Personalized Management of Exacerbation

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Today`s Table

- Personalized management of exacerbation
  - Heterogeneity of AECOPD
    - Sputum color, Sputum purulence, Sputum microbiome, blood eosinophil, and FeNO
  - Personalized management of AECOPD
    - Antibiotics
    - Systemic corticosteroid
    - Comorbid condition: CHF, DD

What is personalized management?

Personalized means...

Definition of personalized medicine?

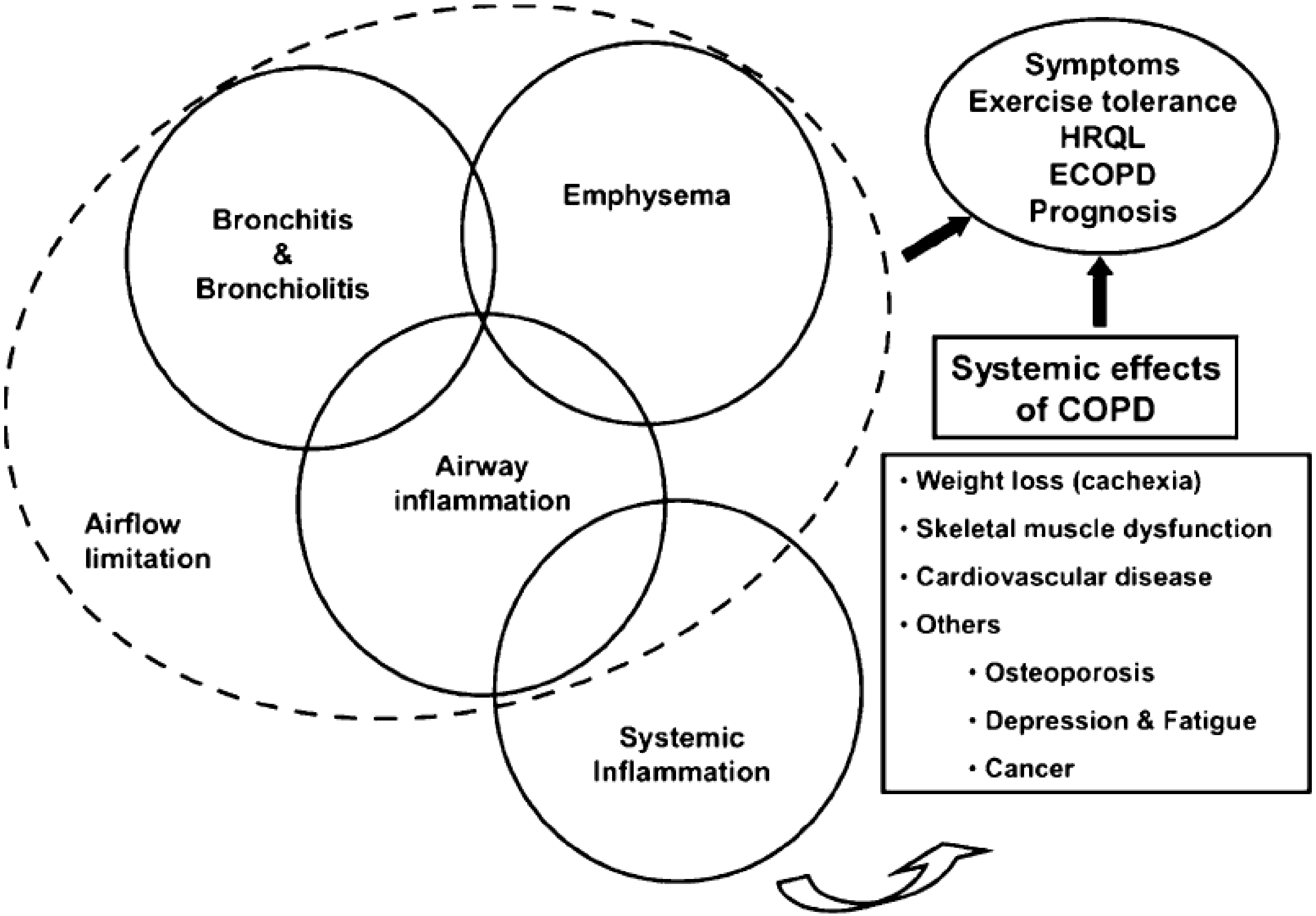
- "Therapeutic approach involving the use of an individual's genetic and epigenetic information to tailor drug therapy or preventive care."

– Nature review

- "특정 질병에 대한 민감성 또는 특정 치료에 대한 반응에서 차이를 보이는 개인을 소집단으로 분류하여 집단에 속하는 개인별 특성을 고려한 의료"

– 미 대통령 과학기술자문위원회

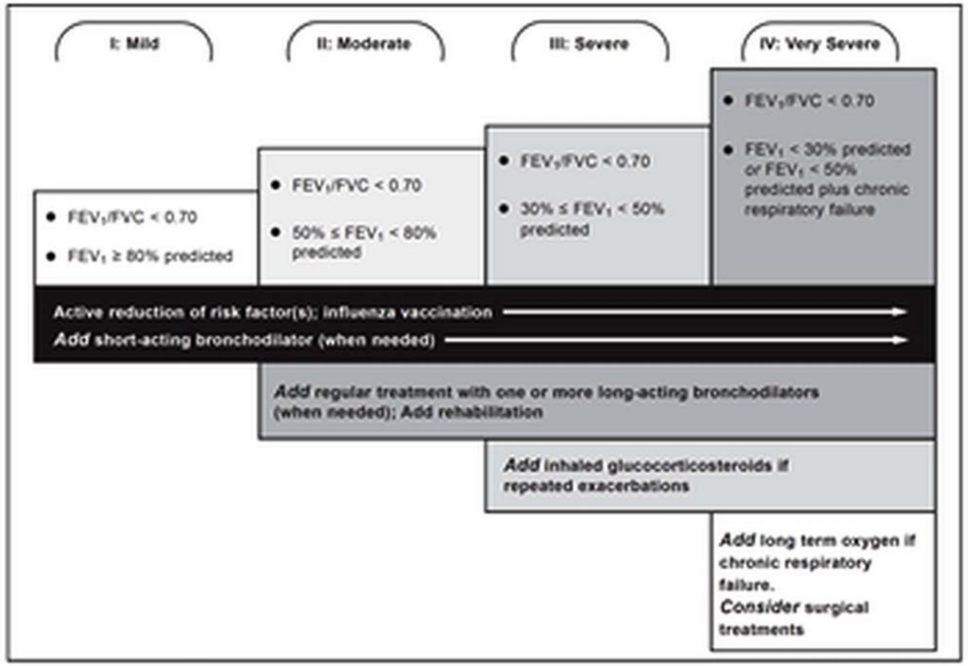
Personalized aspects of COPD: Heterogeneity



Agusti et al. Am J Respir Crit Care Med Vol 183. pp 1129–1137, 2011

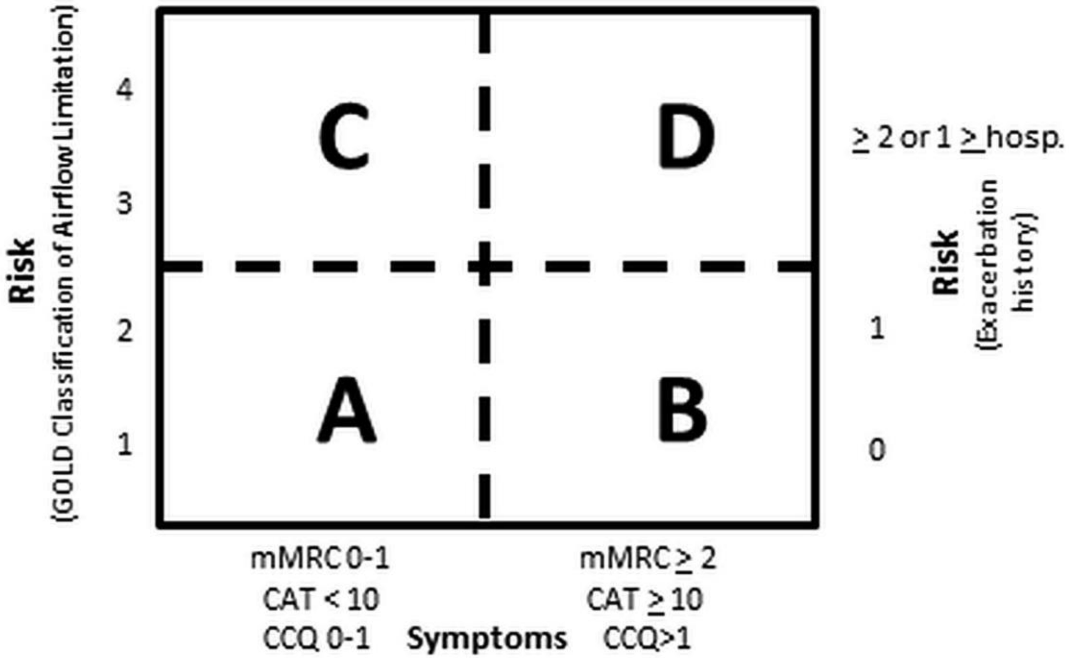
Personalized aspects of COPD: History

2006



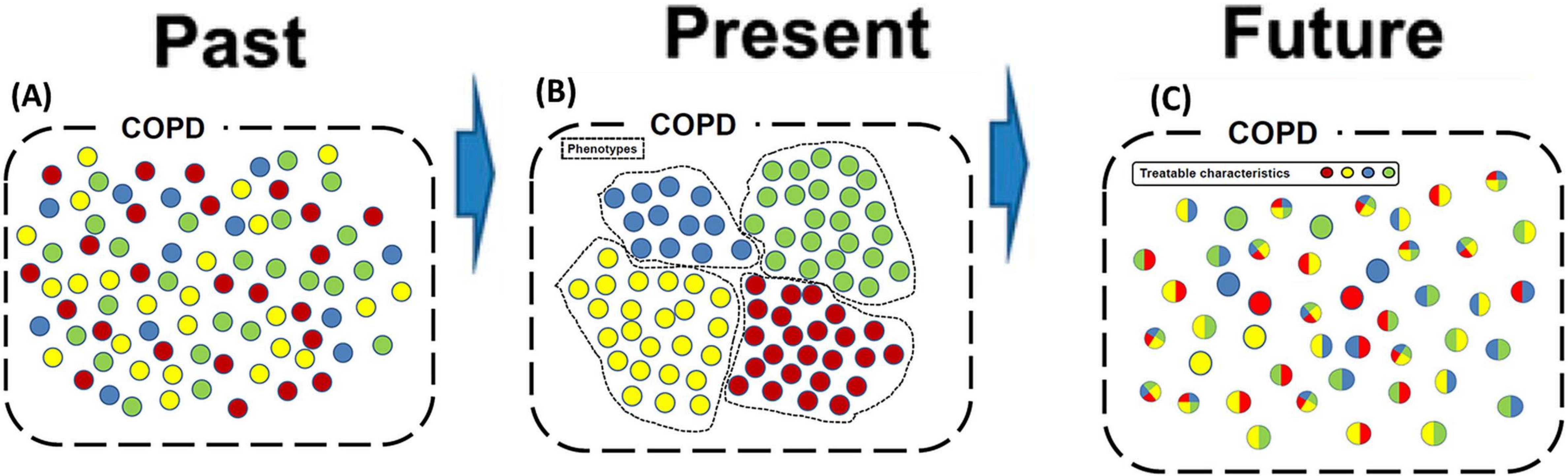
*Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.

