

# XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

## OVIEDO

17-20 Noviembre 2010

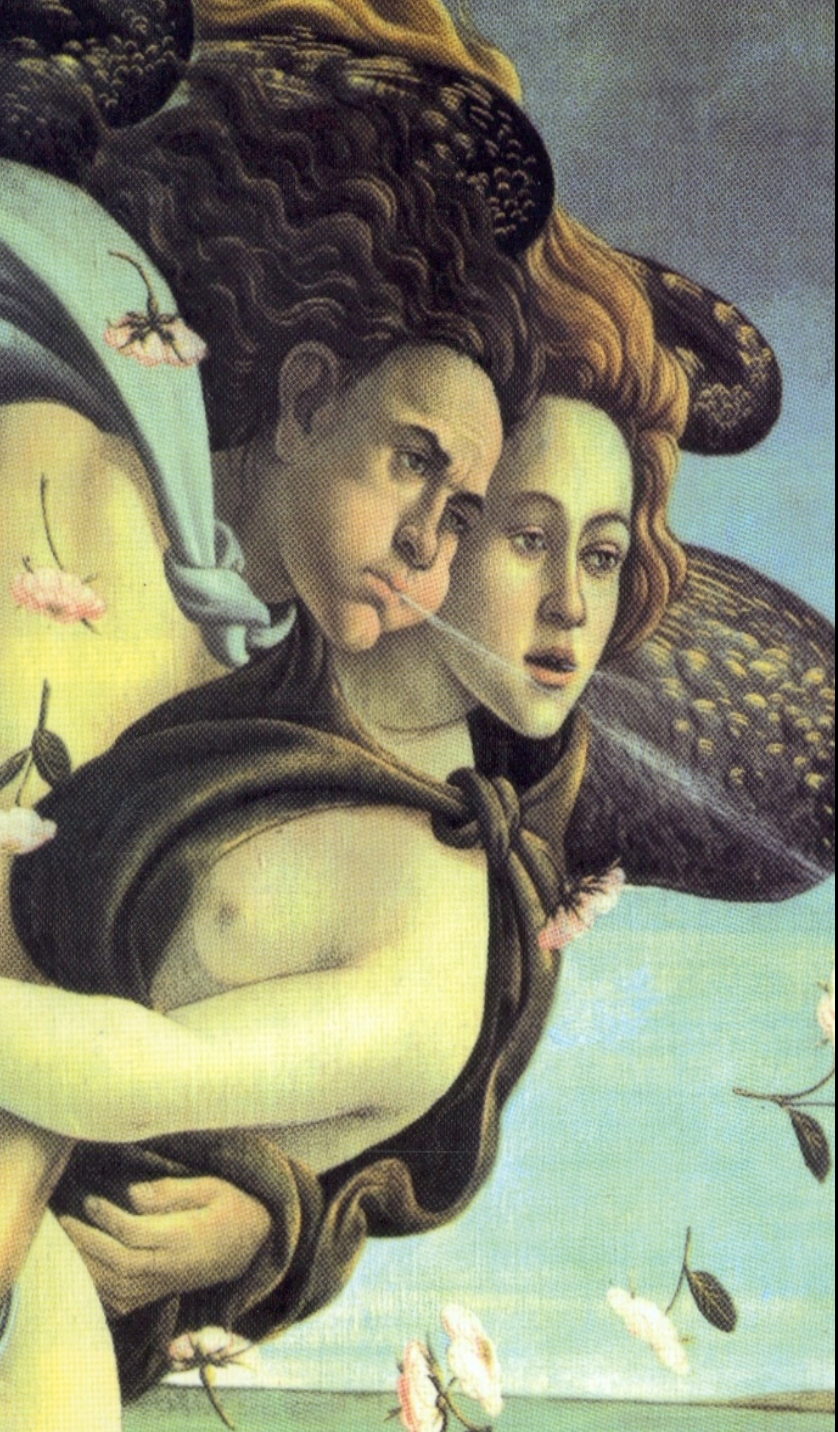
Auditorio-Palacio de Congresos  
"Príncipe Felipe"

## II Congreso Ibérico de Medicina Interna

VII Congreso de la Sociedad  
Asturiana de Medicina Interna

# ANTIBIÓTICOS EN LAS EXACERBACIONES DE LA EPOC. TEORÍA Y REALIDAD

P. Almagro  
Hospital Universitario Mútua de Terrassa

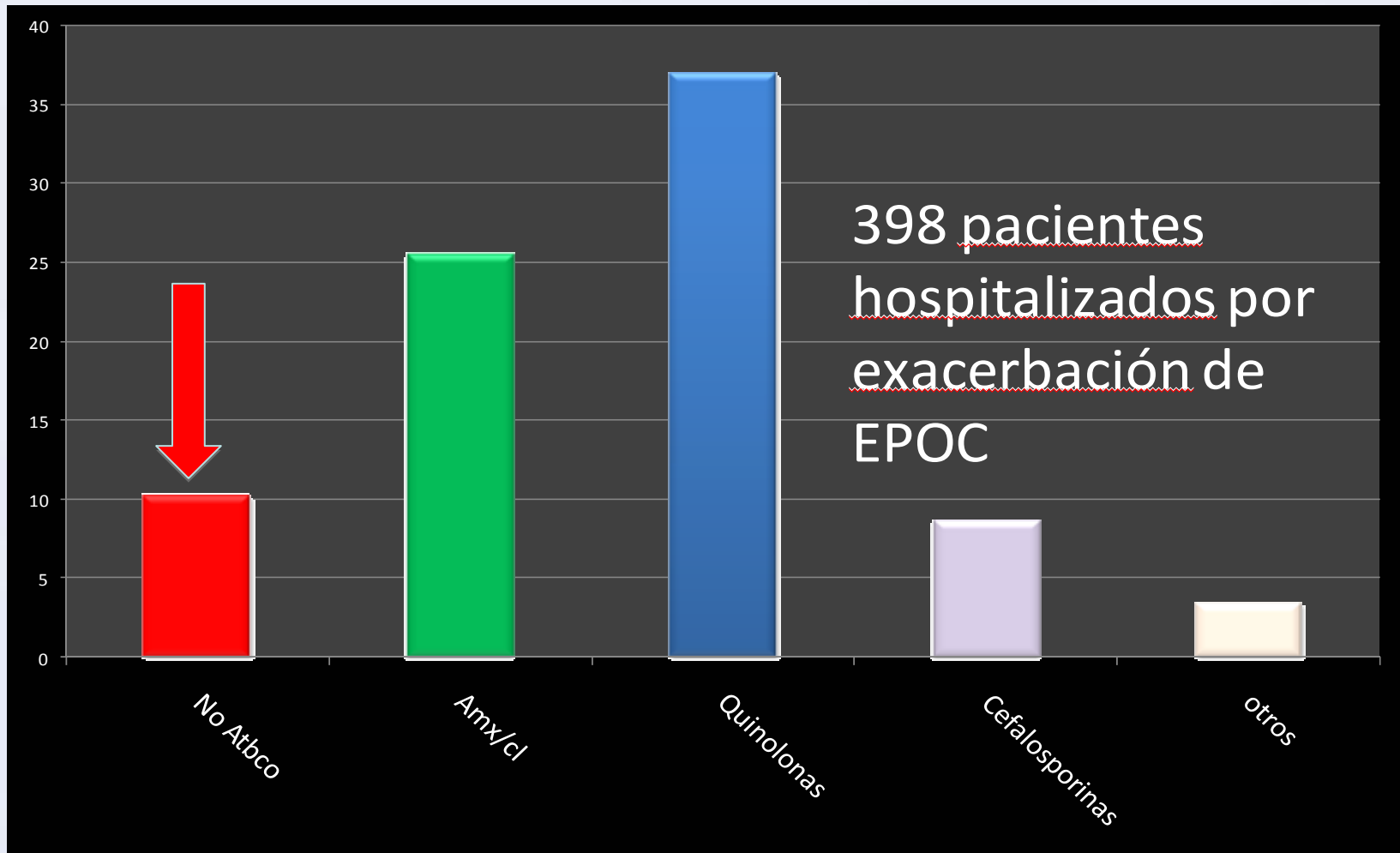






# Práctica

# ESTUDIO ECCO. GRUPO EPOC



# **Antibióticos para las exacerbaciones de la enfermedad pulmonar obstructiva crónica**

**Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC**

Reproducción de una revisión Cochrane, traducida y publicada en *La Biblioteca Cochrane Plus*, 2008, Número 2

- Recomendado en pacientes con EAEPOC y
  - mayor tos y purulencia del esputo que están moderada o gravemente enfermos.
- Los resultados deben ser interpretados con cuidado debido a:
  - diferencias en la selección de pacientes
  - el número pequeño de ensayos
  - la falta de control de las intervenciones que influyen en el resultado, como el uso de corticosteroides sistémicos.

