CORSO AGGIORNAMENTO ECM 2018

Tubercolosi e Micobatteriosi Atipiche: un impegno globale

Imbarcadero
Castello Estense
Ferrara
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BPCO e Tubercolosi: un binomio pericoloso

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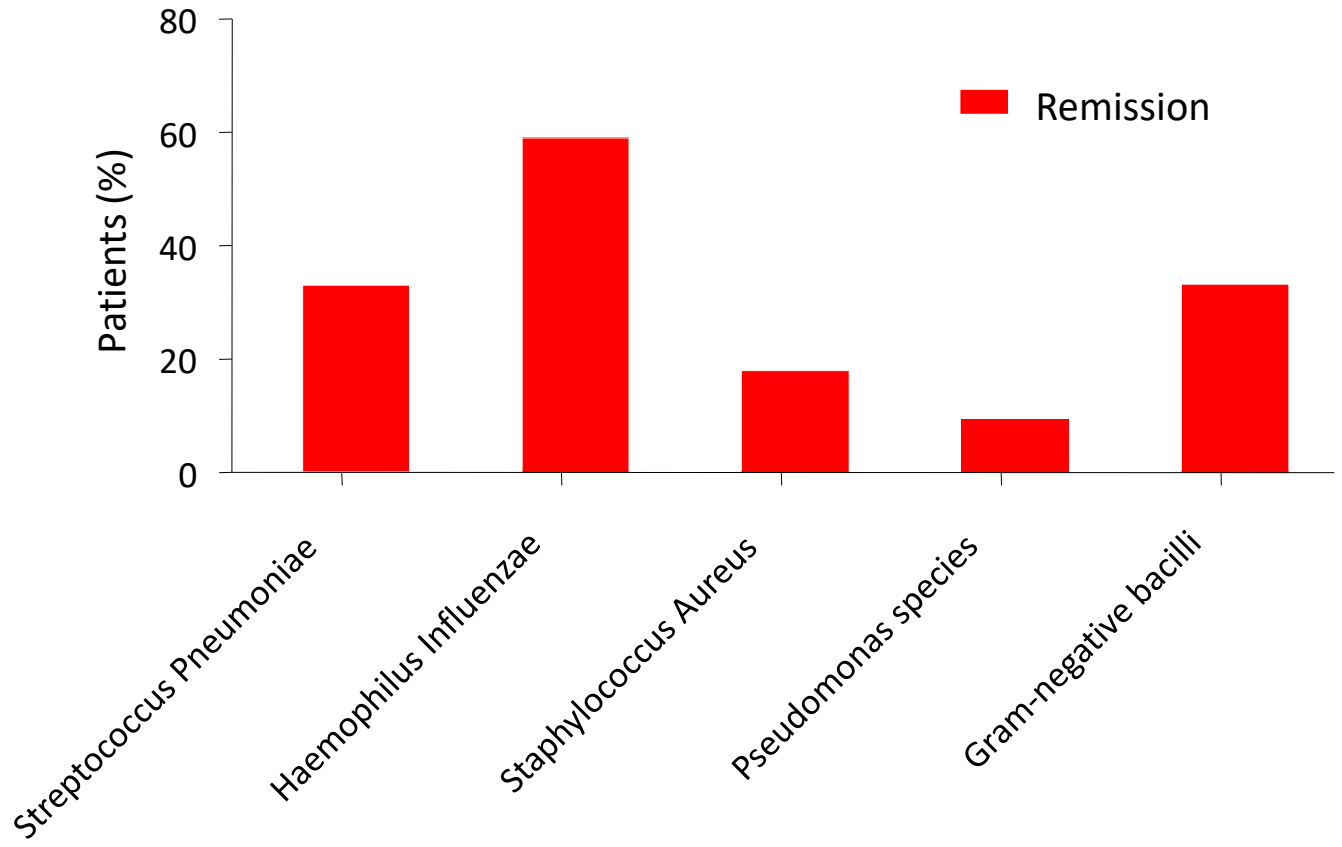
BPCO e Tubercolosi: un binomio pericoloso

- BPCO
- Infezioni in BPCO
- TB (e micobatteri) & BPCO
  - RCTs
  - Studi coorte
- Meccanismi

COPD Definition

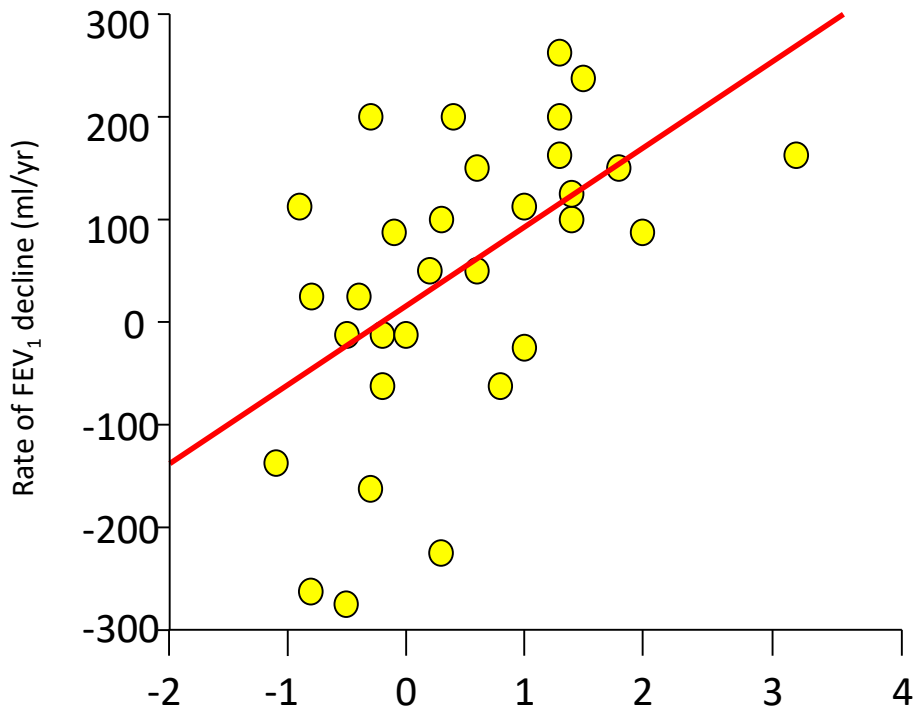
- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is **characterized by persistent respiratory symptoms** and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Role of infections in chronic bronchitis

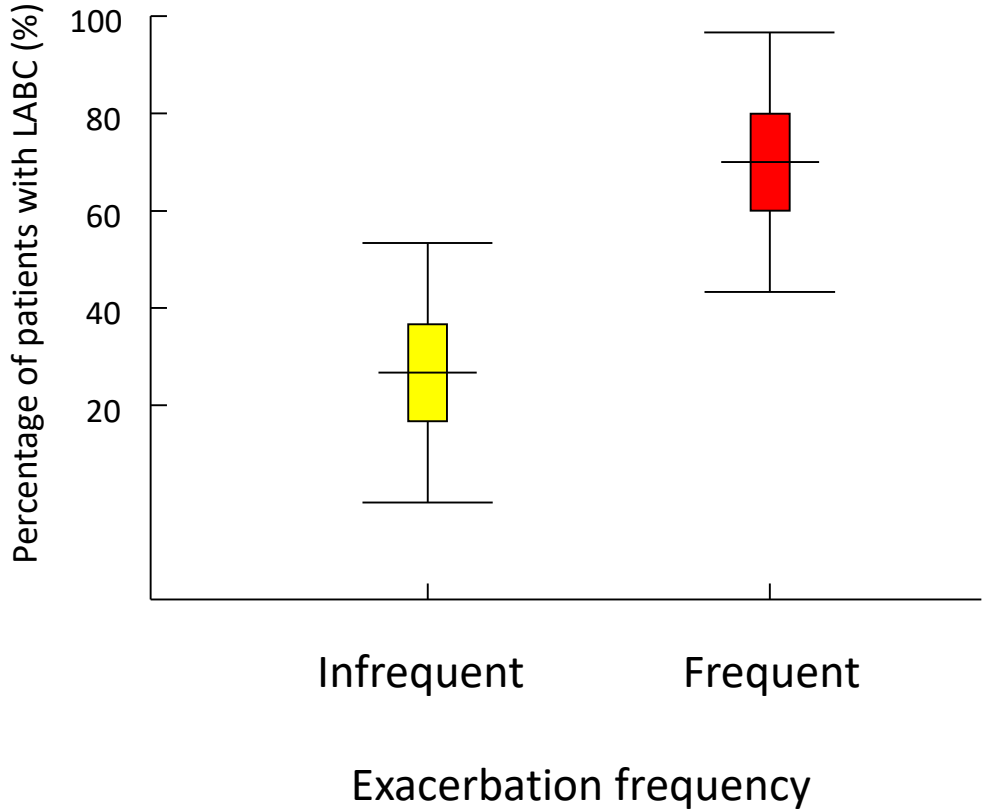


(Gump et al. Am Rev Resp Dis 1976)

