characteristics were balanced. Mean age = 59.6 years, 61.4% were men, and FEV_1 = 1.55 l (53.0% predicted). Improvements at 12 weeks with tiotropium were observed for the primary endpoint FEV_1 area under the curve (AUC) from 0 to 6 h (difference = 186$\pm$24 ml, $p<0.001$) and for morning pre-dose FEV_1 (difference = 98$\pm$23 ml, $p<0.001$). Significant differences in favor of tiotropium were observed for pre-dose FVC (difference = 128$\pm$34 ml, $p<0.001$) and FVC AUC 0–6 h (difference = 232$\pm$35 ml, $p<0.001$). Compared to baseline, the mean weekly number of daily puffs of prn salbutamol was

- **IKS/LABA**
- **LAMA**

- ***LTRA***
- ***METHYLXANTINY***
- ***PDE4 inhibitory***
- ***OMALIZUMAB***
- ***AZITROMYCIN***

- ***STOP SMOKING***
- ***RHB***
- ***DDOT***

3. KROK: Cílená léčba

zaměřená na specifické fenotypy a respirační nedostatečnost

roflumilast	IKS+LABA	subtiuce A1AT	LVRS, bulektomie	mukoaktivní medikace (erostein, NAC)	ATB (makrolidy, chinolony)	BVR
• bronchitický fenotyp • opak. AE • od 3. stupně obstrukce)	• opakov. AE • overlap CHOPN +AB					• chlopně • pára • lepidlo • stenty TBM

Závěry

- AB i CHOPN – komplexní, multifaktoriální nemoci, signifikantní mortalita, morbidita
- Existuje „TYPICKÉ ASTMA“
- Existuje „TYPICKÝ CHOPN“

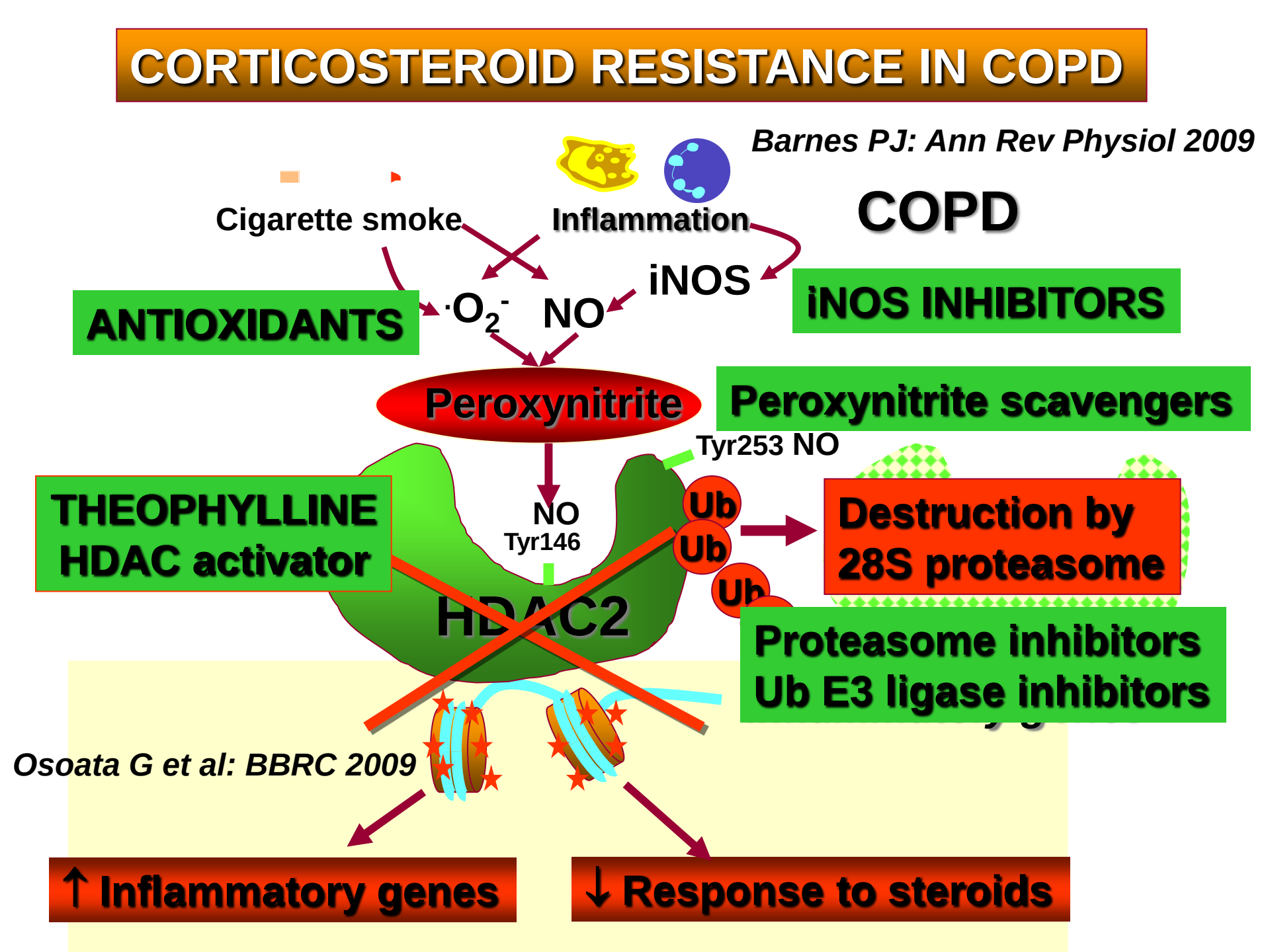
- Překryv AB a CHOPN ale také !
  - CHOPN s astmatem, astma u kuřáků, astma seniorů