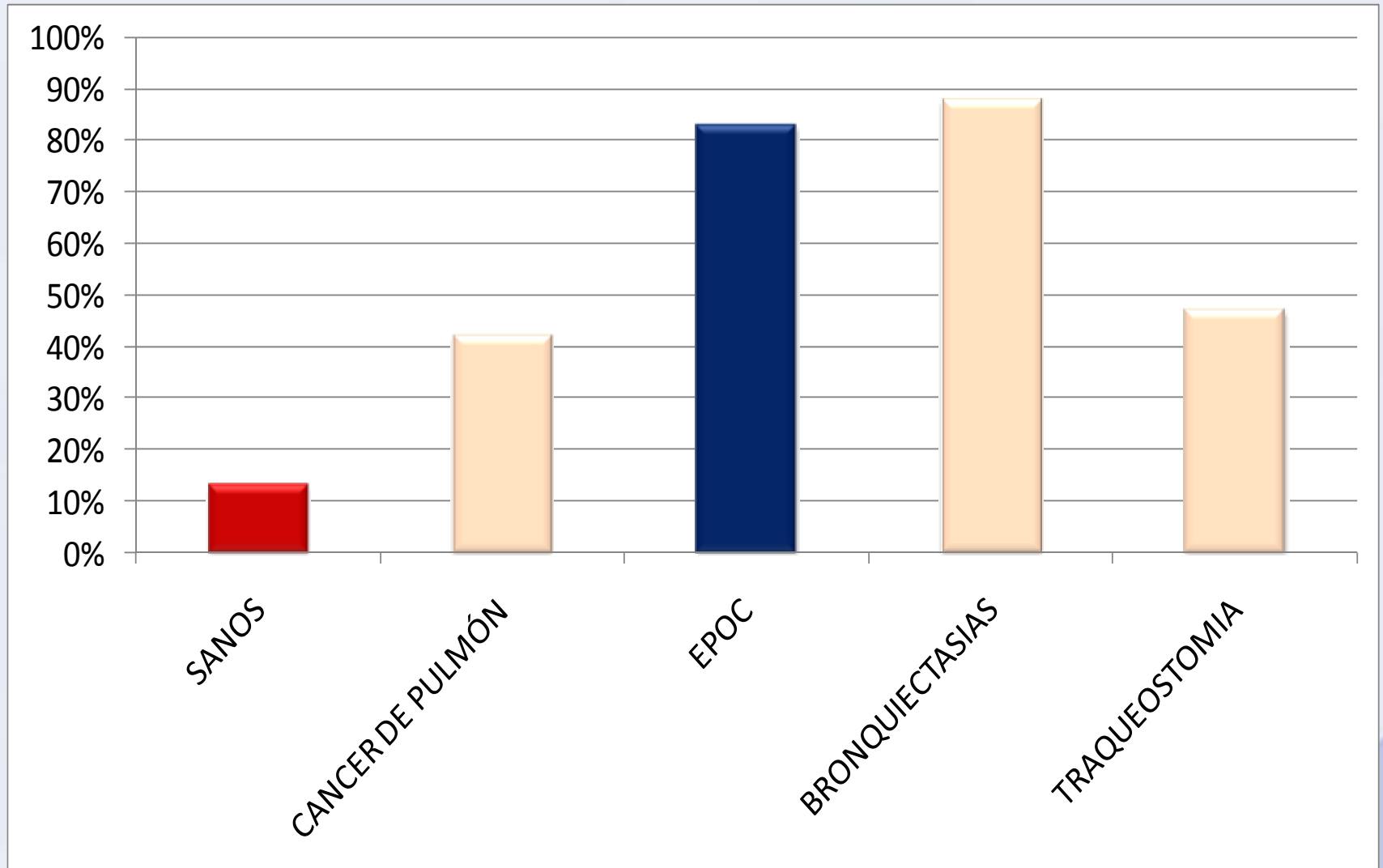




# Bases teóricas

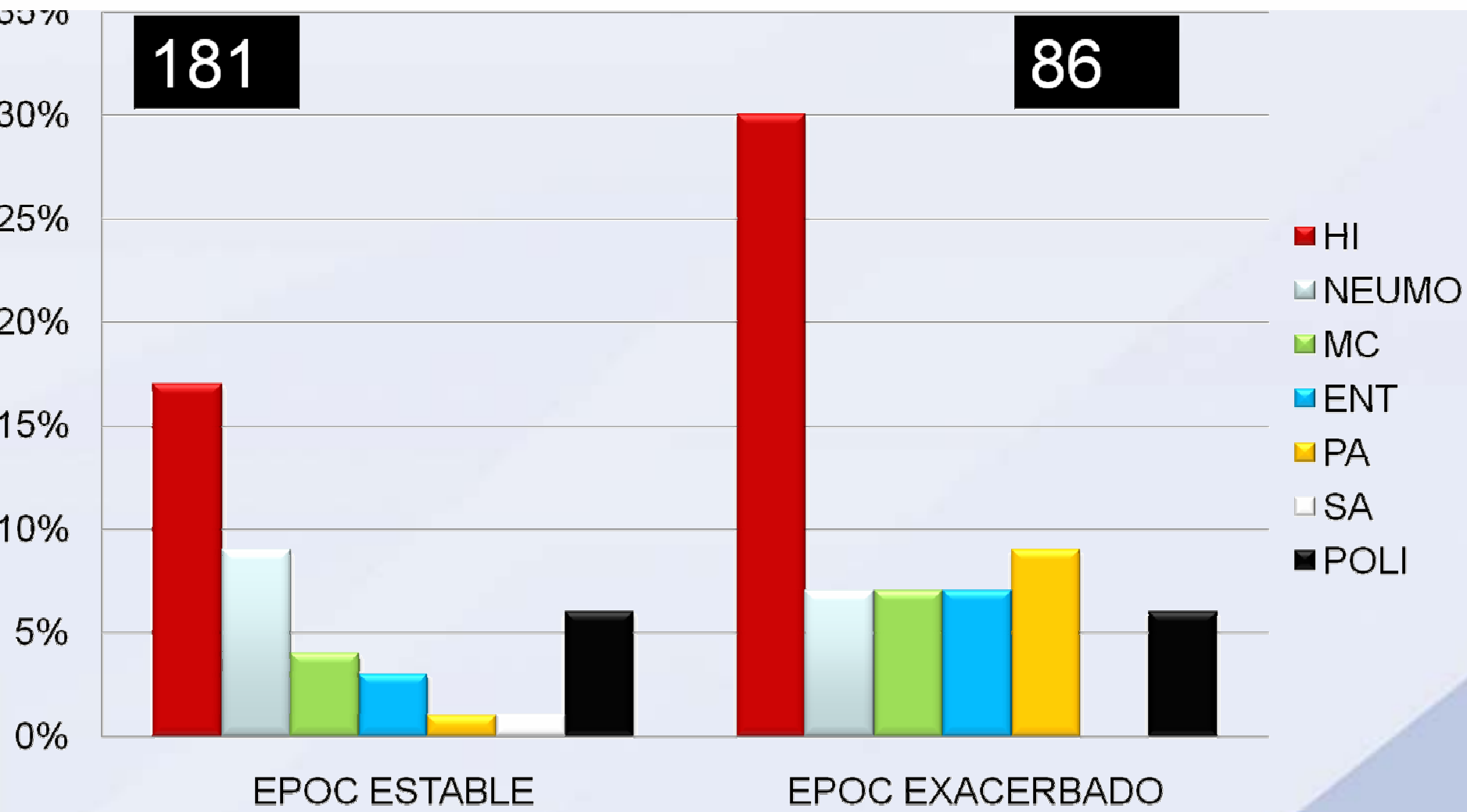
# Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study

Eur Respir J 1997; 10: 1137-1144



# Microbiologic Determinants of Exacerbation in Chronic Obstructive Pulmonary Disease

Antoni Rosell, MD; Eduard Monsó, MD; Néstor Soler, MD; Ferràn Torres, MD; Joaquim Angrill, MD; Gerdt Riise, MD; Rafael Zalacain, MD; Josep Morera, MD; Antoni Torres, MD





# The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 347

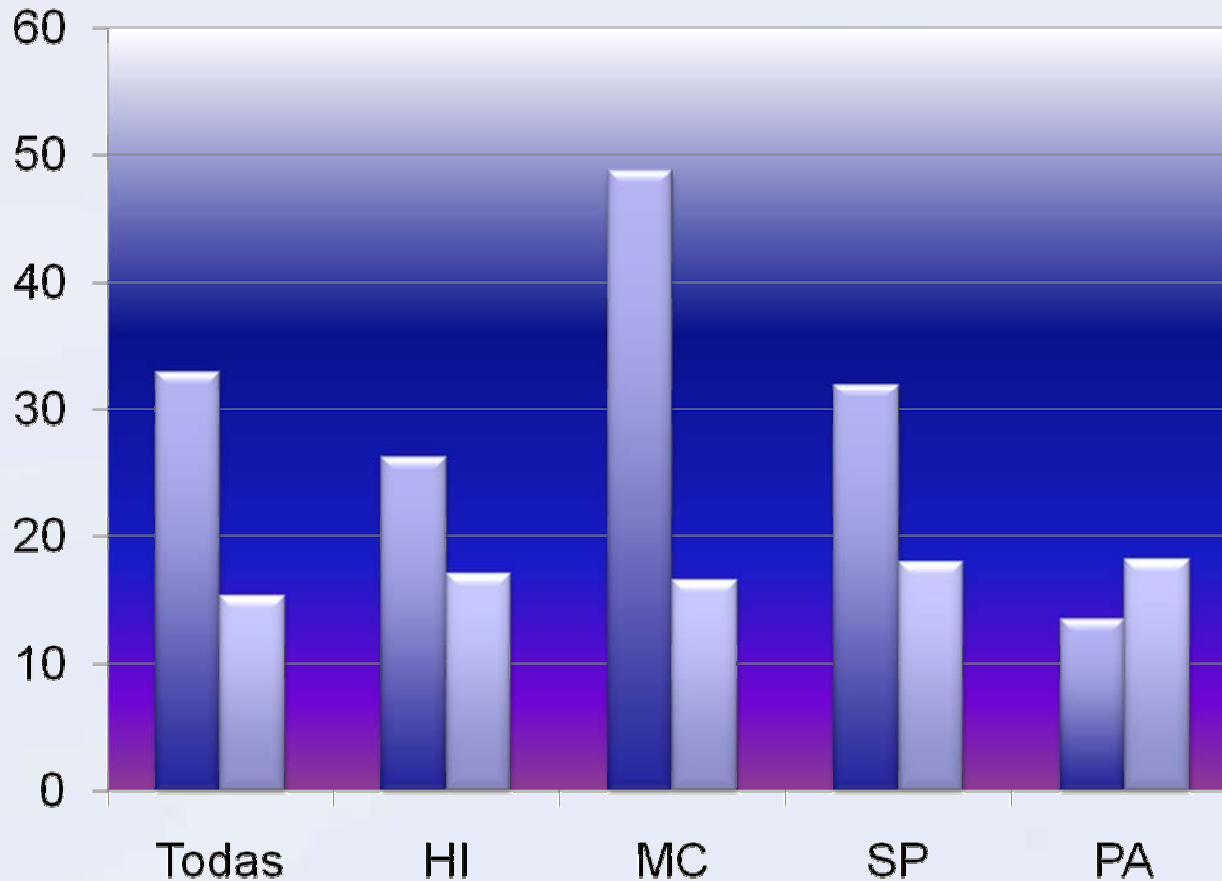
AUGUST 15, 2002

NUMBER 7



## NEW STRAINS OF BACTERIA AND EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

SANJAY SETHI, M.D., NANCY EVANS, R.N., BRYDON J.B. GRANT, M.D., AND TIMOTHY F. MURPHY, M.D.



**Riesgo relativo (95% CI) de exacerbación:**

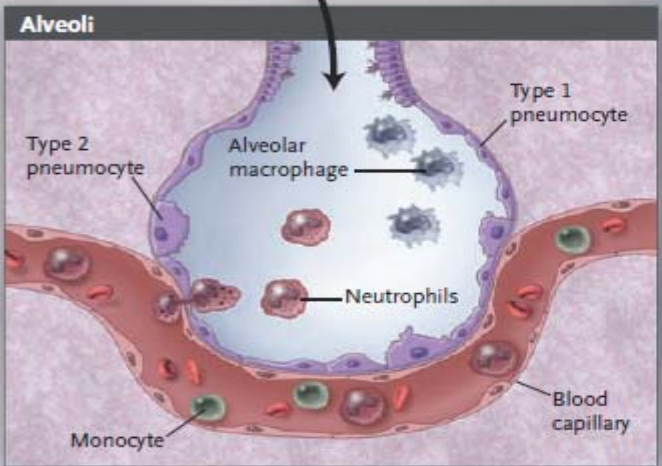
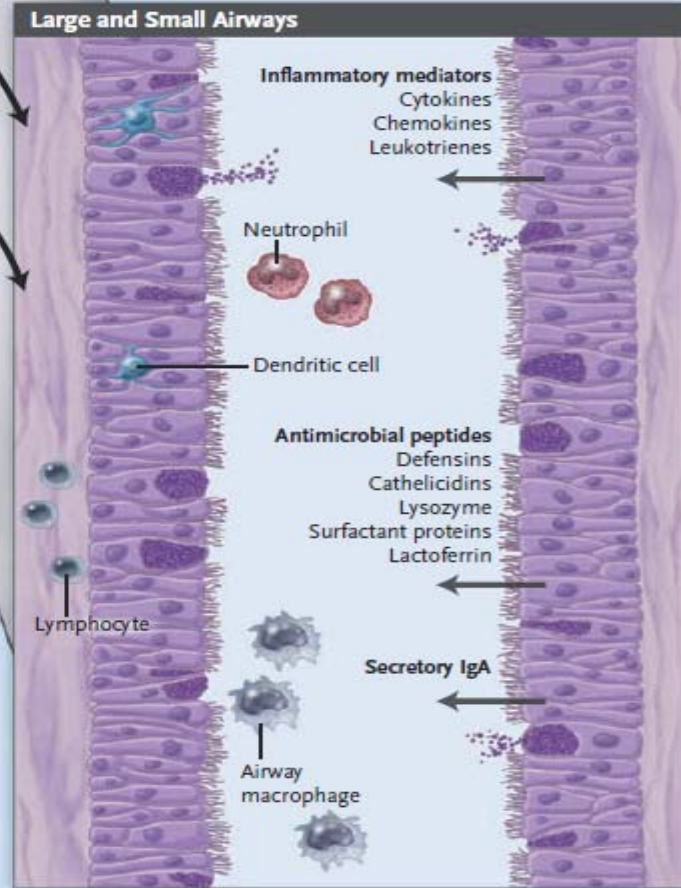
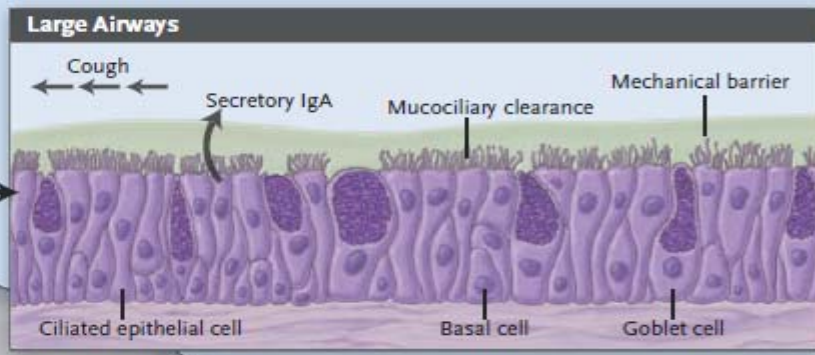
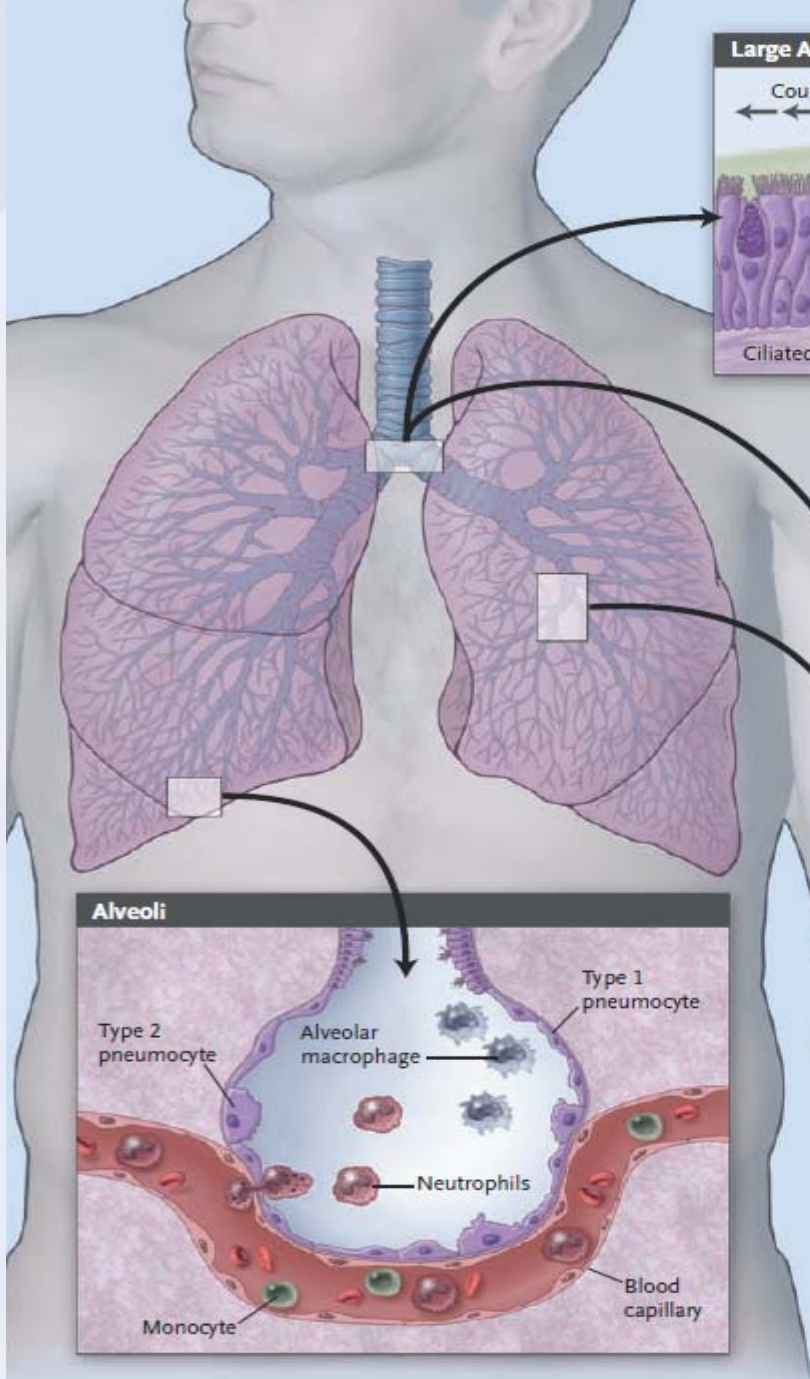
**1 MO 2.15 (1.83-2.63)**