Bacterial colonization and COPD

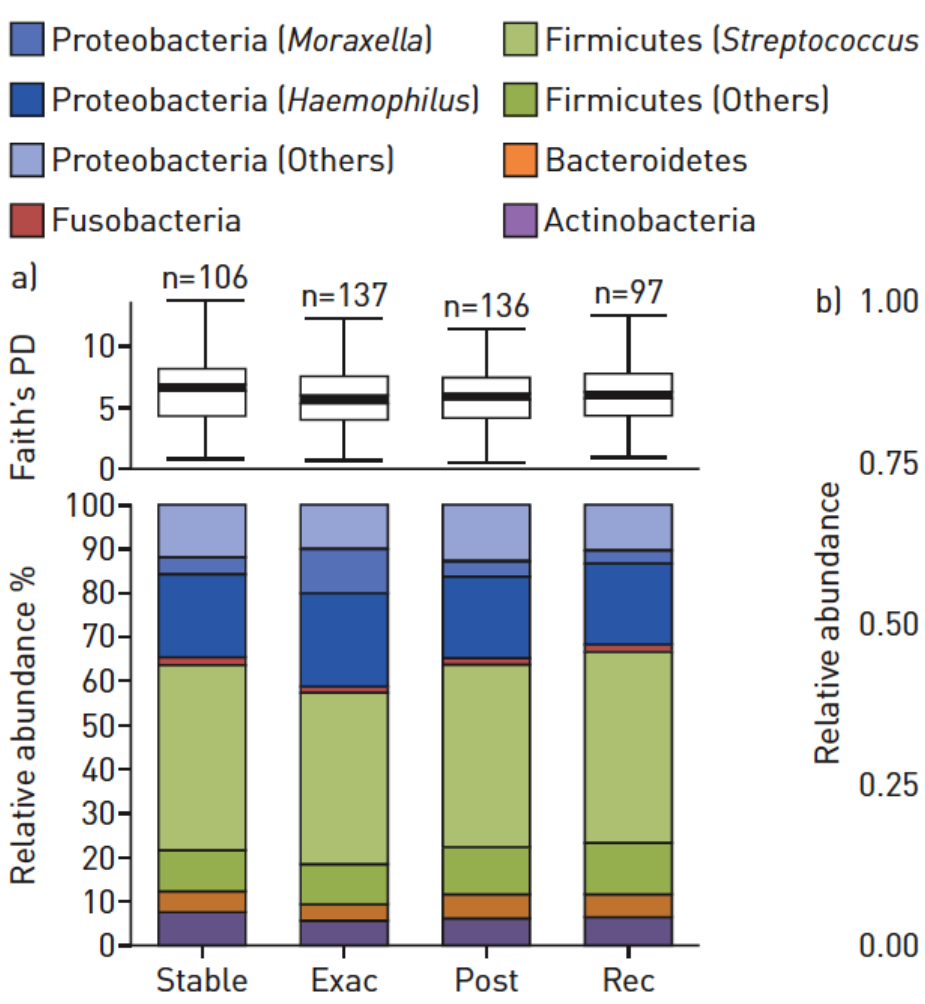


Wilkinson T, AJRCCM 2003

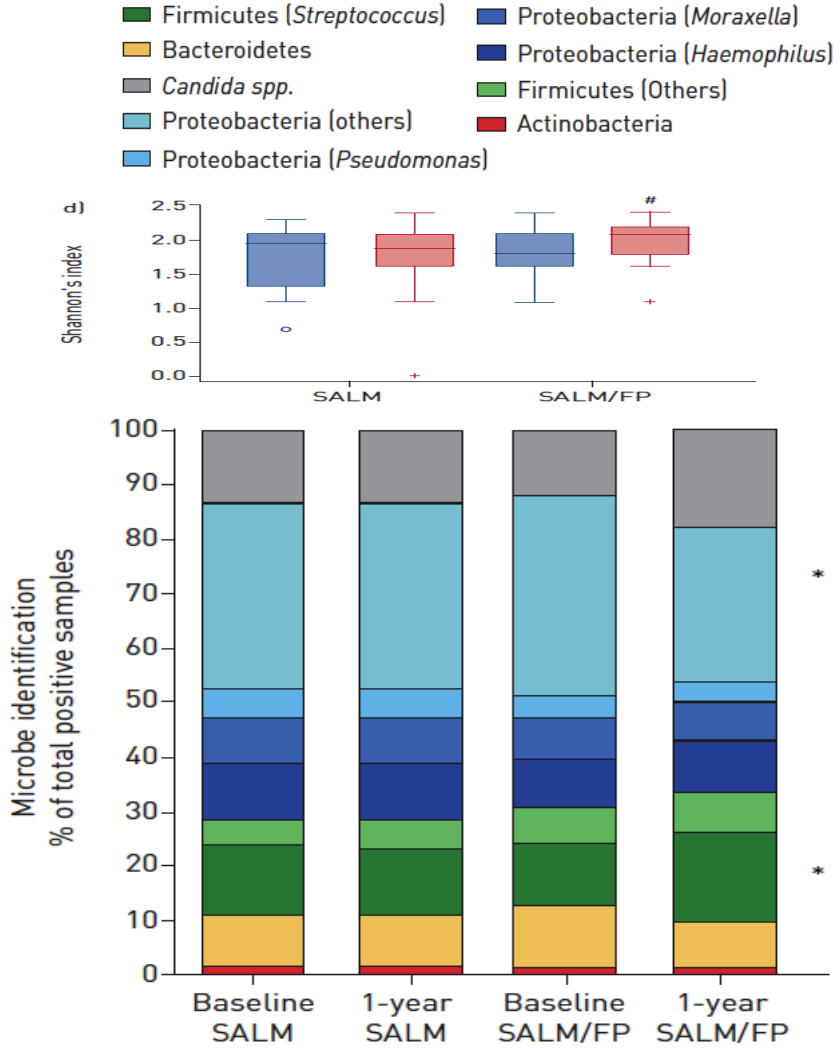


Patel, Thorax 2002

Microbiome in COPD

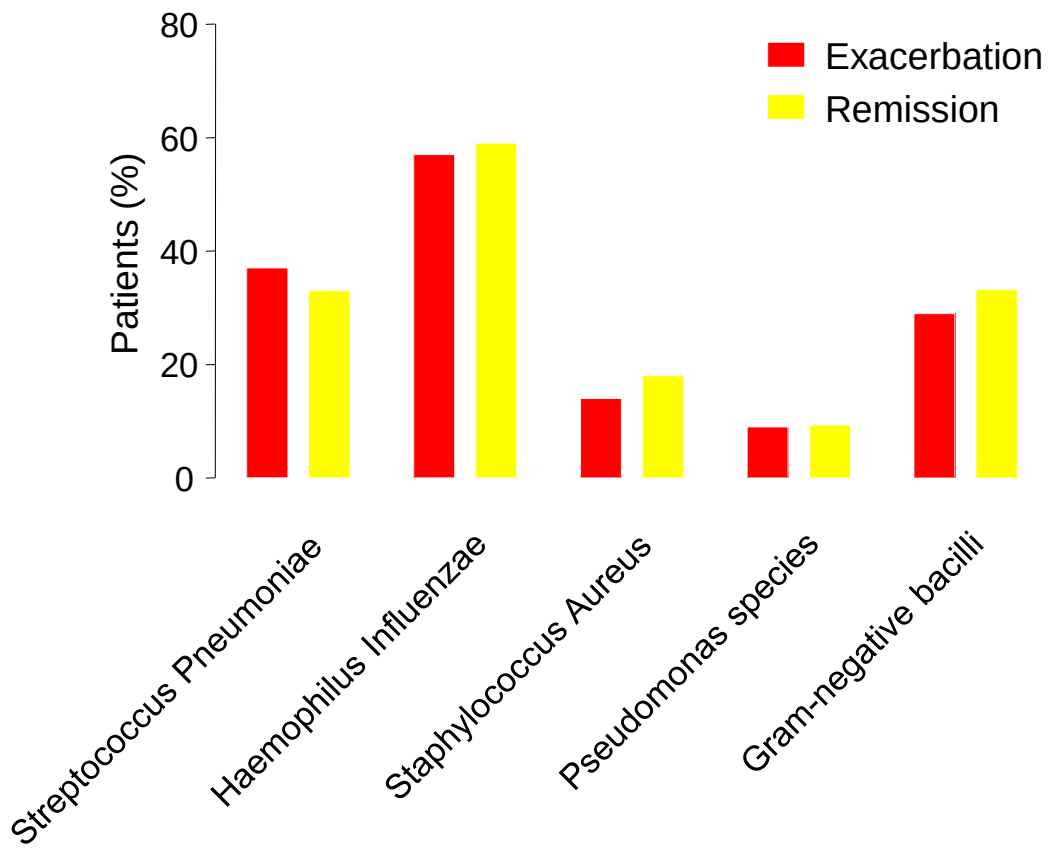


(Wang et al. ERJ 2016)

