Cause di riacutizzazione della BPCO nell’anziano

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Definizione di riacutizzazione

- Variazione dello stato di salute che implica un cambiamento della terapia per la BPCO
  (Cazzola M et al. Eur Respir J 2008; 31: 416–469)
- Variazione dello stato di salute che implica il ricovero ospedaliero.

Esiste il fenotipo “frequente riacutizzatore”? The Eclipse study (Hurst JR et al. N Engl J Med 2010;363:1128-38)

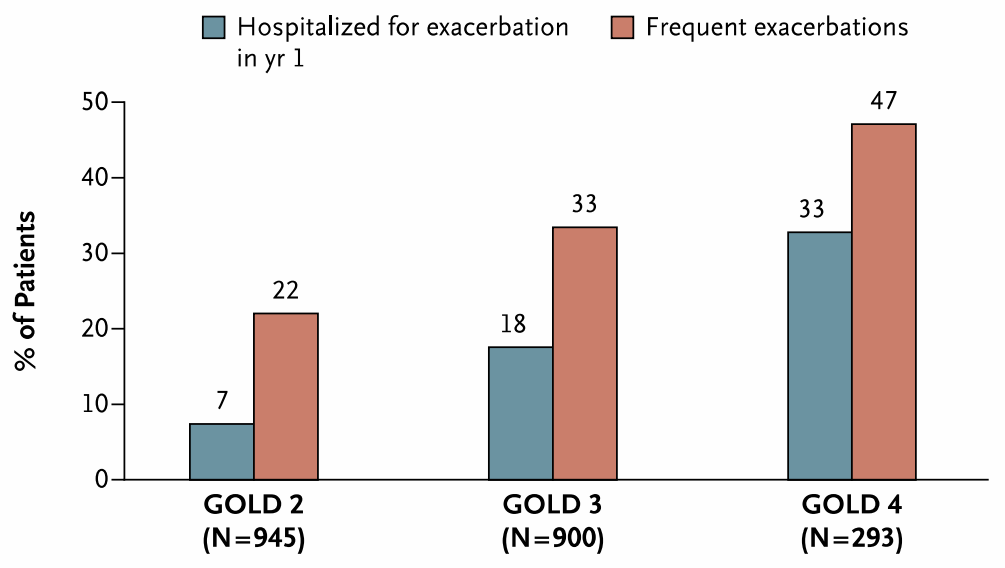


Figure 1. Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease.

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.

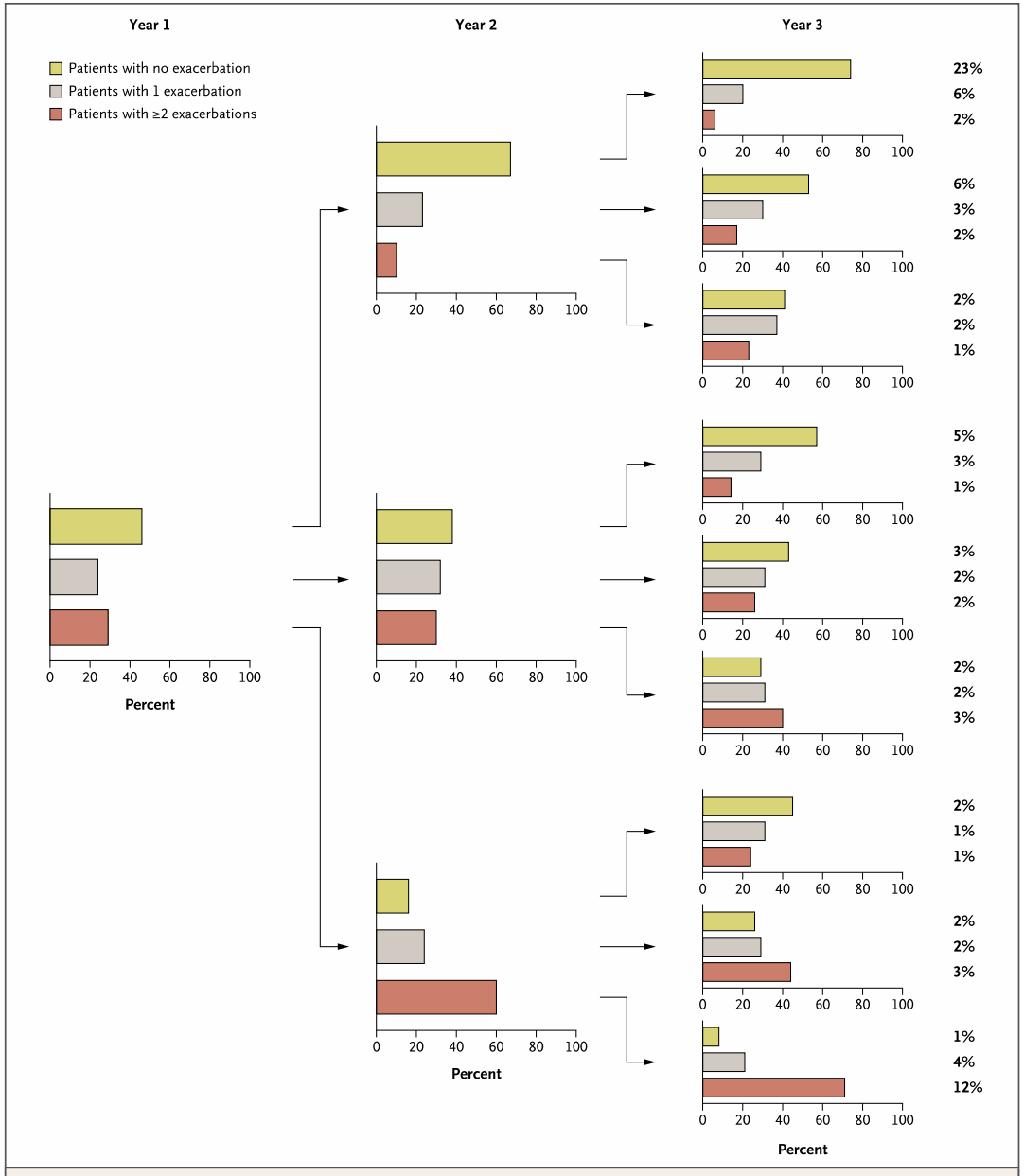


Figure 2. Stability of the Frequent-Exacerbation Phenotype in the 1679 Patients with Chronic Obstructive Pulmonary Disease Who Completed the Study.

The bars at the left show the proportions of patients with no exacerbations, one exacerbation, or two or more exacerbations in year 1. The bars in the middle show the respective incidence of exacerbations for these patients in year 2; the bars at the right show the respective incidence in year 3. The percentages at right denote the proportions of all patients with no exacerbations, one exacerbation, or two or more exacerbations. Numbers do not sum to 100 because of rounding.

Correlati delle frequenti riacutizzazioni: un tratto fenotipico.. (Hurst JR et al. N Engl J Med 2010;363:1128-38)

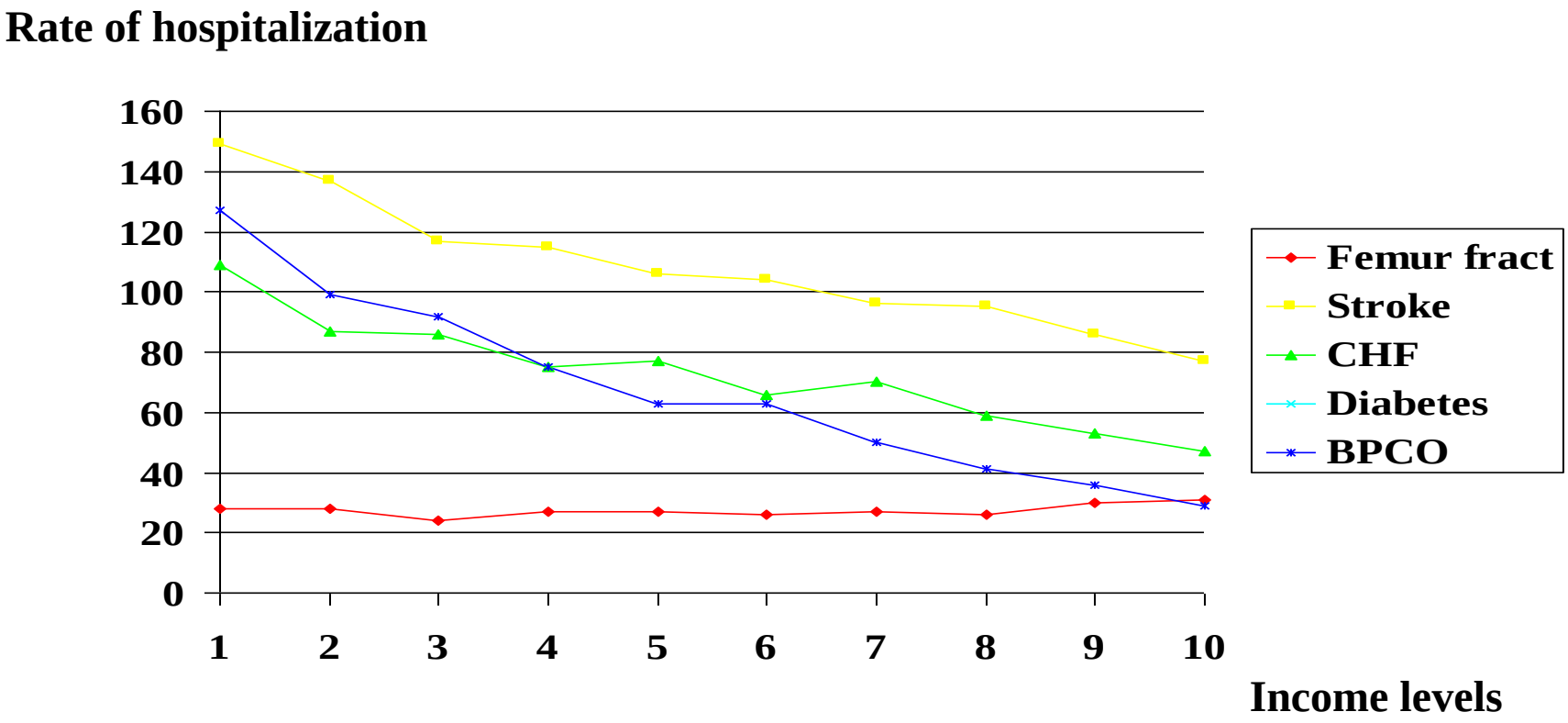
Table 4. Factors Associated with Increased Exacerbation Frequency in Patients with Moderate (GOLD Stage 2) COPD, According to Sex.

