

# Colonización e Inflamación en la EPOC

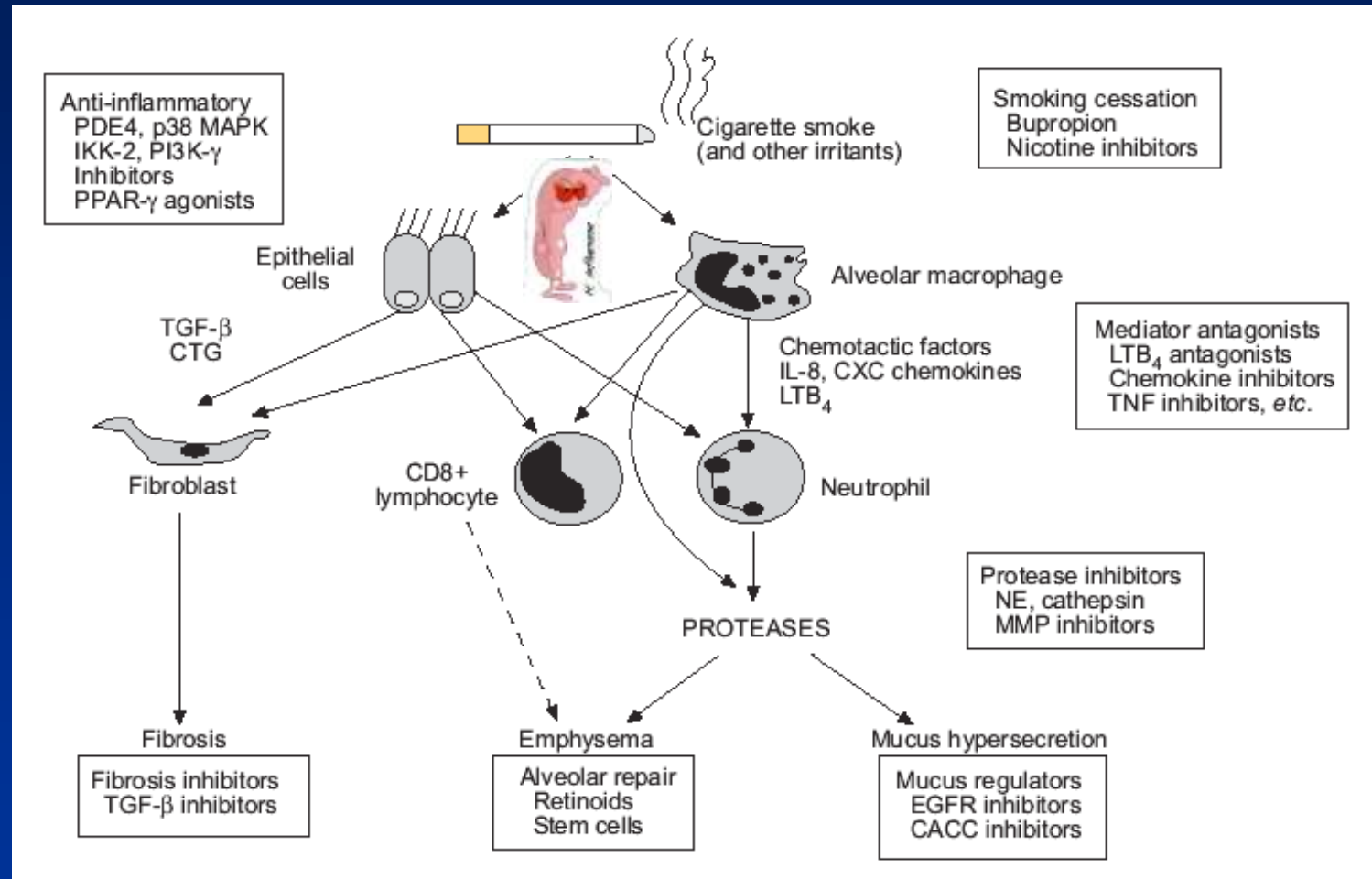
Antoni Torres

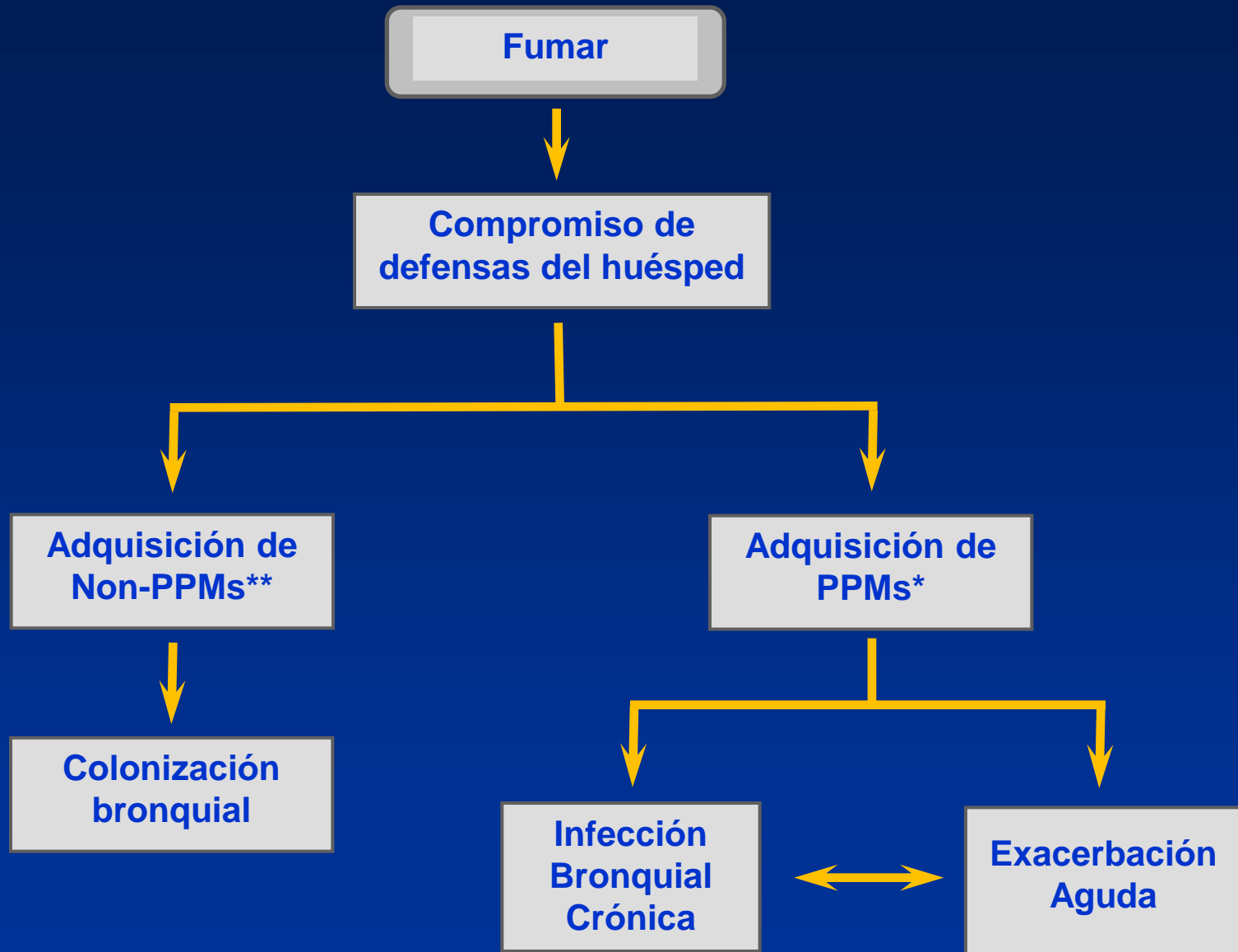
Universidad de Barcelona

Hospital Clinic, IDIBAPS

ALAT 2012, Montevideo

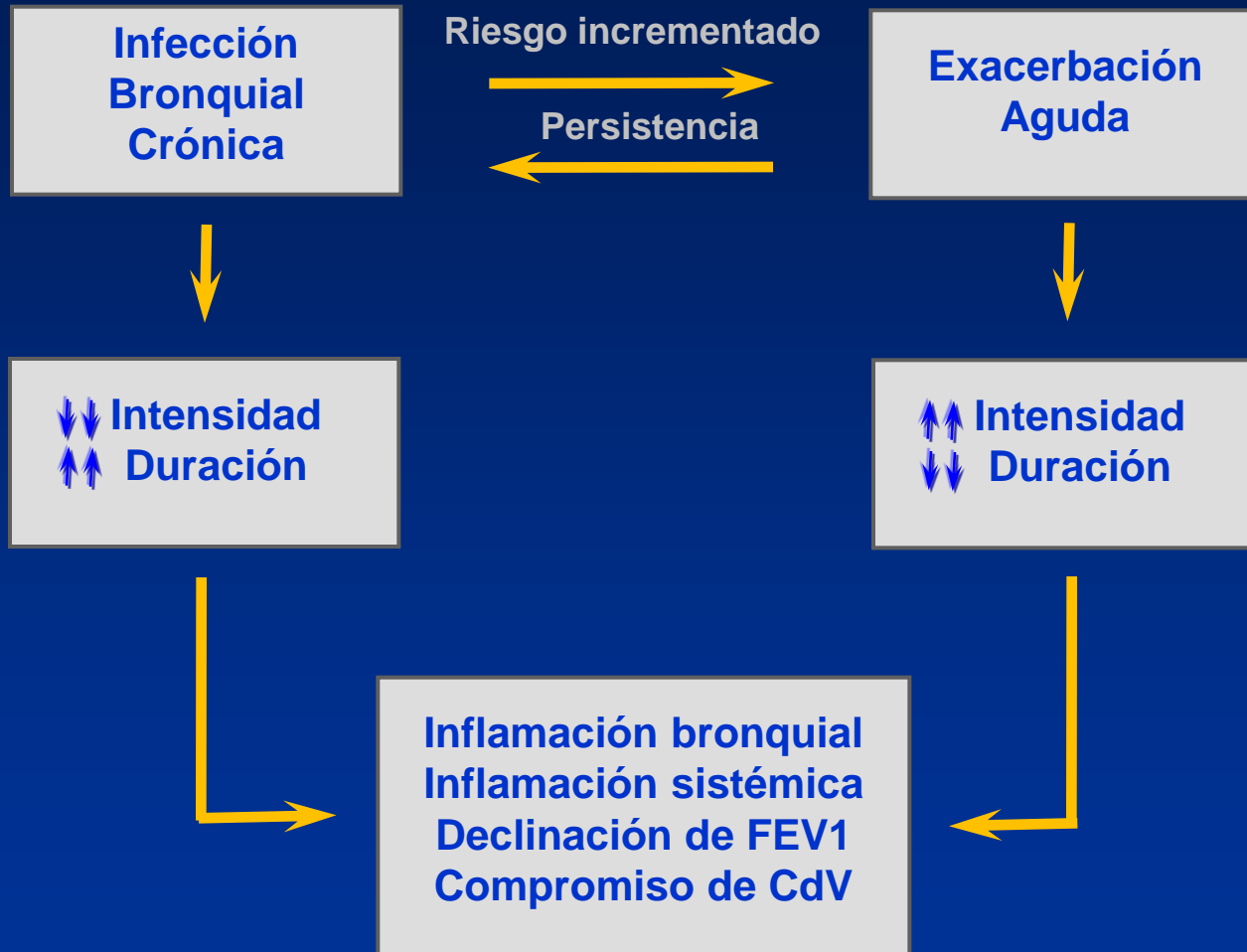
# Patogenia de la EPOC



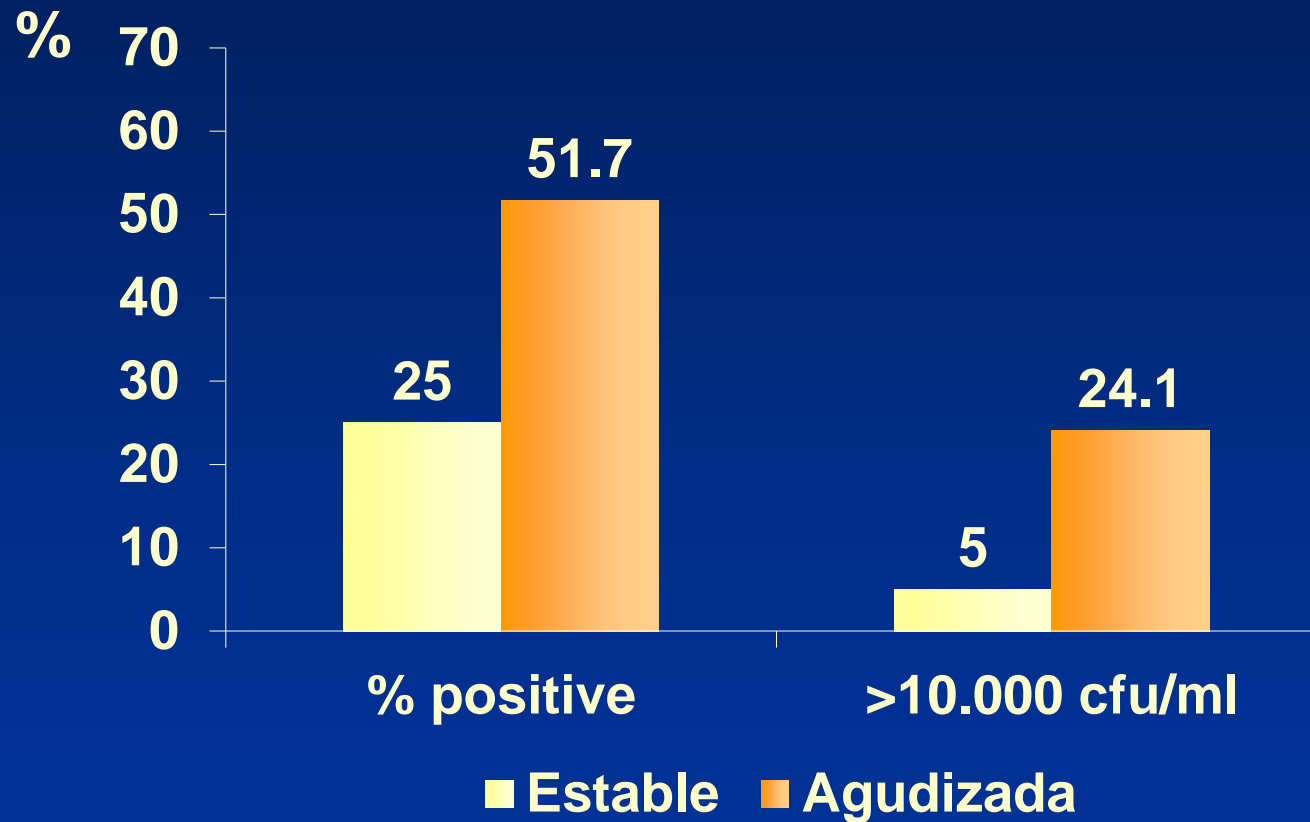


\*PPMs: Microorganismos potencialmente patógenos