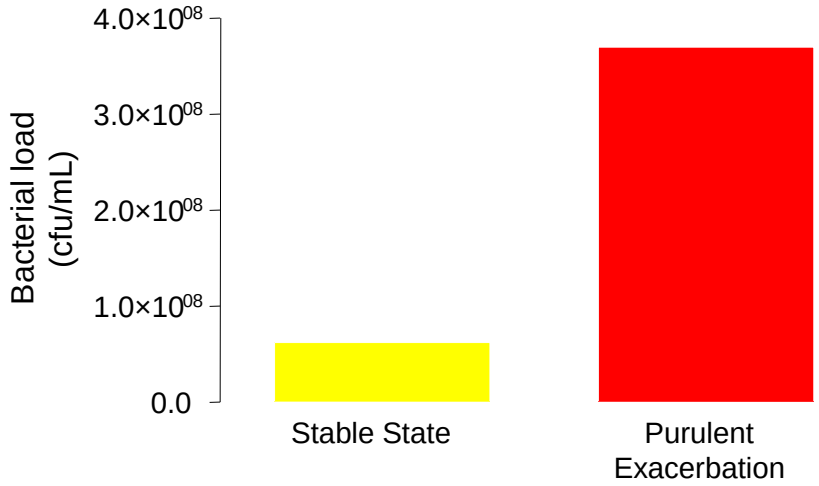


(Contoli, Papi ERJ 2017)

Role of bacterial infections in exacerbations

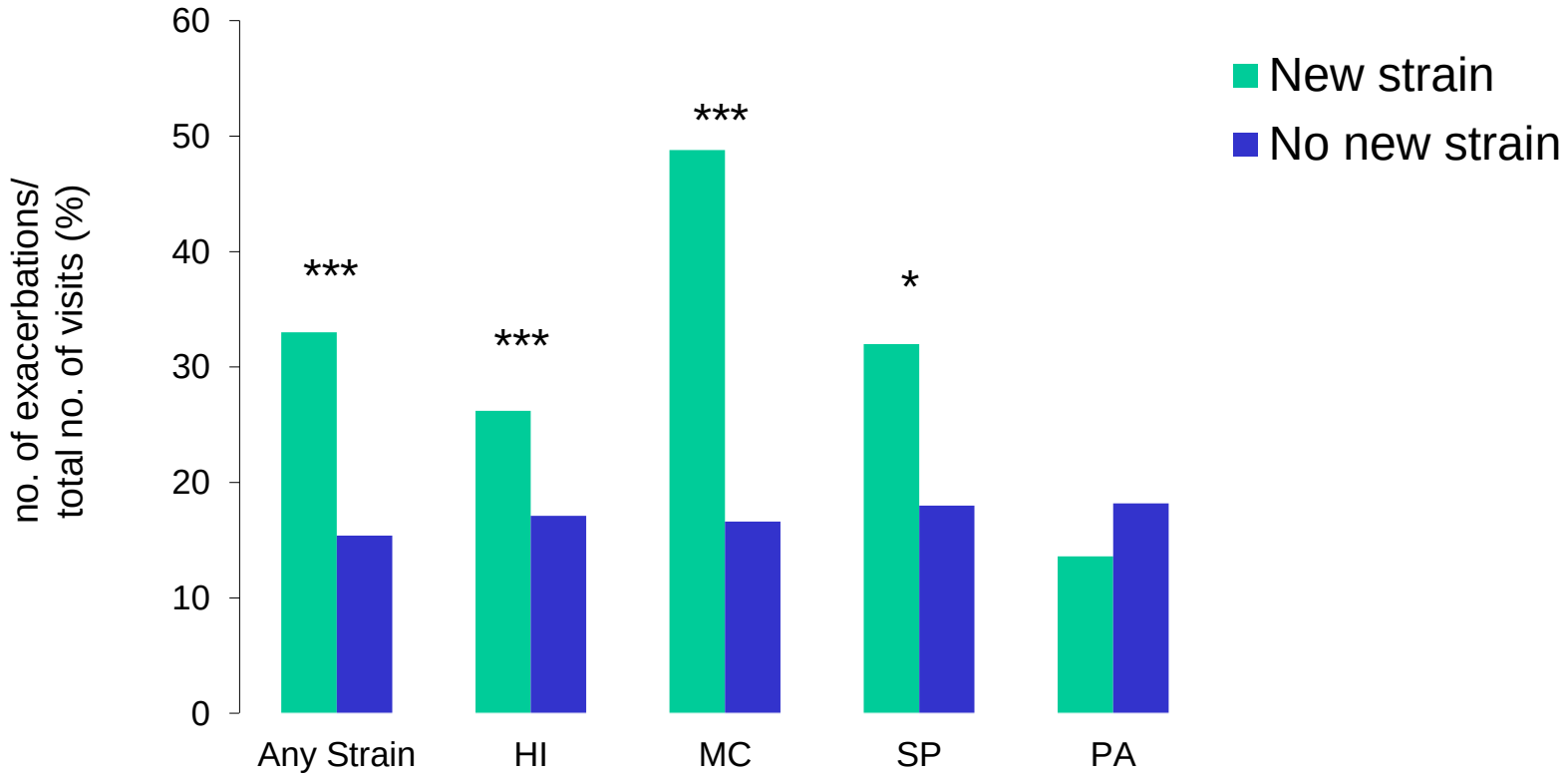


(Gump et al. Am Rev Resp Dis 1976)



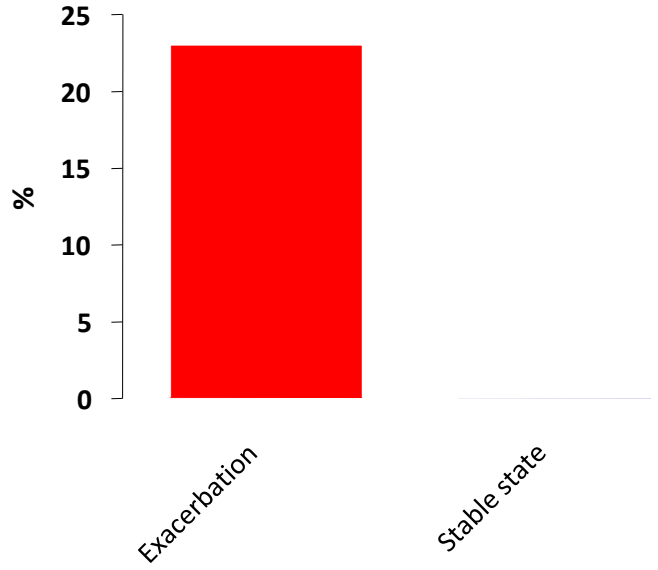
(Stockley R et al. Chest 2000)

New Strains of Bacteria and Exacerbations of COPD

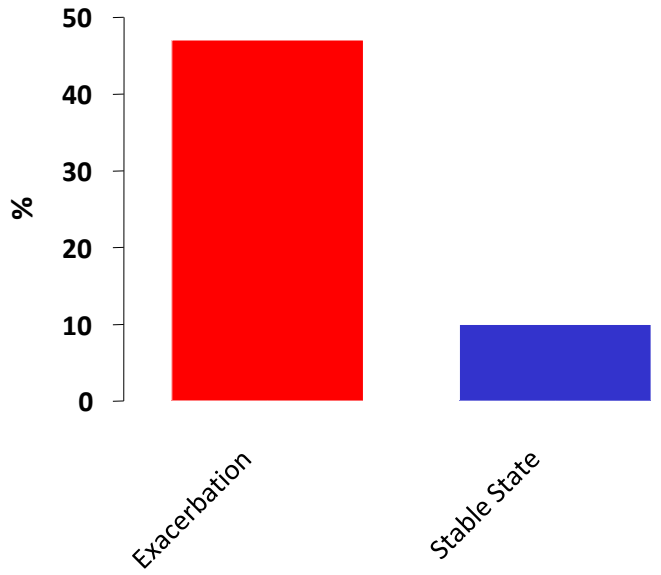


Sethi NEJM 2004

Detection of virus (rhinovirus) in induced sputum at exacerbation of COPD



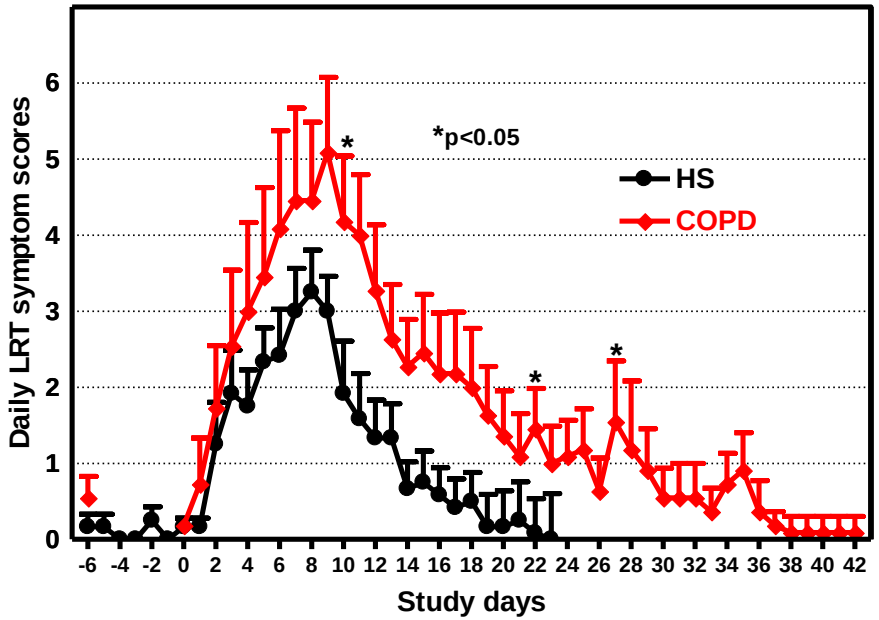
(Seemungal et al. ERJ 2000)