Factor	Number of Exacerbations						Overall P Value
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Women (N = 376)							
Exacerbation during previous year — yes vs. no	8.89 (4.32–18.29)	<0.001	2.28 (1.26–4.11)	<0.006	3.90 (1.82–8.34)	<0.001	<0.001
History of asthma — yes vs. no	3.38 (1.62–7.05)	<0.001	3.00 (1.59–5.66)	<0.001	1.12 (0.53–2.38)	0.76	<0.001
Fibrinogen — per increase of 1 SD on log scale	1.95 (1.28–2.97)	<0.002	1.22 (0.85–1.74)	0.28	1.60 (1.03–2.49)	<0.04	0.008
Men (N = 569)							
Exacerbation during previous yr — yes vs. no	7.38 (4.44–12.27)	<0.001	3.28 (2.09–5.13)	<0.001	2.25 (1.30–3.90)	0.004	<0.001
FEV_1 — per 100-ml decrease*	1.20 (1.11–1.31)	<0.001	1.07 (1.00–1.14)	<0.05	1.13 (1.04–1.23)	<0.006	<0.001
Chronic wheezing — yes vs. no	2.56 (1.55–4.23)	<0.001	1.40 (0.89–2.18)	0.14	1.83 (1.06–3.16)	<0.03	0.001

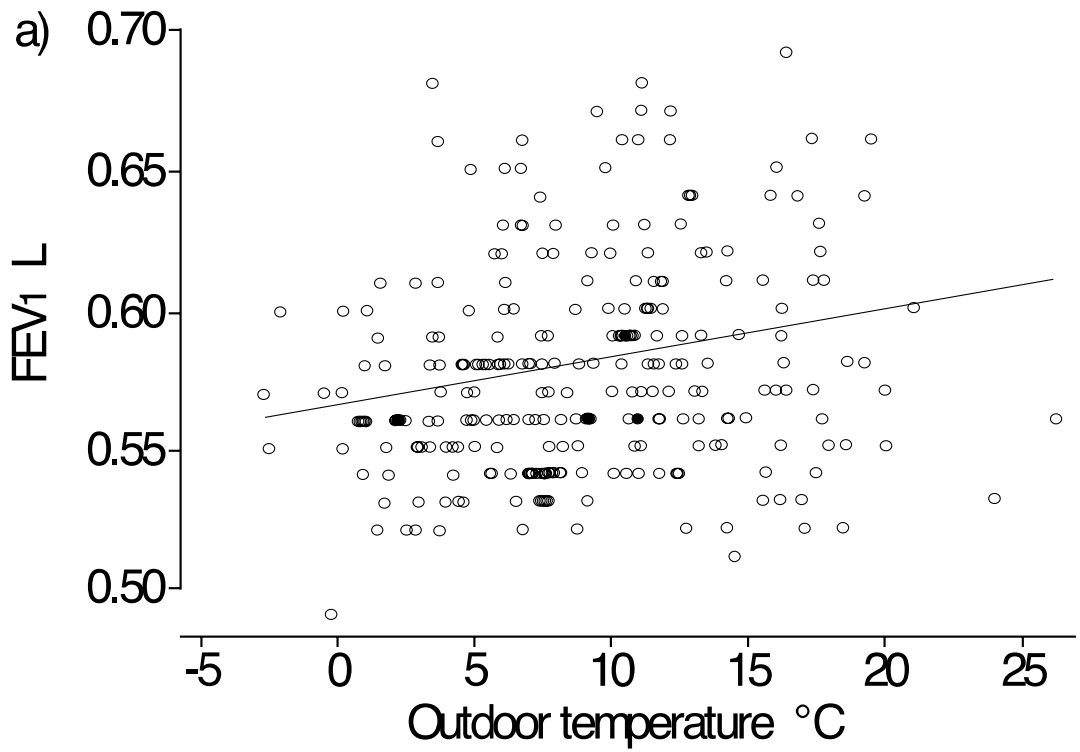
* FEV_1 denotes forced expiratory volume in 1 second, and NS not significant.

O solo una condizione di disagio sociale? Relationship between income and rate of admissions to hospital in males over 75

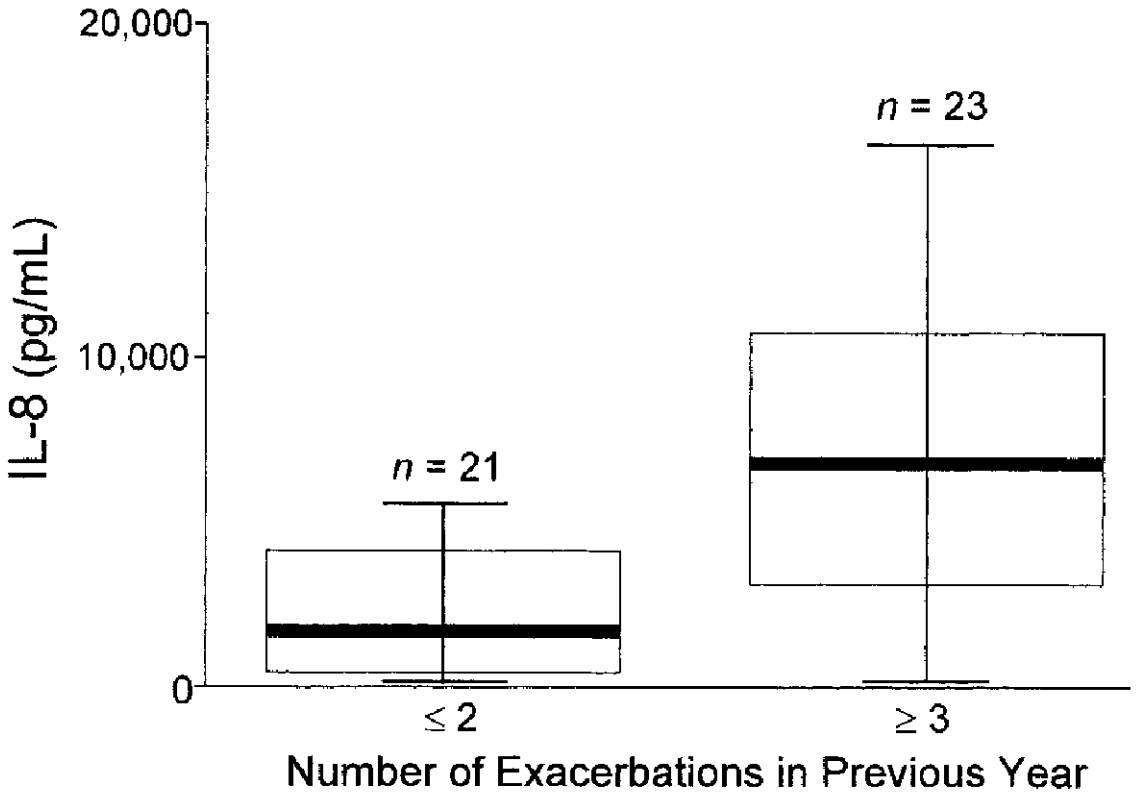
(Antonelli Incalzi R et al. BMC Public Health 2007; 7: 227)



La dimensione sociale potrebbe anche spiegare il link T°-FEV1 (Donaldson GC et al. Eur Respir J 1999; 13: 844-849)

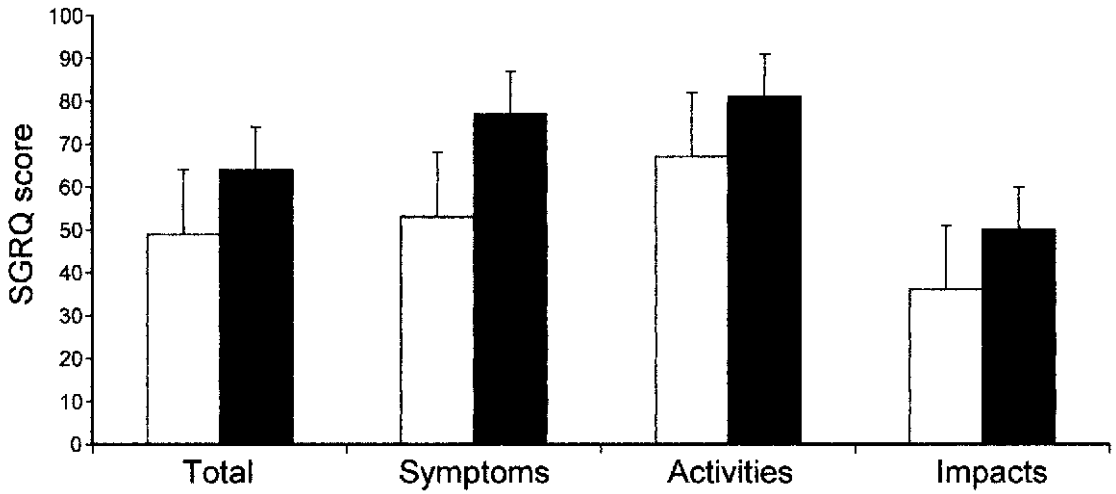


Forte impronta flogistica intercritica nel frequente riacutizzatore (Bhowmik A. Thorax 2000;55(2):114–200)



E peggiore stato di salute

(Bhowmik A. Thorax 2000;55(2):114–200)



Chi è più a rischio di riacutizzazioni?

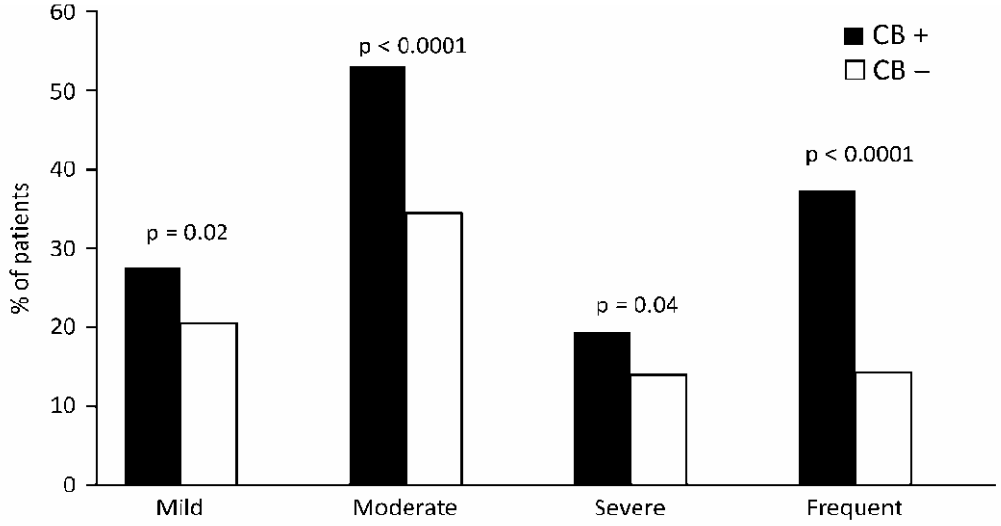
(Miravitlles M. Eur Respir Mon, 2009, 43, 90–110)

Table 1. – Risk factors for frequent exacerbations, relapse and hospital admission following ambulatory treatment of exacerbations of chronic obstructive pulmonary disease

	Risk factors
Frequent exacerbations[#]	Increasing age
	Severity of FEV_1 impairment
	Chronic bronchial mucus hypersecretion
	Frequent past exacerbations
	Daily cough and wheezing
	Bronchitic symptoms
Relapse	Coexisting cardiopulmonary disease
	Increasing number of previous visits to GP for respiratory problems
	Increasing number of previous exacerbations
	Increasing baseline dyspnoea
	Severity of FEV_1 impairment
	Use of home oxygen
Hospital admission	Significant comorbid conditions
	Severity of FEV_1 impairment
	High admission rates for previous exacerbations
	Three or more admissions in previous year
	Increasing age
	Underprescription of LTOT
	Lack of or reduction in physical activity

FEV_1: forced expiratory volume in one second; GP: general practitioner; LTOT: long-term oxygen therapy. [#]: >2 exacerbations$\cdot yr^{-1}$.

L'impronta bronchitica come fattore di rischio per riacutizzazione...(Corhay JL et al. Int J Clin Pract, 2013, 67: 1294)



...e ricovero ospedaliero (Corhay JL et al. Int J Clin Pract, December 2013, 67, 12, 1294–1301)

Table 4 Hospitalisations in chronic obstructive pulmonary disease (COPD) patients with (CB+) and without chronic bronchitis (CB−)

	CB+ N = 622	CB− N = 352	p-value	N#
Hospital visits related to COPD†				
Emergency department without hospitalisation	0.04 ± 0.24	0.03 ± 0.25	0.3445	968
Hospitalisation without stay at ICU	0.28 ± 0.75	0.15 ± 0.43	0.0027*	969
Hospitalisation with stay at ICU	0.05 ± 0.26	0.03 ± 0.16	0.1247	967
All-cause hospitalisations†	0.52 ± 0.91	0.38 ± 0.83	0.0185**	964

*$p < 0.01$, **$p < 0.05$. †The number of hospitalisations per patient per year is expressed as mean ± SD. N#, number of patients with available data; CB, chronic bronchitis; ICU, intensive care unit.

Cause di riacutizzazione

	Proportion	Cause of exacerbation
Infectious exacerbations	60–80% of exacerbations	
Frequent	70–85% of infectious exacerbations	*Haemophilus influenzae* *Streptococcus pneumoniae* *Moraxella catarrhalis* Viruses (influenza/parainfluenza viruses, rhinoviruses, coronaviruses)
Infrequent	15–30% of infectious exacerbations	*Pseudomonas aeruginosa*[#] Opportunistic Gram-negatives *Staphylococcus aureus* *Chlamydia pneumoniae* *Mycoplasma pneumoniae*
Noninfectious exacerbations	20–40% of exacerbations	Heart failure Pulmonary embolism Nonpulmonary infections Pneumothorax
Precipitating factors		Cold air Air pollution Allergens Tobacco smoking Noncompliance with respiratory medication

[#]: in patients with severe forced expiratory volume in one second impairment and other known risk factors (see Aetiology of exacerbations section and table 4). Modified from [34].