\*\* Non-PPMs: Microorganismos potencialmente no patógenos

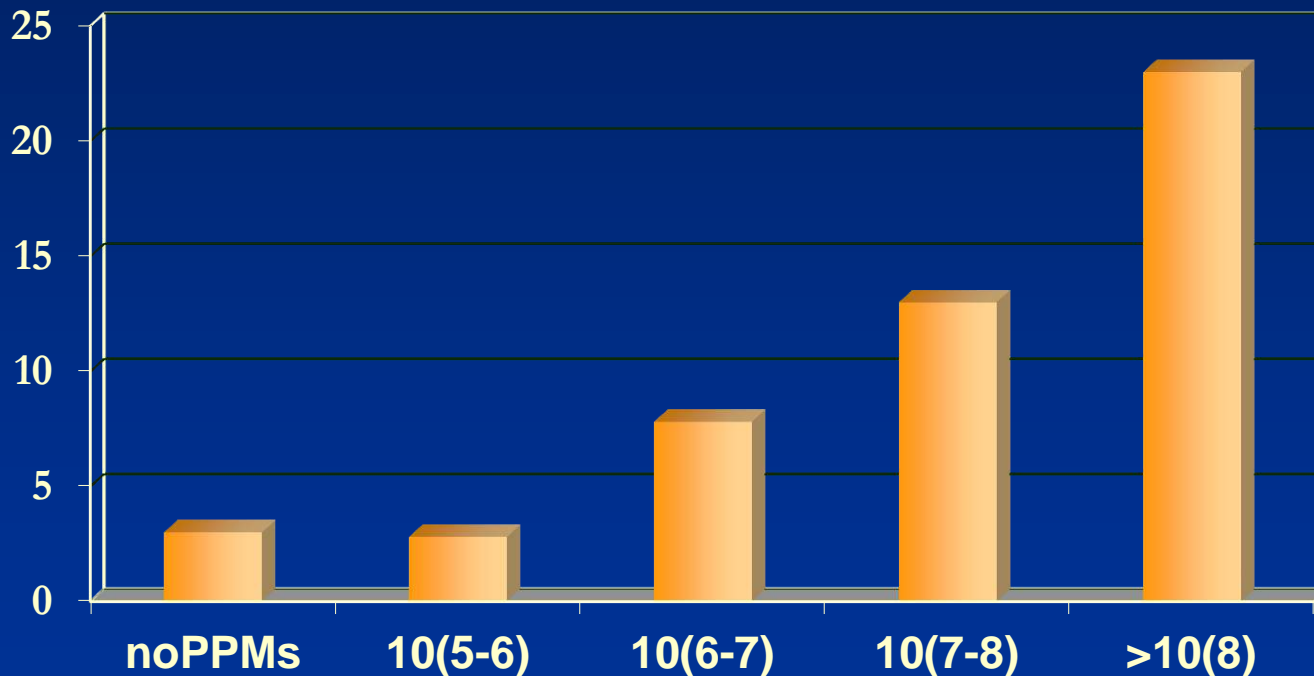


# Cultivos de cepillo protegido en EPOC estable y agudizada



# Colonización e inflamación

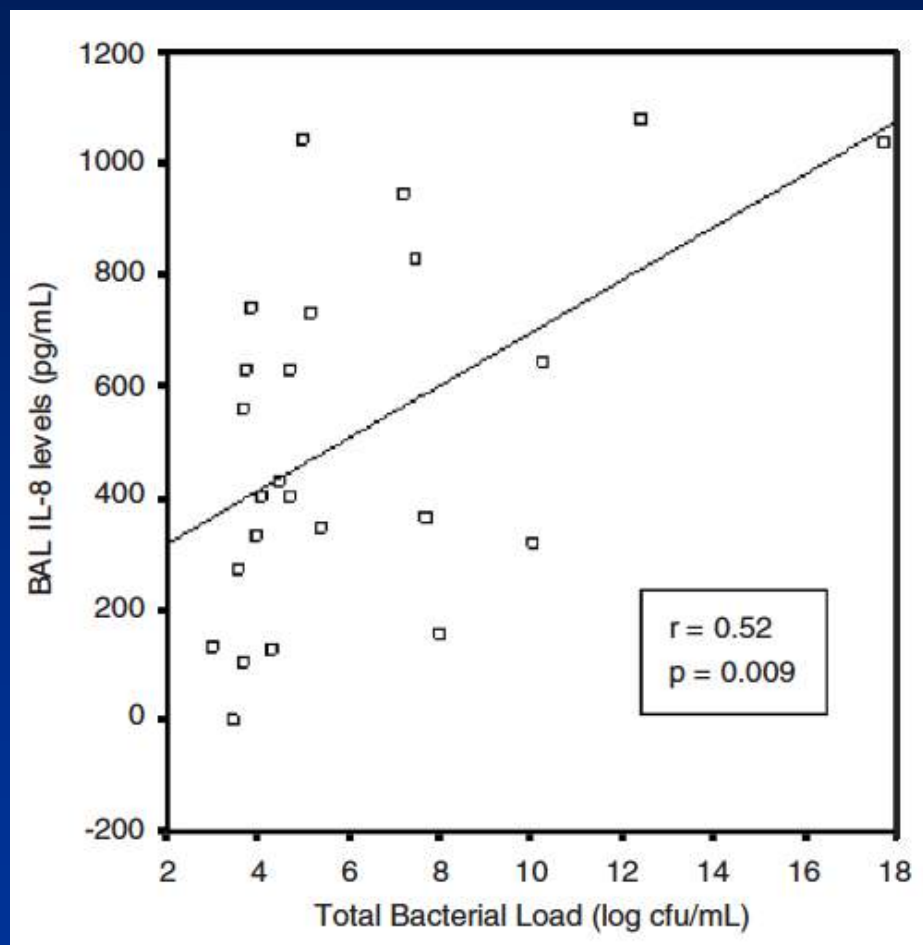
IL-8 (nM)



Cultivo  
cuantitativo  
de esputo en  
160  
pacientes en  
fase estable