2011



Agusti A. Thorax 2014;69:857–864. doi:10.1136/thoraxjnl-2014-205507

Classic → Stratified → Personal



Agusti A. Thorax 2014;69:857–864. doi:10.1136/thoraxjnl-2014-205507

Personalized management of Exacerbation

Management of AECOPD

- **Keys of AECOPD**
  - Bronchodilator
  - **Systemic corticosteroid** ↔ increase of mortality
  - **Antibiotics**
    - Only to mod-severe AECOPD with increased cough and sputum prulence (GOLD guideline)
    - Non-infectious cause: ~ 20%

↔ increase of multi-drug resistant pathogen

→ Understand of phenotypes in AECOPD

Heterogeneity of AECOPD

AECOPD phenotype?

- Etiology
  - Bacteria (purulence, high CRP or PCT), virus (high IL-6, low CRP), environmental, unknown (1/3)
- Inflammatory: CRP, PCT, eosinophil, serum amyloid A, SP-D, fibrinogen etc.
- Comorbidity: Congestive heart failure, Diaphragm dysfunction etc.
- Frequent exacerbation

Zhou et al. International Journal of COPD 2017:12 1009–1018

Heterogeneity of AECOPD: definition

Pauwels et al. Respiratory Medicine (2004) 98,99–107

Table 1 Definitions of exacerbation used in interventional studies.

Study (author and intervention)	Definition	Basis of definition	
		Event	Symptom
Anthonisen et al., 1987; antibiotic therapy[19]	Type 1 The occurrence of increased dyspnea, sputum volume and sputum purulence Type 2 When two of these symptoms were present Type 3 When one of the three symptoms was present in addition to at least one of the following: upper respiratory infection within the past 5 days fever without other cause increased wheezing or cough increase in respiratory rate or heart rate by 20% as compared with baseline	—	√
Thompson et al., 1996; oral prednisone[40]	Subjective worsening of chronic baseline dyspnea or cough for more than 24 hours duration, necessitating a hospital visit; >25% increase in inhaled β-agonist use for more than 24 h or an increase in sputum production (more than one-fourth cup per day over baseline) and/or purulence (more than 25 neutrophils/field)	√	√
Niewoehner et al., 1999 (SCCOPE study); systemic	Hospital admission with clinical diagnosis of exacerbation	√	—

The Anthonisen classification of AECOPD, 1987

Table 1. Anthonisen classification of AECOPD

Type I (most severe)	Type II	Type III
All three symptoms (i.e., increased sputum volume, increased sputum purulence and increased dyspnea).	Any two symptoms present	One symptom present plus at least one of the following: • An upper respiratory tract infection in the past 5 days • Increased wheezing • Increased cough • Fever without an obvious source • A 20% increase in respiratory rate • Heart rate above baseline

Zhou et al. BC MEDICAL JOURNAL VOL. 50 NO. 3, APRIL 2008

Heterogeneity of AECOPD: biologic factors

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Identification of Biologic Clusters and Their Biomarkers

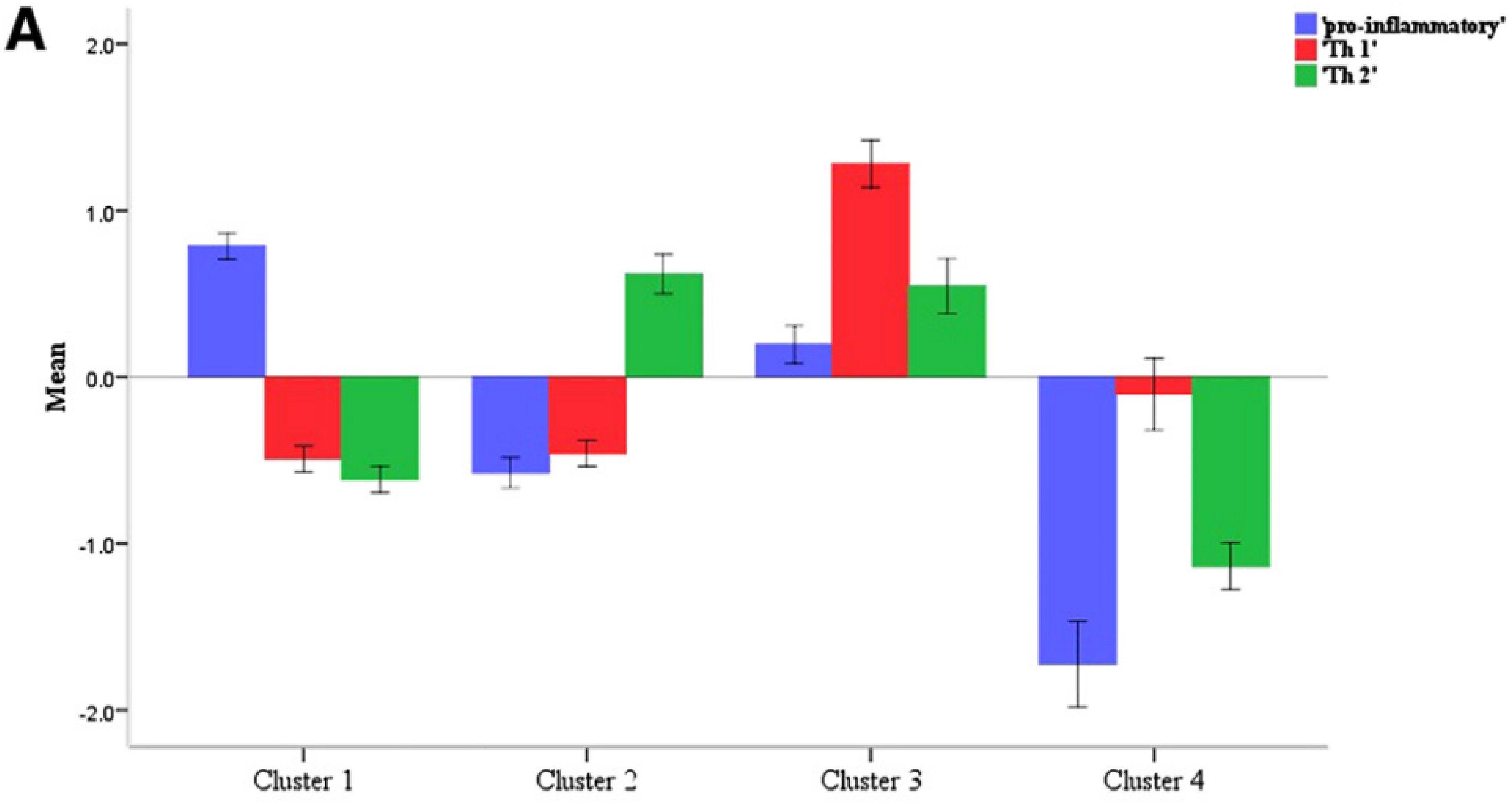
Mona Bafadhel[1,2], Susan McKenna[1], Sarah Terry[1], Vijay Mistry[1,2], Carlene Reid[1], Pranabashis Haldar[2], Margaret McCormick[3], Koirobi Haldar[2], Tatiana Kebadze[4], Annelyse Duvoix[5], Kerstin Lindblad[6], Hemu Patel[7], Paul Rugman[3], Paul Dodson[3], Martin Jenkins[3], Michael Saunders[3], Paul Newbold[3], Ruth H. Green[1], Per Venge[6], David A. Lomas[5], Michael R. Barer[2,7], Sebastian L. Johnston[4], Ian D. Pavord[1], and Christopher E. Brightling[1,2]

Clustered by

- Bacteria- : positive on one of H.influenza, M.catarrhalis, S.pneumoniae, S.aureus, P.aeruginosa
  aerobic CFU > 10^7cell
- Virus- : viral PCR (+)
- Sputum Eosinophilic- : 3%

Bafadhel et al. Am J Respir Crit Care Med Vol 184. pp 662–671, 2011

Heterogeneity of AECOPD: biologic factors



Bacteria-predominant

Eosinophil-predominant

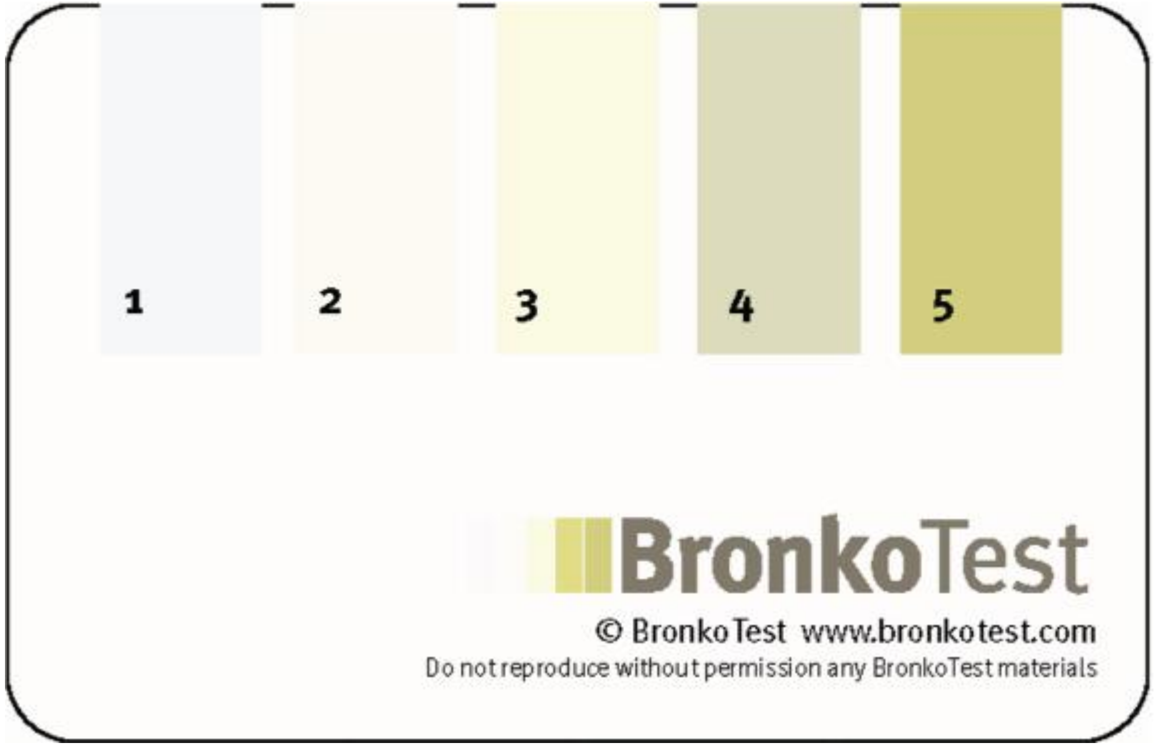
Virus-predominant

Pauci-inflammatory

Bafadhel et al. Am J Respir Crit Care Med Vol 184. pp 662–671, 2011

AECOPD classification - Sputum color/purulence

Sputum color chart



Sputum color chart – inflammation marker

Respirology

Murray et al. Eur Respir J August 2009 34:361–364;doi:10.1183
GOEMINNE et al. Respirology (2014)19, 203–210doi: 10.1111/resp.12219