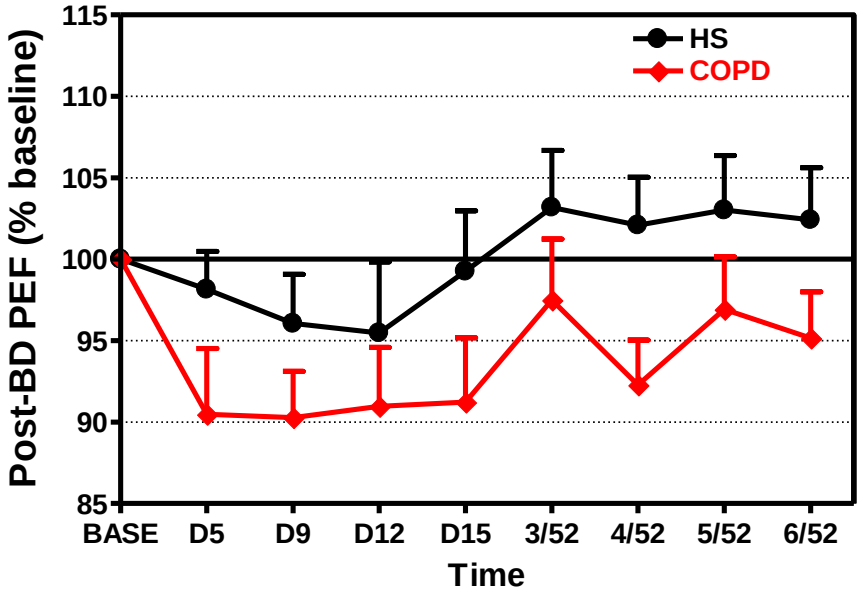


(Rohde G et al. Thorax 2002)

Experimental Rhinovirus Infection as a Human Model of Chronic Obstructive Pulmonary Disease Exacerbation

Patrick Mallia[1,2], Simon D. Message[1,2], Vera Gielen[1], Marco Contoli[1,3], Katrina Gray[1,2], Tatiana Kebadze[1], Julia Aniscenko[1], Vasile Laza-Stanca[1], Michael R. Edwards[1], Louise Slater[1], Alberto Papi[3], Luminita A. Stanciu[1], Onn M. Kon[1,2], Malcolm Johnson[4], and Sebastian L. Johnston[1,2]

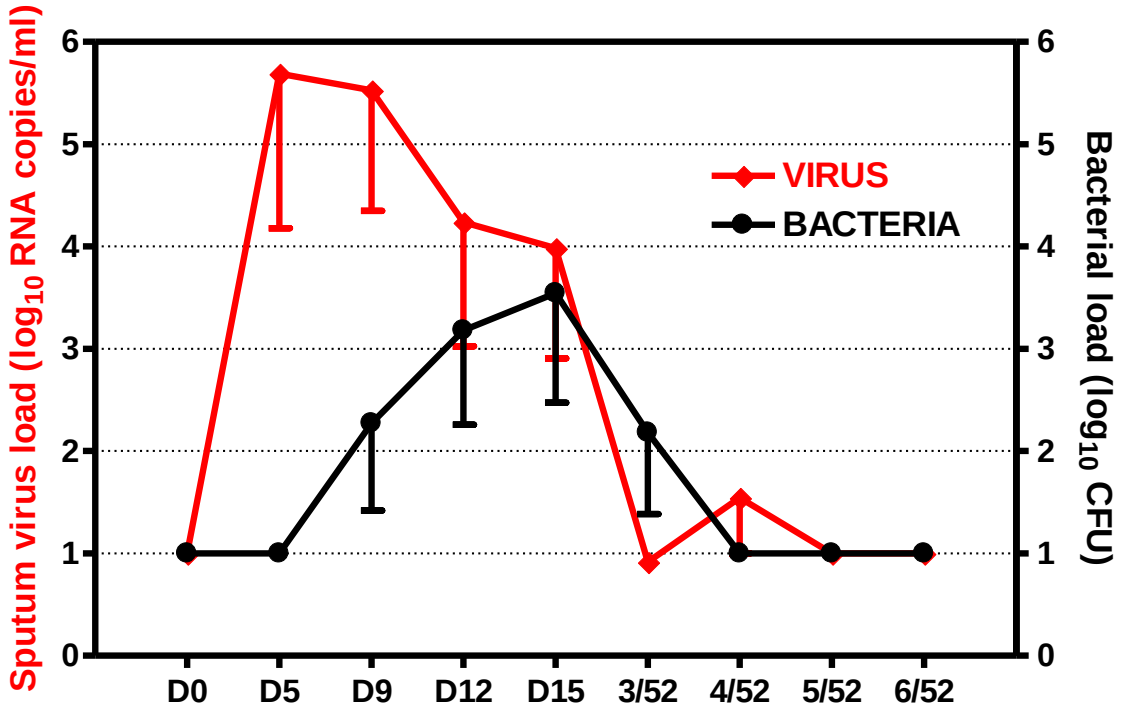




(AJRCCM 2011)

Rhinovirus Infection Induces Degradation of Antimicrobial Peptides and Secondary Bacterial Infection in Chronic Obstructive Pulmonary Disease

Patrick Mallia[1,2,3*], Joseph Footitt[1,2,3*†], Rosa Sotero[1,4], Annette Jepson[2], Marco Contoli[1,5], Maria-Belen Trujillo-Torralbo[1,2], Tatiana Kebadze[1], Julia Aniscenko[1], Gregory Oleszkiewicz[1], Katrina Gray[1,2], Simon D. Message[1], Kazuhiro Ito[6], Peter J. Barnes[6], Ian M. Adcock[6], Alberto Papi[5], Luminita A. Stanciu[1], Sarah L. Elkin[1,2], Onn M. Kon[1,2,3], Malcolm Johnson[7], and Sebastian L. Johnston[1,2,3]



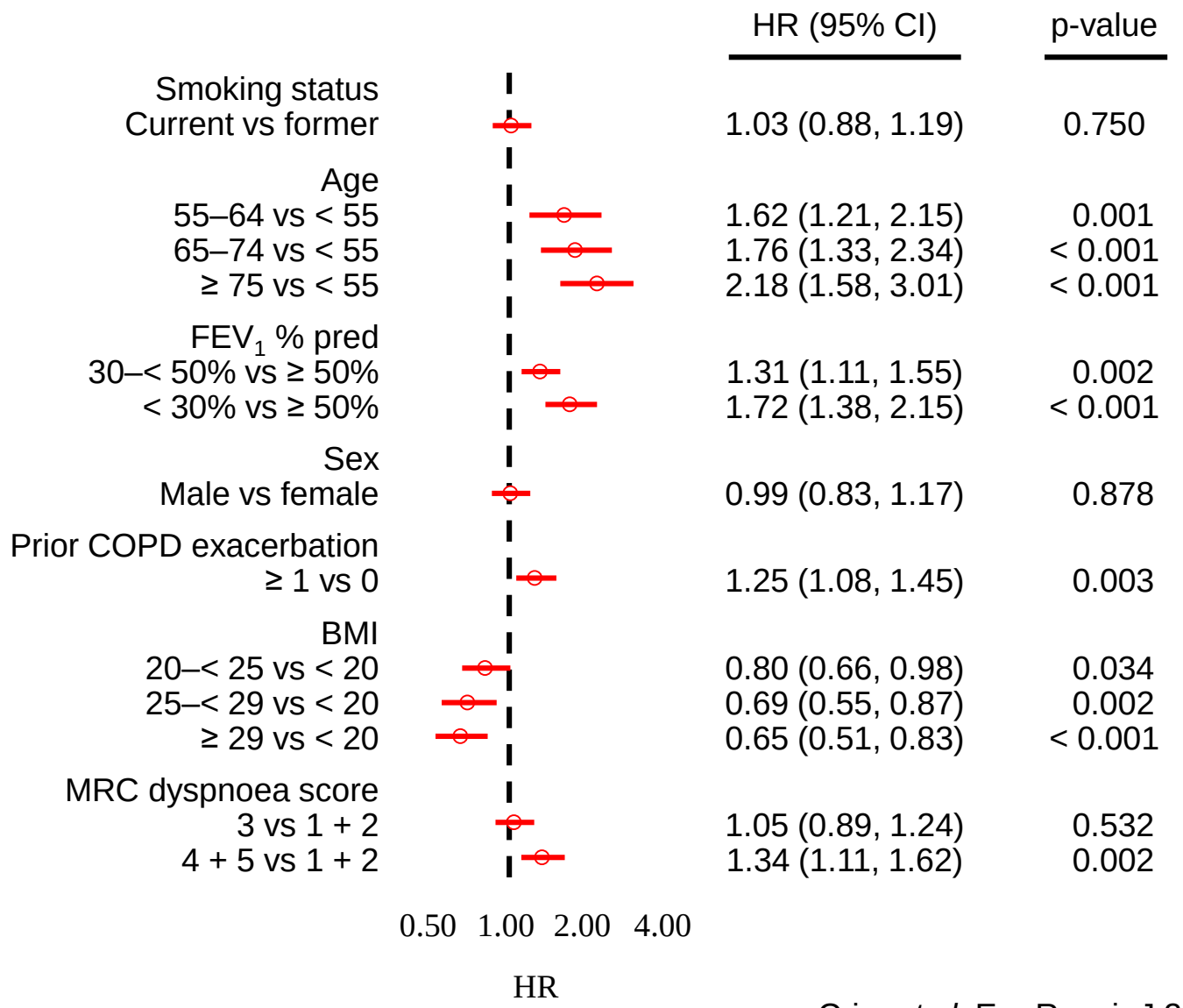
(AJRCCM 2012)