# Inflamación pulmonar y carga bacteriana

Correlación entre carga total bacteriana del BAL y niveles de BAL IL-8 en pacientes con EPOC

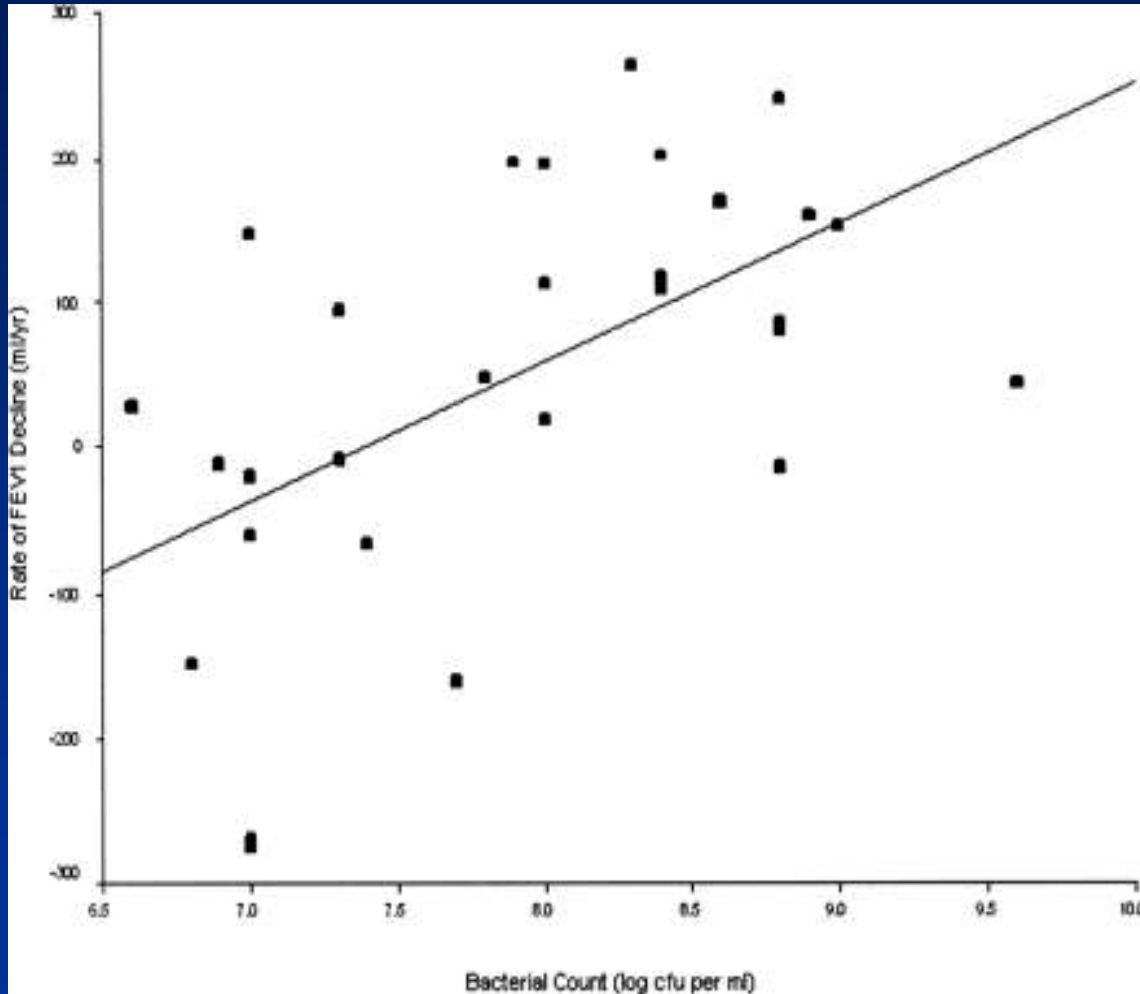


# Prevalencia de la colonización en la EPOC

- 35,2% en muestras de PSB por broncoscopia
  - 11,5% Leve ( $FEV_1$  65-79% teórico)
  - 27,8% Moderada ( $FEV_1$  50-64% teórico)
  - 53,8% Grave ( $FEV_1$  <50% teórico)