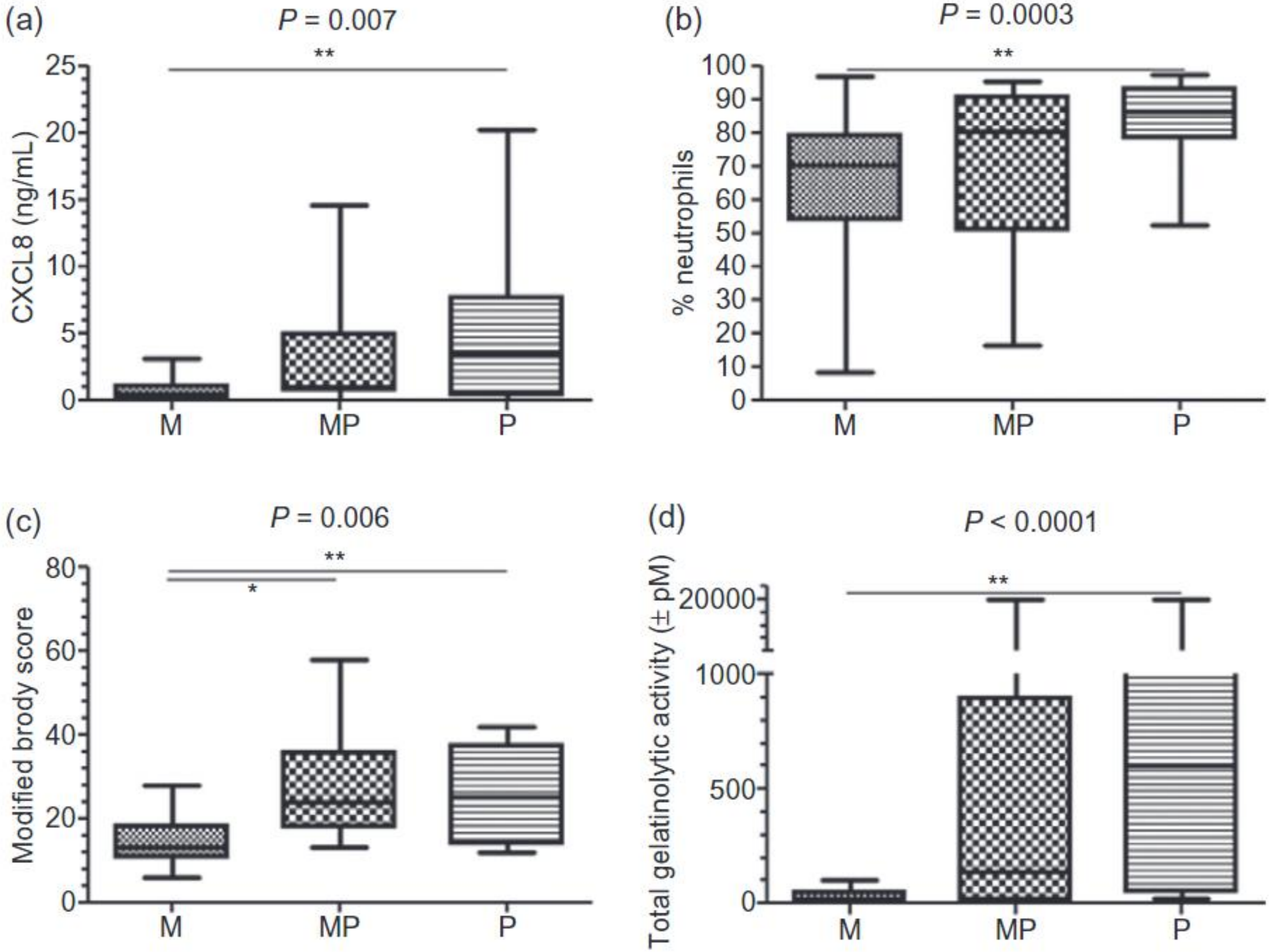
ORIGINAL ARTICLE

The Sputum Colour Chart as a predictor of lung inflammation, proteolysis and damage in non-cystic fibrosis bronchiectasis: A case–control analysis

M

MP

P

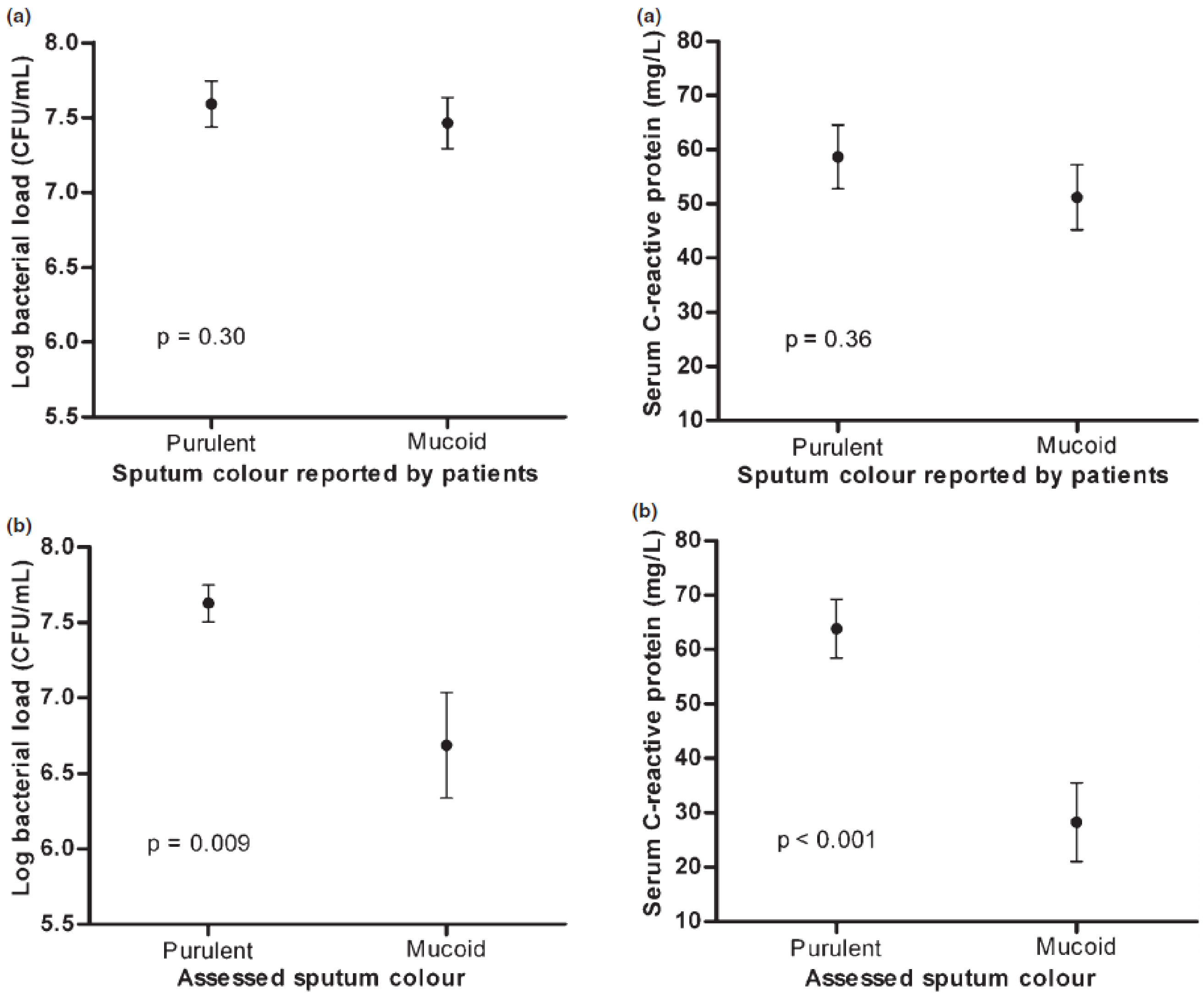


Sputum color for bacterial AECOPD – reliable?

	Sputum color grading (581 sputum samples/845 isolates)			
Bacterial growth				
Gram positive [#*S. pneumoniae*/*S.* spp./*S. aureus*]	107 (62.9%) [92/12/3]	214 (44.6%) [182/9/21]	36 (22.6%) [32/2/2]	7 (18.9%) [3/-/4]
Gram negative [#*H. influenzae*/*H. parainfluenzae*/*M. catarrhalis*]	32 (18.8%) [10/-/22]	239 (49.9%) [167/24/48]	62 (39%) [33/9/20]	14 (37.8%) [9/2/3]
P. aeruginosa/ *Enterobacteriaceae*	31 (18.2%)	26 (5.4%)	61 (38.3%)	16 (43.2%)
No bacterial growth [54/581 (9.2%) sputum samples]	32/145 (22%)	10/322 (2.1%)	7/93 (7.5%)	5/21 (23.8%)

Allegra et al. Respiratory Medicine (2005) 99, 742–747

Sputum color for bacterial COPD: not reliable?