The TORCH paradox

Adverse Event	Placebo Group (N=1544)	Salmeterol Group (N=1542)	Fluticasone Group (N=1552)	Combination-Therapy Group (N=1546)
Reported during treatment — % of patients				
Any event	90	90	90	89
Serious event	41	40	42	43
Drug-related event	13	12	19	18
Event resulting in withdrawal or discontinuation of study medication	24	20	23	18
Total exposure to study medication — yr	3278	3531	3555	3700
Most commonly reported event during treatment — rate per yr				
COPD exacerbation	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Of specific interest during treatment — % of patients*				
Pneumonia	12.3	13.3	18.3†	19.6‡

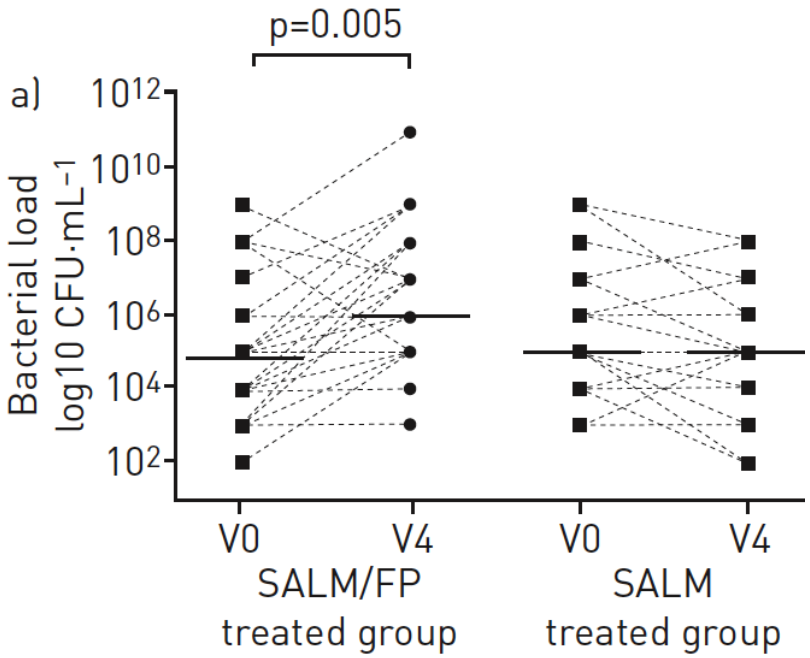
Calverley et al. *N Engl J Med.* 2007;356:775-789.

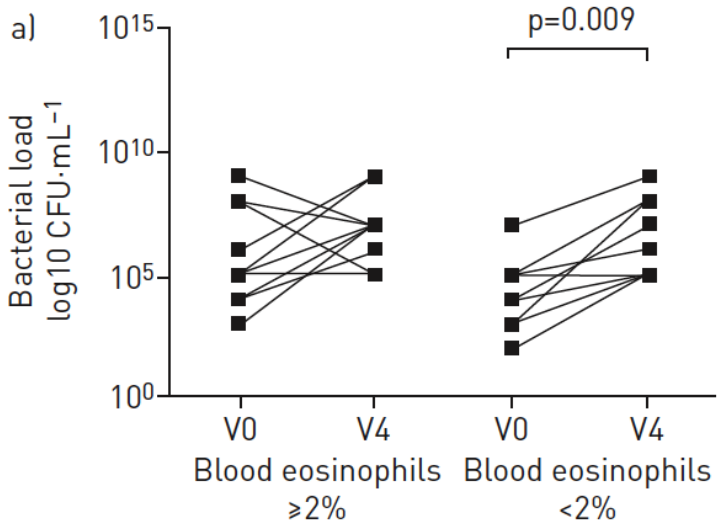
Risk factors for pneumonia

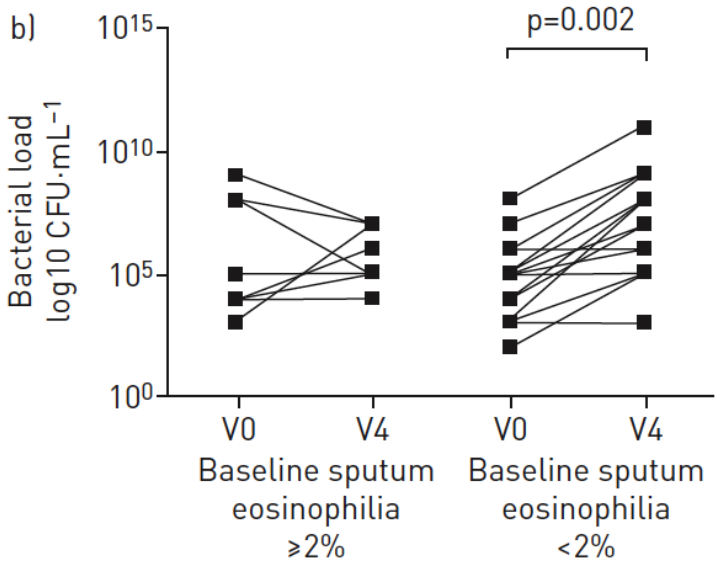


Crim *et al.* Eur Respir J 2009; 34: 641–647

Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD



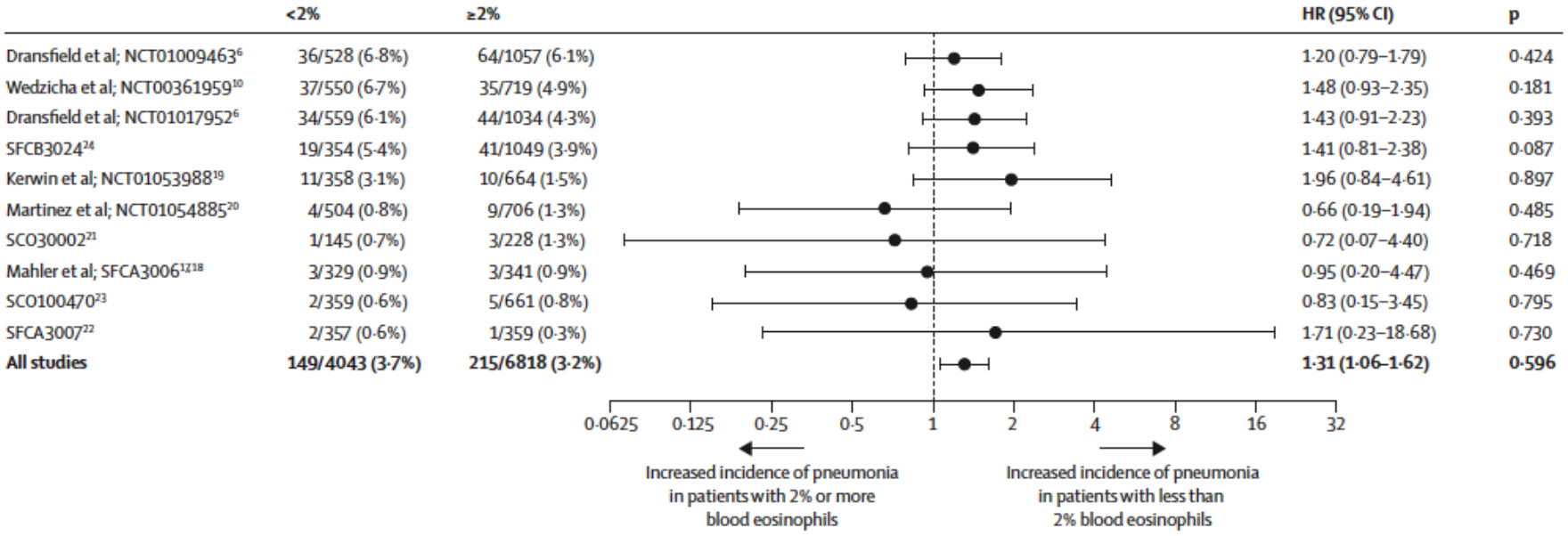




(Contoli, Papi et al. ERJ 2017)

Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis

Interpretation Using 2% baseline eosinophil count as a threshold, patients with COPD with lower blood eosinophil counts had more pneumonia events than did those with higher counts. The magnitude of this increased risk was small and should be further explored in large, prospective studies. These data should be considered when making treatment decisions, alongside existing evidence that patients with COPD and baseline blood eosinophil counts less than 2% have a poorer response to inhaled corticosteroids.