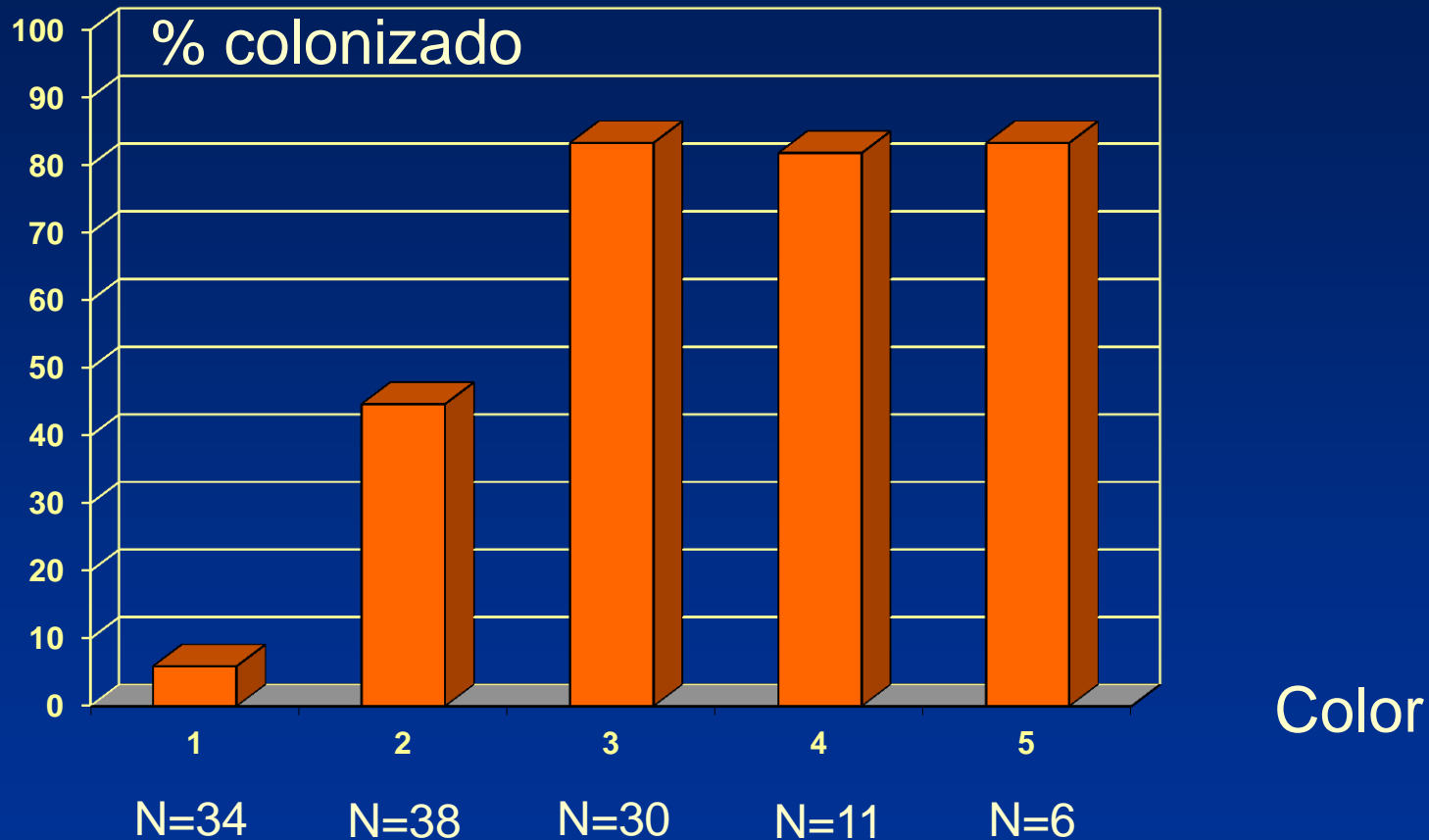


# Colonización y función pulmonar



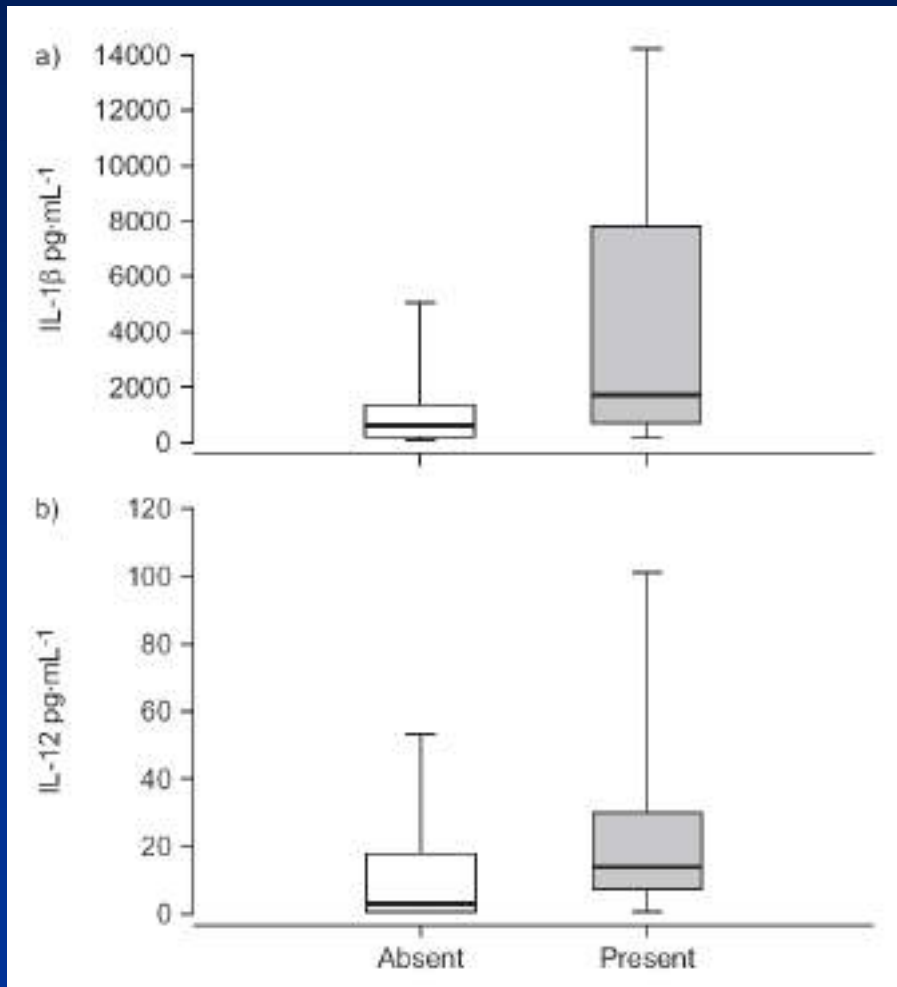
Correlación entre  
caída de FEV1 y  
carga bacteriana.  
 $R= 0,56$ ;  $p=0,001$

# Colonización y Purulencia



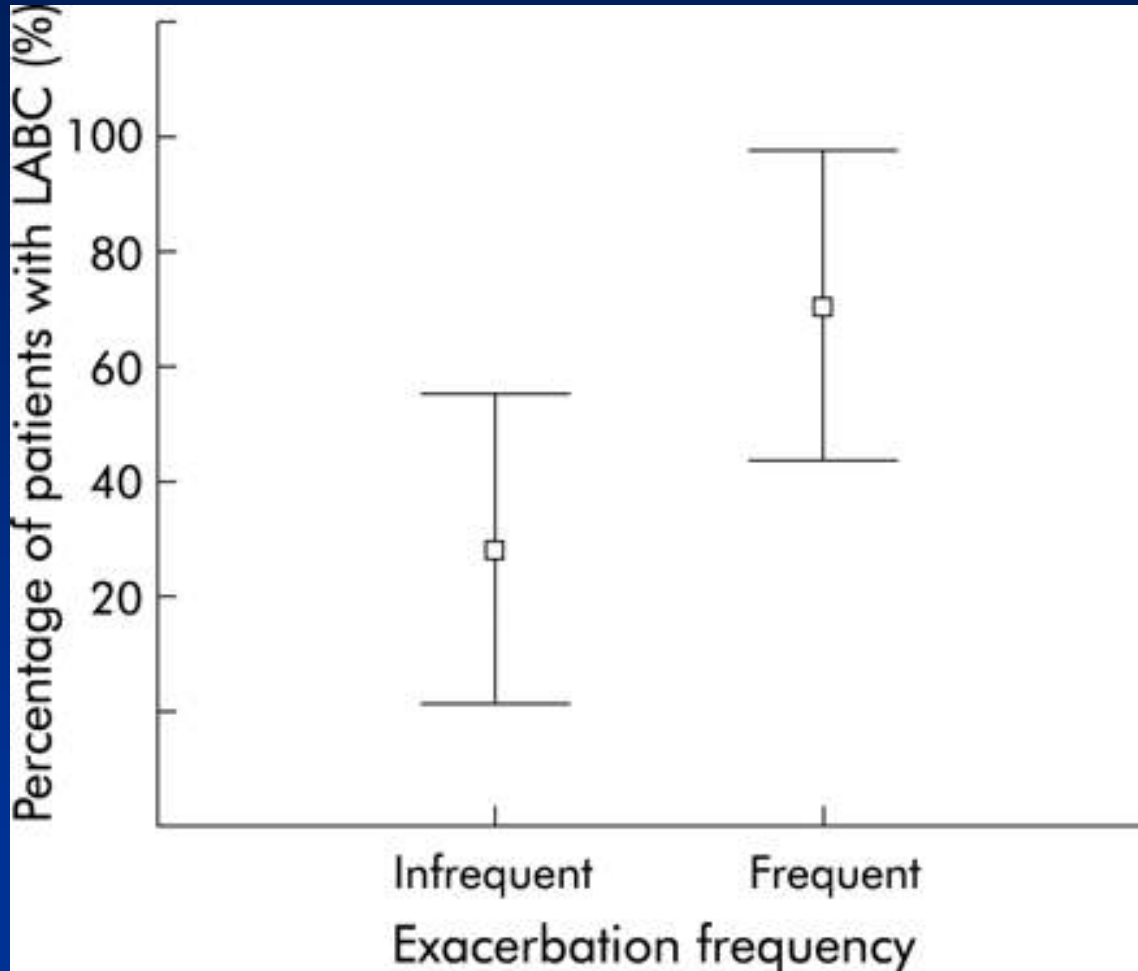
Mucoide = 61.4% Purulento/mucopurulento = 38.6%

# Colonización por *Haemophilus* e inflamación



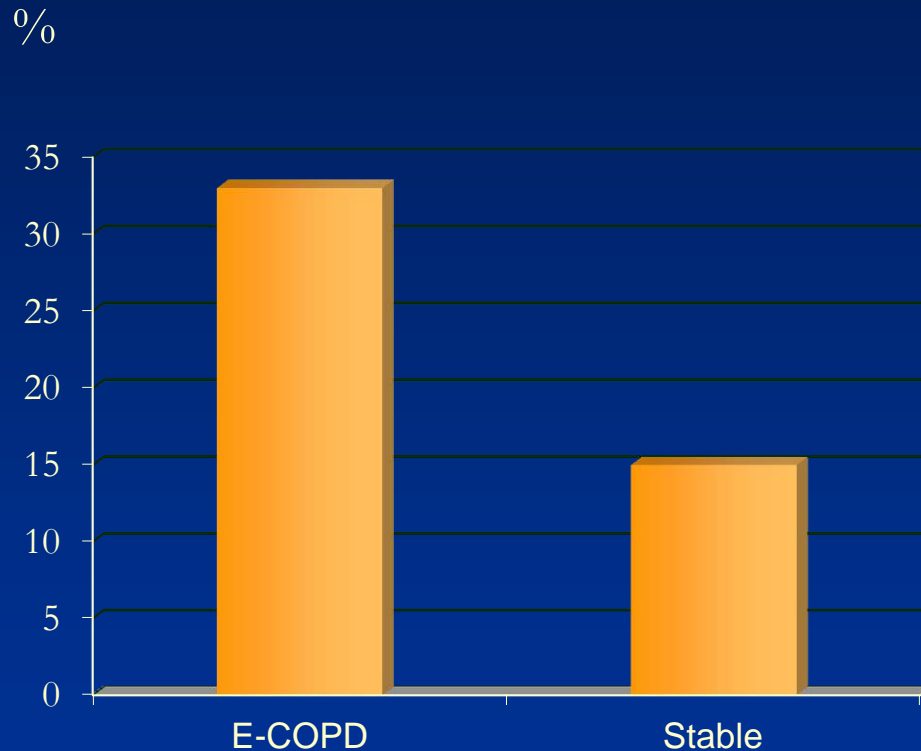
Interleukina-1  $\beta$  e IL-12 son marcadores de inflamación en esputo según la presencia de colonización bronquial por *Haemophilus influenzae*.