- Overlap AB a CHOPN sdílí vlastní charakteristiky
  - deklinace FEV1, QoL, exacerbace
  - vyžaduje specifickou léčbu (ČPFS, GesEPOC)

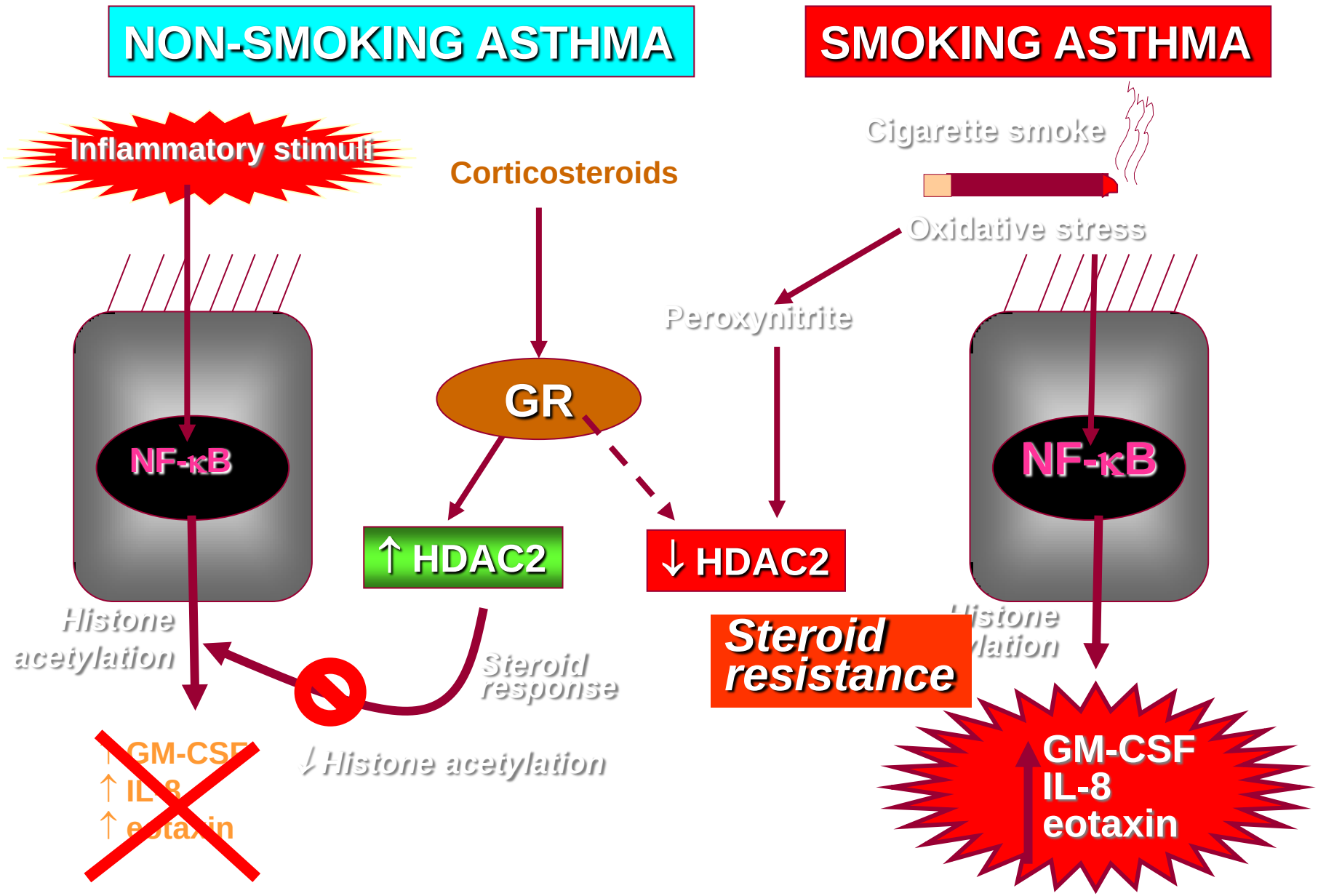
"Upozornujem vas, este jeden uder pod pas a zoberiem vam body!"