Daniels et al. Clinical Microbiology and Infection, Volume 16 Number 6, June 2010

Sputum color for bacterial AECOPD: Chronic bronchitis

Eur Respir J 2012; 39: 1354–1360
DOI: 10.1183/09031936.00042111

Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis

Marc Miravitlles*, Frank Kruesmann[#], Daniel Haverstock[¶], Renee Perroncel[¶], Shurjeel H. Choudhri[+] and Pierre Arvis[§]

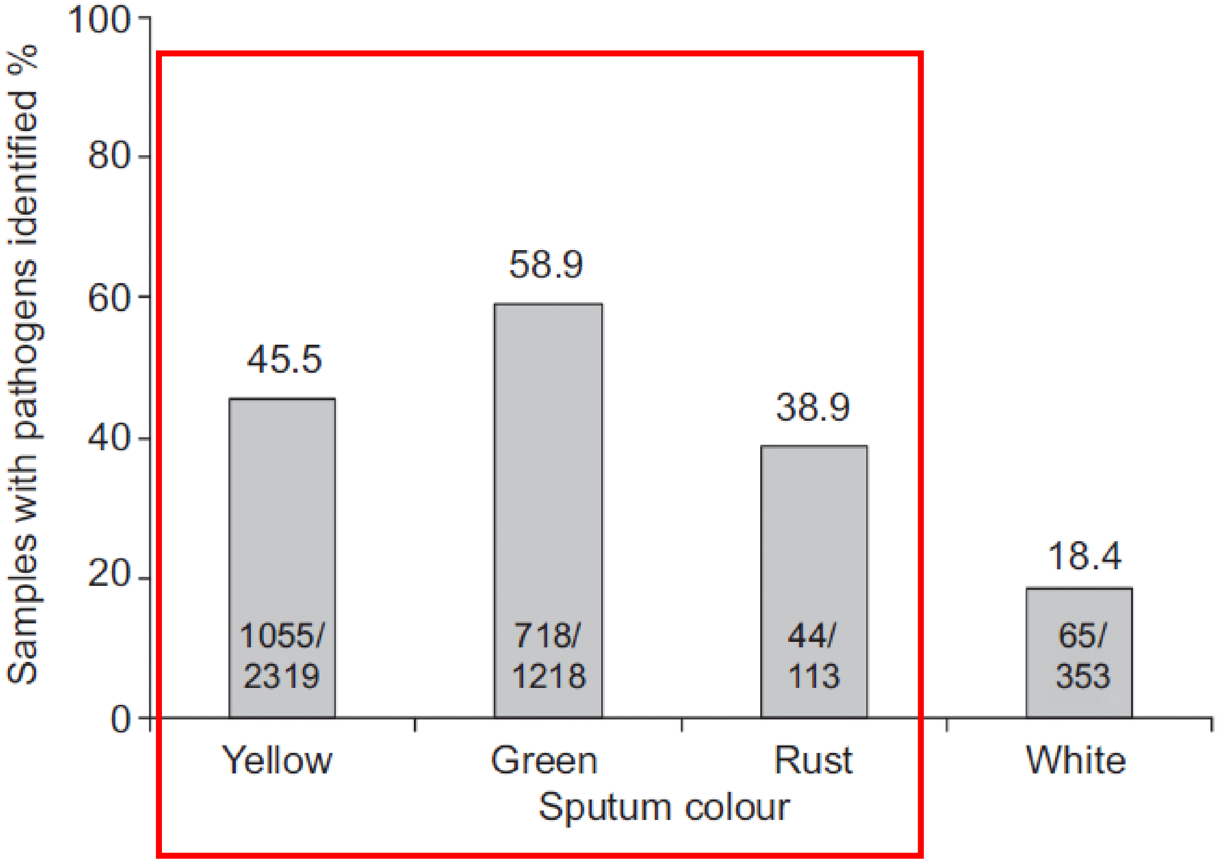
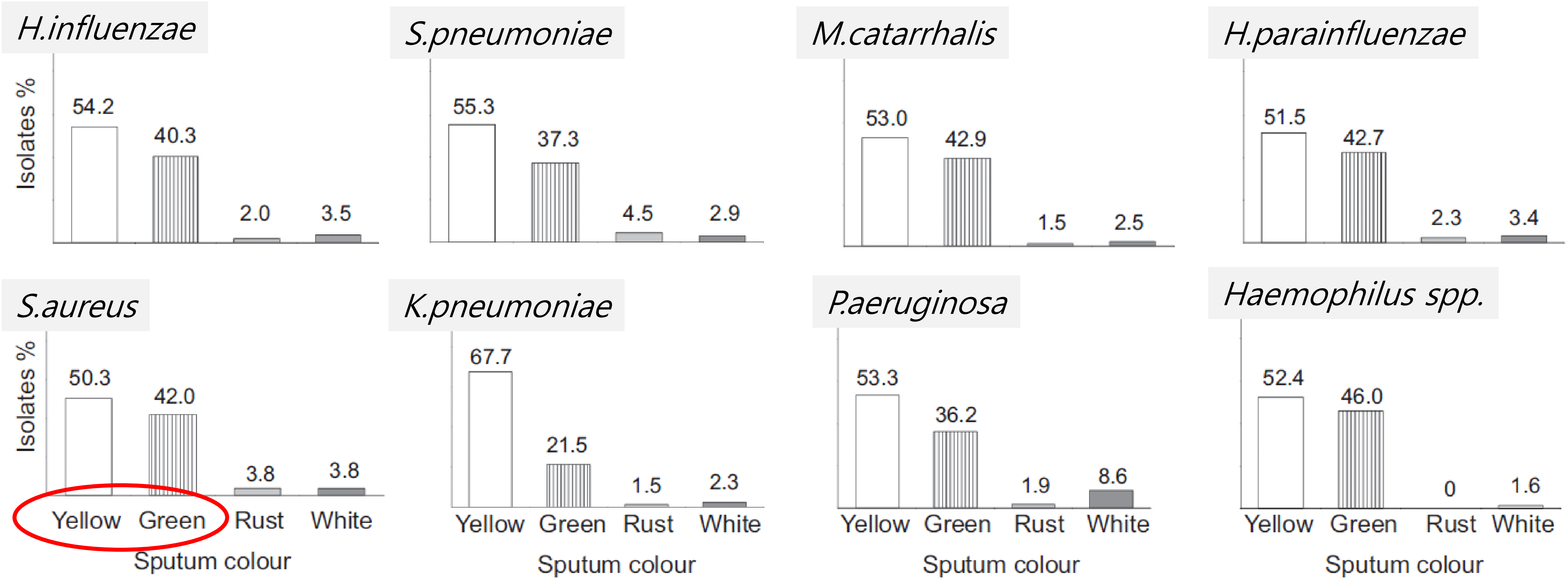


FIGURE 1. Percentage of sputum samples with an identified pathogen according to sputum colour. Data in the bars are presented as n/N.

Miravitlles et al. Eur Respir J 2012; 39: 1354–1360

Sputum color for bacterial AECOPD: Chronic bronchitis



Miravitlles et al. Eur Respir J 2012; 39: 1354–1360

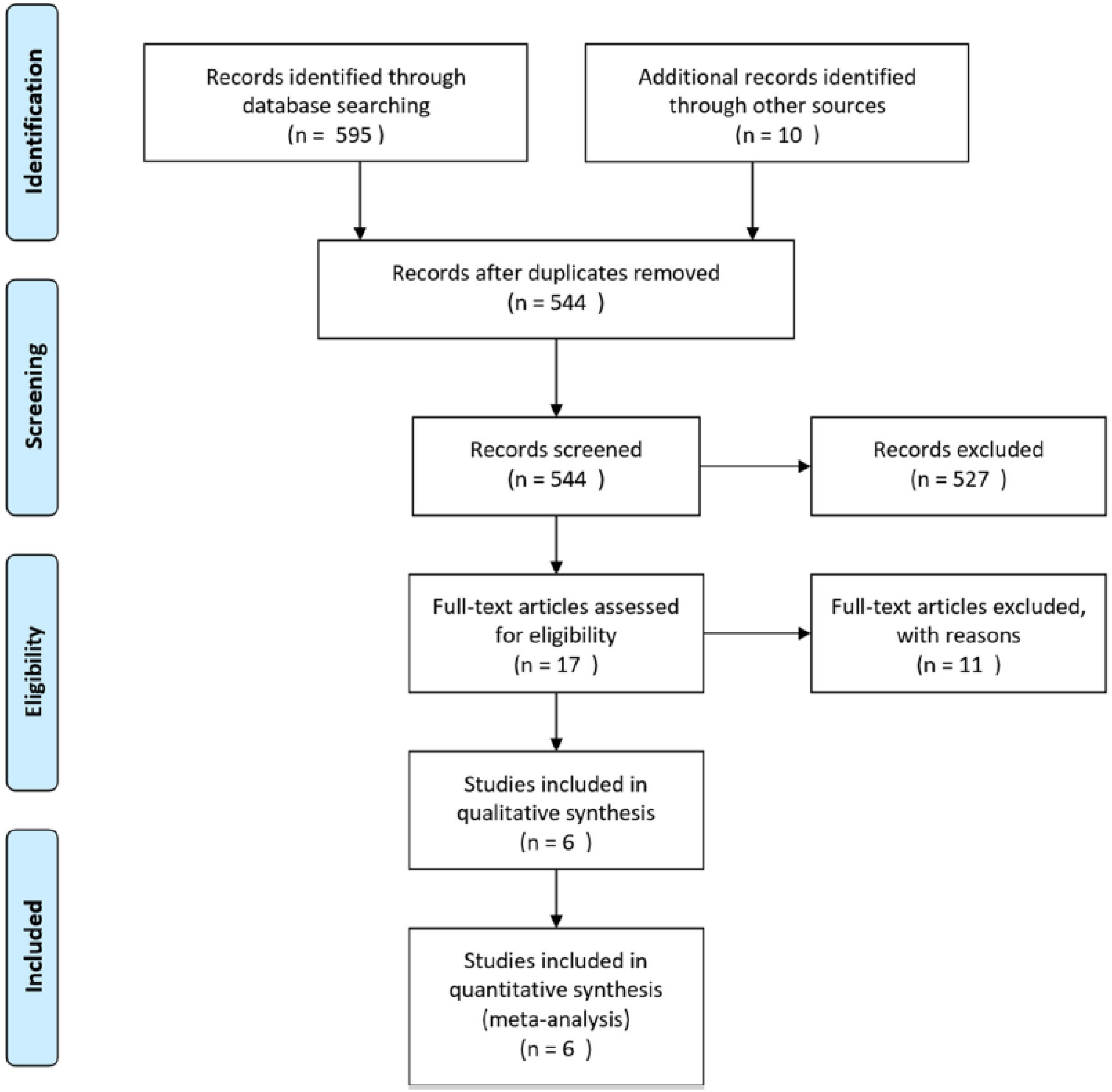
Sputum color for bacterial AECOPD: Chronic bronchitis

- Regression analyses of predicting the potential microorganism in sputum

Variable	Wald Chi-squared	p-value	OR point estimate (95% CI)
Sputum colour	108.4	<0.001	
Yellow *versus* white			3.2 (2.3–4.2)
Green *versus* white			4.9 (3.6–6.8)
Rust *versus* white			2.3 (1.4–3.7)
Sputum aspect	27.0	<0.001	
Purulent *versus* mucoid			2.0 (1.6–2.5)
Purulent *versus* mucopurulent			1.1 (1.0–1.2)
Dyspnoea	6.6	0.036	
Increased *versus* not increased			1.27 (1.1–1.5)
Fever	14.8	0.001	
Absent *versus* present			1.3 (1.1–1.6)

Miravitlles et al. Eur Respir J 2012; 39: 1354–1360

Sputum purulence for bacterial AECOPD – Systematic review and meta-analysis



Chen et al. COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2020, VOL. 17, NO. 3, 311–317

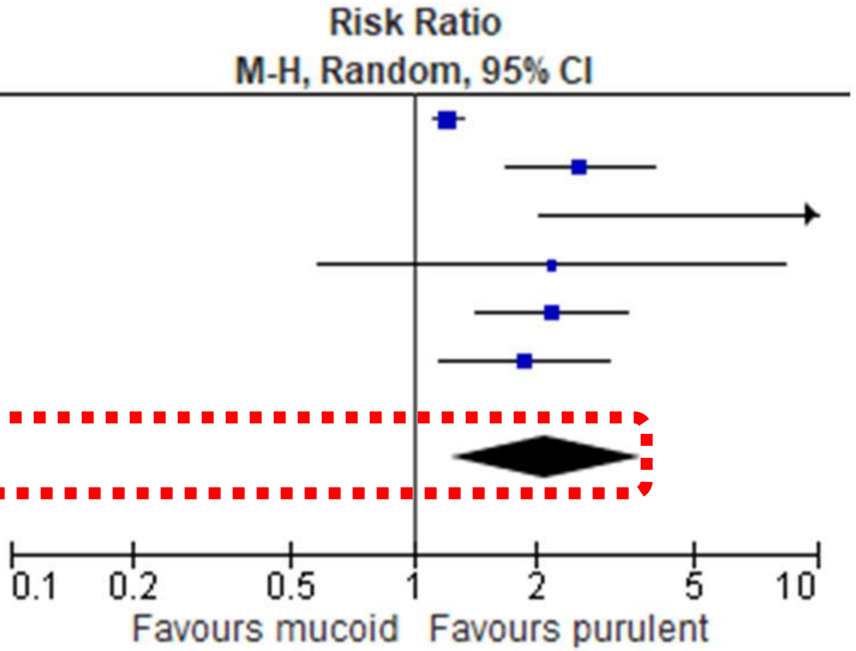
Sputum purulence for bacterial AECOPD – Systematic review and meta-analysis

- Forest plot of purulent versus mucoid sputum samples on sputum culture results.