**HI 1.69 (1.37-2.09)**

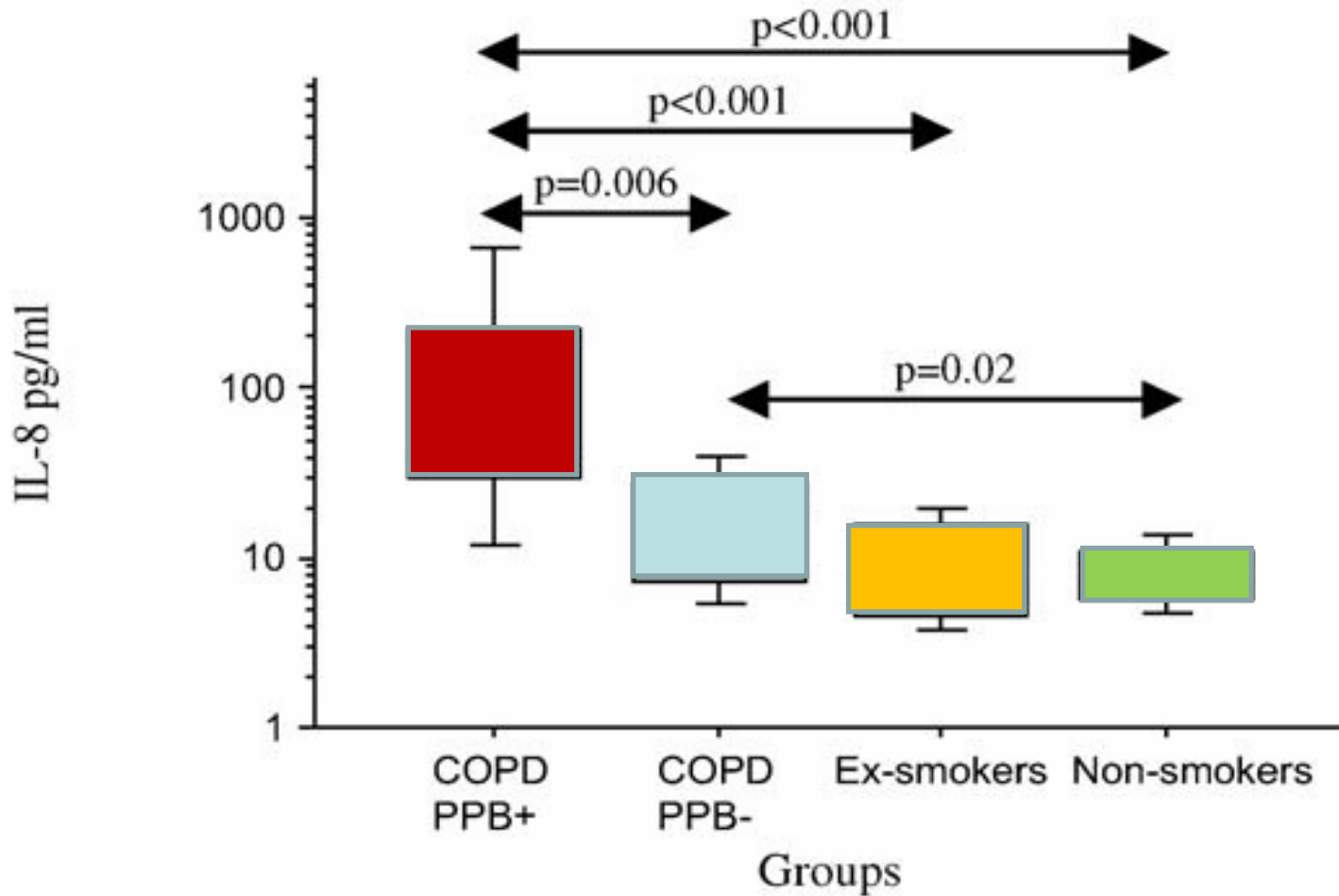
**MC 2.96 (2.39-3.67)**

**SP 1.77 (1.14-2.75)**

**PA 0.61 (0.21-1.82)**

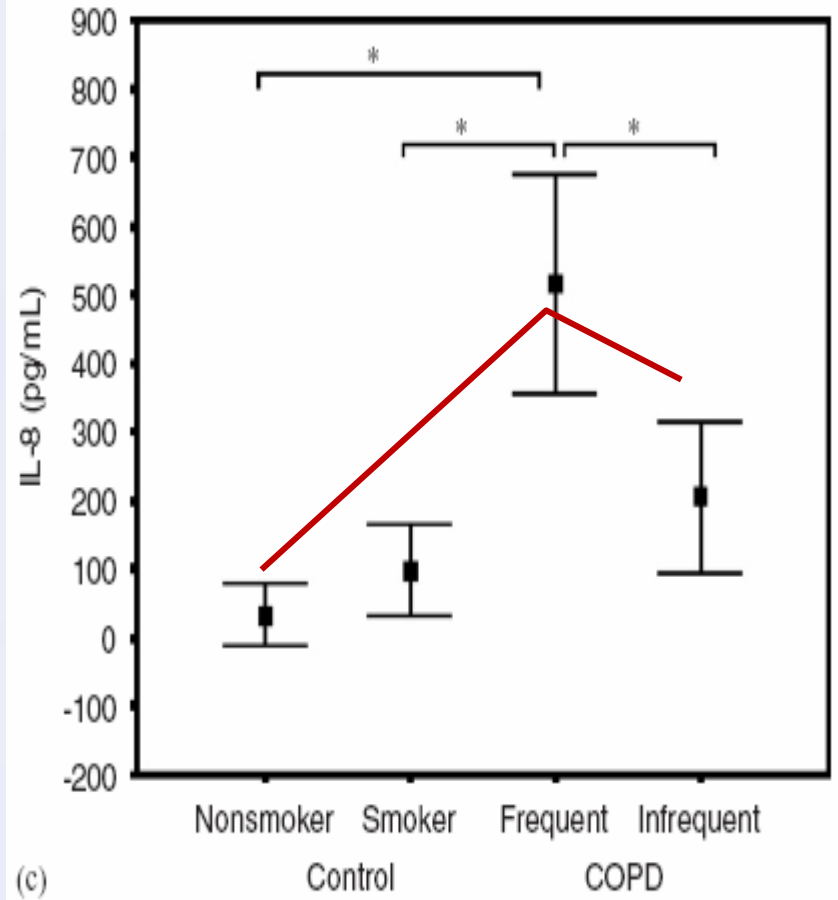
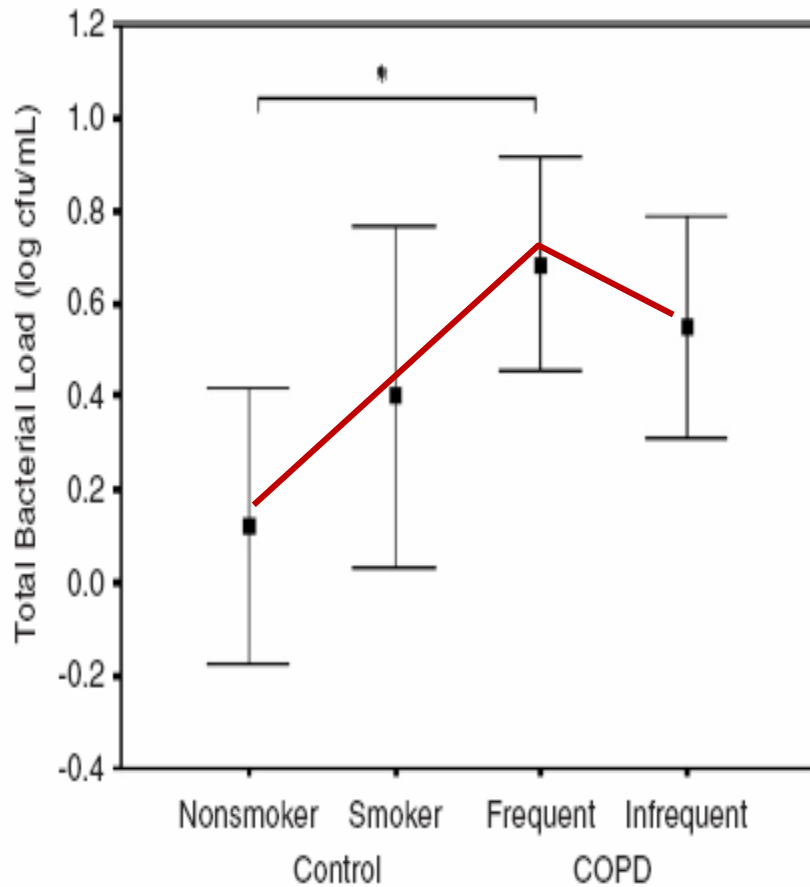