# Colonización y Agudización



Relación entre colonización bacteriana y frecuencia de las agudizaciones.

# La evidencia en contra de la colonización como factor de agudización



81 pacientes ambulatorios seguidos hasta por 56 meses: 374 Exacerbaciones de EPOC. Se tomaron muestras de esputo cada mes en la fase estable y durante la exacerbación de EPOC

Porcentaje de adquisición de nuevas cepas

RR=2.15 (1.8-2.5);  $p < 0.01$

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# Colonización bronquial

¿o no?

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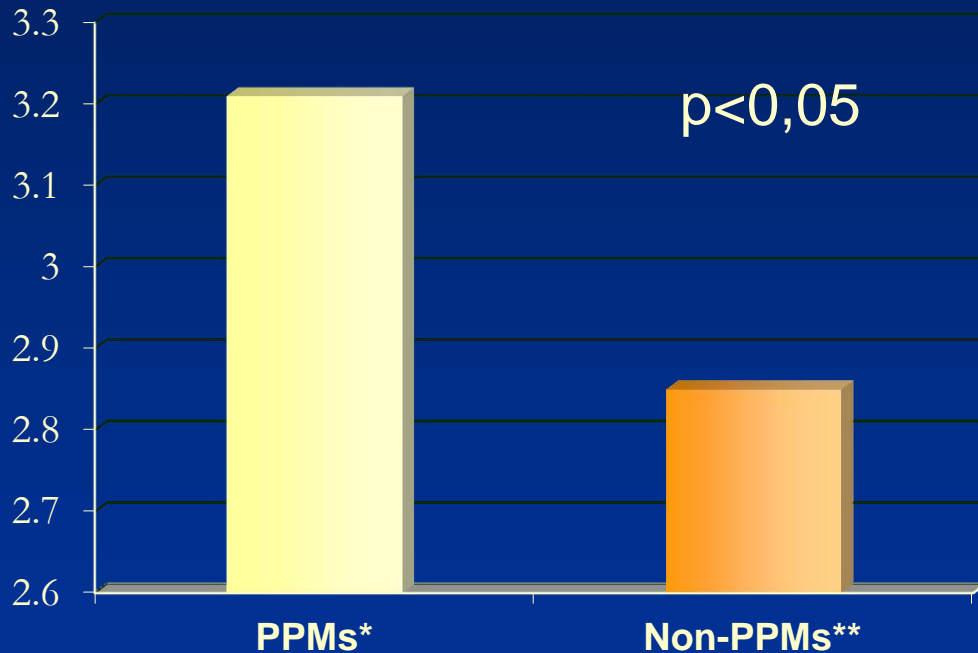
**Colonización:**  
La presencia y multiplicación de  
microorganismos sin invasión o  
daño tisular

Mosby's Medical Dictionary. 8th Edition

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# Colonización e inflamación sistémica

g/L



Concentraciones plasmáticas de **fibrinógeno** en 27 pacientes colonizados frente a 40 pacientes no colonizados

\*PPMs: Microorganismos potencialmente patógenos

\*\* Non-PPMs: Microorganismos potencialmente no patógenos



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

Alvar Agusti<sup>1,2\*</sup>, Lisa D. Edwards<sup>3</sup>, Stephen I. Rennard<sup>4</sup>, William MacNee<sup>5</sup>, Ruth Tal-Singer<sup>6</sup>, Bruce E. Miller<sup>6</sup>, Jørgen Vestbo<sup>7,8</sup>, David A. Lomas<sup>9</sup>, Peter M. A. Calverley<sup>10</sup>, Emiel Wouters<sup>11</sup>, Courtney Crim<sup>3</sup>, Julie C. Yates<sup>3</sup>, Edwin K. Silverman<sup>12</sup>, Harvey O. Coxson<sup>13</sup>, Per Bakke<sup>14</sup>, Ruth J. Mayer<sup>3</sup>, Bartolome Celli<sup>12</sup>, for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators

**Methods and Findings:** Six inflammatory biomarkers in peripheral blood (white blood cells (WBC) count and CRP, IL-6, IL-8, fibrinogen and TNF- $\alpha$  levels) were quantified in 1,755 COPD patients, 297 smokers with normal spirometry and 202 non-smoker controls that were followed-up for three years. We found that, at baseline, 30% of COPD patients did not show evidence of systemic inflammation whereas 16% had persistent systemic inflammation. Even though pulmonary abnormalities were similar in these two groups, persistently inflamed patients during follow-up had significantly increased all-cause mortality (13% vs. 2%,  $p < 0.001$ ) and exacerbation frequency (1.5 (1.5) vs. 0.9 (1.1) per year,  $p < 0.001$ ) compared to non-inflamed ones. As a descriptive study our results show associations but do not prove causality. Besides this, the inflammatory response is complex and we studied only a limited panel of biomarkers, albeit they are those investigated by the majority of previous studies and are often and easily measured in clinical practice.

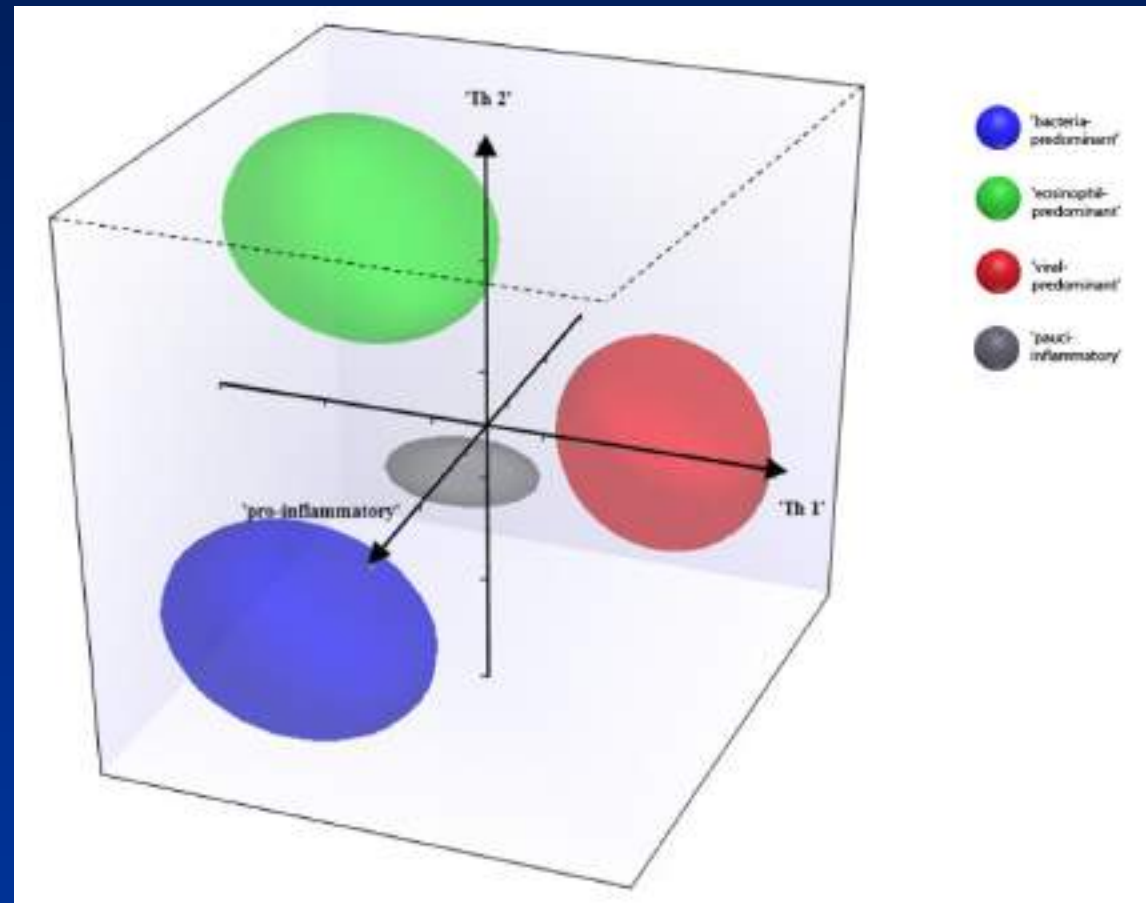
# Fenotipos exacerbadores

Estudio sobre 182  
exacerbaciones  
en 86 pacientes:

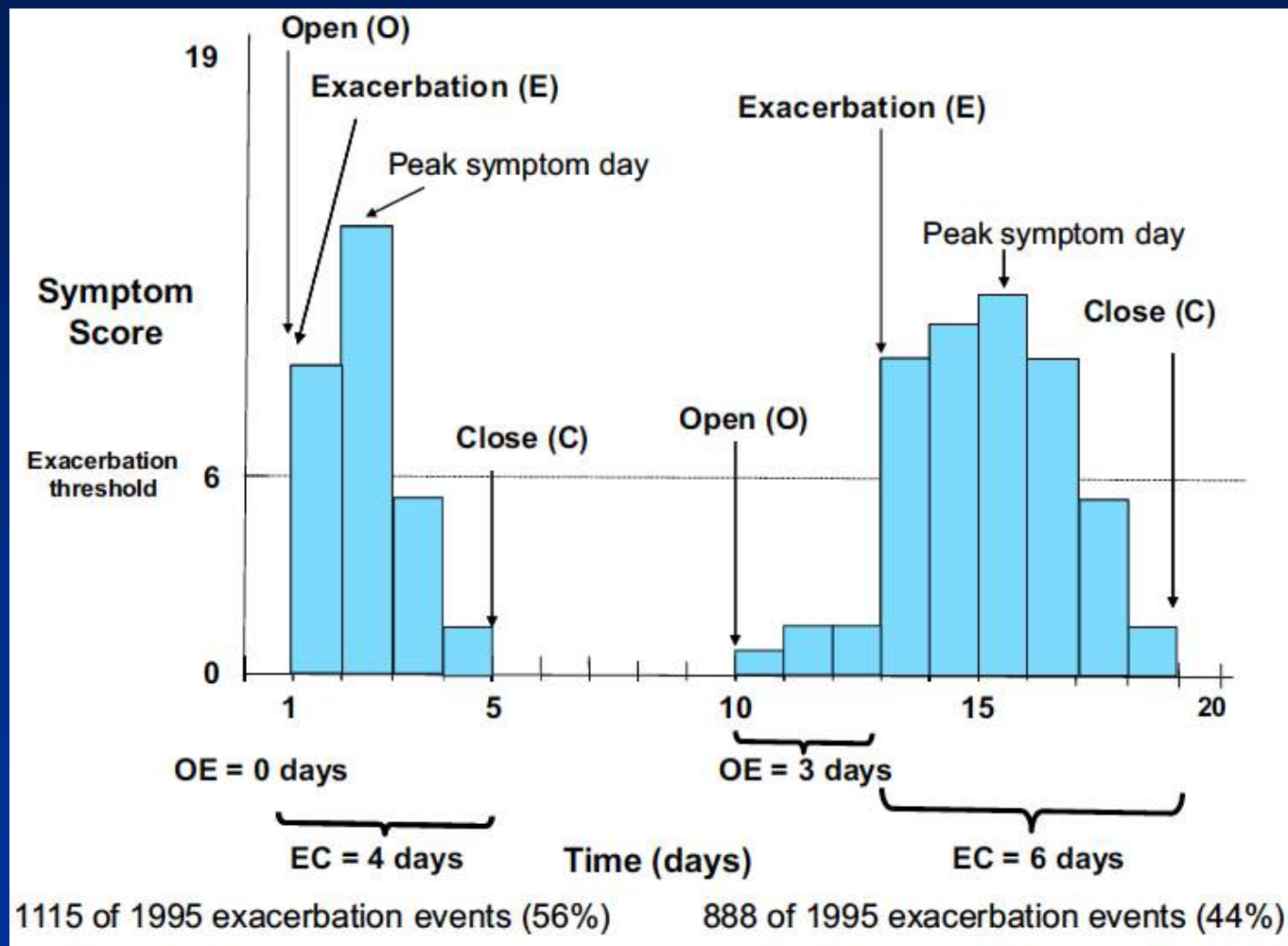
Atópicos 20%.

Colonizados 28%.

Inflamación  
eosinofílica de la vía  
aérea 27%

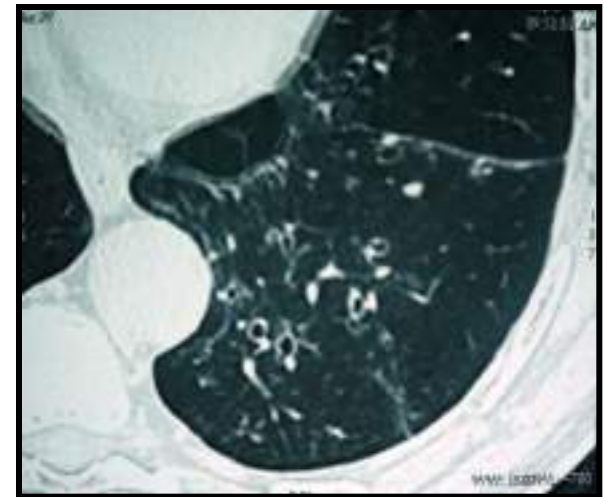
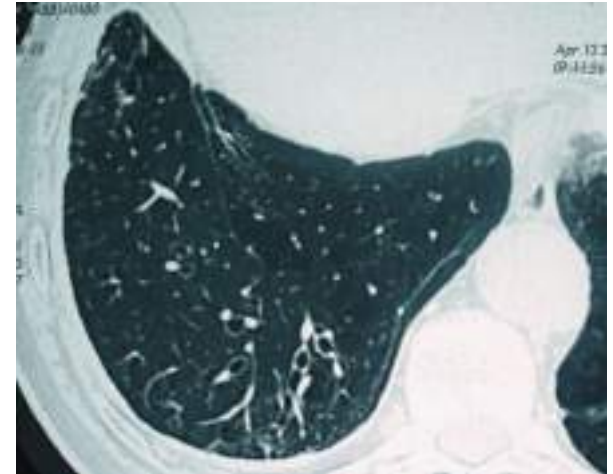


# Fenotipos Exacerbadores



# EPOC y Bronquiectasias

<b>Patients with bronchiectasis n (%)</b>	53 (57.6%)
<b>Type, n (%)<sup>+</sup></b>	
-Cilindrical	48 (90.6%)
-Cystic	10 (18.9%)
<b>Location, n (%)</b>	
-Only upper lobes	6 (11.3%)
-Only lower lobes	32 (60.4%)
-Only lingula or middle lobule	15 (28.3%)
-Only right	7 (13.2%)
-Only left	5 (9.4%)
-Bilateral	41 (77.4%)
-Central bronchiectasis	2 (3.8%)
<b>Extension, n (%)</b>	
-Localized (only 1 lobule)	8 (15.1%)
-Disseminated (4 or more lobules)	10 (18.9%)
-Nº affected lobules, mean (SD)	2.1 (2.2)
-Nº affected segments, mean (SD)	3.8 (4.6)