Più in dettaglio (Sethi S et al. N Engl J Med 2008;359:2355-65)

Table 1. Microbial Pathogens in COPD.*

Microbe	Role in Exacerbations	Role in Stable Disease
Bacteria		
Haemophilus influenzae	20–30% of exacerbations	Major role
Streptococcus pneumoniae	10–15% of exacerbations	Minor role
Moraxella catarrhalis	10–15% of exacerbations	Minor role
Pseudomonas aeruginosa	5–10% of exacerbations, prevalent in advanced disease	Probably important in advanced disease
Enterobacteriaceae	Isolated in advanced disease, pathogenic significance undefined	Undefined
H. haemolyticus	Isolated frequently, unlikely cause	Unlikely
H. parainfluenzae	Isolated frequently, unlikely cause	Unlikely
Staphylococcus aureus	Isolated infrequently, unlikely cause	Unlikely
Viruses		
Rhinovirus	20–25% of exacerbations	Unlikely
Parainfluenza virus	5–10% of exacerbations	Unlikely
Influenza virus	5–10% of exacerbations	Unlikely
Respiratory syncytial virus	5–10% of exacerbations	Controversial
Coronavirus	5–10% of exacerbations	Unlikely
Adenovirus	3–5% of exacerbations	Latent infection seen, pathogenic significance undefined
Human metapneumovirus	3–5% of exacerbations	Unlikely
Atypical bacteria		
Chlamydophila pneumoniae	3–5% of exacerbations	Commonly detected, pathogenic significance undefined
Mycoplasma pneumoniae	1–2% of exacerbations	Unlikely
Fungi		
Pneumocystis jiroveci	Undefined	Commonly detected, pathogenic significance undefined

* References for this table are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Una sintesi delle cause infettive (Kurai D et al. **Frontiers in Microbiology** | Virology October 2013 | Volume 4 | Article 293 | **2**)

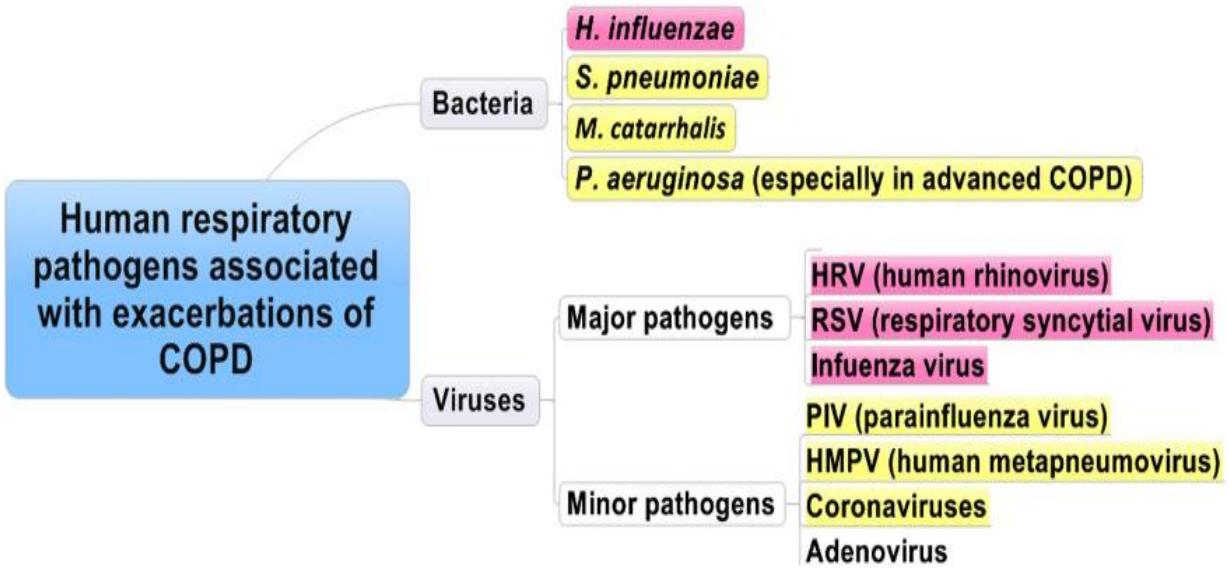


FIGURE 2 | Human respiratory pathogens associated with exacerbations of COPD. Red and yellow columns are the most relevant pathogens in order.

I virus sembrano pesare meno che nelle riacutizzazioni asmatiche

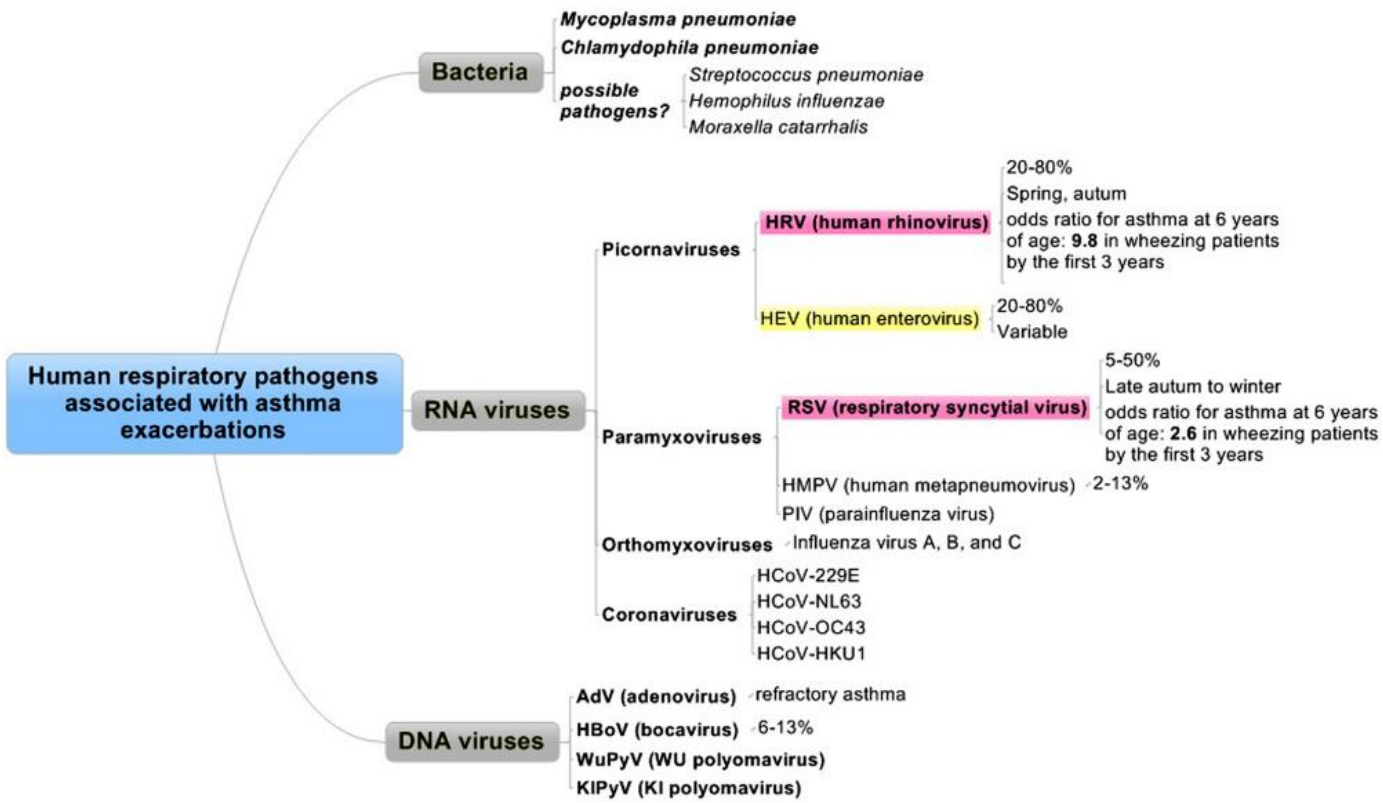


FIGURE 1 | Human respiratory pathogens associated with asthma exacerbations. Pathogens are divided into three categories as bacteria, RNA viruses, or DNA viruses. Red and yellow columns are the most relevant pathogens in order.

...ma cercando bene

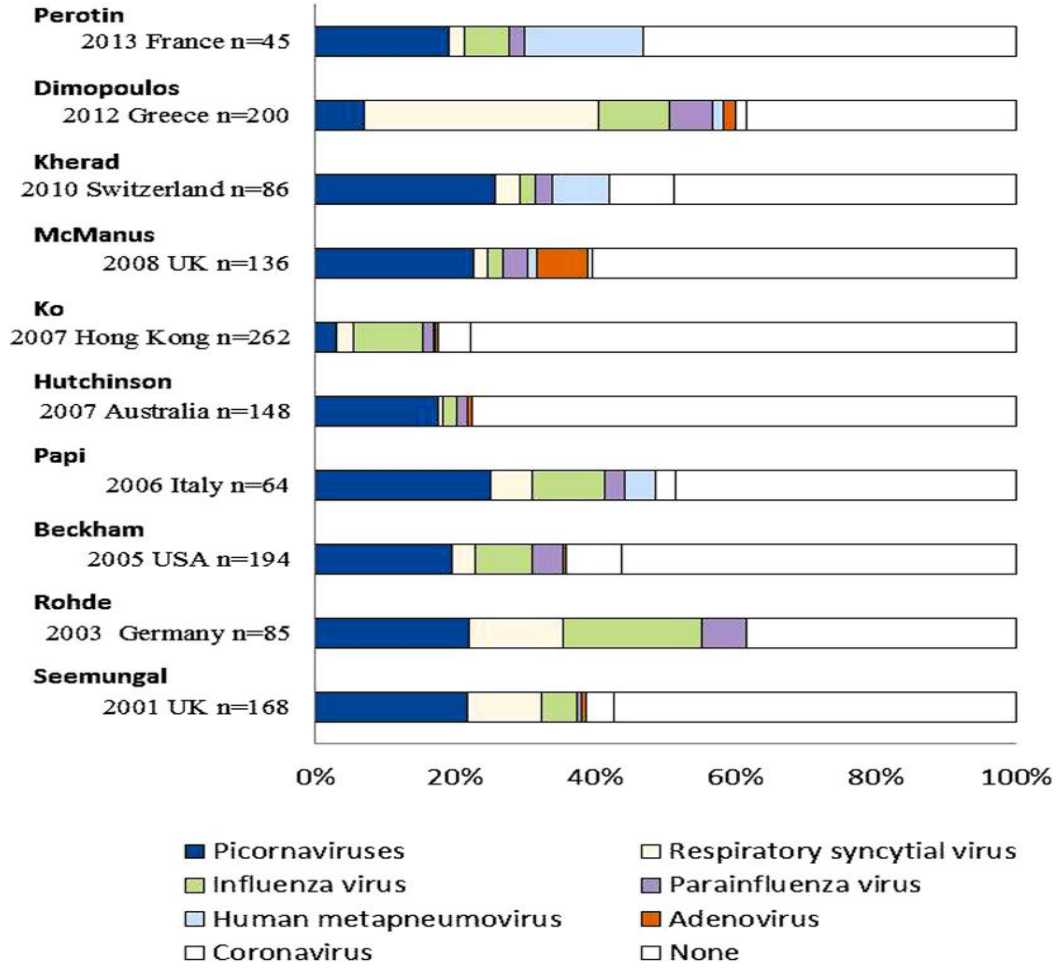


FIGURE 4 | Viral detection in exacerbations of COPD using PCR or RT-PCR methods in recent studies. Picornaviruses include human rhinovirus and human enterovirus. Multiple viruses were detected in individual patients per one episode.