(Pavord et al. Lancet Resp Med 2016)

What do we know from the «big RCTs»?

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

* Adverse events of special interest are based on an analysis of a group of prespecified adverse events that are associated with the use of inhaled glucocorticoids, long-acting muscarinic antagonists, or long-acting β_2-agonists. See Table S15 in the Supplementary Appendix for the full listing of adverse events of special interest. CNS denotes central nervous system.

Lipson DA et al. N Engl J Med 2018;378:1671-1680

The NEW ENGLAND JOURNAL of MEDICINE

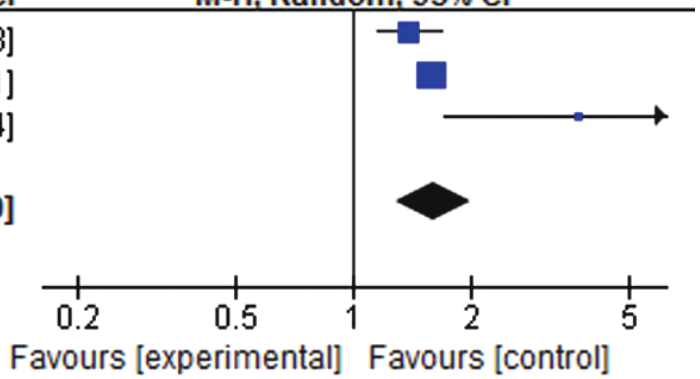
Inhaled corticosteroids (ICS) and risk of mycobacterium in patients with chronic respiratory diseases: a meta-analysis

Five studies involving 4,851 cases and 28,477 controls

	cases		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Brassard P 2011	96	422	722	4405	40.2%	1.39 [1.15, 1.68]	
Lee CH 2013	671	4139	2109	20583	52.6%	1.58 [1.46, 1.71]	
Shu CC 2010	5	16	45	538	7.1%	3.74 [1.71, 8.14]	
Total (95% CI)		**4577**		**25526**	**100.0%**	**1.60 [1.28, 1.99]**	
Total events	772		2876				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.44$, $df = 2$ ($P = 0.04$); $I^2 = 69\%$

Test for overall effect: $Z = 4.12$ ($P < 0.0001$)



Relationship between mycobacterium and high-dose ICS. ICS, inhaled corticosteroids.

(Songshi et al. J Thorac Dis 2014)

The risk of mycobacterial infections associated with inhaled corticosteroid use

population-based nested case–control study using linked laboratory and health administrative databases in Ontario, Canada, including adults aged ⩾66 years with treated obstructive lung disease (i.e. asthma, chronic obstructive pulmonary disease (COPD) or asthma–COPD overlap syndrome) between 2001 and 2013.

Among 417494 older adults with treated obstructive lung disease, we identified 2966 cases of NTM-PD and 327 cases of TB.

(Brode et al. ERJ 2017)

	NTM-PD cases	Controls	p-value
Subjects	2966	11 851	
Female	1341 (45.2)	5360 (45.2)	0.99
Age	76.6±6.36	76.6±6.35	0.943
Income quintile			0.893
1 (lowest)	760 (25.6)	2939 (24.8)	
2	688 (23.2)	2617 (22.1)	
3	523 (17.6)	2254 (19.0)	
4	470 (15.8)	2104 (17.8)	
5 (highest)	517 (17.4)	1868 (15.8)	
Missing	8 (0.3)	69 (0.6)	
Rural residency[#]	76 (2.6)	1472 (12.4)	<0.001
Suburban	267 (9.0)	3188 (26.9)	
Urban	2623 (88.4)	7191 (60.7)	
ADGs	10.5±3.71	9.83±3.96	<0.001
Comorbidities			
Bronchiectasis	483 (16.3)	559 (4.7)	<0.001
Chronic kidney disease	297 (10.0)	1444 (12.2)	0.001
Diabetes mellitus	723 (24.4)	3608 (30.4)	<0.001
GORD	704 (23.7)	2818 (23.8)	0.961
HIV[¶]	⩽5	⩽5	0.264
Interstitial lung disease	277 (9.3)	504 (4.3)	<0.001
Rheumatoid arthritis	121 (4.1)	412 (3.5)	0.115
Prior TB	22 (0.7)	8 (0.1)	<0.001
Last COPD hospitalisation			<0.001
<6 months	281 (9.5)	1143 (7.7)	
6 months–5 years	661 (22.3)	3131 (21.1)	
>5 years or never	2024 (68.2)	10 543 (71.2)	

The role of tuberculosis in COPD

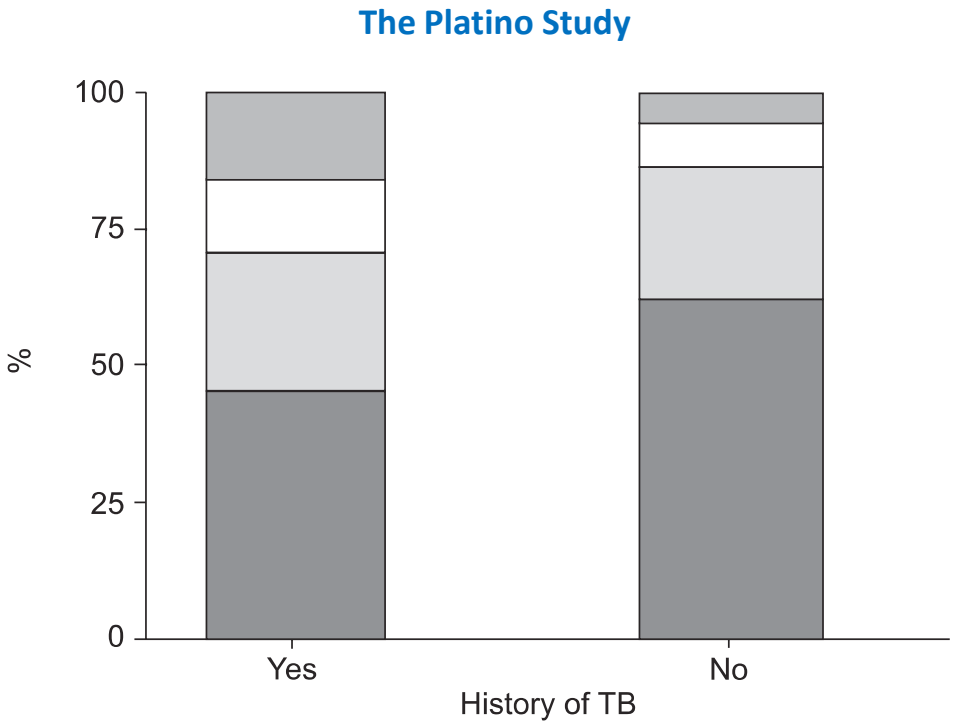


FIGURE 1. Prevalence of different stages of chronic obstructive pulmonary disease (COPD) severity according to medical history of tuberculosis (TB). ■: no COPD; ■: stage 0; □: stage I; ■: stage II–IV.

(Menezes et al. ERJ 2007)