	Purulent		Mucoid			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Allegra 2005	414	436	113	145	23.5%	1.22 [1.11, 1.33]
Daniels 2010	138	168	15	47	20.6%	2.57 [1.69, 3.93]
Soler 2007	17	22	1	18	5.9%	13.91 [2.04, 94.70]
Soler 2012	12	30	2	11	9.7%	2.20 [0.58, 8.30]
Stockley 2000	73	87	13	34	20.4%	2.19 [1.42, 3.40]
Tsimogianni 2009	16	28	20	66	19.8%	1.89 [1.16, 3.07]
Total (95% CI)		**771**		**321**	**100.0%**	**2.14 [1.25, 3.67]**
Total events	670		164			

Heterogeneity: Tau² = 0.32; Chi² = 41.42, df = 5 (P < 0.00001); I² = 88%

Test for overall effect: Z = 2.76 (P = 0.006)



Chen et al. COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2020, VOL. 17, NO. 3, 311–317

Sputum purulence for bacterial AECOPD – Systematic review and meta-analysis

- GOLD - Sputum purulence → antibiotics for acute exacerbations

- In this study,
  - Sputum purulence - by visual assessment (subjectively or by a colored chart)
    → green or yellow sputum
  - Purulent vs. mucoid sputum: positive bacterial culture (RR = 2.14, 95%CI [1.25, 3.67], p = 0.006)

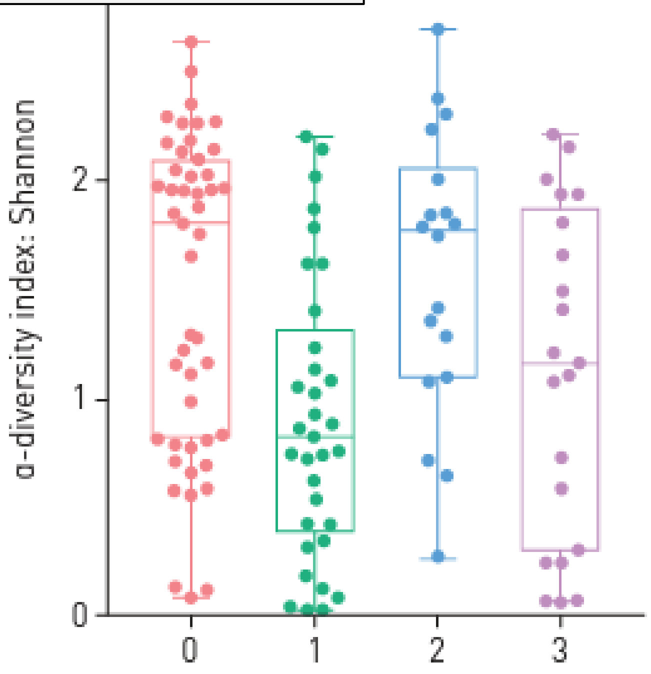
→ Supporting GOLD report

Chen et al. COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2020, VOL. 17, NO. 3, 311–317

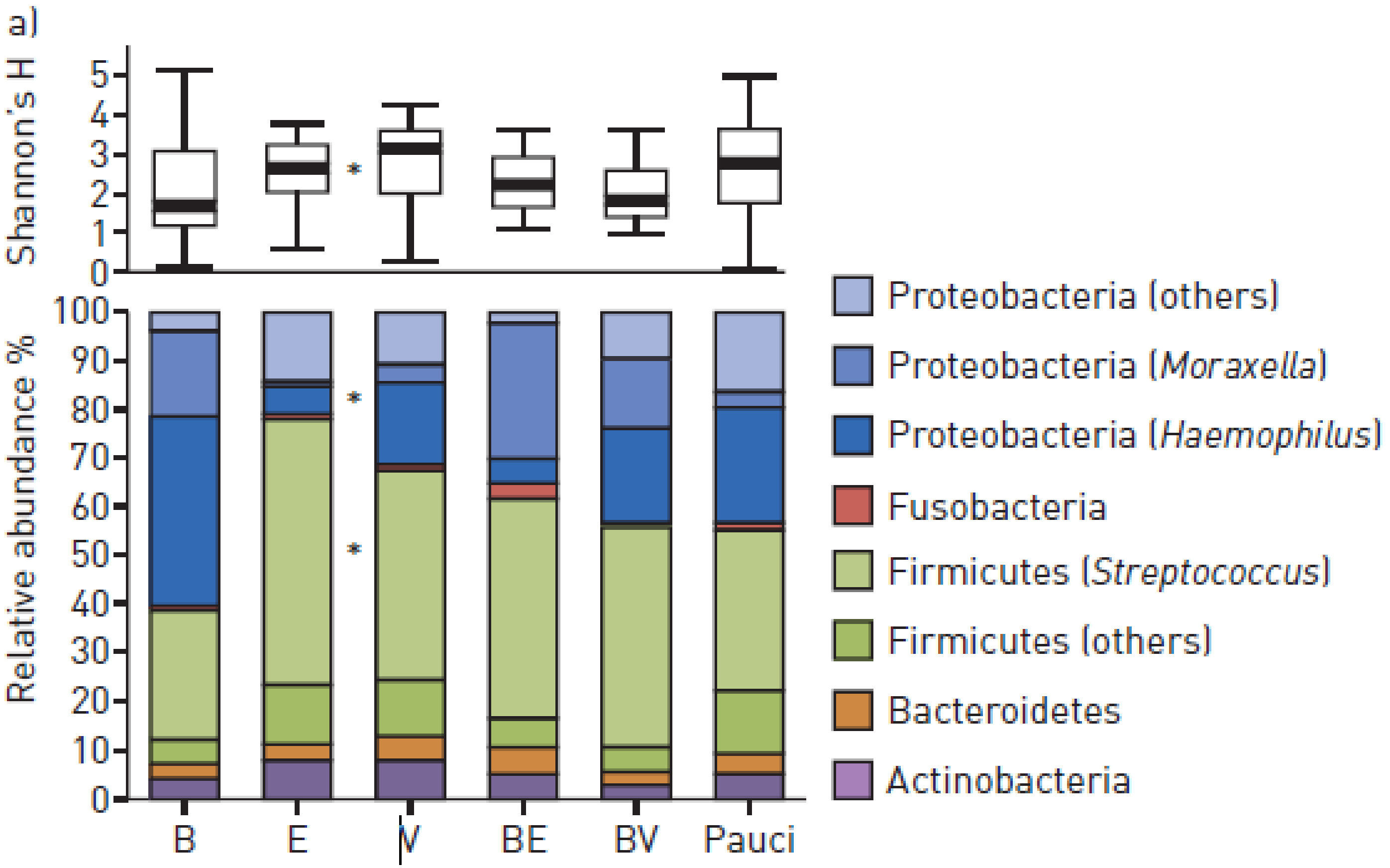
AECOPD classification - Sputum microbiome

Sputum microbiome in AE: by AE phenotype

α-diversity index



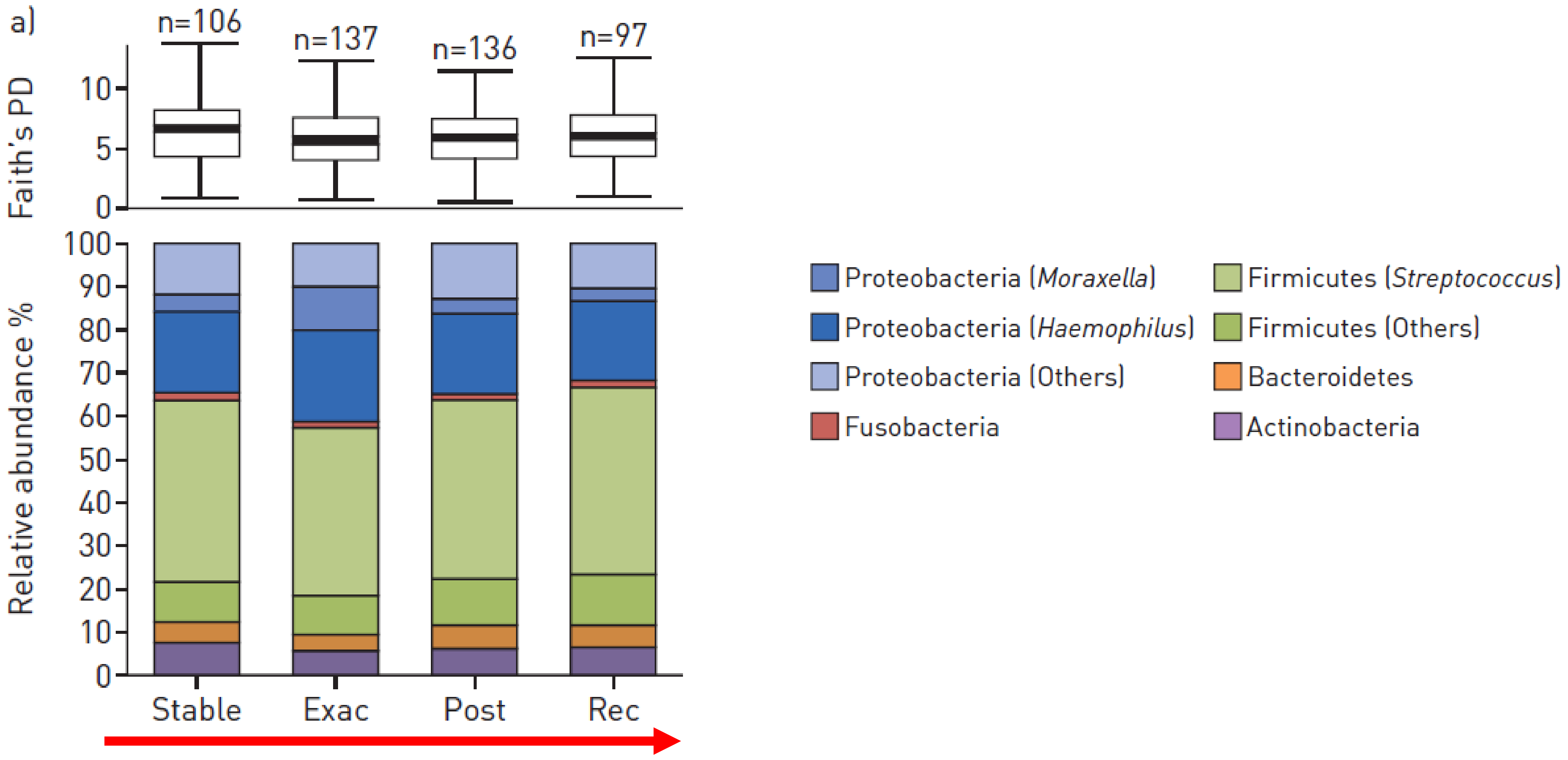
Types of AE
- 0=stable
- 1=bacterial exacerbation
- 2=eosinophilic exacerbation
- 3=viral exacerbation
  or unexplained exacerbation