Inoltre i virus potrebbero spiegare in parte l'efficacia preventiva dell'azitromicina (Albert RK et al. N Engl J Med 2011;365:689)

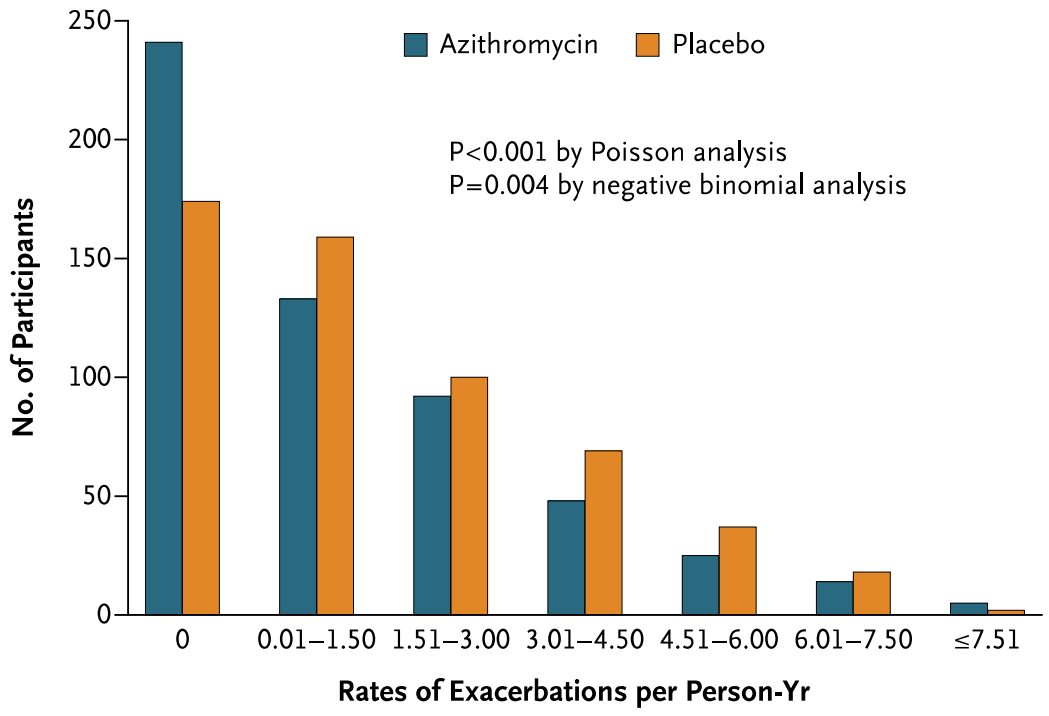
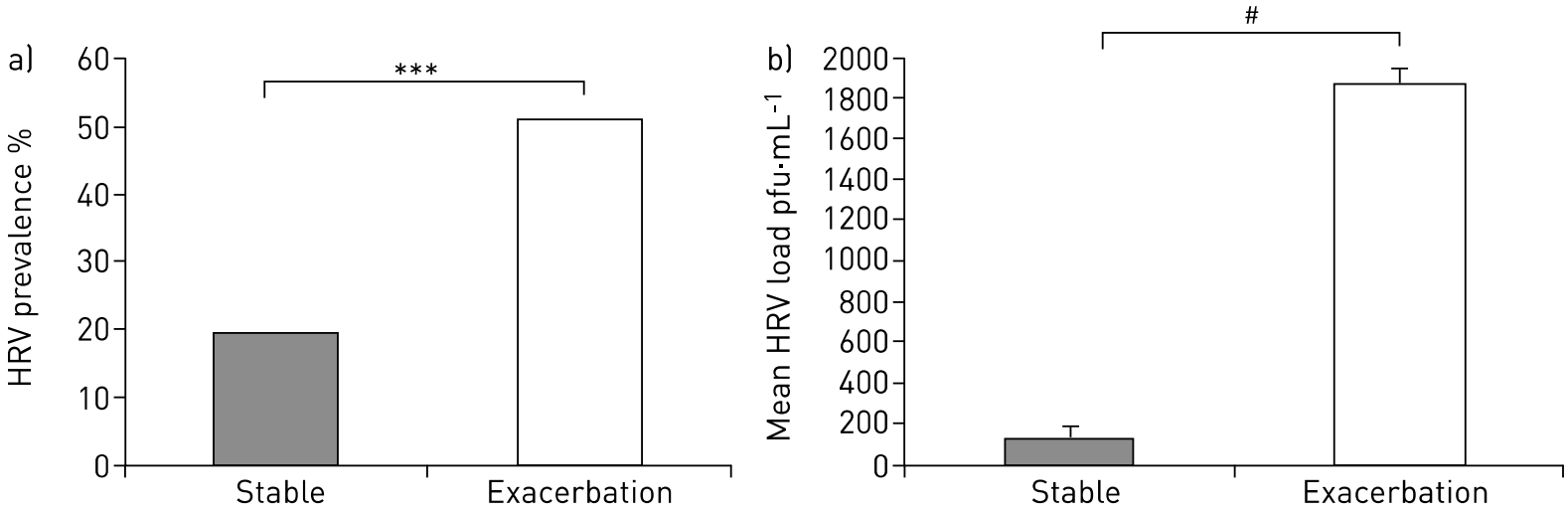
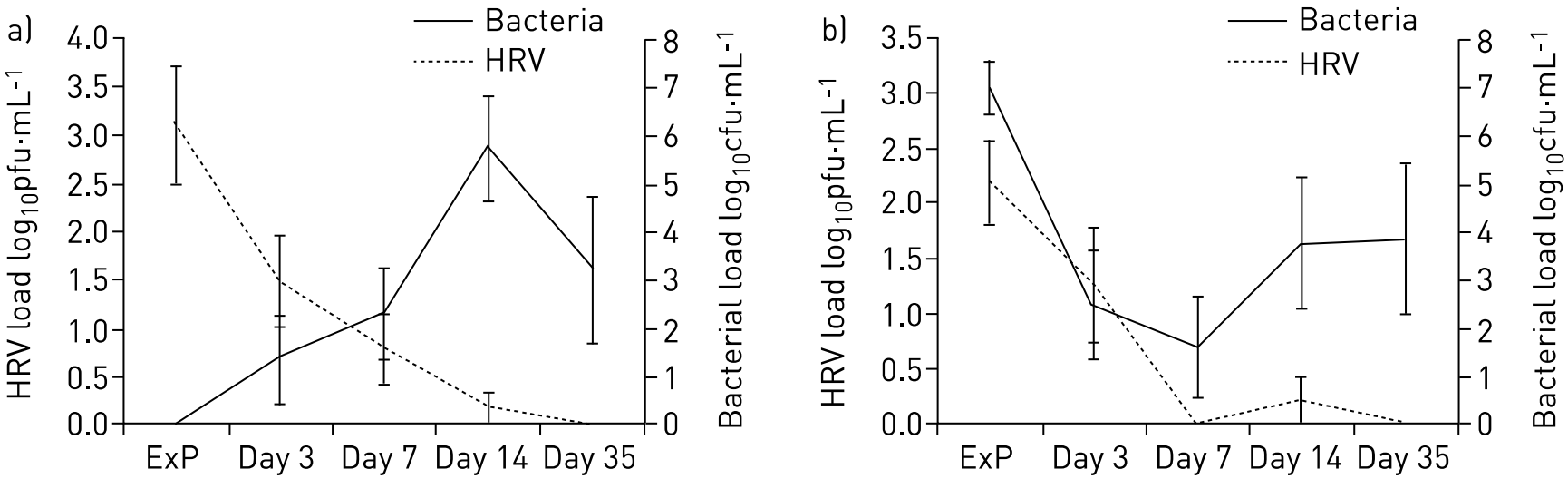


Figure 3. **Rates of Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group.**

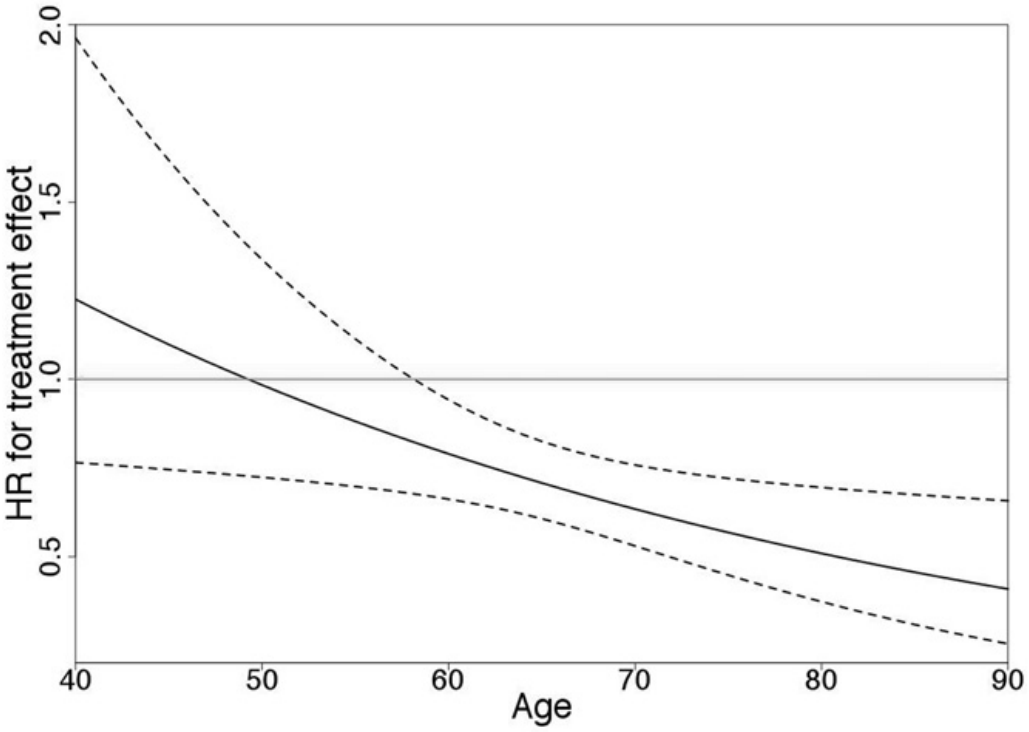
Rinovirus: più importanti di quanto si creda (George SN et al. Eur Respir J. 2014; 44: 87)



E i batteri spesso seguono i Rinovirus dopo anche 14 giorni (George SN et al. Eur Respir J. 2014; 44: 87)



L'età è predittore positivo di risposta alla profilassi con azitromicina (Han MK et al. Am J Respir Crit Care Med 2014; 189: 1503)