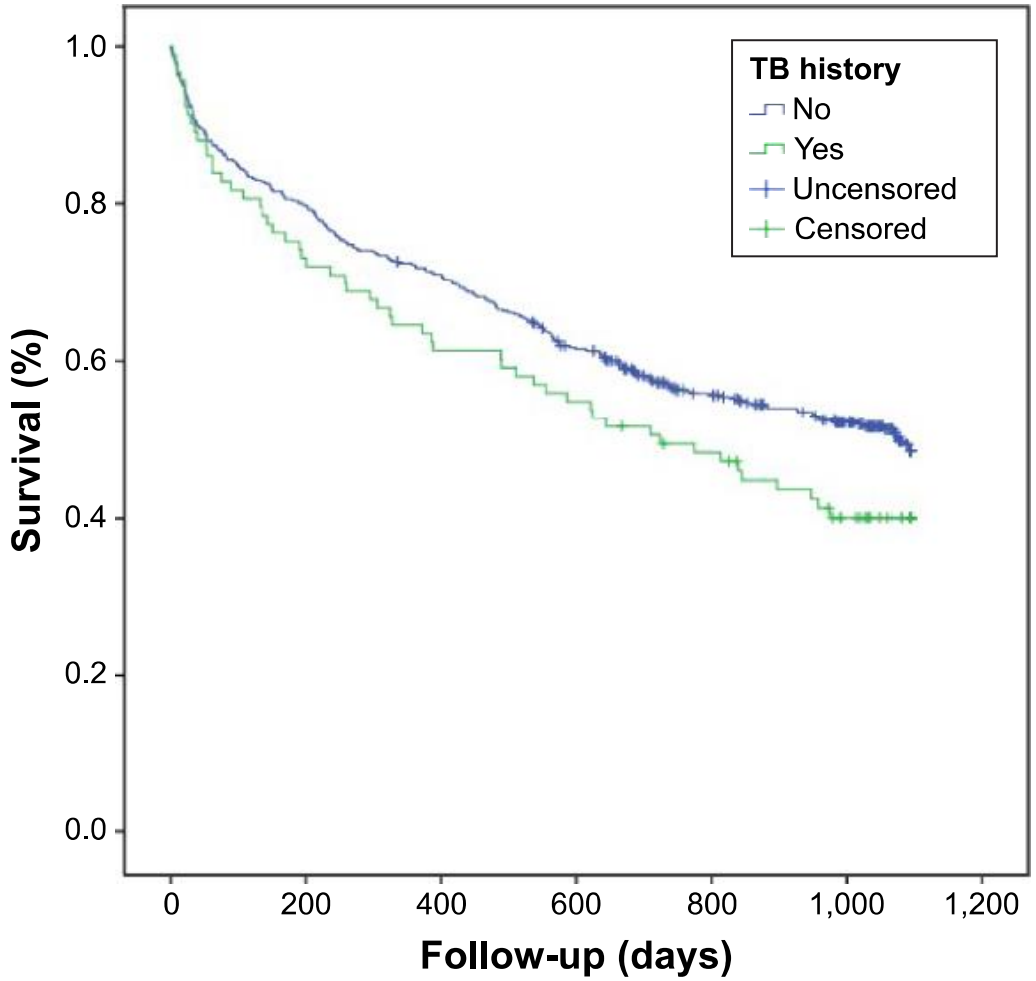
	COPD	No COPD	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Subjects	87	409				
Tuberculosis	9 (10.3)	9 (2.2)	5.13 (1.97–13.33)	<0.0001	5.93 (2.05–17.18)	0.001
Smoker	33 (37.9)	92 (22.5)	2.11 (1.29–3.44)	0.003	1.39 (0.77–2.53)	0.28
Male	57 (65.5)	206 (50.4)	1.87 (1.16–3.03)	0.01	1.09 (0.61–1.95)	0.782
Female	30 (34.5)	203 (49.6)				
Age recode years						
30–40	3 (3.4)	20 (4.9)				
41–50	16 (18.4)	220 (53.8)	4.78 (1.34–17.10)	0.016	4.02 (1.10–14.66)	0.035
51–60	25 (28.7)	109 (26.7)	9.85 (5.19–18.71)	<0.0001	9.35 (4.79–18.25)	<0.0001
>60+	43 (49.4)	60 (14.7)	3.13 (1.74–5.61)	<0.0001	3.18 (1.73–5.83)	<0.0001

(Ng'weina et al. ERJ 2018)

The role of tuberculosis in COPD

	All patients	TB history (–)	TB history (+)	*P*-value
Subject	598	505	93	
Age (years)	69.5±10.6	70.1±10.4	66.3±11.3	0.002
Sex (F/M)	154/444	135/370	19/74	0.20
COPD duration (years)	7.0±4.3	6.8±4.3	7.7±4.1	0.07
Age of COPD diagnosis (years)	62.5±11.5	63.2±11.2	58.6±12.3	<0.001
Smoking history (current/ex/none)	53/412/133	45/342/118	8/70/15	0.28
Cigarettes smoked (pack-years)	40.0±33.0	39.5±33.3	42.7±31.2	0.39
Length of hospital stay (days)	8.7±4.6	8.6±4.6	8.9±4.6	0.58
FEV_1% predicted	39.4±17.4	40.2±17.1	34.8±18.6	0.069
PaO_2 (mmHg)	57.5±13.1	57.7±13.0	55.8±13.9	0.26
$PaCO_2$ (mmHg)	48.8±12.3	48.1±11.9	52.2±14.0	0.008
BMI (kg/m^2)	26.4±5.8	26.6±5.8	25.0±5.7	0.09
Charlson comorbidity index	1.25±1.26	1.32±1.30	0.83±0.90	<0.001

(Yakar et al. Int J COPD 2017)



Inhaled Corticosteroids and Risk of Tuberculosis in Patients with Respiratory Diseases

A cohort of patients (n=427648) with airways disease was formed using the Quebec databases

Role of the disease

	Cases	Control Subjects
No.	564	5,640
Age, yr, mean ± SD	69.4 ± 17.0	69.3 ± 16.9
Follow-up, yr, mean ± SD	3.2 ± 3.3	3.2 ± 3.3
Male, %	54.1	42.7
In the year before index date:		
Hospitalization for COPD and/or asthma, %	7.3	2.9
Respiratory drugs, mean number of Rx ± SD	5.0 ± 7.4	3.4 ± 6.2
Oral corticosteroids, mean number of Rx ± SD	0.8 ± 2.3	0.4 ± 2.4
Oral corticosteroids, cumulative dose, mg, mean ± SD	271.4 ± 846.7	98.7 ± 458.3
Traditional DMARDS, %	2.7	1.5
Diabetes, %	9.0	9.9
Other comorbid conditions, %	5.1	3.5

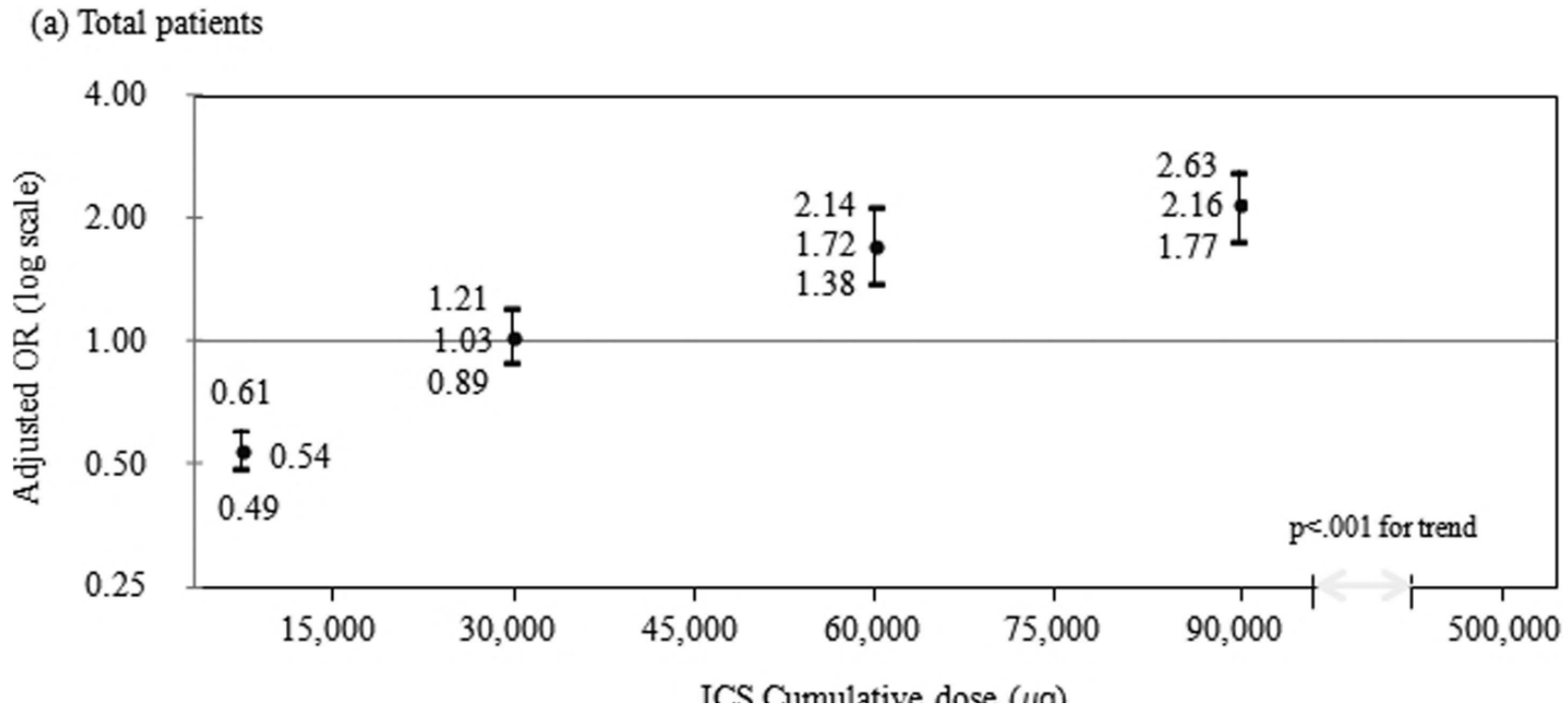
Role of the treatment on top of the disease

				Adjusted*	
	Cases	Controls	Crude RR	RR	95% CI
No. of subjects	564	5,640			
No use, %	54.4	62.7	1.00	1.00	Reference
Any use, %	45.6	37.3	**1.43**	**1.27**	**1.05–1.53**
Current use, 30 d, %	20.4	15.4	**1.58**	**1.33**	**1.04–1.71**
High dose, %	5.0	3.2	**1.94**	1.55	0.99–2.44
Medium dose, %	12.1	9.6	**1.50**	1.25	0.93–1.68
Low dose, %	3.4	2.7	1.49	1.40	0.84–2.33
Past use, 31–365 d, %	25.2	21.9	**1.33**	1.23	0.98–1.53

(Brassard et al. AJRCCM 2011)