Děkuji za pozornost

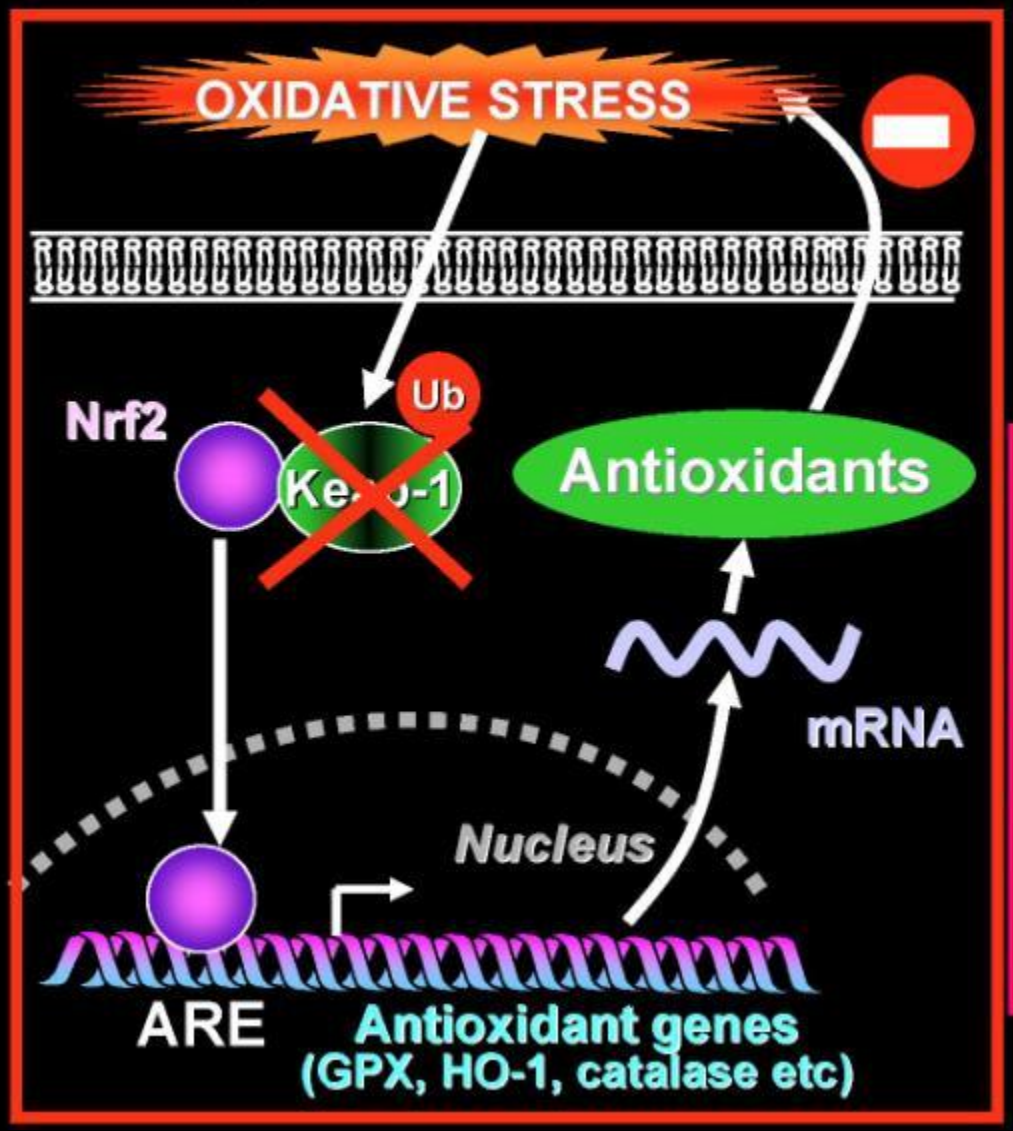
CORTICOSTEROID RESISTANCE IN COPD



STEROID RESISTANCE IN SMOKING ASTHMATICS



Nrf2 AND ANTIOXIDANT GENE REGULATION



BZip transcription factor

Nrf2(-/-): ↑ emphysema in smoking mice

Rangasamy T et al: :JCI 2004;
Ishii et al: J Immunol 2005

Nrf2 activity in lung