Types of AE
- B=Bacteria, E=Eosinophilic, V=Viral, Pauci=Pauci-inflammatory

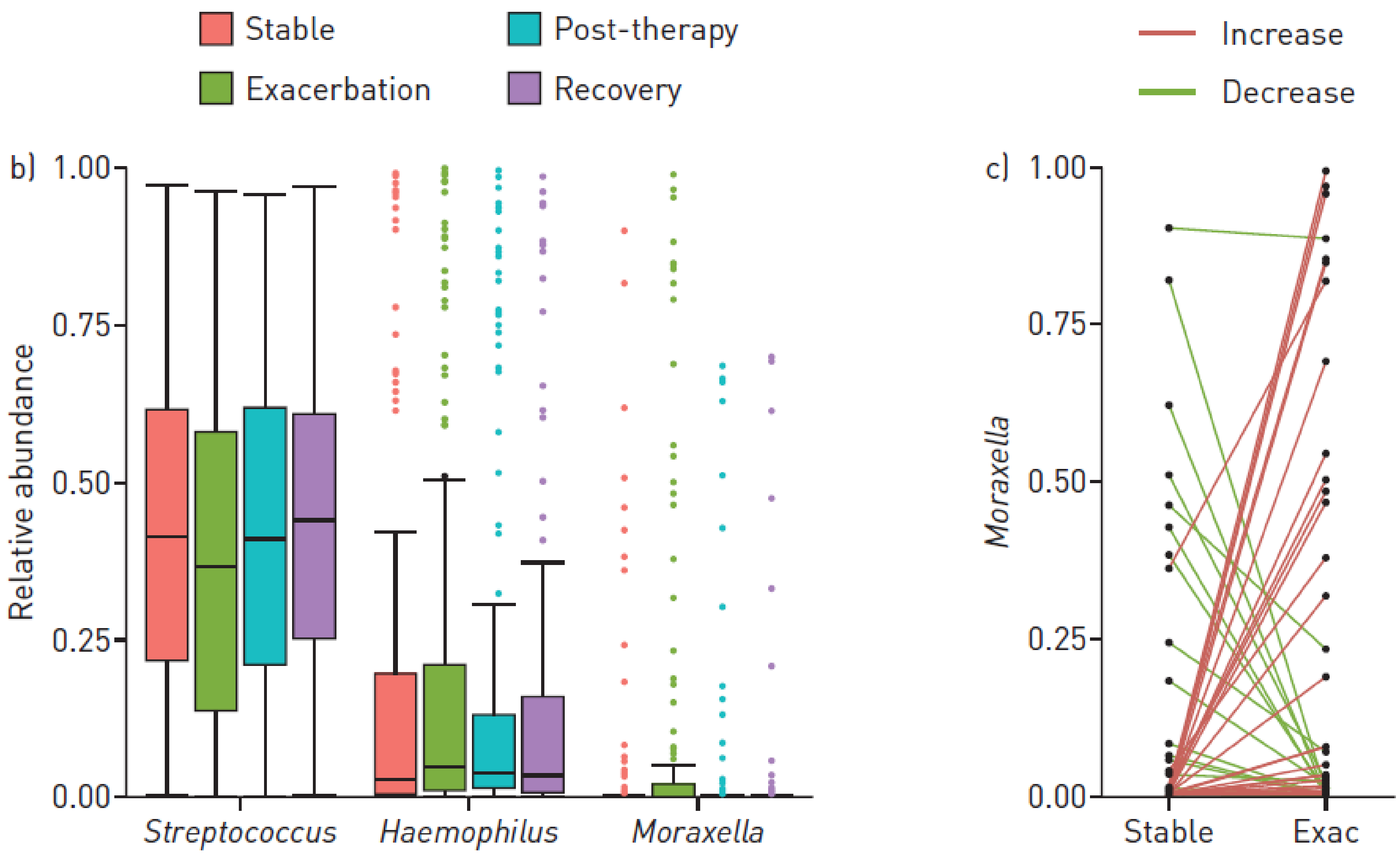
H.R. KEIR ET AL. Eur Respir J 2020; 56: 2000391
Z. WANG ET AL. Eur Respir J 2016; 47: 1034–1036

Sputum microbiome in AE: shifts during AE



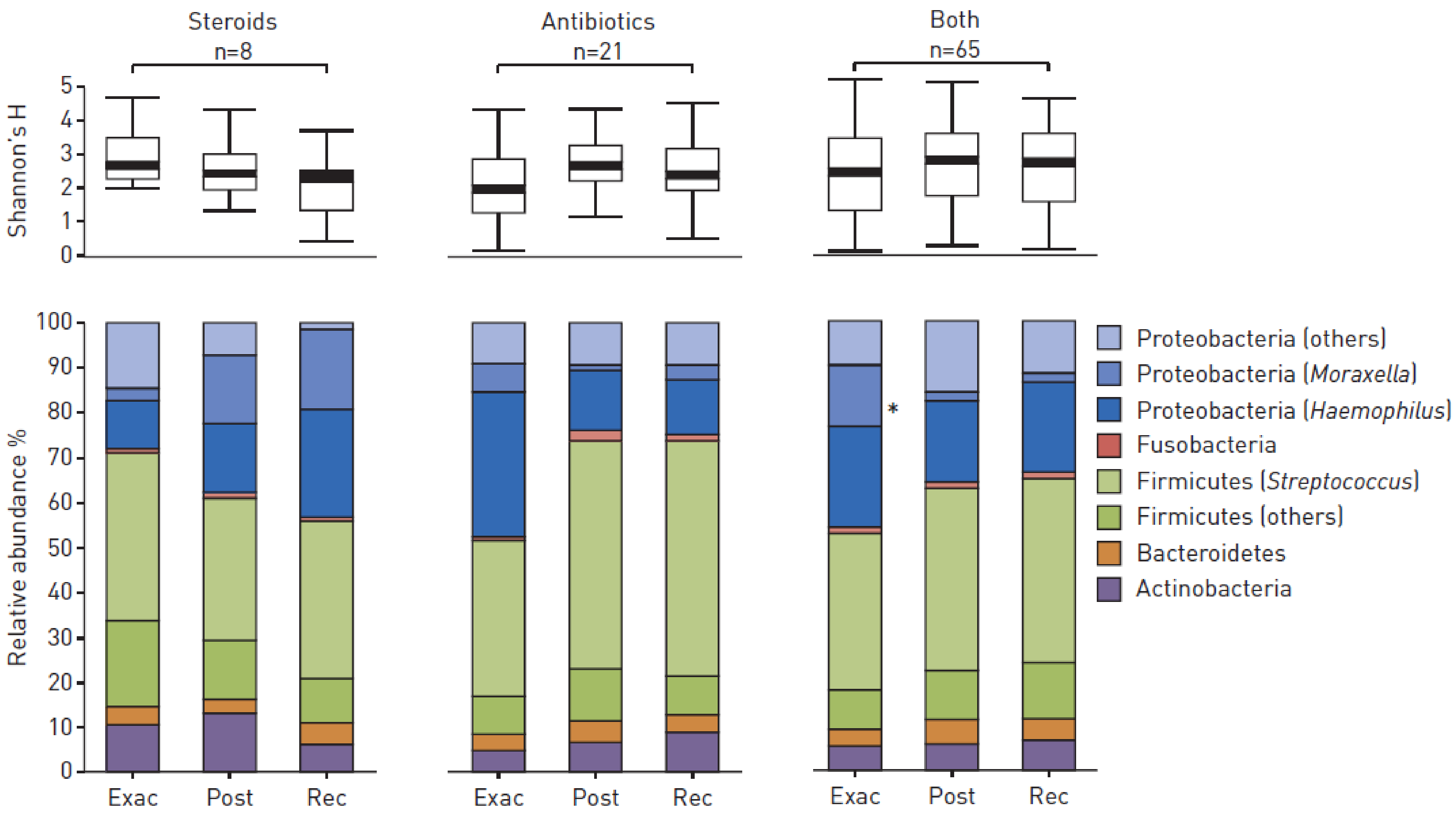
Z. WANG ET AL. Eur Respir J 2016; 47: 1034–1036

Sputum microbiome in AE: shifts during AE



Z. WANG ET AL. Eur Respir J 2016; 47: 1034–1036

Sputum microbiome in AE: by medication



Z. WANG ET AL. Eur Respir J 2016; 47: 1034–1036

Sputum microbiome in AE: by inflammatory endotype

ORIGINAL ARTICLE

Inflammatory Endotype–associated Airway Microbiome in Chronic Obstructive Pulmonary Disease Clinical Stability and Exacerbations
A Multicohort Longitudinal Analysis

Zhang Wang[1], Nicholas Locantore[2], Koirobi Haldar[3], Mohammadali Yavari Ramsheh[3], Augusta S. Beech[4], Wei Ma[5], James R. Brown[6], Ruth Tal-Singer[7], Michael R. Barer[3], Mona Bafadhel[8], Gavin C. Donaldson[9*], Jadwiga A. Wedzicha[9*], Dave Singh[4], Tom M. A. Wilkinson[10], Bruce E. Miller[2‡], and Christopher E. Brightling[3‡]