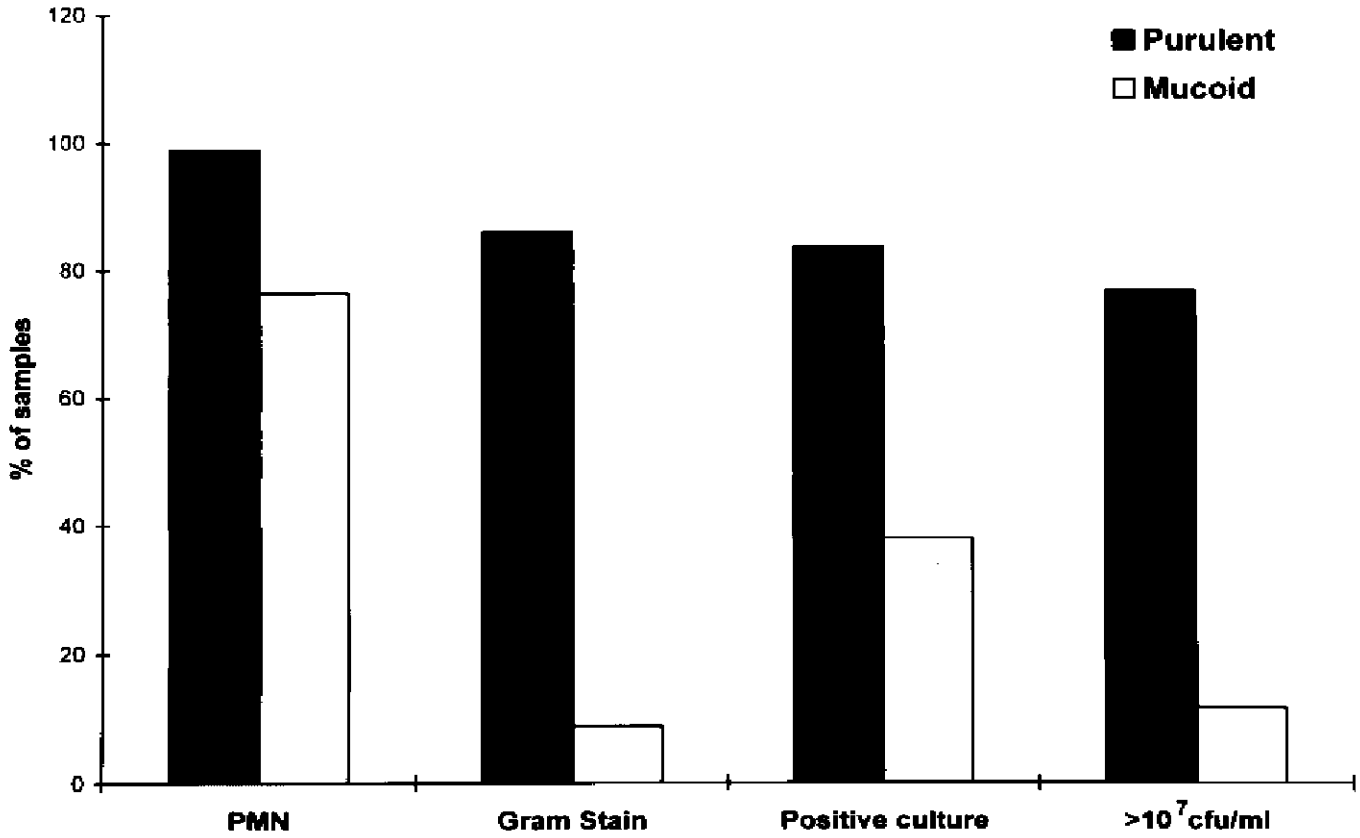


Accertamento dell’eziologia infettiva possibile se…

- VIRUS
- Colture cellulari
- Sierologia
- PCR

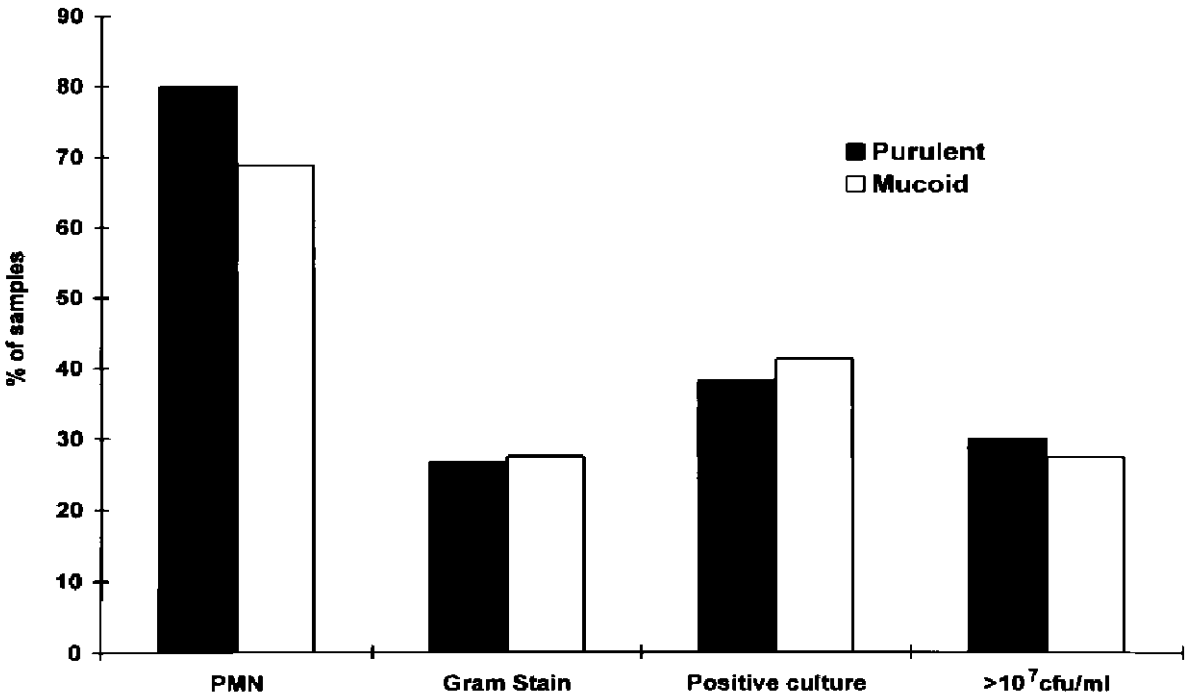
- BATTERI
- Esame microscopico e colturale dell’escreato
- BAL protetto

La conferma dell'eziologia batterica se l'escreato è purulento (Stockley RA et al. Chest 2000; 117: 1638)



Ma la coltura può essere positiva in fase stabile

(Stockley RA et al. Chest 2000; 117: 1638)



Riacutizzazioni mortali nell'anziano: cause infettive in minoranza (Zvezdin B et al. CHEST 2009; 136:376–380)

Characteristics	Cardiac Failure (n = 16)	Pneumonia (n = 12)	PTE (n = 9)	Respiratory Failure Secondary to COPD (n = 6)	p Value	Total
Age, yr	70 (64–75)	69 (67–72)	70 (59–74)	74 (67–85)	0.44	
Male gender	12 (75)	8 (66)	6 (66)	5 (83)	0.86	
History of tobacco smoking	12 (75)	11 (92)	7 (70)	3 (50)	0.47	
Duration of illness, yr	5 (3–12)	10 (5–10)	10 (5–18)	13 (10–16)	0.23	
Hospitalization in a previous year	8 (50)	5 (41)	3 (33)	3 (50)	0.83	
Comorbidities						
Chronic heart failure	12 (75)	6 (50)	2 (22)	5 (83)		25 (58)
Diabetes mellitus	3 (16)	2 (17)	3 (33)	1 (17)		9 (21)
Liver cirrhosis	0 (0)	2 (17)	0 (0)	0 (0)		2 (5)
Osteoporosis	1 (6)	0 (0)	0 (0)	1 (17)		2 (5)
Peptic ulcer	4 (25)	2 (17)	1 (11)	2 (33)		9 (21)
Carcinomas	4 (25)	1 (8)	1 (11)	0 (0)		6 (14)
Atherosclerosis	10 (63)	5 (42)	0 (0)	4 (66)		19 (44)

Values are given as median (IQR) or No. (%), unless otherwise indicated.

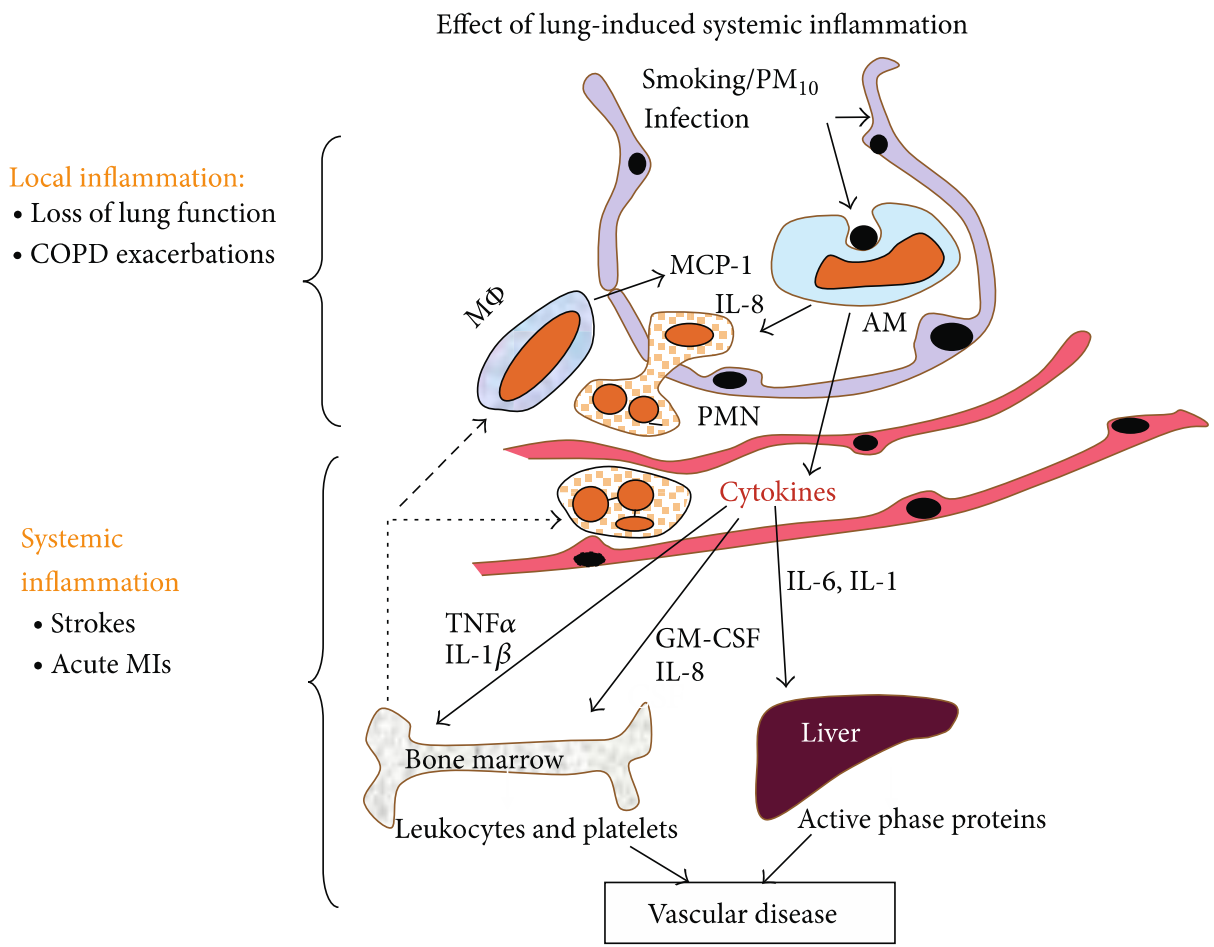
Ruolo della comorbilità nel profilo di rischio

(Yoo J et al. J Korean Med Sci 2011; 26: 1606-1612)

Table 5. A multivariate logistic regression model for the risk factors of COPD exacerbation using conventional clinical and physiological information

Variables	Odds ratio	95% CI	*P* value
Age (yr)	1.05	1.01-1.09	0.02
Hospitalization due to exacerbation during past one year	2.34	0.87-6.30	0.09
Charlson index score	2.07	1.04-4.11	0.04
Post-bronchdilator FEV_1 (% predicted)	0.97	0.96-0.99	0.002

La riacutizzazione può innescare un danno cardiovascolare (BioMed Res Int Volume 2014, Article ID 528789)



Il razionale per ischemia coronarica e cerebrale in corso di riacutizzazione di BPCO (Laratta CR et al. BioMed Res Int Volume 2014, Article ID 528789)

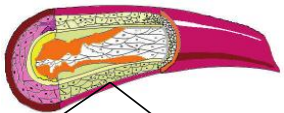
AECOPD destabilize atherosclerotic plaques

COPD lung inflammation + infection

↓

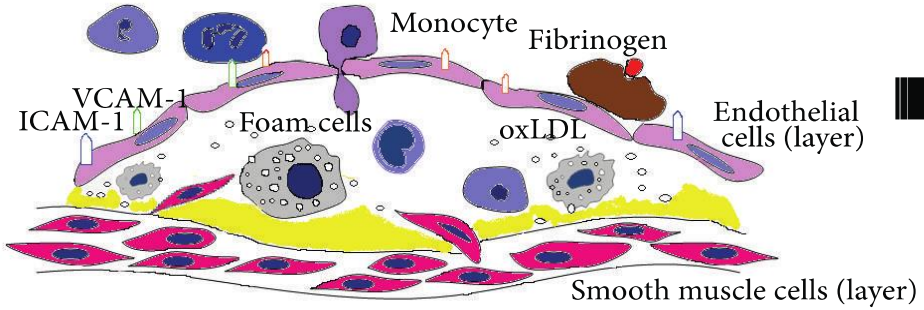
Systemic inflammation

- CRP and fibrinogen
- Cytokines (TNFα, IL-1β, IL-6)
- Leukocytes and platelets



Blood vessel activation and endothelial dysfunction

- ↑ Endothelial permeability
- ↑ ROS and uptake of oxLDL
- ↑ ET-1, ↓ NO
- ↓ Vasodilatation



Atherosclerotic plaque

Cause and destabilize plaques:
- ↑ Adhesion molecule expression
- ↑ Monocyte recruitment
- ↑ Plaque cellularity
- ↑ Foam cells and plaque lipid content
- ↑ Smooth muscle cell proliferation
- ↑ Proteinase activity (MMP's)
- ↓ Fibrous cap of plaques

↓

Heart attacks and strokes

Rischio di riacutizzazione da Pseudomonas

First author [Ref.]	Risk factors
Eller [36]	FEV_1 of <35% pred
	Pretreatment with antibiotics
Miravitlles [37]	FEV_1 of <50% pred
Monsó [38]	Low FEV_1
	Oral corticosteroid use
	Antibiotics in previous 3 months
	Protective effect of antiinfluenza vaccine
Allegra [39]	FEV_1 of <35% pred
Lode [40]	FEV_1 of <35% pred
	Systemic steroid use
	Antibiotics in previous 3 months

FEV_1: forced expiratory volume in one second.