Use of inhaled corticosteroids and the risk of tuberculosis

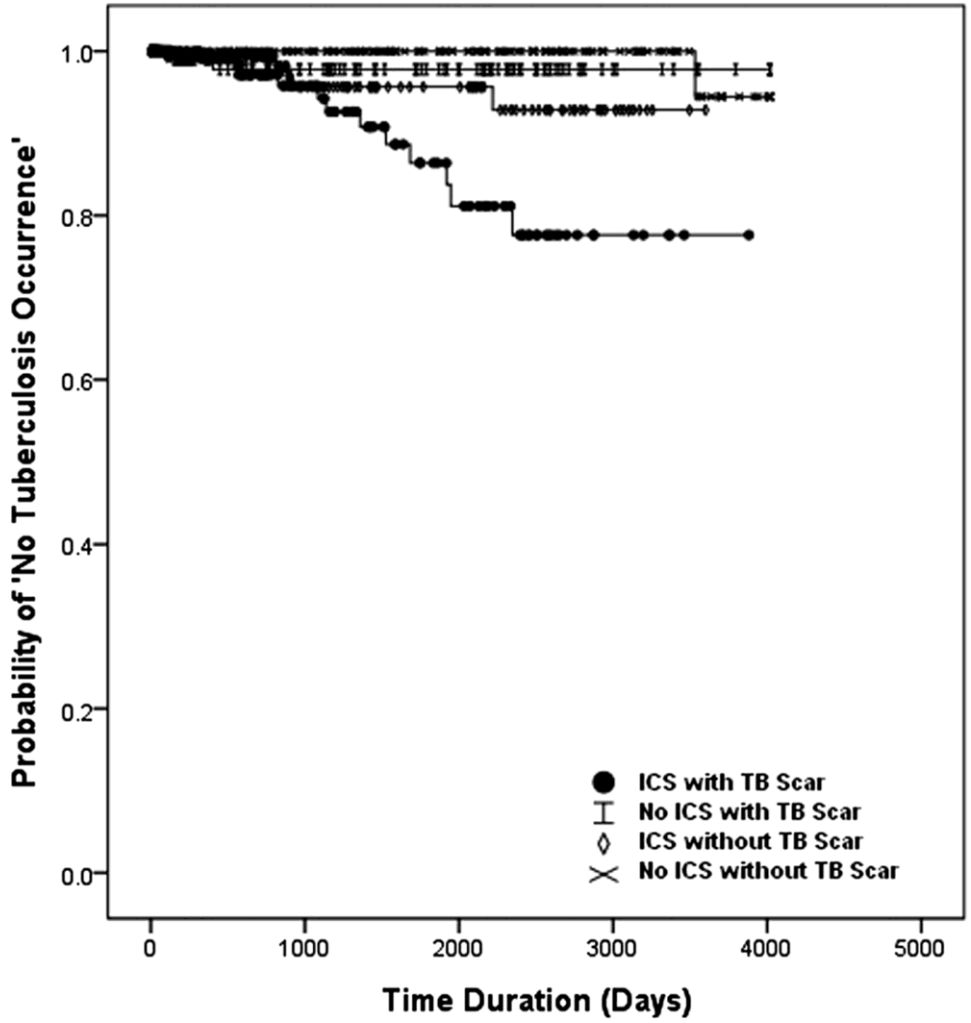
The eligible cohort consisted of 853439 new adult users in South Corea of inhaled respiratory medications between 1 January 2007 and 31 December 2010.



(Lee et al. Thorax 2013)

Inhaled Corticosteroid Is Associated With an Increased Risk of TB in Patients With COPD

A retrospective cohort study (South Corea) was performed. Between January 1, 2000, and December 31, 2005, a total of 778 patients who had COPD were recruited



(Jung-Hyun Kim et al Chest 2013)

BPCO e Tubercolosi: un binomio pericoloso

- BPCO
- Infezioni in BPCO
- TB (e micobatteri) & BPCO
  - RCTs
  - Studi coorte
- Meccanismi

Effects of ICS on pulmonary host defence

1) inhibition of macrophage antimicrobial activity *(Stolberg et al. J Immunol 2015)*
2) inhibition of the macrophage release of cytokines such as TNF and IP-10 *(Patterson et al Respir Res 2012)*
3) downregulation of the expression of MHC class II molecules in macrophages *(Van de Garde et al. J Immunol 2012)*
4) reduction of adaptive immune responses *(Lee et al. FASEB 2012)*

Effects of eosinophils on immune response to pathogens

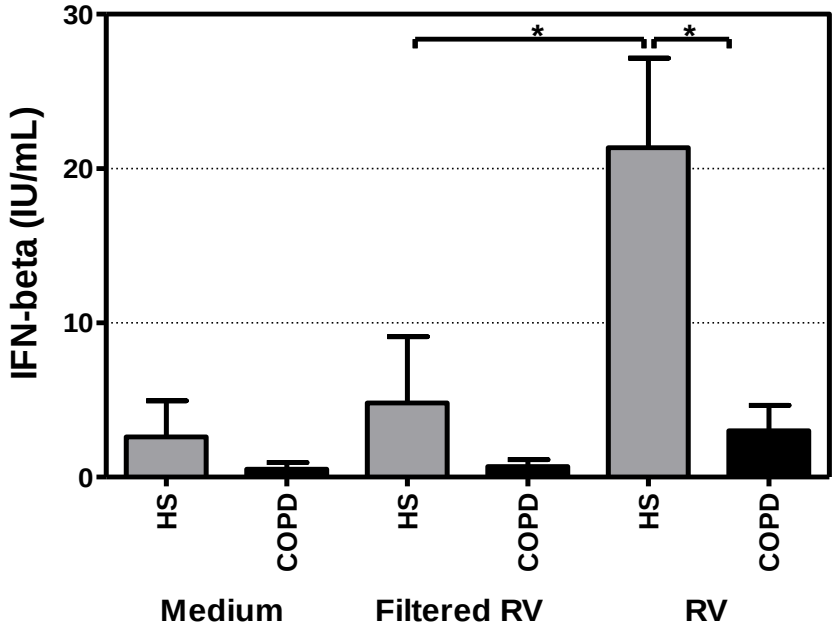
1) antigen-presenting cells to CD4+ T-cells *(Shi et al. J Leukoc Biol 2004)*
2) bactericidal activity through the release of eosinophil cationic protein (ECP) and major basic protein (MBP) *(Malik et al Crit Rev Microbiol 2012).*

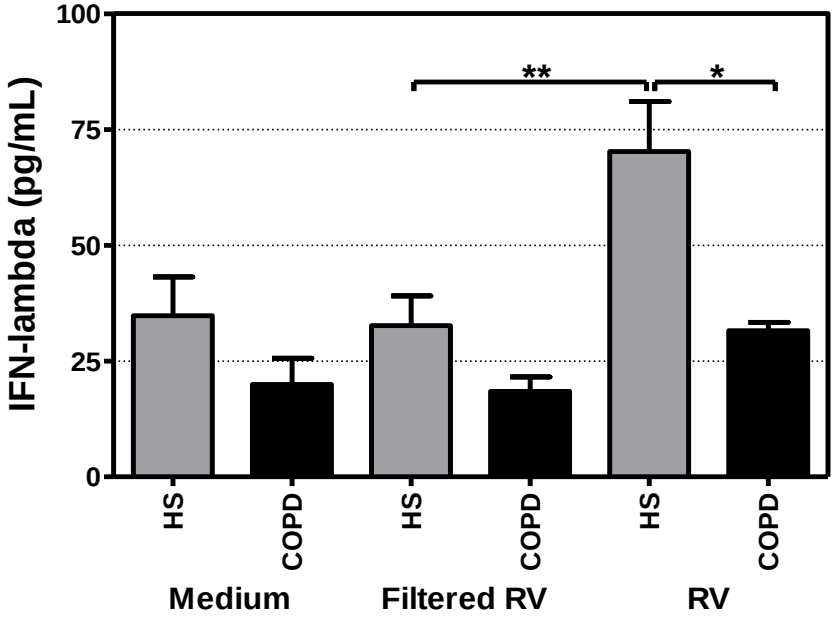
- eosinopenia is an independent predictor of poor clinical outcomes of:
  - severe infection, such as bacteraemia *(Terradas et al. PLoS ONE 2012)*
  - COPD exacerbations *(Steer et al. Thorax 2012)*

Experimental Rhinovirus Infection as a Human Model of Chronic Obstructive Pulmonary Disease Exacerbation

Patrick Mallia[1,2], Simon D. Message[1,2], Vera Gielen[1], Marco Contoli[1,3], Katrina Gray[1,2], Tatiana Kebadze[1], Julia Aniscenko[1], Vasile Laza-Stanca[1], Michael R. Edwards[1], Louise Slater[1], Alberto Papi[3], Luminita A. Stanciu[1], Onn M. Kon[1,2], Malcolm Johnson[4], and Sebastian L. Johnston[1,2]

Mechanisms of susceptibility to infections





(AJRCCM 2011)

BPCO e Tubercolosi: un binomio pericoloso

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Conclusioni

COPD & TB: YES

- Deranged innate immune response in COPD

PARTICULARLY IF:

- Elderly/comorbid patients
- Previous history of TB
- Low eos count
- On high dose of ICS (Fluti)