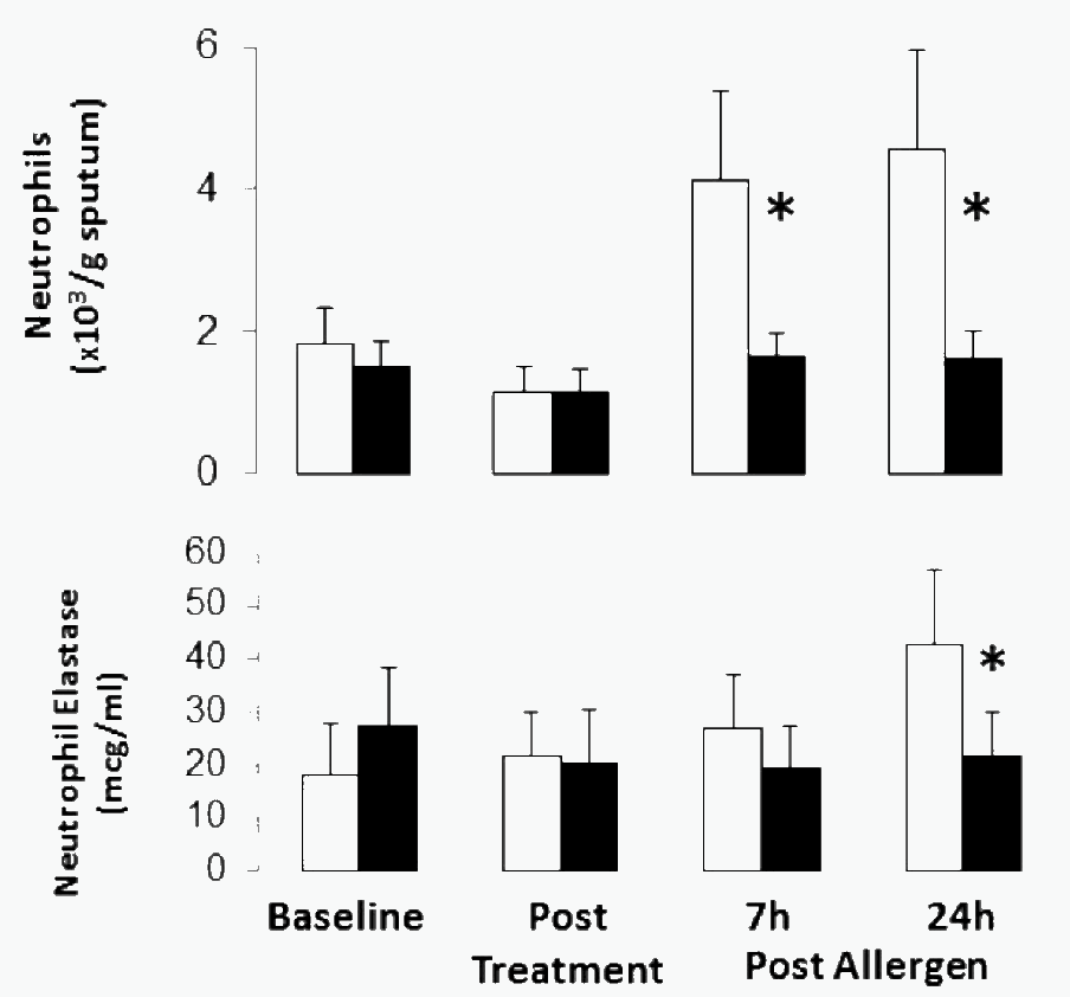
↑ in normal smokers
↓ in COPD patients

Malhotra et al: AJRCCM 2008

No ↑ with ox stress in COPD
Due to Nrf2 acetylation
(linked to ↓HDAC2 and SIRT1)

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

Phosphodiesterase 4 inhibitors in asthma



- *Gauvreau et al, Respiratory Research: 2011, 12. Used with permission.*