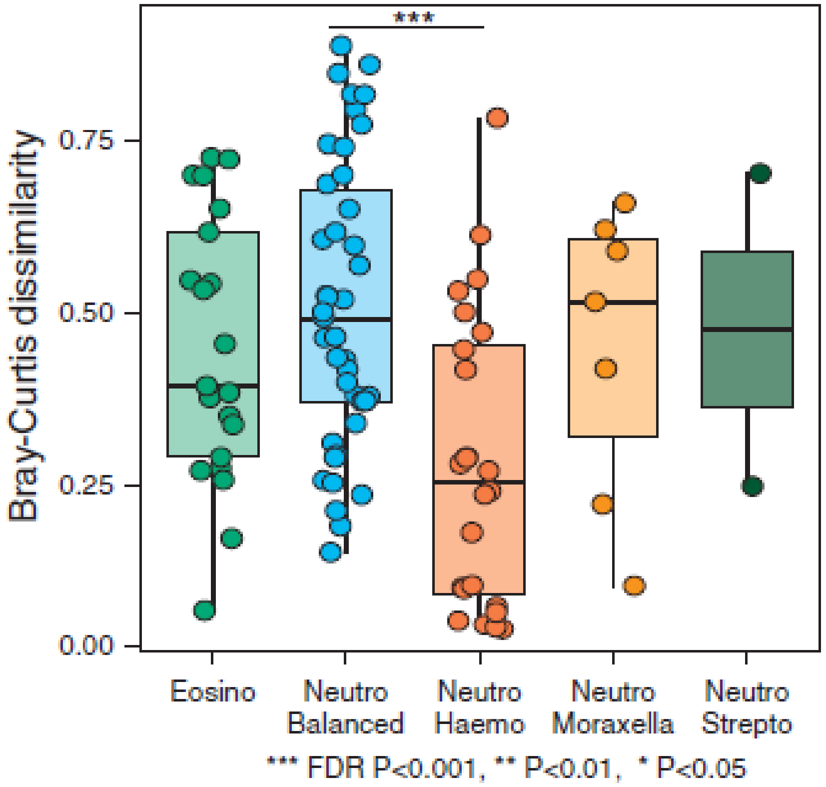
COPDMAP			AERIS	BEAT-COPD
Leicester ($N = 303$)	London ($N = 300$)	Manchester ($N = 180$)	Southampton ($N = 583$)	Leicester ($N = 340$)

- Community grouped by inflammatory endotype: neutron-, eosino-, mixed-, pauci-
- Subgroup by dominant community microbiome type: Balanced-, Haemophillus-, Moraxella-, Strepto-

Wang et al. Am J Respir Crit Care Med Vol 203, Iss 12, pp 1488–1502, Jun 15, 2021

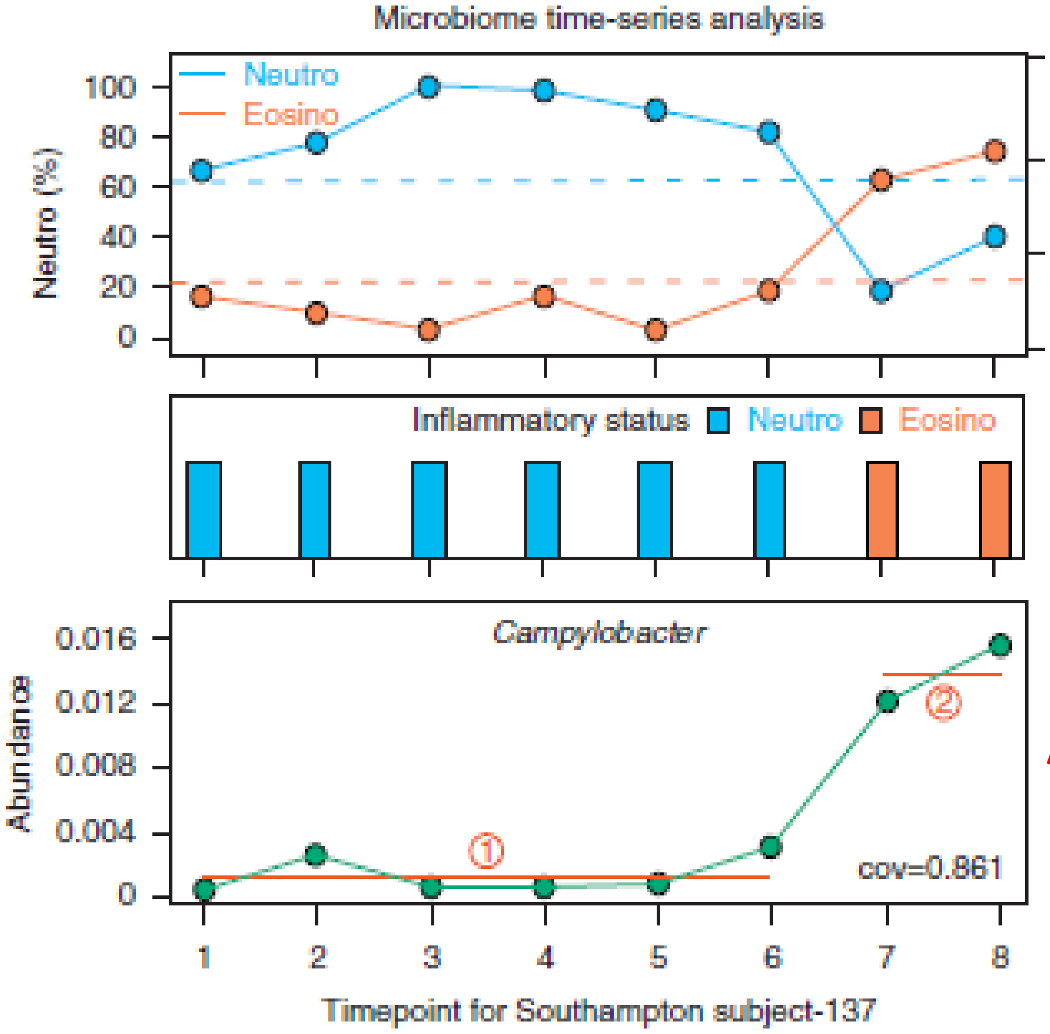
Sputum microbiome in AE: by inflammatory endotype

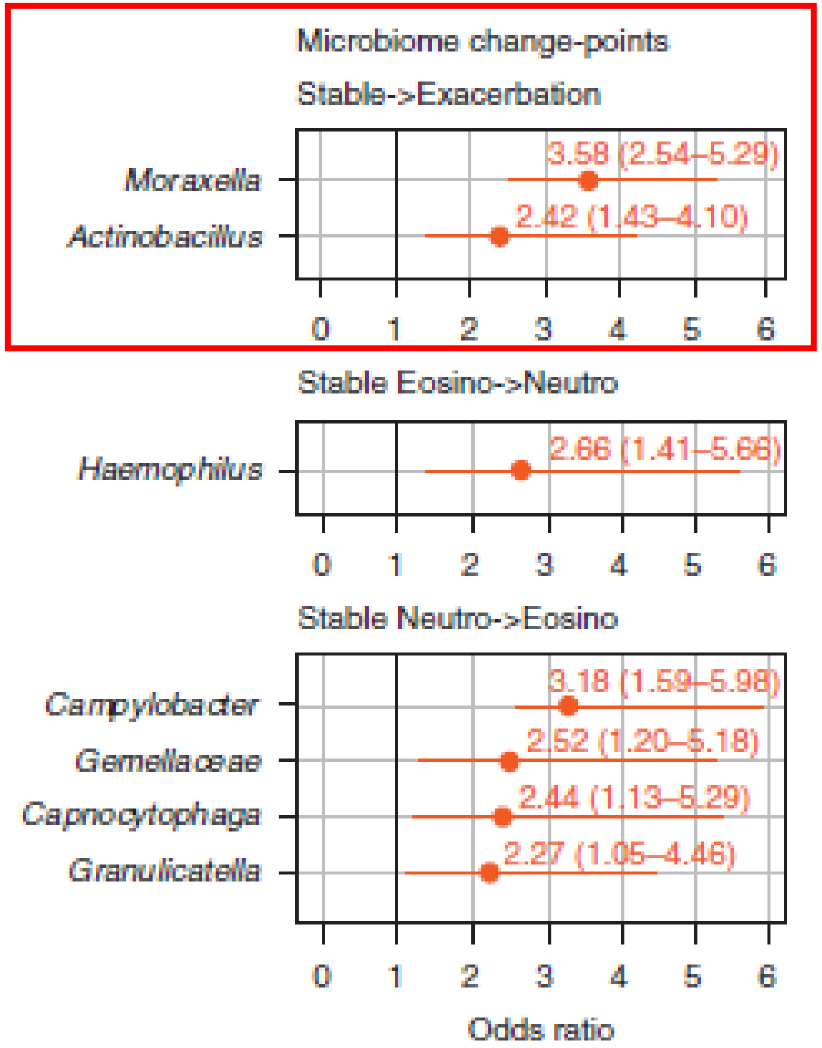
Dysbiosis at AE by subgroup



Wang et al. Am J Respir Crit Care Med Vol 203, Iss 12, pp 1488–1502, Jun 15, 2021

Sputum microbiome in AE: by inflammatory endotype





Wang et al. Am J Respir Crit Care Med Vol 203, Iss 12, pp 1488–1502, Jun 15, 2021

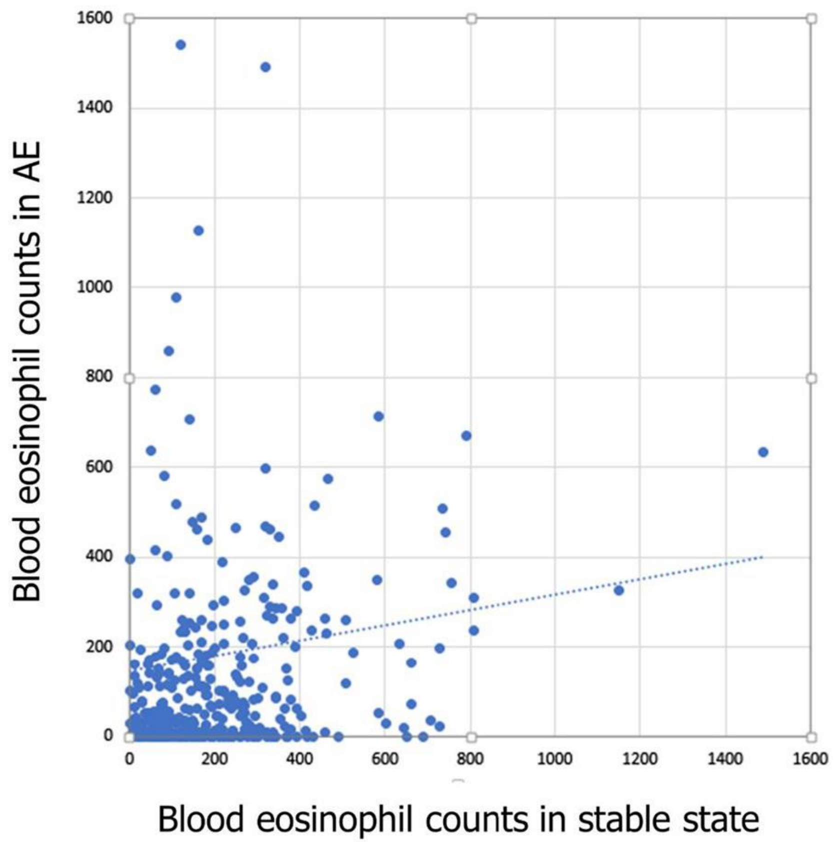
AECOPD classification – blood eosinophils

Stable blood eosinophil → Eosinophilic AE

RESEARCH ARTICLE Open Access

The association between eosinophilic exacerbation and eosinophilic levels in stable COPD