Le bronchiectasie: una causa sottostimata di infezione da Pseudomonas nella BPCO (Ringshausen FC et al. PLOS One 2013; 8: e71109)

Table 2. Secondary diagnoses when bronchiectasis is the primary diagnosis during hospitalization, classified by putative infectious and non-infectious complications as well as diagnoses commonly associated with bronchiectasis (n = 12,251).

ICD-10	Secondary diagnosis	Frequency	Percentage
Putative infectious and non-infectious bronchiectasis-associated complications			
J96	Respiratory failure	2,831	23.1
J20–J22, J40–J42	Bronchitis and bronchiolitis	1,955	16.0
R04	Hemoptysis	1,831	14.9
J09–J18	Influenza and pneumonia	1,074	8.8
I27	Pulmonary heart diseases	598	4.8
R64	Cachexia	358	2.9
Diagnoses commonly associated with bronchiectasis			
J43–J44	COPD and emphysema	4,799	39.2
J45–J46	Asthma	787	6.4
J32	Chronic sinusitis	461	3.8
K21	Gastroesophageal reflux disease	412	3.4
J84	Interstitial lung disease	336	2.7
D38	Airway or chest neoplasm of uncertain or unknown behavior	320	2.6

GER: una causa di riacutizzazione misconosciuta

(Terada K et al. Thorax 2008;63:951–955)

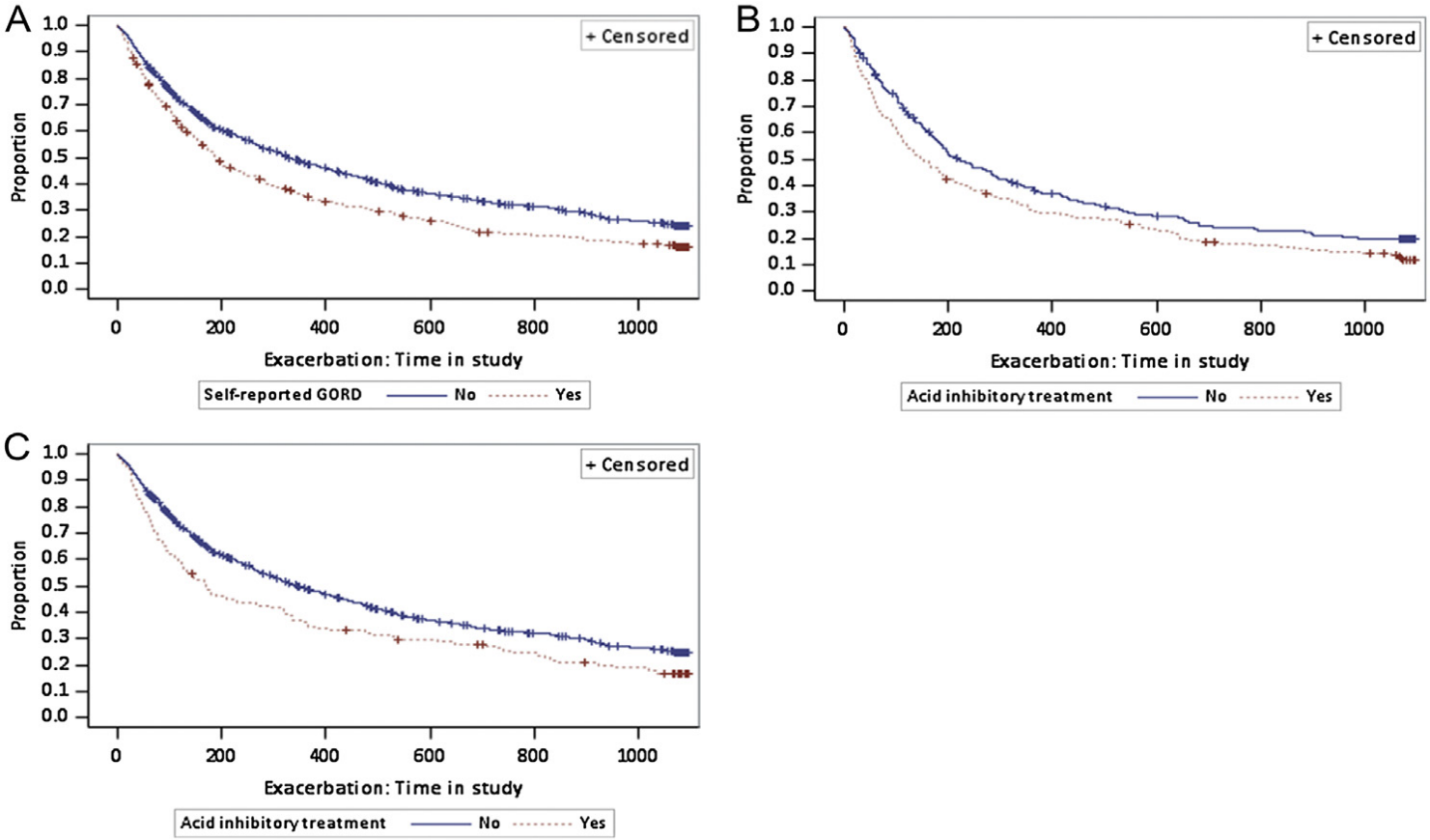
Table 3 Associations between exacerbations and GORD symptoms in patients with COPD

GORD symptoms	COPD exacerbation		Exacerbation frequency over 6 months
	Did not occur	Did occur	
Negative	36	24	0.70 (1.20
Positive	5	17	1.73 (1.58
p Value	<0.01		<0.01

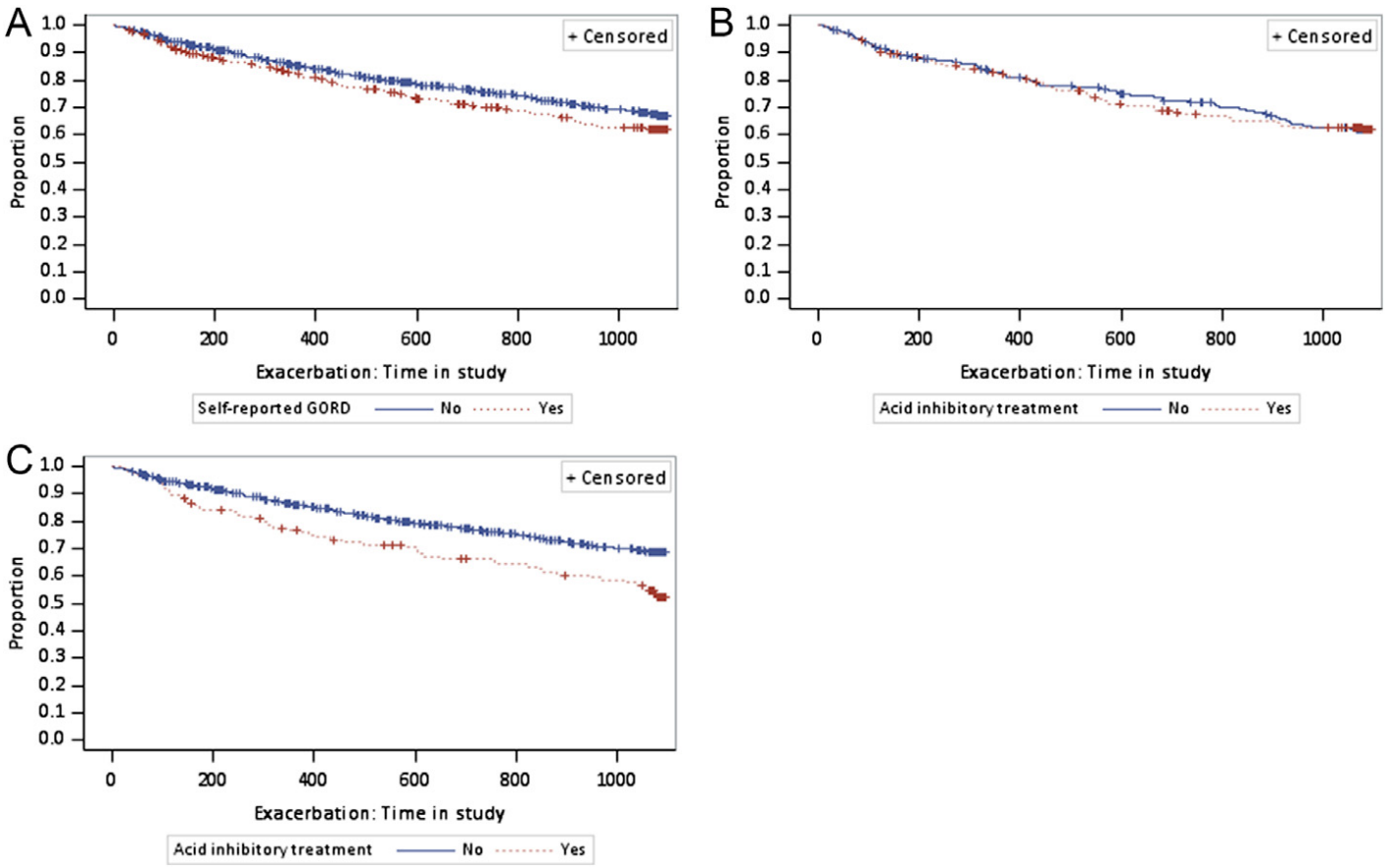
Data were evaluated by the χ^2 test and the unpaired t test. The relative risk for the occurrence of exacerbation in patients with GORD symptoms compared with patients without such symptoms was 1.93 (95% CI 1.32 to 2.84; $p<0.01$).
COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease.

Ma PPI non migliorano la situazione in una coorte Eclipse (età media 63 anni)

V.S. Benson et al. / Respiratory Medicine 109 (2015) 1147–1154



…anzi, aumentano il rischio di ricovero



Non così nel Copenaghen Health Study (T.S. Ingebrigtsen et al. Respirology 20 (2015) 101e107)

Table 2 Gastro-esophageal reflux disease and risk of exacerbations in COPD

	Risk of exacerbations		Subgroup analysis: GOLD 2–4	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Coexisting night-time and daytime gastro-esophageal reflux disease and no regular use of acid inhibitory treatment†	2.7 (1.3–5.4)	0.006	2.6 (1.2–5.8)	0.02
Coexisting night-time and daytime gastro-esophageal reflux disease and regular use of acid inhibitory treatment†	1.2 (0.6–2.7)	0.63	0.8 (0.3–2.3)	0.68
Either night-time or daytime gastro-esophageal reflux disease but not coexisting, and no regular use of acid inhibitory treatment†	1.7 (1.0–3.0)	0.05	1.2 (0.6–2.5)	0.55
Either night-time or daytime gastro-esophageal reflux disease but not coexisting, and regular use of acid inhibitory treatment†	0.3 (0.05–2.4)	0.28	0.4 (0.05–2.6)	0.32
No gastro-esophageal reflux disease but regular use of acid inhibitory treatment†	1.8 (0.9–3.5)	0.08	1.4 (0.6–3.2)	0.46

Altre conferme sul ruolo del GER

Study	Age (y)	Yearly exacerbations
Rogha M J Gastrointestin Liver Dis September 2010 Vol.19 No 3, 253-256	68	2.1 vs 1.4 ($p<0.001$)
Rascon-Aguilar I et al. CHEST 2006; 130:1096–1101	67	3.2 vs 1.6

Though being symptomatic, only a half of the subjects with severe COPD are properly labelled

	Criteria of COPD	Diagnosed (%)
NHANES III, USA	(BTS)	37
IBERPOC, Spain	ERS	22
DIMCA, Netherlands	(CNSLD)	35
OLIN, Sweden	BTS	31
	GOLD	18
An European assumption	(clinical)	25

Though being symptomatic, only a half of the subjects with severe COPD are properly labelled Lindberg A. et al., Respir. Med., 2005; 100: 264-72

Come prevenire le riacutizzazioni

(Rabe KF et al. Am J Respir
Crit Care Med 2007; 176: 532–555)

Proven efficacy
Quitting smoking
LABAs: salmeterol, formoterol
Tiotropium
Combination therapy: LABA/ICS
Anti-influenza vaccine
Antipneumococcal vaccine[#]
Rehabilitation
Physical exercise
Self-management plans
LVRS in selected patients
Questionable efficacy
Theophyllines
Prophylactic antibiotic in selected patients
Immunomodulators
Mucolytic agents
Antioxidants

LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; LVRS: lung volume reduction surgery. [#]: efficacy demonstrated in prevention of pneumonia, but not in prevention of exacerbations.