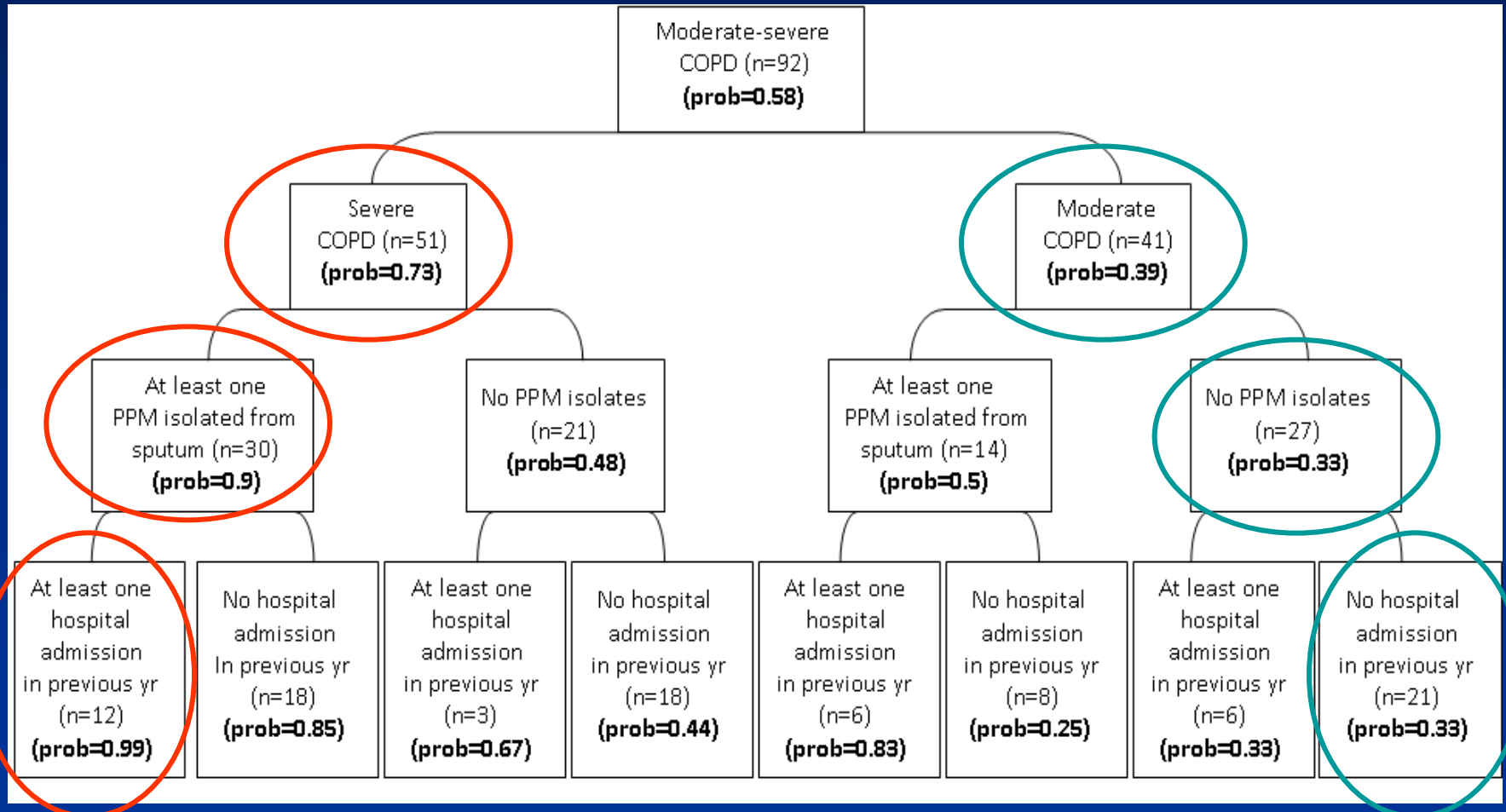


# EPOC y Bronquiectasias

Variables in the equation	Univariate analysis		Adjusted multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Severe COPD (FEV1 $\leq$ 50%)	4.13 (1.71-9.94)	0.001	<b>3.87 (1.38-10.5)</b>	<b>0.01</b>
PPM isolates*	5.19 (2.08-12.9)	0.001	<b>3.59 (1.3-9.9)</b>	<b>0.014</b>
At least one hospital admission in the previous year	3.07 (1.09-8.65)	0.024	<b>3.07 (1.07-8.77)</b>	<b>0.037</b>
At least four acute antibiotic treatments	4.73 (1.26-17.7)	0.012	3.1 (0.58-15.5)	0.18
Chronic expectoration	4.89 (1.5-15.86)	0.004	2.8 (1.02-7.7)	0.054
Home oxygen therapy	4.12 (1.38-12.3)	0.007	1.1 (0.25-4.9)	0.89
Fibrinogen (mg/dl)	1.01 (1-1.01)	0.011	1.1 (0.99-1.01)	0.49
Albumin (mg/dl)	0.21 (0.05-0.86)	0.03	0.5 (0.08-3.02)	0.28

# EPOC y Bronquiectasias

Probabilidad (pretest) de tener bronquiectasias de acuerdo a las características de la EPOC



# EPOC y Bronquiectasias

Parámetro	LL BC*	LL BC*	p
	No	Si	
IL-8 en esputo en estado estable	3.6 (1.9-4.6)	4.6 (3.2-5.8)	0.001
IL-6 en esputo en estado estable	62.6 (13-178)	96.2 (19-219)	0.03
Tiempo para la recuperación después de la exacerbación, días	10	12	0.001

EPOC (n=54), FEV1 media = 0.97 L.

Frecuencia de bronquiectasias 50%, en Lóbulo Inf 33%

\* LL BC : Lower Lobe Bacterial Colonisation (Colonización Bacteriana del Lóbulo Inferior)

# Riesgo de colonización por *P.aeruginosa*

<b>Autor, año</b>	<b>Factores de riesgo</b>
<b>Eller, 1998</b>	FEV1 < 35% Pretratamiento con antibióticos
<b>Miravittles, 1999</b>	FEV1 < 50%
<b>Monsó, 2003</b>	FEV1 bajo Uso de esteroides orales Antibióticos en los 3 meses previos Efecto protector de la vacuna contra influenza
<b>Allegra, 2005</b>	FEV1 < 35%
<b>Lode, 2007</b>	FEV1 < 35% Uso de esteroides sistémicos Antibióticos en los 3 meses previos
<b>García-Vidal, 2009</b>	Índice de BODE empeorado Admisiones en el año anterior Esteroides sistémicos Aislamiento previo de <i>P. aeruginosa</i>

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# Estrategias contra la colonización (¿infección?) crónica

1-ESTRATEGIAS ANTIBIÓTICAS

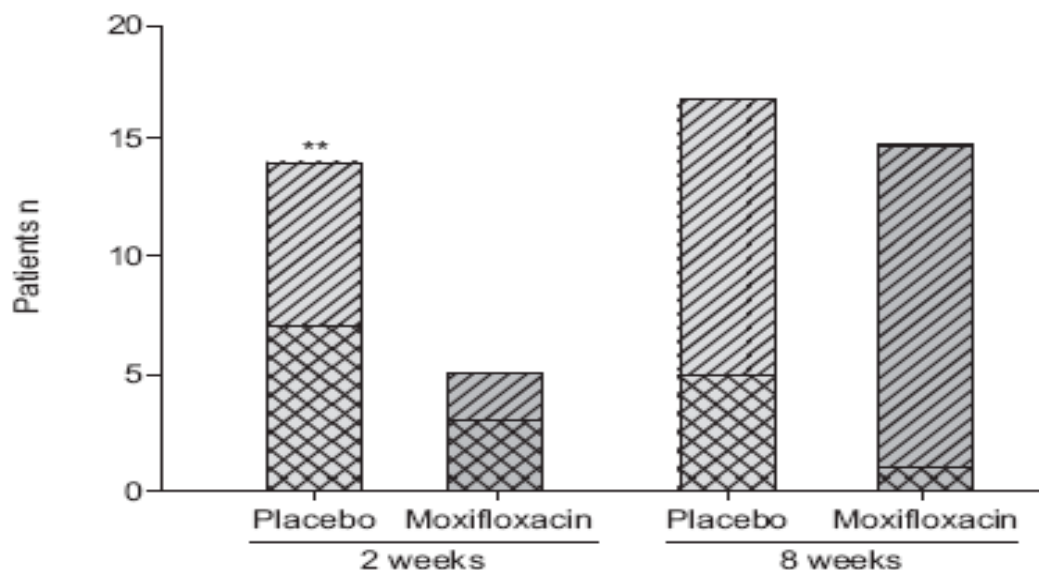
2-ESTRATEGIAS PARA MEJORAR LA  
FUNCIÓN CELULAR

3-ESTRATEGIAS PARA MEJORAR LA  
INMUNIDAD HUMORAL



## Efficacy of moxifloxacin in the treatment of bronchial colonisation in COPD

M. Miravittles\*, A. Marín<sup>†</sup>, E. Monsó<sup>†</sup>, S. Vilà\*, C. de la Roza\*, R. Hervás<sup>†</sup>,  
C. Esquinas\*, M. García<sup>†</sup>, L. Millares<sup>†</sup>, J. Morera<sup>†</sup> and A. Torres<sup>‡</sup>



**FIGURE 1.** Number of patients with positive isolation of potentially pathogenic microorganisms (PPMs) in sputum at 2 and 8 weeks after randomisation. Numbers are the result of adding the percentage of patients with persistent (▨) and newly acquired (▧) strains identified by sputum culture and detection of the DNA of PPMs by PCR (table 2). \*\*:  $p=0.01$ .

RESEARCH

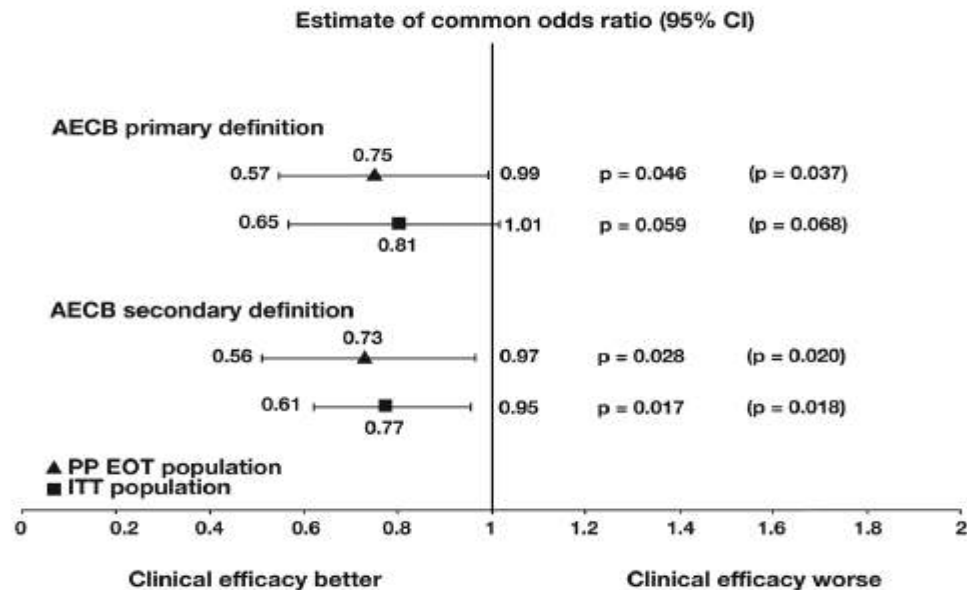
Open Access

## Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial

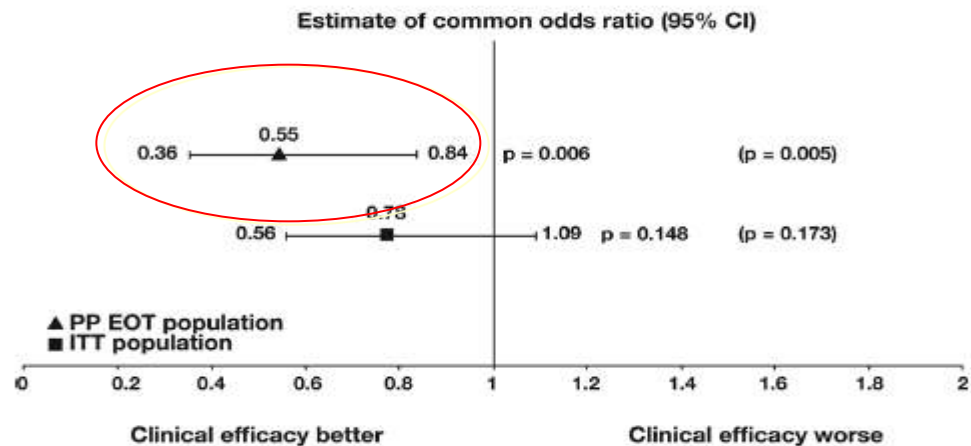
Sanjay Sethi<sup>1\*</sup>, Paul W Jones<sup>2</sup>, Marlize Schmitt Theron<sup>3</sup>, Marc Miravittles<sup>4</sup>, Ethan Rubinstein<sup>5</sup>, Jadwiga A Wedzicha<sup>6</sup>, Robert Wilson<sup>7</sup>, the PULSE Study group

**Methods:** Stable patients with COPD were randomized in a double-blind, placebo-controlled trial to receive moxifloxacin 400 mg PO once daily (N = 573) or placebo (N = 584) once a day for 5 days. Treatment was repeated every 8 weeks for a total of six courses. Patients were repeatedly assessed clinically and microbiologically during the 48-week treatment period, and for a further 24 weeks' follow-up.