# Colonización bacteriana en la EPOC





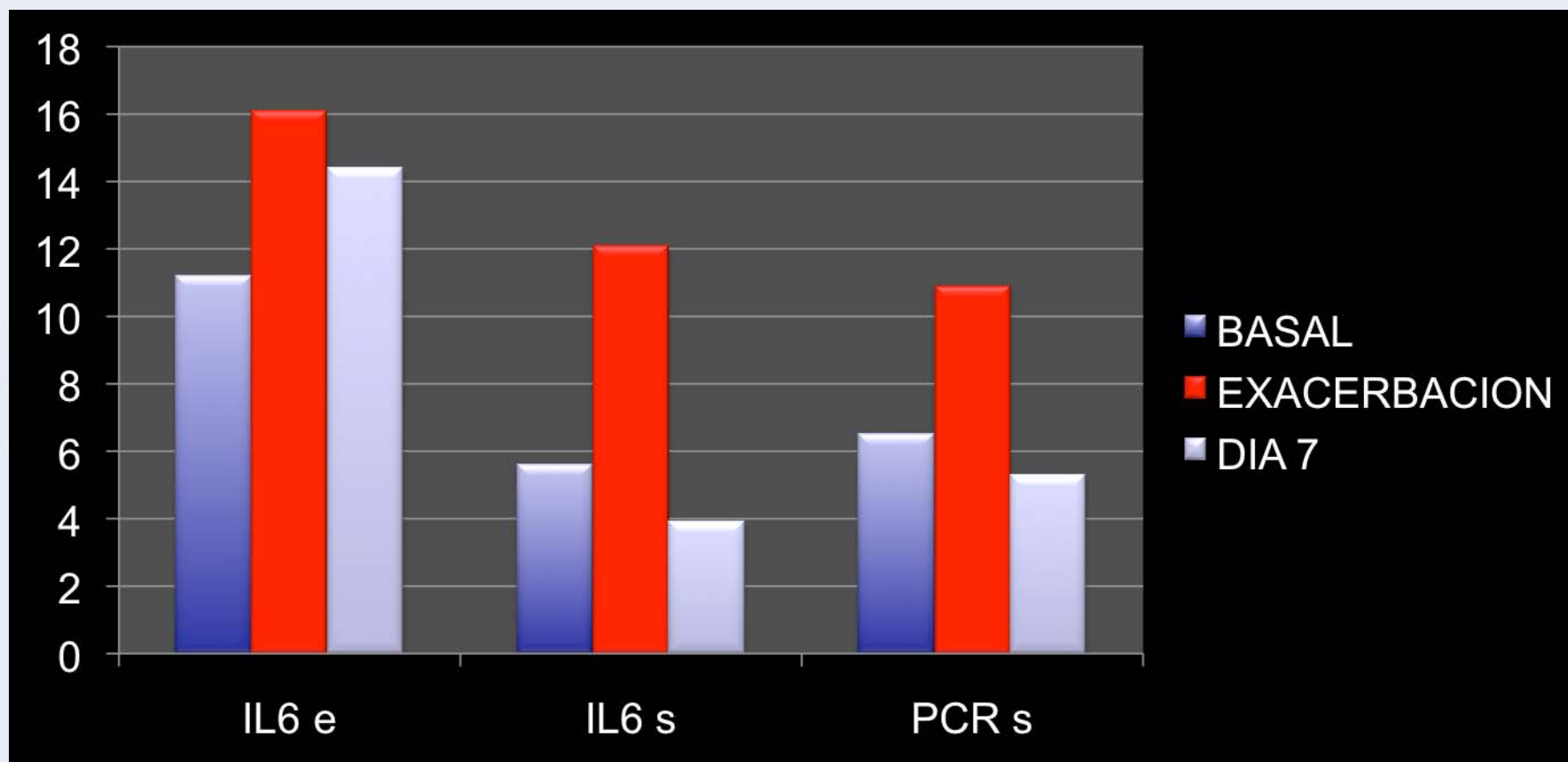
# Colonización bacteriana en la EPOC



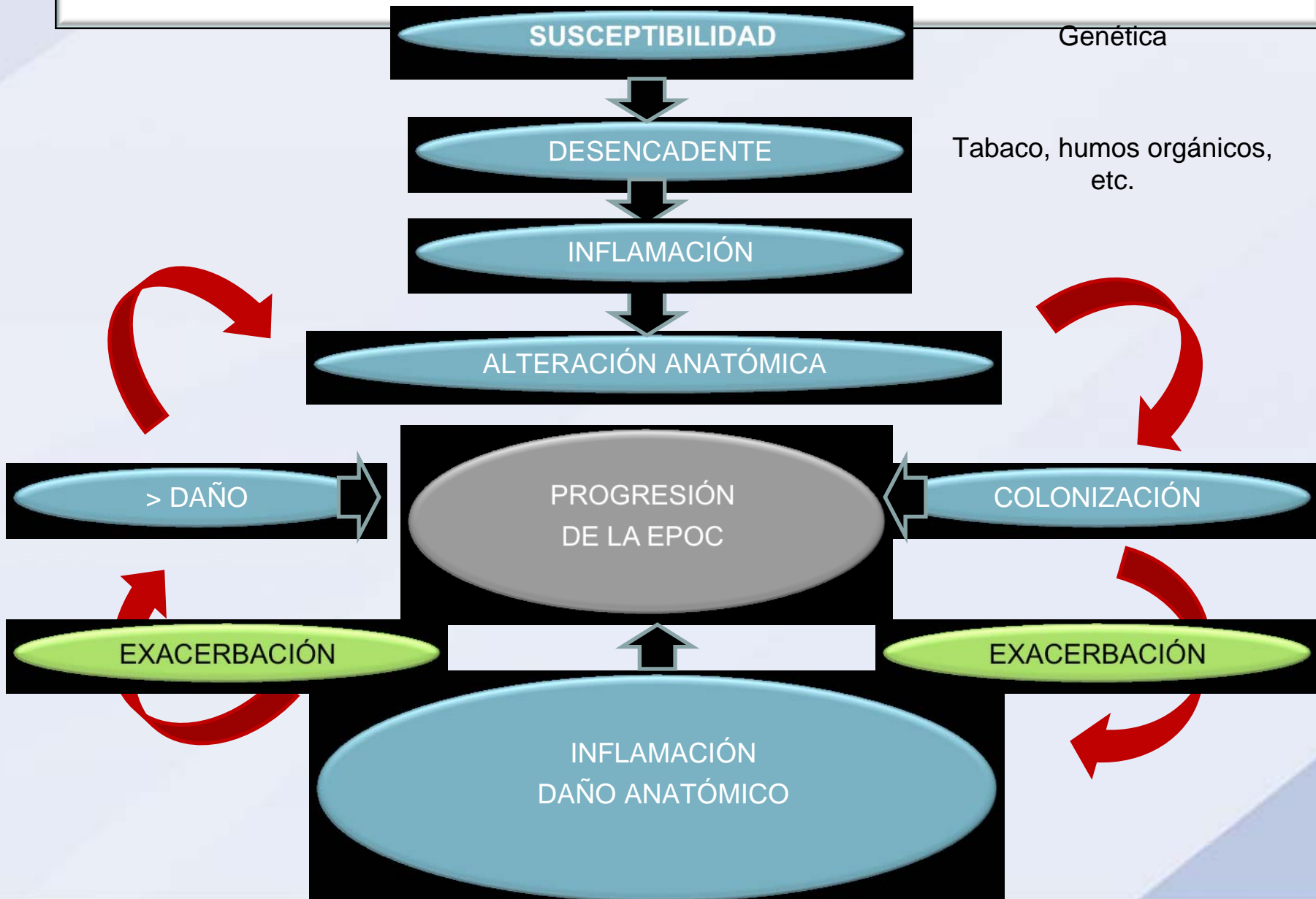
Tumkaya M, Atis S, Ozge C, Delialioglu N, Polat G, Kanik A. Relationship between airway colonization, inflammation and exacerbation frequency in COPD. *Respir Med.* 2007;101(4):729-37. Epub 2006 Sep 26.

# Inflammatory changes, recovery and recurrence at COPD exacerbation

W.R. Perera\*, J.R. Hurst\*, T.M.A. Wilkinson\*, R.J. Sapsford\*, H. Müllerova#,  
G.C. Donaldson\* and J.A. Wedzicha\*



# EL CIRCULO VICIOSO EN LA EPOC







Evidencia científica

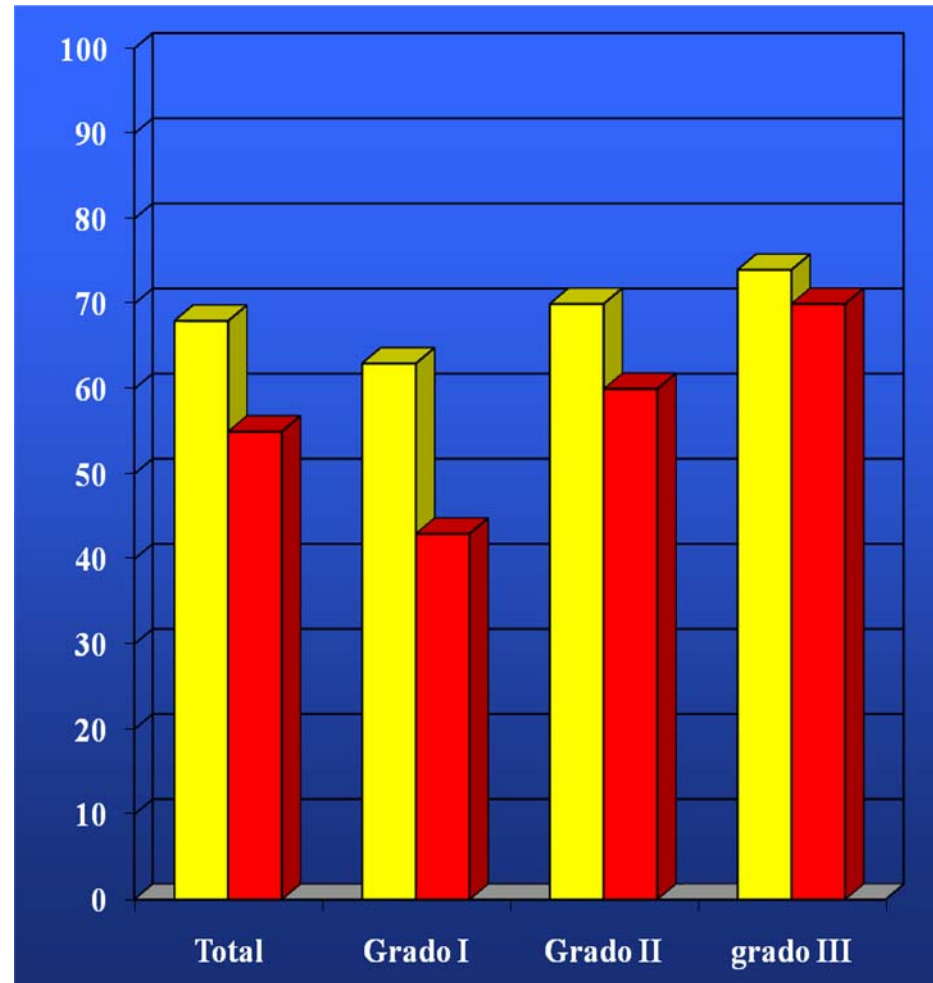
# Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary

## Disease

Annals of Internal Medicine. 1987;106:196-204.

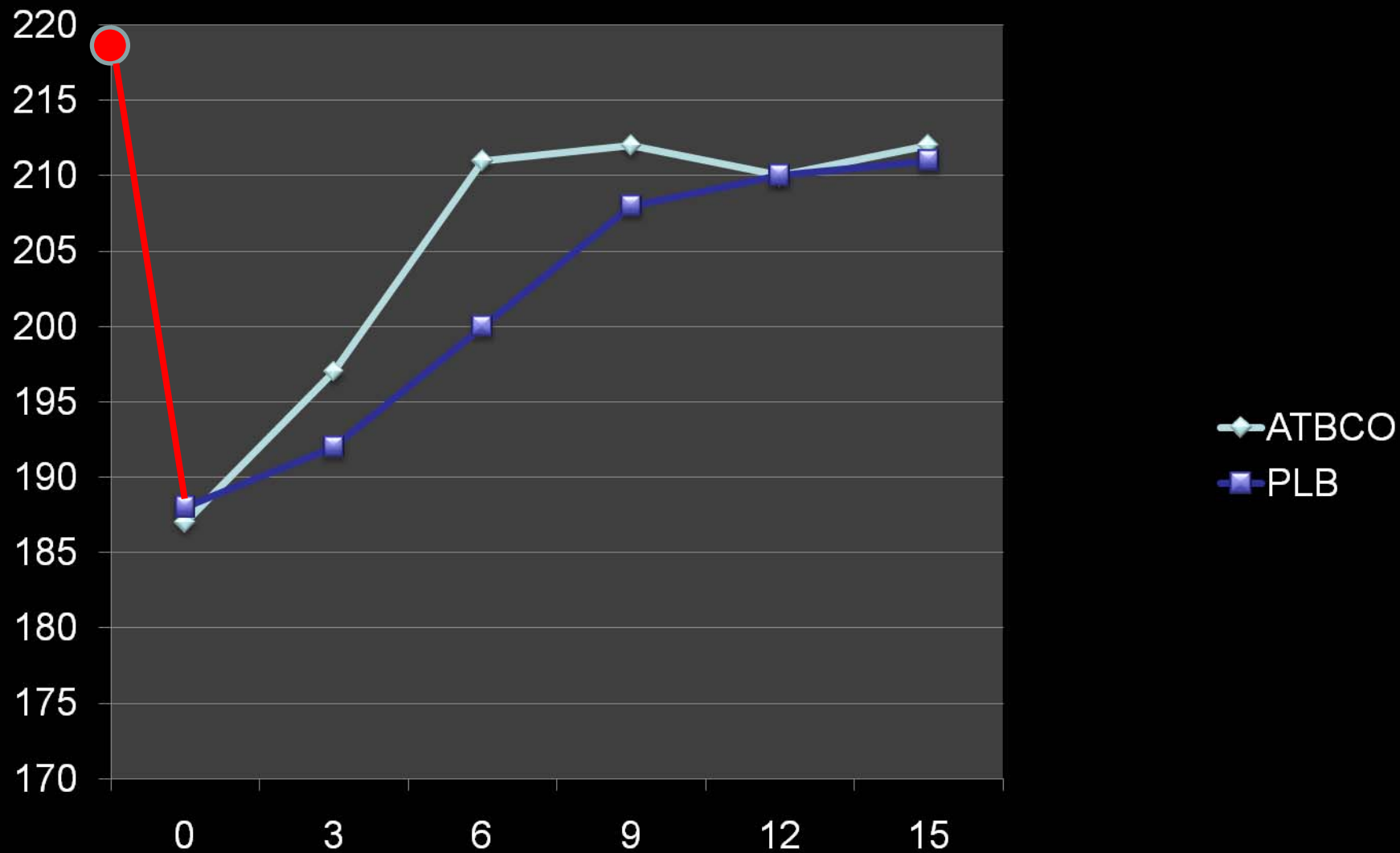
N. R. ANTHONISEN, M.D.; J. MANFREDA, M.D.; C. P. W. WARREN, M.D.; E. S. HERSHFELD, M.D.; G. K. M. HARDING, M.D.; and N. A. NELSON, Ph.D.; Winnipeg, Manitoba, Canada