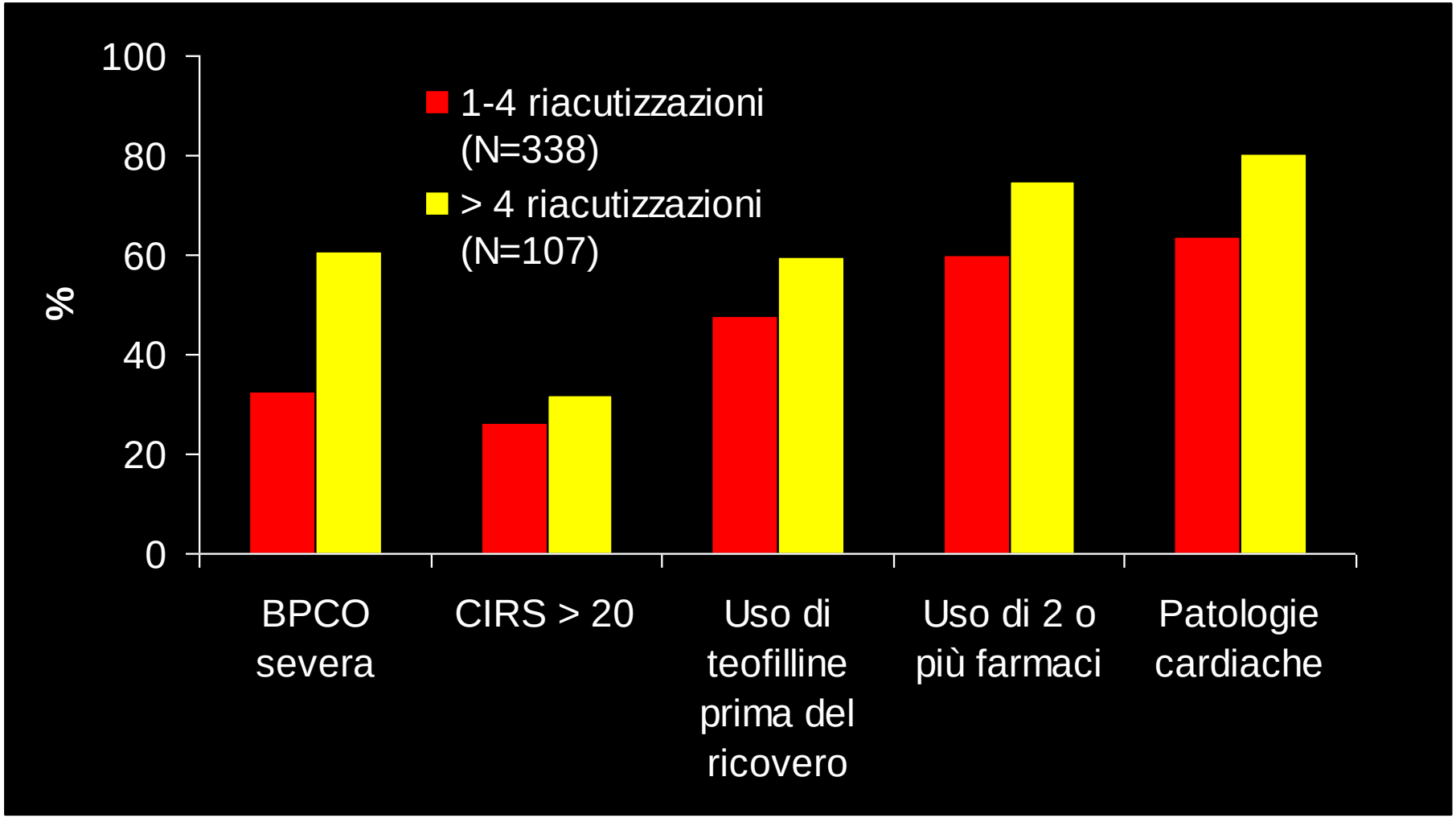
Il profilo di rischio per riacutizzazione: il contributo dello studio OLD-COPD (N=810)

Età (anni)	76.2 ± 6.8
Sesso (M)	511 (63.1)
BMI (Kg/m^2)	27.0 ± 11.2
BPCO nuova diagnosi	50 (6.2)
BPCO vecchia diagnosi	760 (93.8)
Durata BPCO (anni)	15.5 ± 9.6
Gravità della BPCO	
Lieve	139 (17.2)
Moderata	376 (46.4)
Grave	231 (28.5)

Comorbilità della BPCO nella popolazione OLD-COPD (N=810)

Cardiopatie	576 (71.1)
Ipertensione	525 (64.8)
Patologie genitourinarie	294 (36.3)
Patologie del tratto gastroenterico superiore	275 (34.0)
Patologie endocrino-metaboliche	267 (33.0)
Patologie del sistema muscolo-scheletrico	265 (32.7)
Patologie vascolari periferiche	263 (32.5)

Correlati del rischio di riacutizzazioni frequenti: analisi univariata (N=445)



Correlati del rischio di riacutizzazioni frequenti: modello di regressione logistica (N=445)

		OR	95%CI
Età (anni)		0.99	0.95-1.03
Sesso (F)		0.92	0.55-1.24
Grave vs. lieve-moderata		**2.36**	**1.40-3.99**
SGRQ totale			
	<50	**1.0**	
	50-70	**4.12**	**1.62-10.4**
	>70	**7.52**	**3.02-18.7**
Patologie cardiache		**1.81**	**1.01-3.25**

Calcolo dello score

Frazione attribuibile (AF=1-OR/OR)

BPCO severa=57.6%

SGRQ totale 50-70=75.7%

SGRQ totale>70=86.7%

Cardiopatie=44.7%

Score parziale=AF/10 (approssimato all'unità)

BPCO severa=6

SGRQ totale 50-70=8

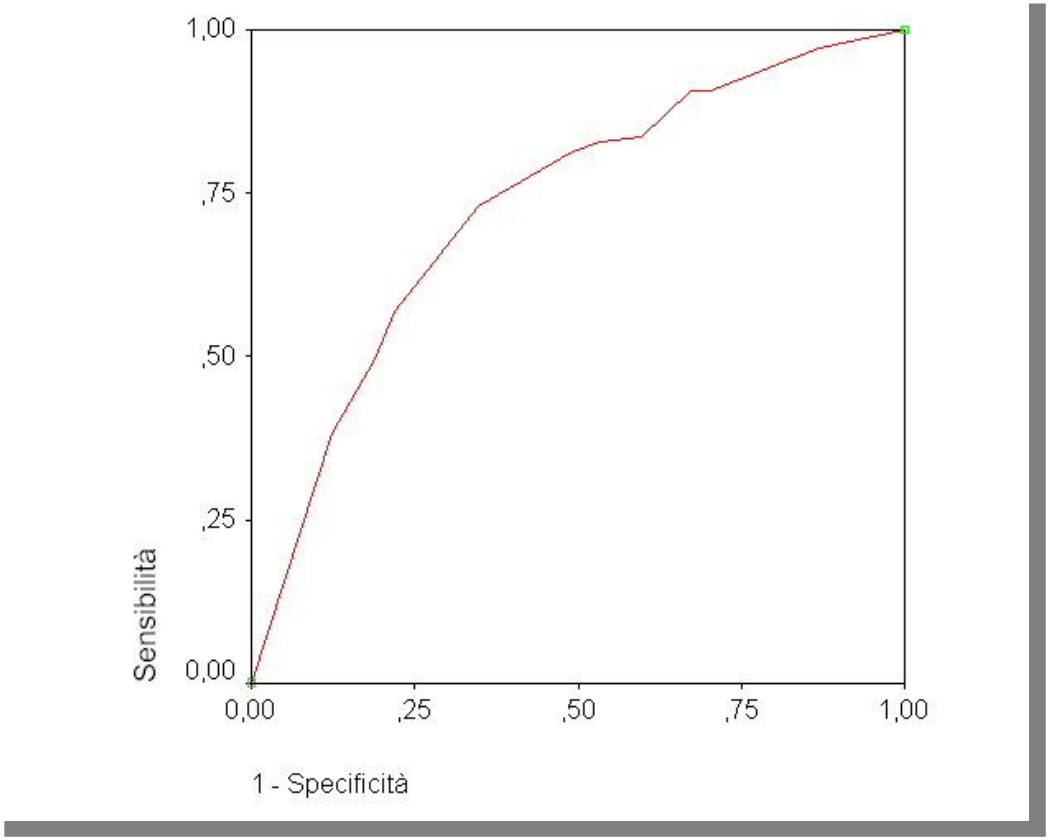
SGRQ totale>70=9

Cardiopatie=5

Score totale=somma dei singoli scores parziali

Esempio - paziente con BPCO severa, SGRQ totale=80 e cardiopatia; score totale = 6+9+5 = 20

Analisi della curva ROC



Valore	Sensibilità	1-Specificità
-1,0	1,0	1,0
2,5	,972	,870
5,5	,907	
7,0	,907	,672
8,5	,841	,595
10,0	,832	,533
12,0	,813	,491
13,5	**,729**	**,346**
14,5	,570	,219
17,0	,495	,189
19,5	,383	,124
21,0	,000	,000

Rischio di ricovero per BPCO: modelli disponibili

- **Due predittori:**
  - Patologia cardiorespiratoria
  - >4 esacerbazioni nell'ultimo anno

  Sensibilità: 75%

  Specificità: 47%

Ball P et al, Q J Med 1995; 88: 61.

- **Due predittori:**
  - CHF, CAD o Diabete;
  - FEV1%

  AUC: 0.633

Miravitlles M et al, Respiration 2000; 67: 495

Rischio di esacerbazioni frequenti: evidenze disponibili.

- <u>Tre predittori</u>
  - Età (per decade);
  - FEV1% (ogni 10 unità);
  - Ipersecrezione mucosa;

  AUC (ROC): 0.633

Miravitlles M et al, Respiration 2000; 67: 495.