(A) PP EOT and ITT population



(B) Mucopurulent/purulent sputum subgroup



**Figure 3** Clinical efficacy of moxifloxacin vs placebo. (a) Per-protocol end-of-treatment (PP EOT) and intent-to-treat (ITT) populations according to the primary and secondary definitions of an exacerbation, and (b) patients with purulent/mucopurulent sputum at baseline (PP EOT and ITT populations using the primary definition of an exacerbation). The first set of p-values on the graphs are from logistic regression analysis using the median value for patients missing at 48 weeks. Corresponding p-values for logistic regression analysis using last observation carried forward are given in brackets. AECEB, acute exacerbation of chronic bronchitis.

# The NEW ENGLAND JOURNAL of MEDICINE

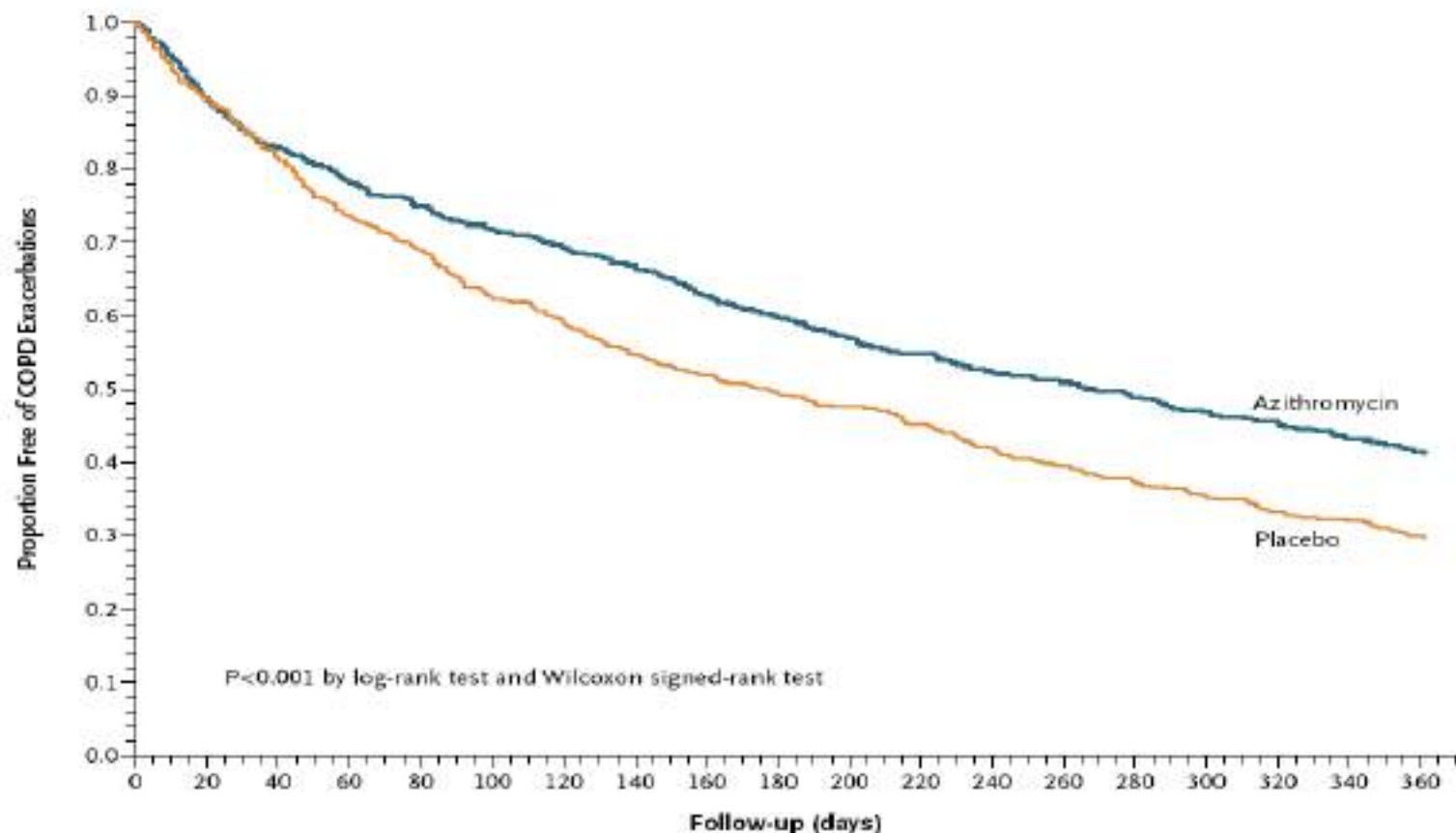
ESTABLISHED IN 1812

AUGUST 25, 2011

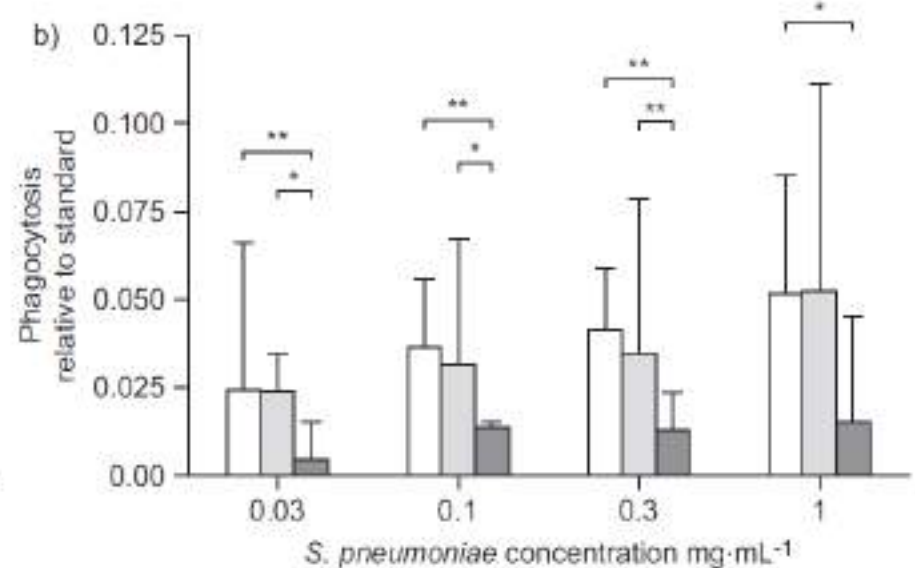
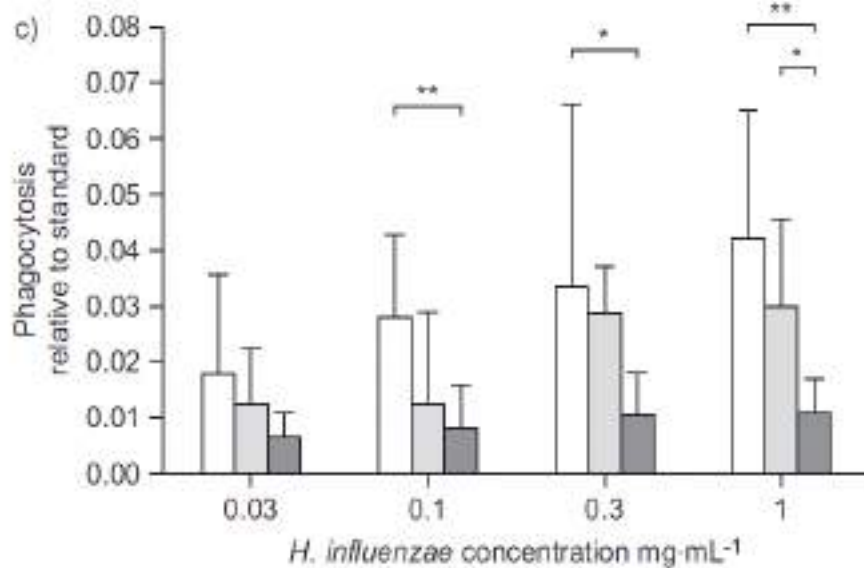
VOL. 365 NO. 8

## Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., Mei-Lan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porszasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network



# Alteraciones de la fagocitosis de los macrófagos en la EPOC



Respuestas fagocitarias de los macrófagos derivados de monocitos de no fumadores, exfumadores y pacientes con EPOC

# Conclusiones

1-La colonización bronquial es frecuente en el paciente EPOC estable

2-Las consecuencias de ello se traducen en mayor inflamación, más agudizaciones y pérdida de función pulmonar

3-Las estrategias antibióticas han sido parcialmente efectivas

4-La existencia asociada de bronquiectasias y los defectos en la inmunidad pueden jugar un papel importante