The effects of broad-spectrum antibiotic and placebo therapy in patients with chronic obstructive pulmonary disease in exacerbation were compared in a randomized, double-blinded, crossover trial. Exacerbations were defined in terms of increased dyspnea, sputum production, and sputum purulence. Exacerbations were followed at 3-day intervals by home visits, and those that resolved in 21 days were designated treatment successes. Treatment failures included exacerbations in which symptoms did not resolve but no intervention was necessary, and those in which the patient's condition deteriorated so that intervention was necessary. Over 3.5 years in 173 patients, 362 exacerbations were treated, 180 with placebo and 182 with antibiotic. The success rate with placebo was 55% and with antibiotic 68%. The rate of failure with deterioration was 19% with placebo and 10% with antibiotic. There was a significant benefit associated with antibiotic. Peak flow recovered more rapidly with antibiotic treatment than with placebo. Side



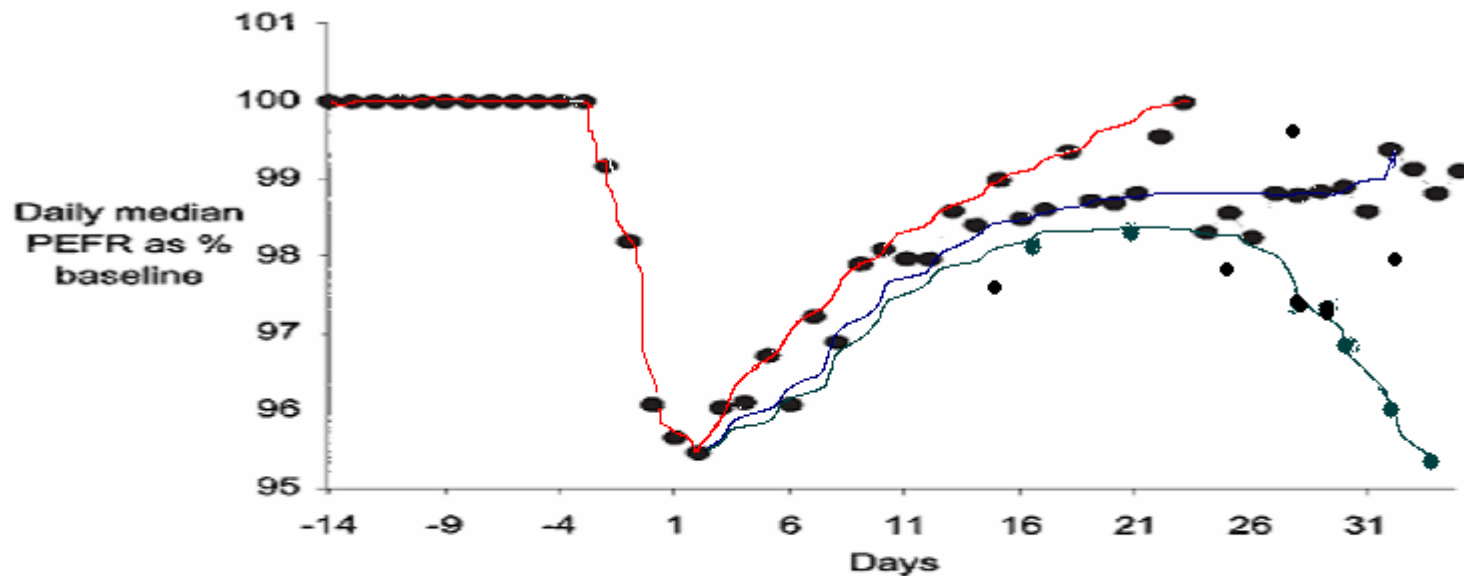
# Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease

N. R. ANTHONISEN, M.D.; J. MANFREDA, M.D.; C. P. W. WARREN, M.D.; E. S. HERSHFIELD, G. K. M. HARDING, M.D.; and N. A. NELSON, Ph.D.; Winnipeg, Manitoba, Canada












# PERDIDA DE FUNCIÓN PULMONAR

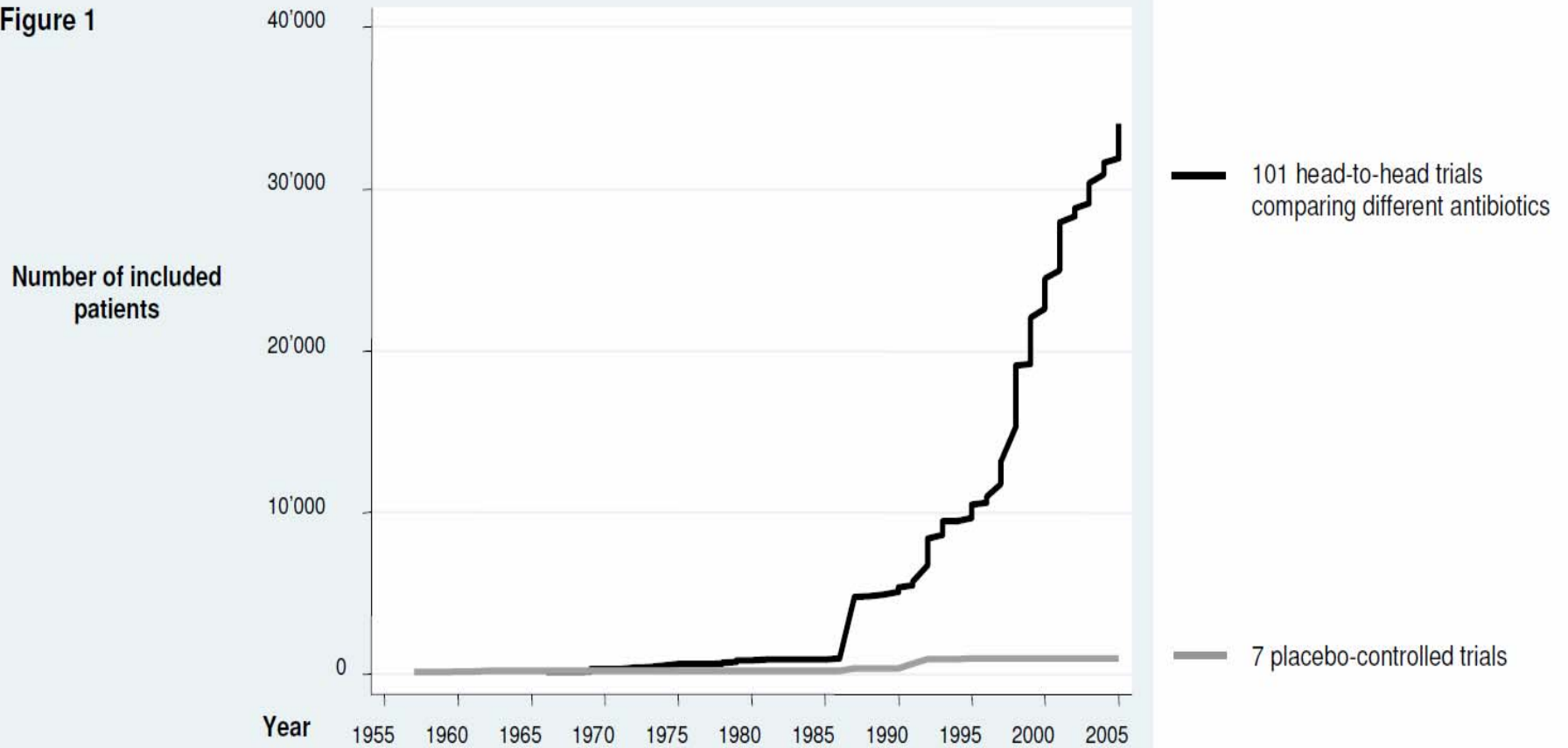


*Figure 3.* Median peak flow expressed as a percentage of baseline peak flow from 14 d before, to 35 d after onset of exacerbation for 504 exacerbations in 91 patients.

# ALGUNOS METAANÁLISIS SOBRE EL USO DE ANTIBIÓTICOS VS. PLACEBO EN LA EPOC

- 1.-Saint S. Antibiotics in COPD. A meta-analysis. JAMA 1995. 
- 2.-Snow V. Evidence Base for Management of Acute Exacerbations of COPD. Annals Inter Med 2001. 
- 3.-McCorry DC. Management of Acute Exacerbations of COPD. A Summary and Appraisal of Published Evidence. Chest 2001. 
- 4.-Ram FVF. Antibióticos para las exacerbaciones de la EPOC. Cochrane 2005. 
- 5.-Puhan M. Exacerbations of COPD: when are antibiotics indicated? A systematic review. Resp Res 2007.  **GRAVES**
- 6.-Quon BS. Contemporary Management of Acute Exacerbations of COPD.A Systematic Review and Metaanalysis. Chest 2008. 
- 7.-Puhan M. Where is the supporting evidence for treating mild to moderate COPD with antibiotics? A systematic review. BMC 2008. 

**Figure 1**



**Number of trials**

Placebo-controlled	0	2	3	3	3	3	3	4	7	7	7
Head-to-head	0	0	0	5	9	13	14	22	43	76	101

# Contemporary Management of Acute Exacerbations of COPD\*

## A Systematic Review and Metaanalysis

CHEST 2008; 133:756-766

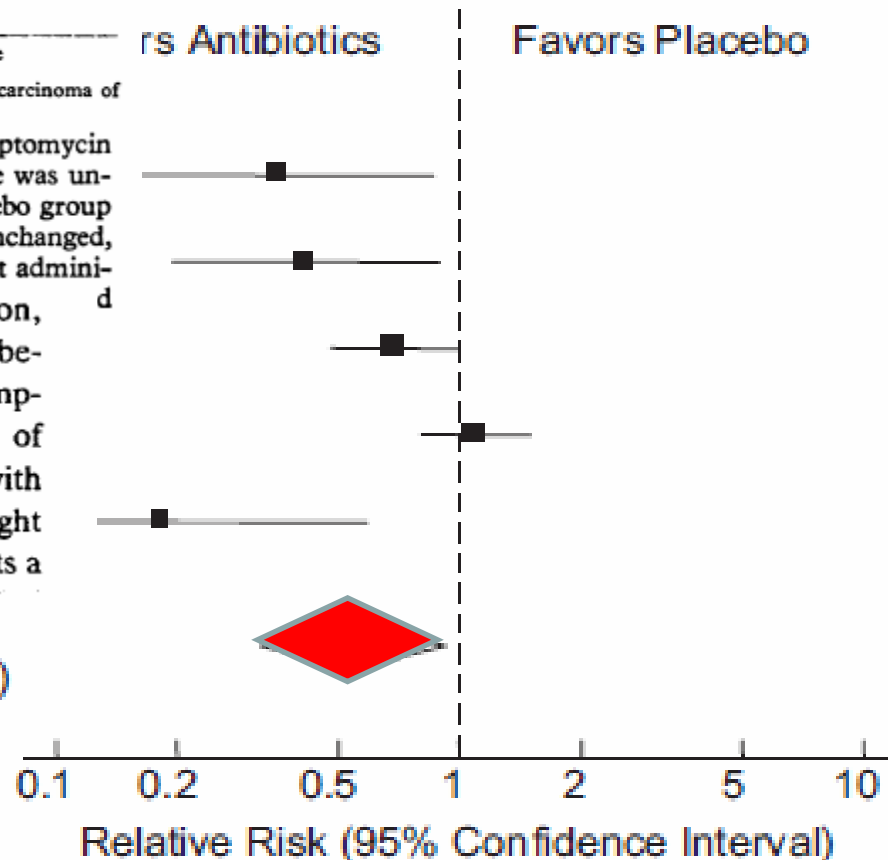
TABLE IV.—Causes of Death

Treatment Group	Length of Stay Before Death	Cause
Ampicillin	9 days	Haematemesis and respiratory failure
Control	7 days	Pulmonary artery thrombosis
"	23 days	Myocardial infarction (symptomless carcinoma of stomach)
"	3 days	Respiratory failure

Among the group treated with penicillin and streptomycin 10 improved on clinical assessment, in three their state was unchanged, and two deteriorated; one died. In the placebo group three patients improved, in three their state was unchanged, and nine deteriorated, some severely despite the prompt admini-

Based on this definition, no statistically significant difference was found between amoxicillin and placebo. Resolution of symptoms occurred in a significantly higher number of amoxicillin treated patients (25/132) compared with placebo (13/136). We do not feel that this slight improvement in the course of the disease warrants a routine use of antibiotics.