Identificazione dei correlati delle riacutizzazioni frequenti

- L'identificazione dei soggetti a rischio di riacutizzazioni frequenti appare auspicabile al fine di adottare misure preventive in grado di ridurre i costi dell'assistenza
- Il modello sviluppato
  - ha un buon mix di sensibilità e specificità
  - è di facile applicazione non richiedendo l'uso di variabili strumentali
  - permette pertanto di acquisire informazioni prognostiche a costo zero
  - è in corso di validazione prospettica

Progetto OLD - Centri partecipanti

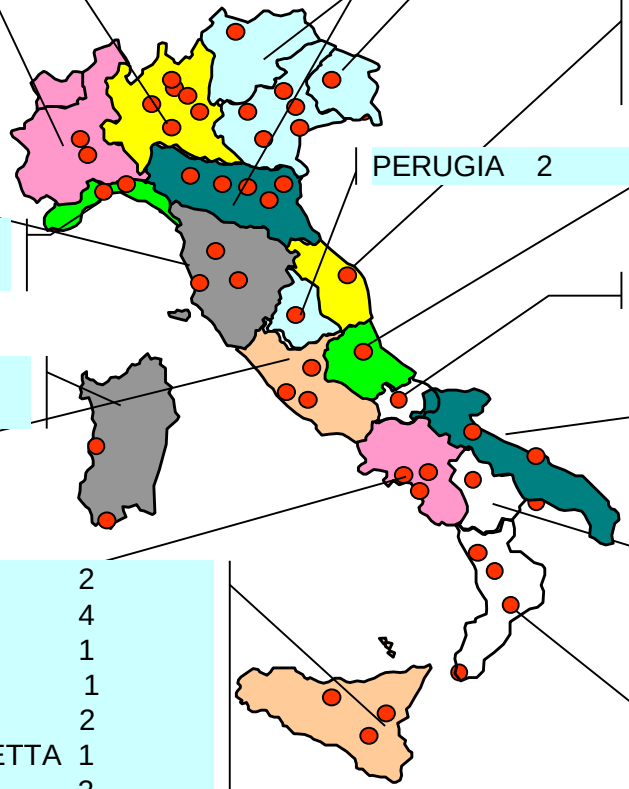
BRESCIA	5
MILANO	4
CREMONA	1
BERGAMO	2
PAVIA	2
MANTOVA	1
LECCO	1
SONDRIO	1

PARMA	1
MODENA	2
RIMINI	1
FORLI'	1
RAVENNA	1

UDINE	1
TRIESTE	1
PORDENONE	1

VENEZIA	2
TREVISO	1
PADOVA	2
BOLZANO	1
VERONA	4
ROVIGO	1

TORINO	3
ASTI	2
CUNEO	1
NOVARA	1



PESARO	1
ASCOLI PICENO	1
MACERATA	2

AREZZO	1
SIENA	1
GROSSETO	2
FIRENZE	1
PISA	1

GENOVA	2
IMPERIA	1

PERUGIA	2

AQUILA	2
PESCARA	2
TERAMO	1

CAMPOBASSO	1

CAGLIARI	1
SASSARI	1

BARI	3
FOGGIA	1
TARANTO	6
LECCE	1

ROMA	8
RIETI	2
FROSINONE	1
VITERBO	1

POTENZA	1

NAPOL I	4
SALERNO	2
CASERTA	3

TRAPANI	2
PALERMO	4
CATANIA	1
MESSINA	1
AGRIGENTO	2
CALTANISSETTA	1
SIRACUSA	2
ENNA	2

COSENZA	1
CATANZARO	1
REGGIO CALABRIA	1

L'ipovitaminosi D fattore di rischio per riacutizzazione? Aspettiamo il PRECOVID

Table 1 Eligibility criteria for the PRECOVID trial

Inclusion criteria	Exclusion criteria
Vitamin D deficiency (serum 25(OH)D < 50 nmol/l)	Severe vitamin D deficiency (serum 25(OH)D <15 nmol/l),
Postbronchodilator $FEV_1/FVC < 0.70$, $FEV_1 < 80$ % and diagnosis COPD confirmed by a physician	Use of a supplement containing more than 400 IU vitamin D per day
Recent COPD exacerbation	Use of maintenance dose oral corticosteroids
≥10 packyears of smoking	Diagnosed asthma
Age ≥ 40 years	Diagnosed osteoporosis
Written informed consent	Self-reported history of hypercalcaemia or nephrolithiasis
Ability to comply with all study requirements.	Self-reported presence of sarcoidosis
	Diagnosed chronic kidney disease stage 4 or higher (eGFR ≤ 29 ml/min/1.73 m2)
	Interfering malignant diseases
	Life expectation of less than 1 year on the basis of concurrent disease
	Current participation in a clinical rehabilitation program
	Pregnant or lactating women, or subjects who intend to become pregnant within the study period
	Potentially unreliable patients and those judged by the investigator to be unsuitable for the study
	Serious mental impairment i.e. preventing to understand the study protocol or comply with the study aim

25(OH)D 25-hydroxyvitamin D, *FEV_1* Forced Expiratory Volume in one second, *FVC* Forced Vital Capacity, *eGFR* estimated Glomerular Filtration Rate with the MDRD formula

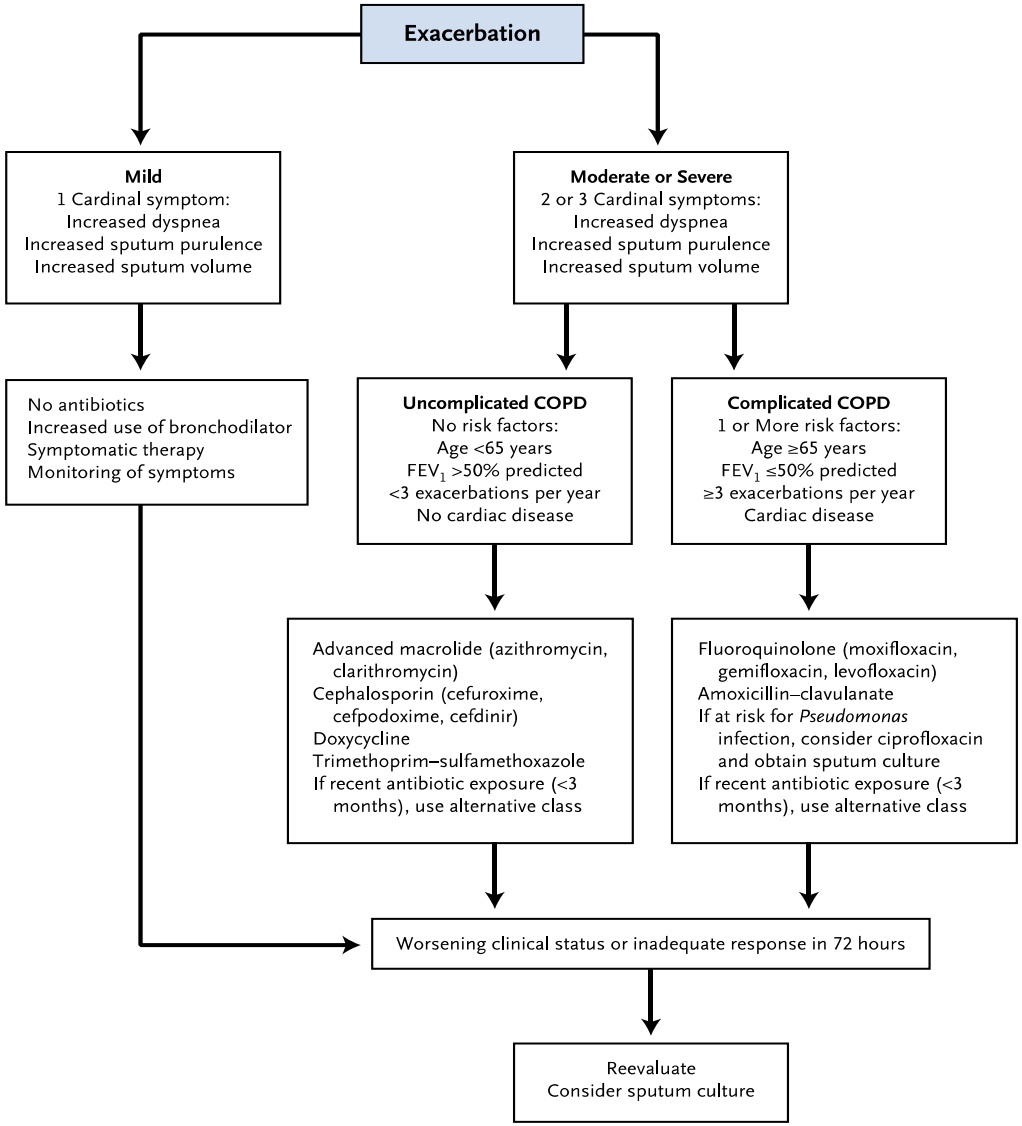


Figure 4. Algorithm for Antibiotic Treatment in Patients with Acute Exacerbations of COPD.
FEV_1 denotes forced expiratory volume in 1 second.

Sethi T et al. N Engl J Med 2008; 359:2355-65.

La riacutizzazione: esordio paziente-specifico

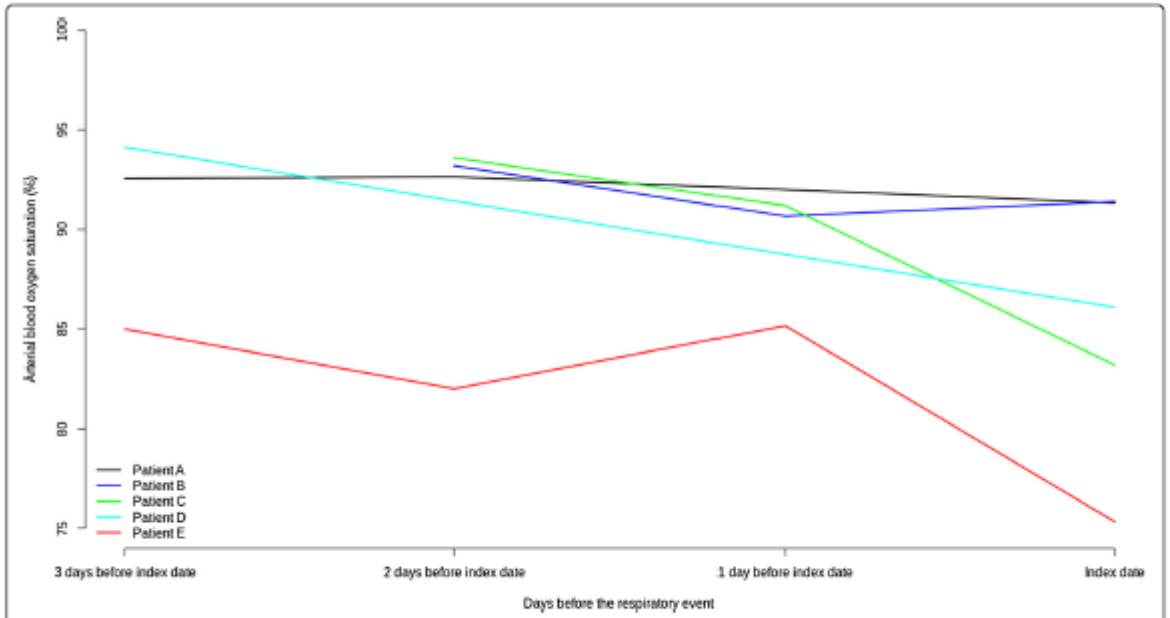


Figure 3 Arterial oxygen saturation in the three days preceding the respiratory event. Trend of the arterial oxygen saturation in the three days before a respiratory event. Each line represents data from a single patient.

Pedone *et al. BMC Health Services Research* 2013, **13**:82
http://www.biomedcentral.com/1472-6963/13/82

Serve quindi un monitoraggio multiparametrico

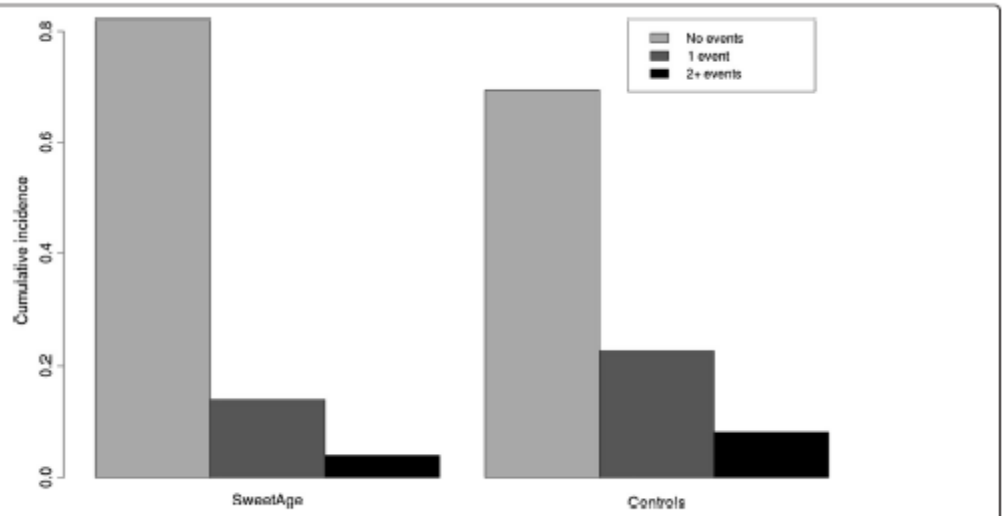


Figure 2 Cumulative incidence of events.

Pedone *et al. BMC Health Services Research* 2013, **13**:82
http://www.biomedcentral.com/1472-6963/13/82

Cause di riacutizzazione nell’anziano: conclusioni

- Non documentati, ma ipotizzabili elementi di specificità per l’anziano
- Cause infettive verosimilmente sottostimate
- Tra le cause infettive ruolo dei Rinovirus e virus in generale forse sottostimato
- In una frazione imprecisato probabile sequenza virus>>batteri
- Segni e sintomi prodromici poco noti
- Dimensione sociale del profilo di rischio ignorata