(RR,0.54; 95% CI, 0.32-0.92)





# Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial

Lancet 2001; 358: 2020–25

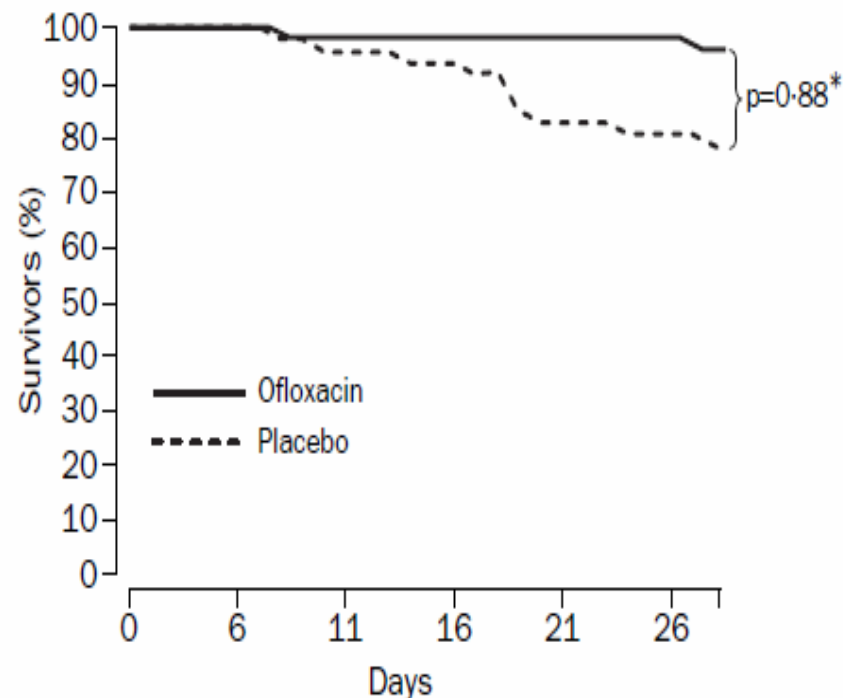
Semir Noura, Soudani Marghli, Makhlouf Belghith, Lamia Besbes, Souheil Elatrous, Fekri Abroug

	<b>Ofloxacin (n=47)</b>	<b>Placebo (n=46)</b>	<b>Absolute risk reduction (95% CI)</b>	<b>p</b>
<b>Primary outcome</b>				
Death				
ICU	2 (4%)	8 (17%)	13.2 (0.8 to 25.6)	0.05
Hospital	2 (4%)	10 (22%)	17.5 (4.3 to 30.7)	0.01
Need for additional antibiotics	3 (6%)	16 (35%)	28.4 (12.9 to 43.9)	0.0006
Combined events	5 (11%)	26 (57%)	45.9 (29.1 to 62.7)	<0.0001
<b>Secondary outcome</b>				
Duration of mechanical ventilation (days)	6.4 (3.1)	10.6 (5.1)	4.2 (2.5 to 5.9)	0.04
Duration of stay (days)				
ICU	9.4 (5.2)	14.5 (6.0)	5.1 (3.9 to 6.3)	0.02
Hospital	14.9 (7.4)	24.5 (8.5)	9.6 (3.4 to 12.8)	0.01

# Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial

Lancet 2001; 358: 2020–25

Semir Noura, Soudani Marghli, Makhlouf Belghith, Lamia Besbes, Souheil Elatrous, Fekri Abroug

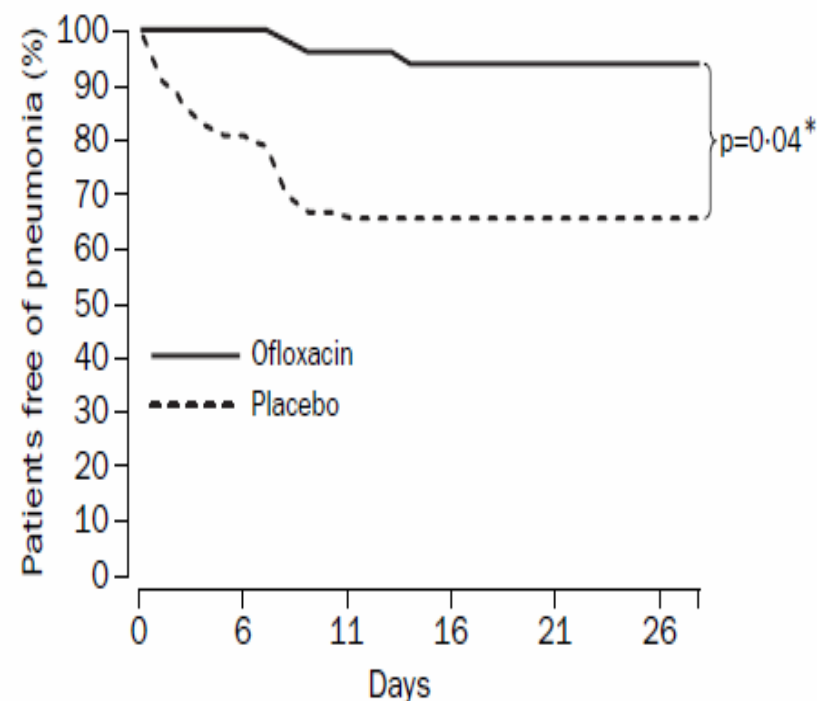


## Number of patients

Ofloxacin	47	47	46	46	46	46
Placebo	46	46	44	43	38	37

Figure 2: Kaplan-Meier survival analysis of deaths in patients given ofloxacin or placebo

\*By log-rank test.



## Number of patients

Ofloxacin	47	47	45	44	44	44
Placebo	46	37	30	30	30	30

Figure 3: Kaplan-Meier survival analysis showing pneumonia-free intervals in patients on ofloxacin or placebo

\*By log-rank test.

- Para una patología tan frecuente como las exacerbaciones de EPOC, la evidencia de estudios randomizados es sorprendentemente escasa. Sólo se han analizado 917 pacientes y todos menos uno de estos estudios son anteriores a 1992.

– *Rothberg MB. Antibiotic Therapy and treatment failure in patients hospitalized for acute exacerbation of COPD. JAMA 2010*



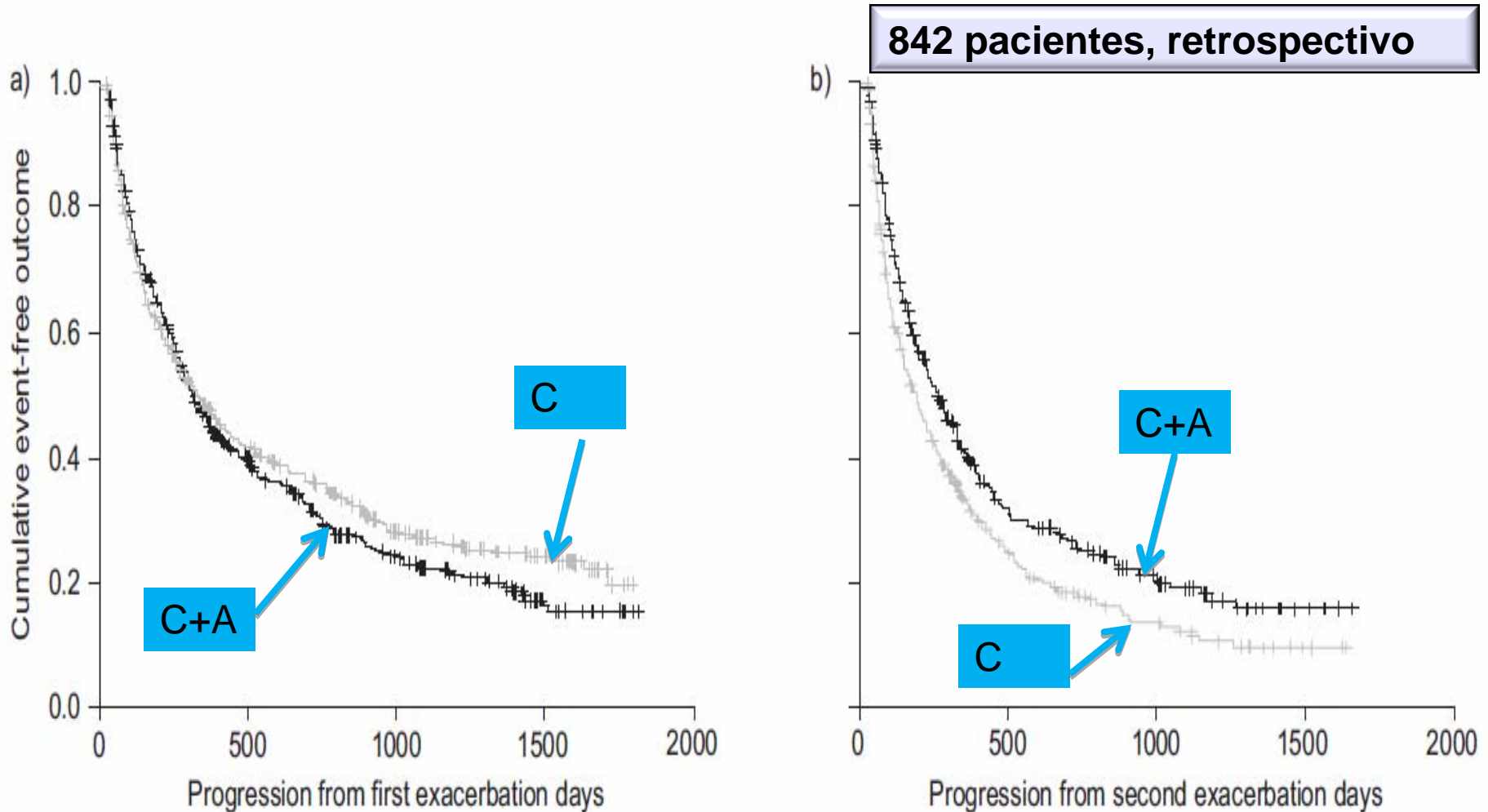
Ultimos estudios





# Reduced risk of next exacerbation and mortality associated with antibiotic use in COPD

B.M. Roede<sup>\*,#</sup>, P. Bresser<sup>†</sup>, J.M. Prins<sup>\*</sup>, F. Schellevis<sup>+,5</sup>,  
T.J.M. Verheij<sup>‡</sup> and P.J.E. Bindels<sup>#</sup>



## Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Michael B. Rothberg; Penelope S. Pekow; Maureen Lahti; et al.

*JAMA*. 2010;303(20):2035-2042 (doi:10.1001/jama.2010.672)

These 2 findings, that all patient groups seemed to benefit from therapy and that harms were minimal, support the notion that all patients hospitalized with acute exacerbations of COPD should be prescribed antibiotics.

# NUEVOS ESTUDIOS SOBRE EL USO DE ANTIBIÓTICOS EAEPOC 2008

NCT00495586 Amox/clv vs. amoxicilina ambulatorios

NCT00170222- Doxiciclina vs placebo.

NCT00190437 - Amox/clav en pacientes intubados //

NCT00255983 Faropenem vs. Pb bronquitis crónica

PULSE Moxifloxacino vs. placebo intermitente

# CHEST<sup>®</sup>

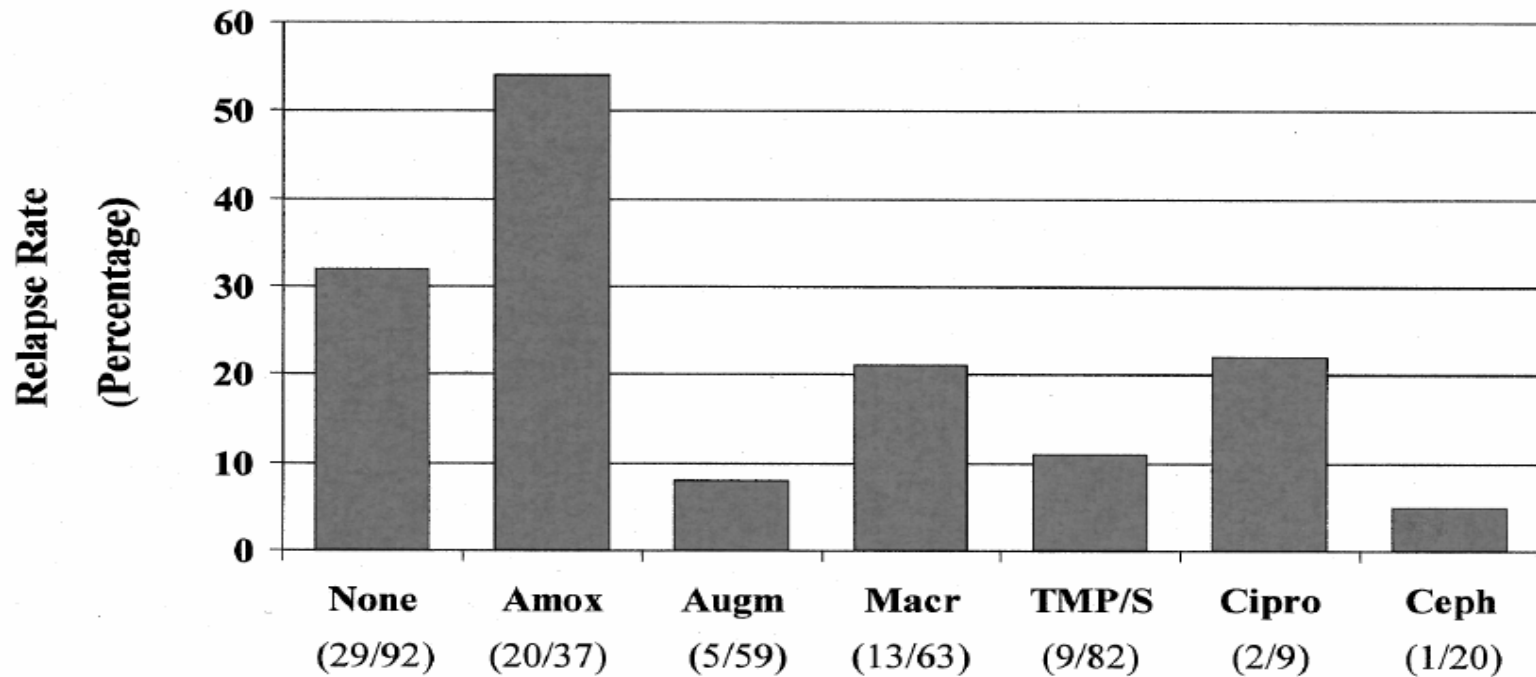
Official publication of the American College of Chest Physicians

CHEST  
ONLINE

## Antibiotics Are Associated With Lower Relapse Rates in Outpatients With Acute Exacerbations of COPD\*

Sandra G. Adams, Jairo Melo, Michael Luther and Antonio Anzueto

*Chest* 2000;117:1345-1352



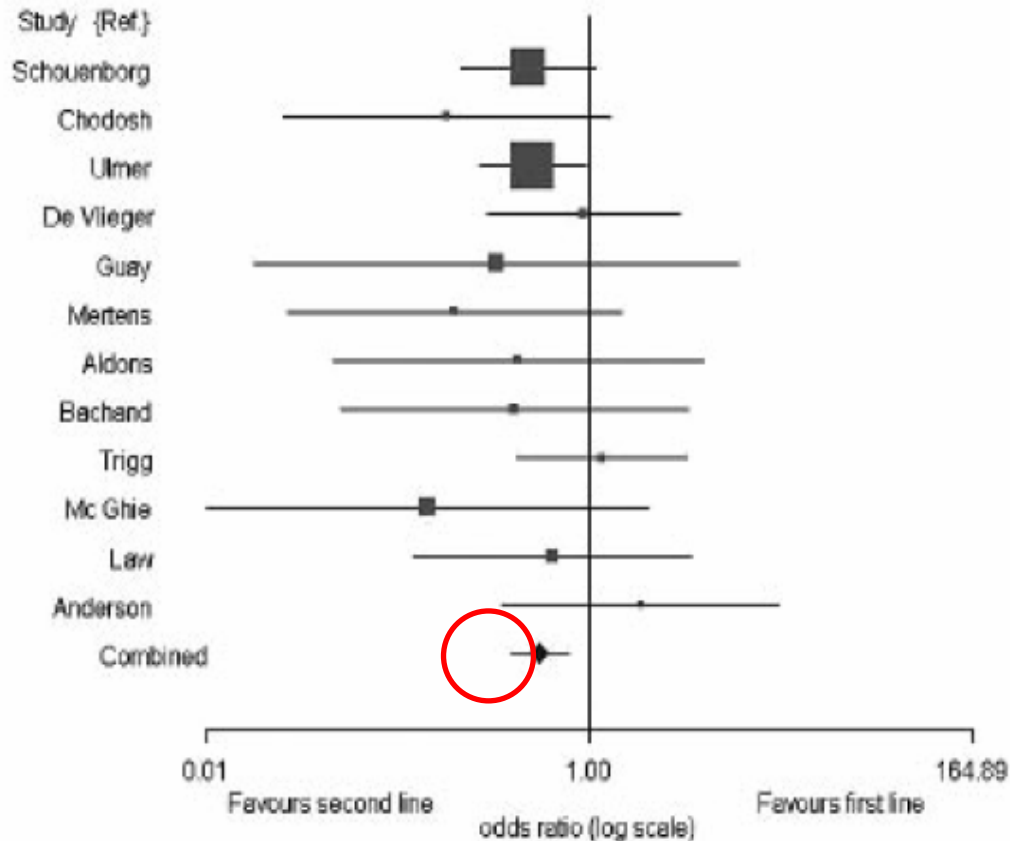


# Comparison of First-Line With Second-Line Antibiotics for Acute Exacerbations of Chronic Bronchitis\*

George Dimopoulos, Ilias I. Siempos, Ioanna P. Korbila, Katerina G. Manta and Matthew E. Falagas

A

(CHEST 2007; 132:447-455)



Amoxicilina  
TMP-SMZ  
Doxiciclina

Amoxy/Clav.  
Macrólidos  
2<sup>a</sup> Cefalosporinas  
3<sup>a</sup> Cefalosporinas  
Quinolonas

# Efficacy of amoxicillin versus amoxicillin/clavulanate in acute exacerbations of chronic pulmonary obstructive disease in primary care

International Journal of COPD 2009:4 45–53

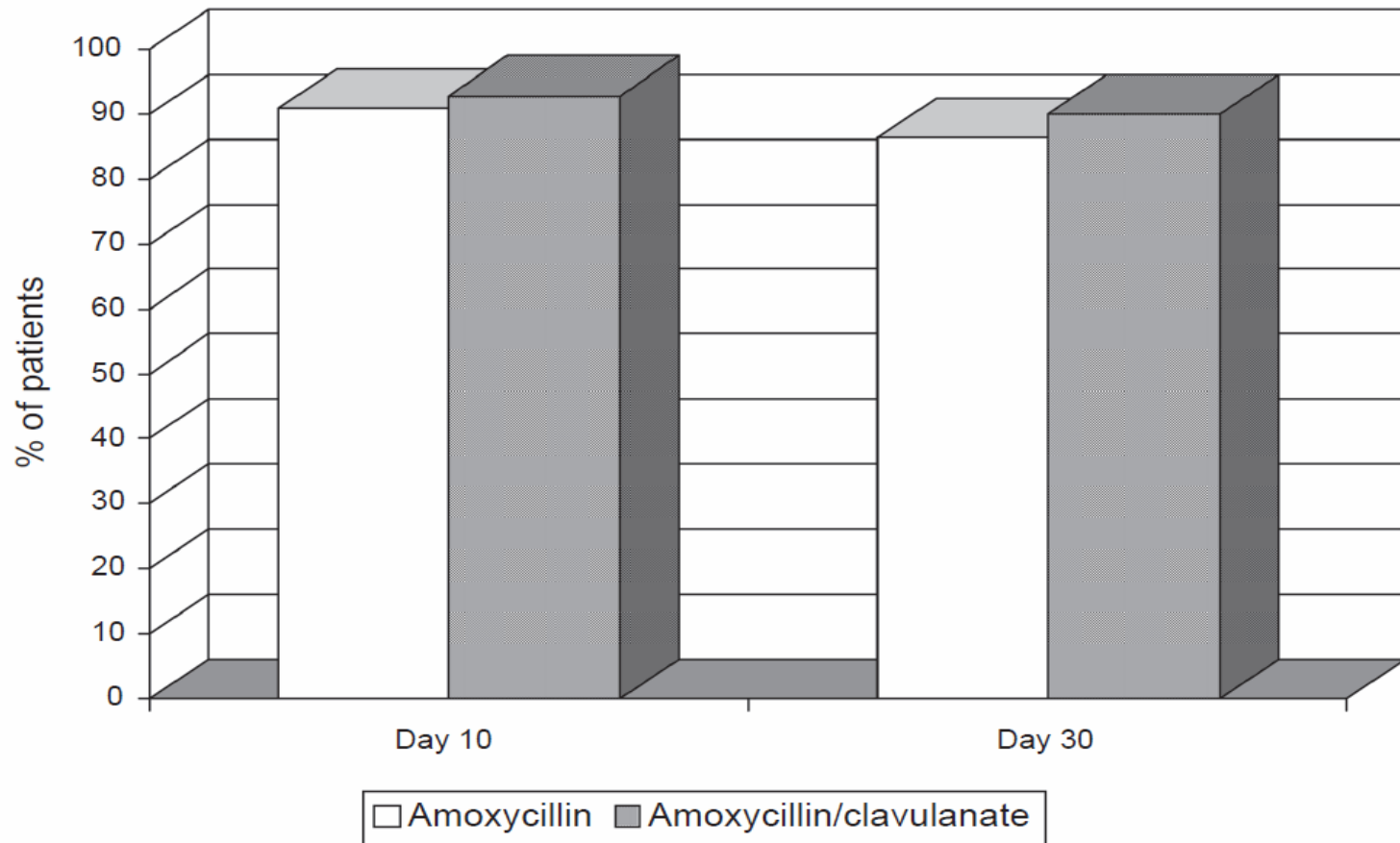


Figure 2 Clinical cure at days 10 and 30 in the evaluable patients with COPD exacerbation.

# Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Johannes M. A. Daniels<sup>1</sup>, Dominic Snijders<sup>1</sup>, Casper S. de Graaff<sup>1</sup>, Fer Vlasplolder<sup>2</sup>, Henk M. Jansen<sup>3</sup>, and Wim G. Boersma<sup>1</sup>

Am J Respir Crit Care Med Vol 181. pp 150–157, 2010

Estudio randomizado, doble ciego en pacientes hospitalizados por exacerbación de EPOC

Brazos: doxiciclina 200 mg /7 días vs.placebo. Todos corticoides sistémicos.

223 pacientes con 265 exacerbaciones.

Edad media 73 años

FEV1 medio 43% del teórico

# Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Johannes M. A. Daniels<sup>1</sup>, Dominic Snijders<sup>1</sup>, Casper S. de Graaff<sup>1</sup>, Fer Vlaspolder<sup>2</sup>, Henk M. Jansen<sup>3</sup>, and Wim G. Boersma<sup>1</sup>

Am J Respir Crit Care Med Vol 181. pp 150–157, 2010

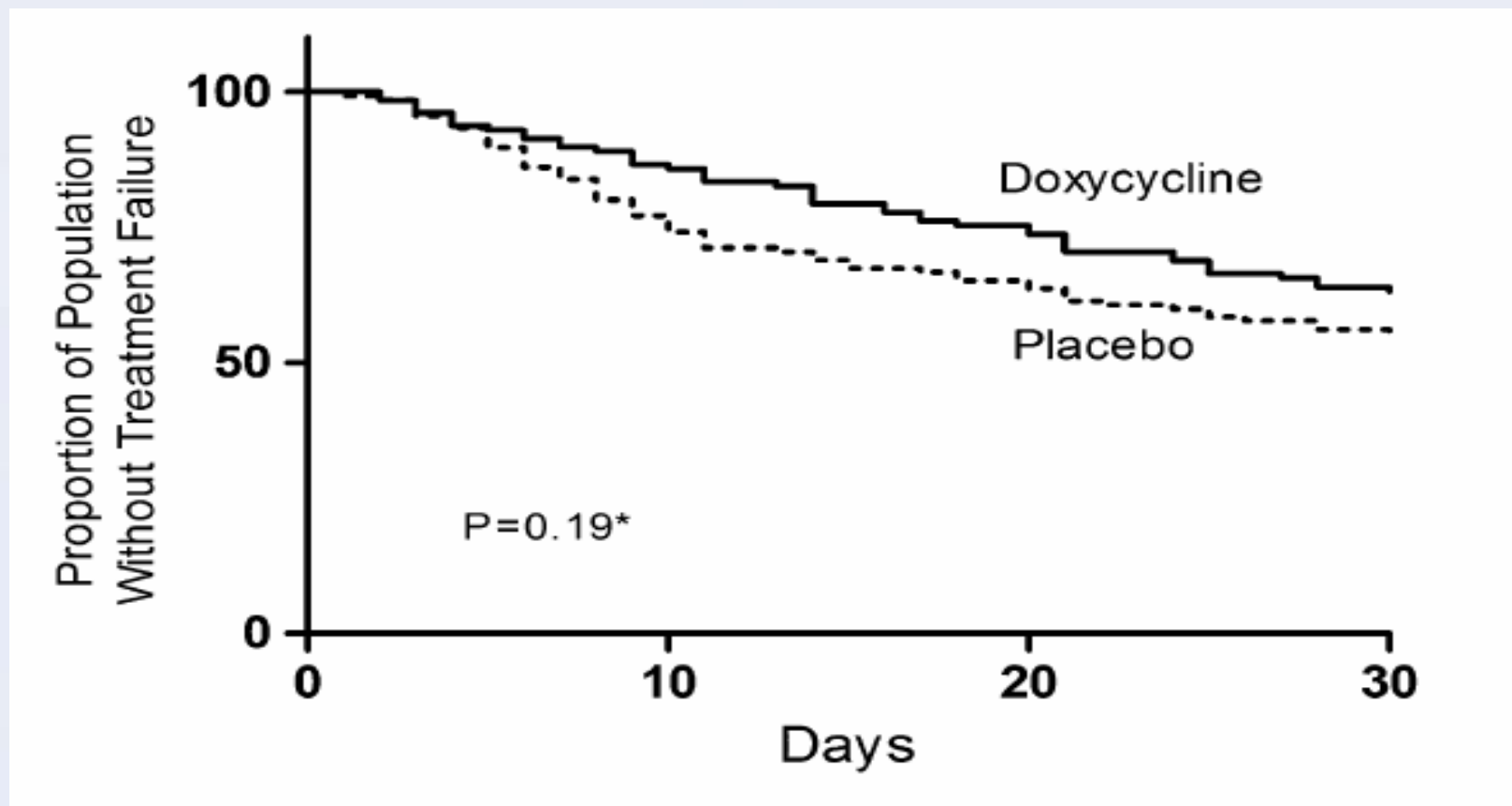
	<b>MEJORI A DIA 10</b>	<b>CURA 10</b>	<b>MEJORIA 30</b>	<b>CURA 30</b>	<b>CAMBIO ANTB</b>	<b>SINT</b>
<b>DOXI</b>	80%	67%	61%	51%	15%	-10
<b>PB</b>	69%	51%	53%	41%	28%	-6
<b>P</b>	<b>0.05</b>	<b>0.01</b>	<b>0,32</b>	<b>0.15</b>	<b>0.01</b>	<b>0.03</b>



# Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Johannes M. A. Daniels<sup>1</sup>, Dominic Snijders<sup>1</sup>, Casper S. de Graaff<sup>1</sup>, Fer Vlasplolder<sup>2</sup>, Henk M. Jansen<sup>3</sup>, and Wim G. Boersma<sup>1</sup>

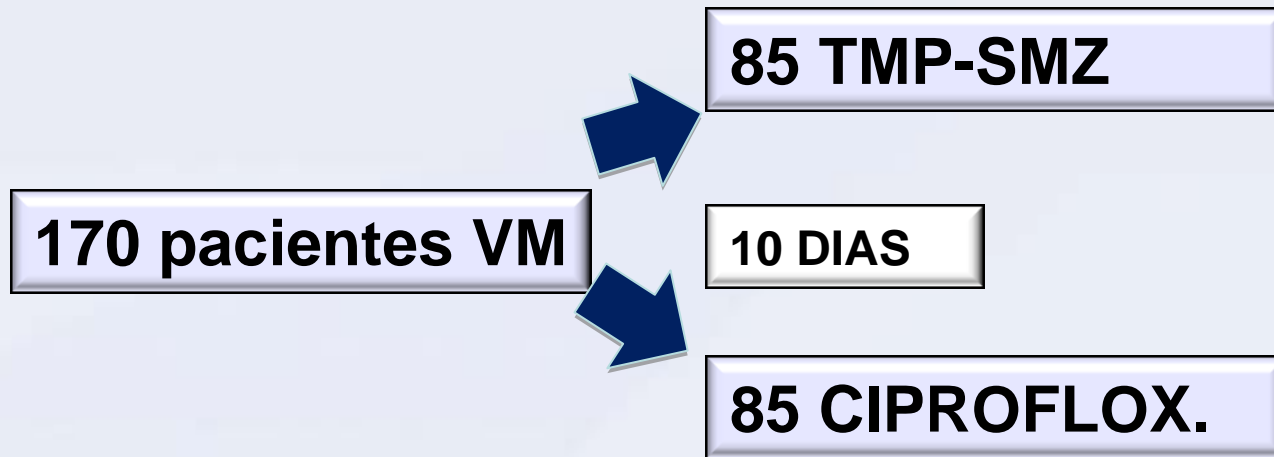
Am J Respir Crit Care Med Vol 181. pp 150–157, 2010



# Standard versus Newer Antibacterial Agents in the Treatment of Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Randomized Trial of Trimethoprim-Sulfamethoxazole versus Ciprofloxacin

Clinical Infectious Diseases 2010;51(2):143-149

Semir Nouira,<sup>1</sup> Soudani Marghli,<sup>1,3</sup> Lamia Besbes,<sup>2</sup> Riadh Boukef,<sup>1</sup> Monia Daami,<sup>2</sup> Nouredine Nciri,<sup>2</sup> Souheil Elatrous,<sup>3</sup> and Fekri Abroug<sup>2</sup>



No hay diferencias en mortalidad, tiempo de VM, cambio de antibiótico, ni tiempo hasta exacerbación posterior

RESEARCH

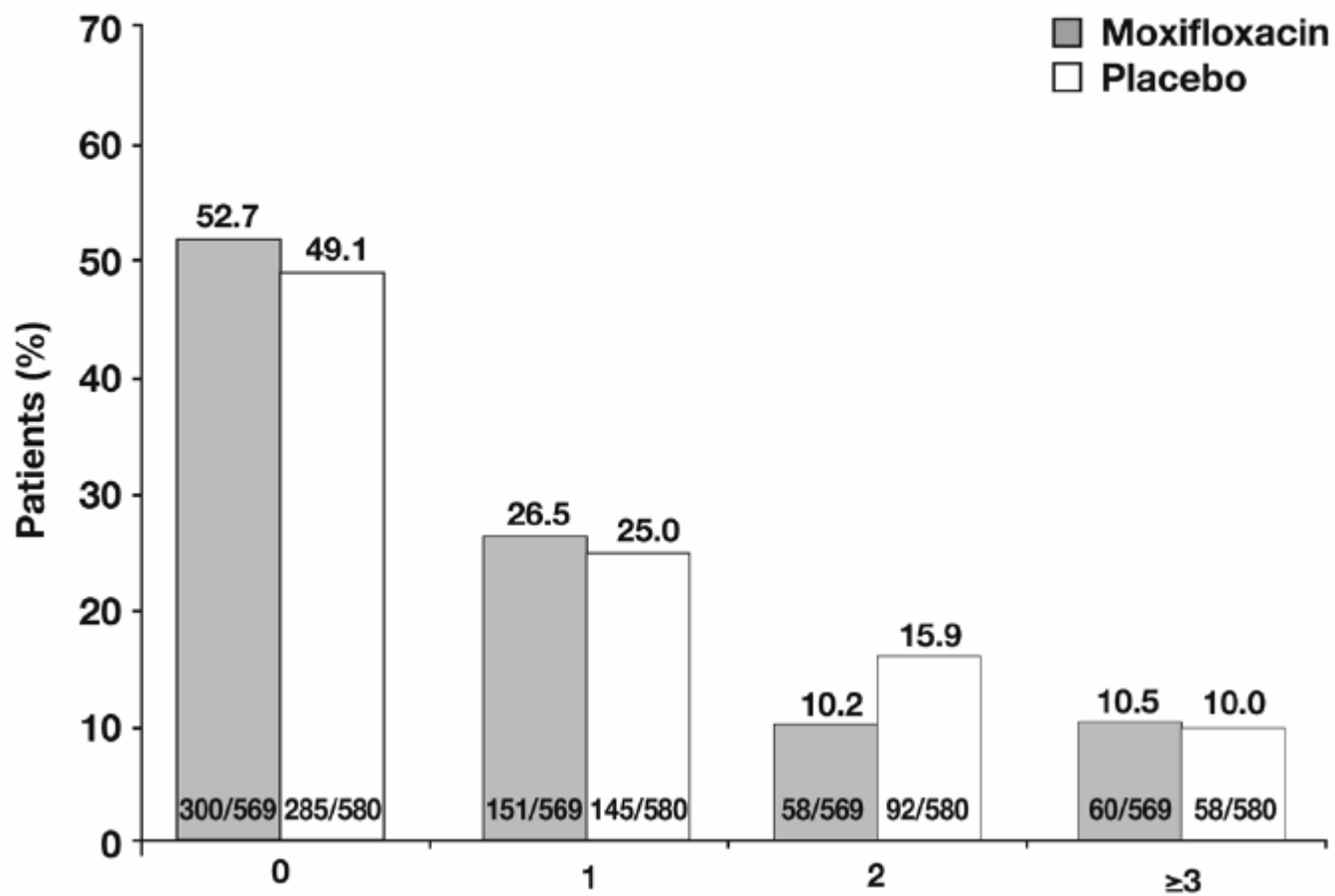
Open Access

## 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

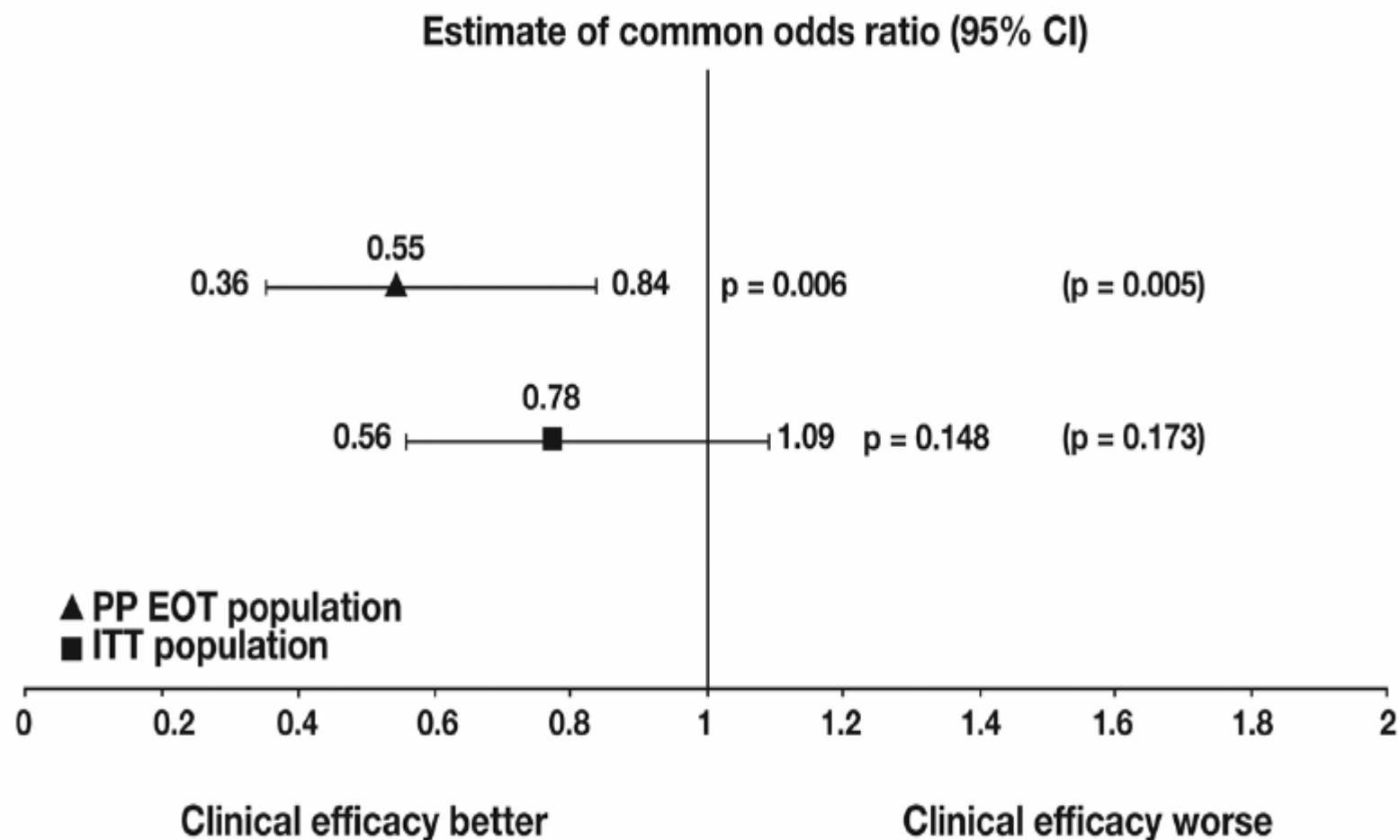
- Pacientes con EPOC estable, con criterios de bronquitis crónica y al menos 2 exacerbaciones en el año previo.
- Randomizados a :
  - (573) Moxifloxacino, 5 días cada 8 semanas durante 48.
  - (584) Placebo

### (B) ITT population





## (B) Mucopurulent/purulent sputum subgroup



- El uso de Moxifloxacino redujo las exacerbaciones a 48 semanas.
- Expectoración purulenta al inicio del estudio, (OR de 0,53; IC 0,35-0,82,  $p < 0,004$  y NNT 7).
- No disminuyó el número de hospitalizaciones, la caída de función pulmonar, ni la mortalidad y sólo marginalmente la calidad de vida.
- No se observó desarrollo de resistencias.

# NUEVOS ESTUDIOS SOBRE EL USO DE ANTIBIÓTICOS EAEOC 2010

NCT01091493 Antibiótico en exacerbaciones no purulentas de la EPOC. Doble ciego, controlado con placebo.

NCT00656747 Moxifloxacino vs. Amoxicilina/clavulánico en bronquitis crónica.

NCT00739648 Completed Fase II, prevención de exacerbaciones con levofloxacino inhalado.

# CONCLUSIONES

- En la práctica clínica, los pacientes con EAEPOC y expectoración purulenta reciben tratamiento antibiótico.
- Posiblemente se consoliden otros marcadores, como PCR o procalcitonina para seleccionar los pacientes que más pueden beneficiarse.



# CONCLUSIONES

- A pesar de ser una enfermedad común, la evidencia científica es limitada.
- Los últimos estudios no encuentran diferencias entre antibióticos de 1 y 2 línea. Pero debe tenerse en cuenta el patrón de resistencias en diferentes zonas.
- El uso de antibiótico intermitente disminuye las exacerbaciones en un subgrupo de pacientes.

# XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

## II Congreso Ibérico de Medicina Interna

# OVIEDO

17-20 Noviembre 2010

Auditorio-Palacio de Congresos  
"Príncipe Felipe"

VII Congreso de la Sociedad  
Asturiana de Medicina Interna

 THORAX

## Antibiotics at COPD exacerbations: the debate continues

Jadwiga A Wedzicha

*Thorax* 2008;63;940-942

# GRACIAS