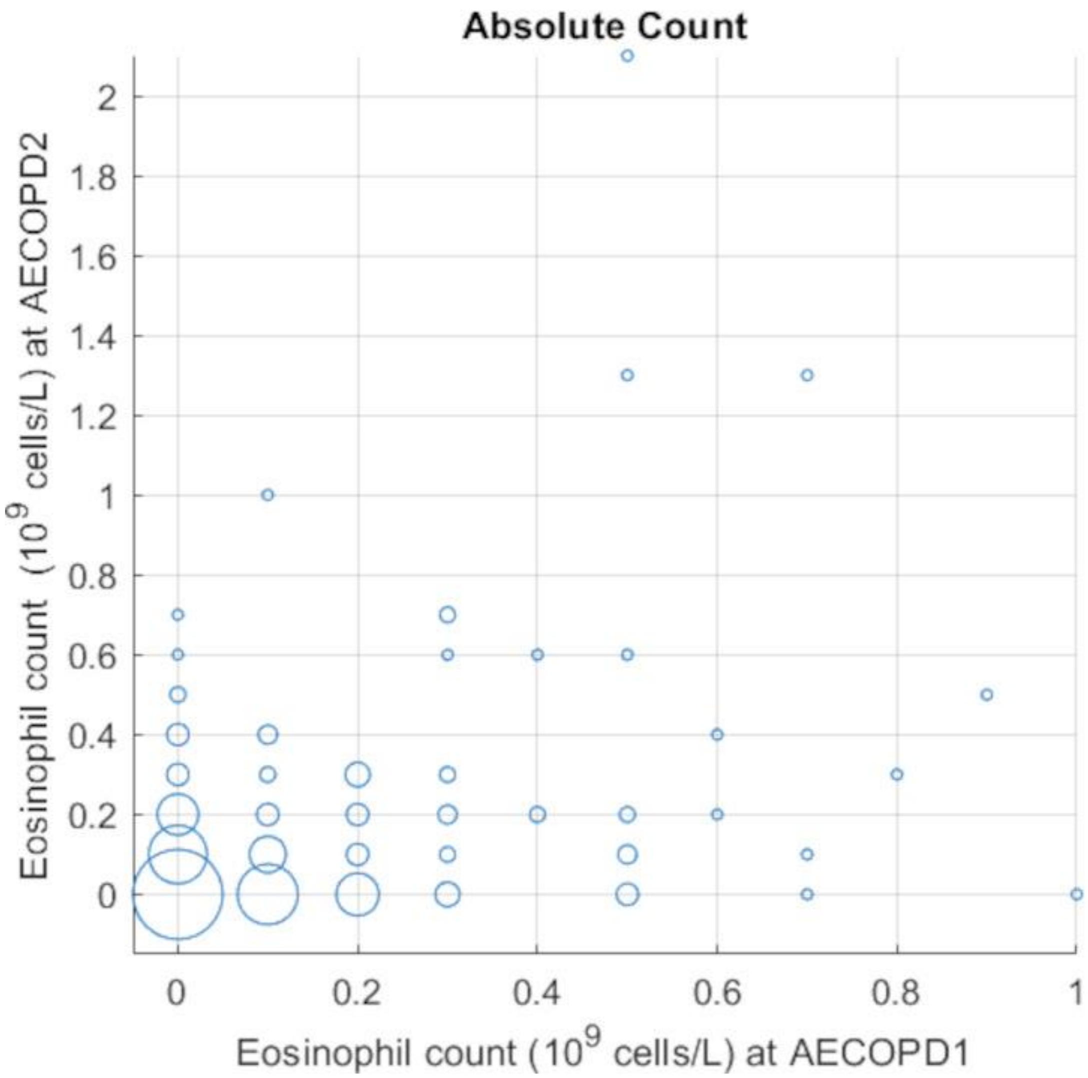
Hye Seon Kang, Sung Kyoung Kim, Yong Hyun Kim, Jin Woo Kim, Sang Haak Lee, Hyung Kyu Yoon and Chin Kook Rhee*



Variables	OR	95% CI	*P* value
Eosinophilic exacerbations (cut off eosinophil 2%)			
Age	0.975	0.949–1.002	0.074
Male	2.542	1.347–4.799	0.004
Post BD FEV_1 (%)	1.008	0.994–1.021	0.252
ICS containing inhaler	2.421	1.446–4.054	0.001
Eosinophilia at stable state (cut off eosihophil 300 cells/uL)	2.962	1.704–5.150	< 0.001
Eosinophilic exacerbations (cut off eosinophil count 300 cells/uL)			
Age	0.951	0.920–0.984	0.003
Male	1.113	0.524–2.366	1.113
Post BD FEV_1 (%)	1.011	0.995–1.028	1.011
ICS containing inhaler	1.921	0.977–3.777	0.059
Eosinophilia at stable state (cut off eosihophil 300 cells/uL)	3.129	1.608–6.089	0.001

Kang et al. BMC Pulm Med (2021) 21:74

Blood eosinophil in AE: diverse



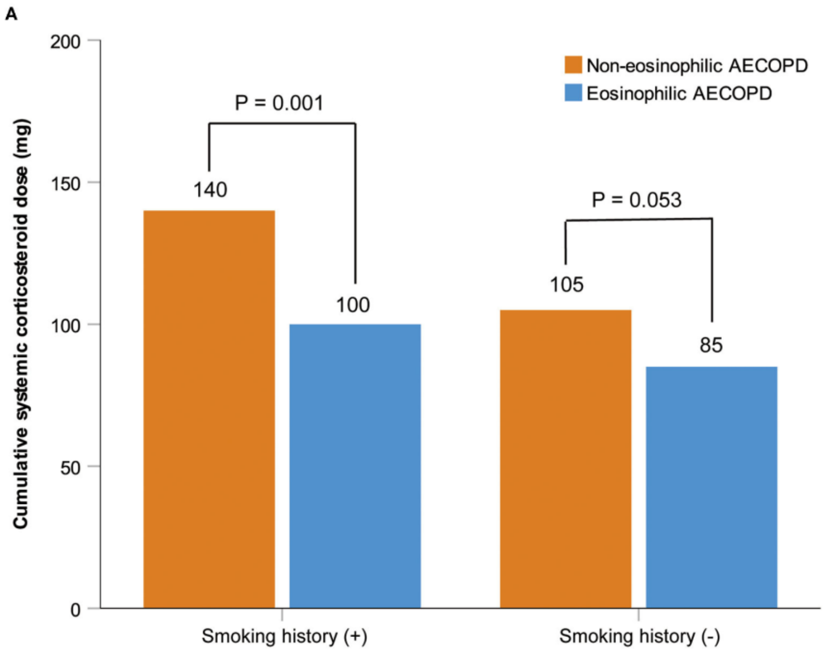
Citgez E, et al. BMJ Open Resp Res 2021;8:e000960.

Blood eosinophil in AE: not promising

Blood Eosinophils and Clinical Outcomes in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Propensity Score Matching Analysis of Real-World Data in China

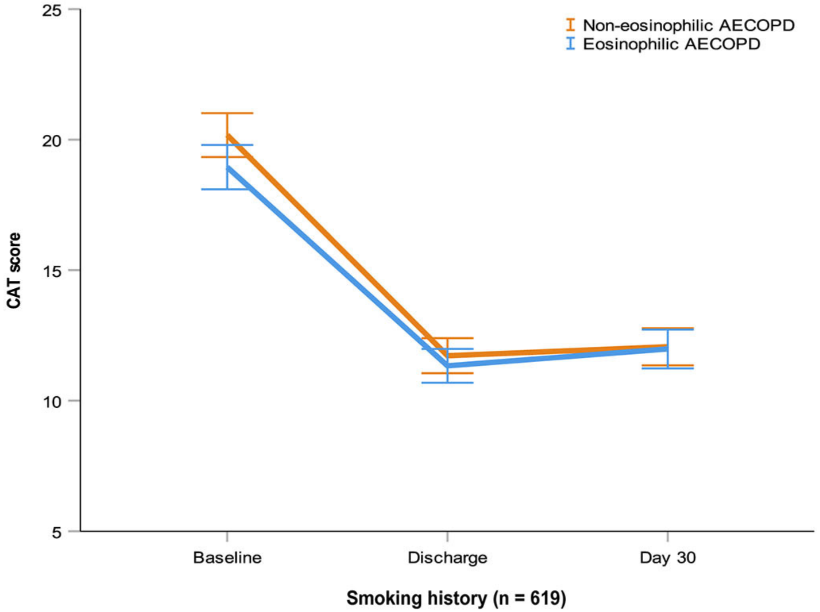
Yanan Cui[1], Zijie Zhan[1], Zihang Zeng[1], Ke Huang[2,3,4], Chen Liang[5], Xihua Mao[5], Yaowen Zhang[5], Xiaoxia Ren[2,3,4], Ting Yang[2,3,4] and Yan Chen[1]**

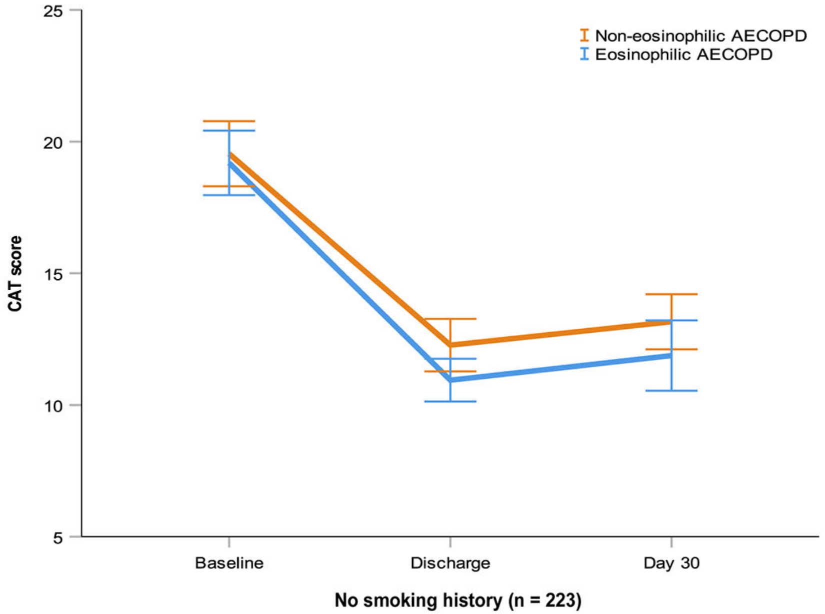
Cumulative steroid exposure



Cui et al. Front. Med. 8:653777.

CAT score





Blood eosinophil in AE: not promising

Re-admission

	Readmission with AECOPD or death within 15 days		Readmission with AECOPD or death within 30 days	
	HR (95% CI)[a]	*P*-value	HR (95% CI)[a]	*P*-value
Overall (*n* = 850)				
Non-eosinophilic AECOPD	1 (Ref)		1 (Ref)	
Eosinophilic AECOPD	1.002 (0.300–3.346)	0.998	1.264 (0.572–2.793)	0.562
Smoking history (*n* = 619)				
Non-eosinophilic AECOPD	1 (Ref)		1 (Ref)	
Eosinophilic AECOPD	1.034 (0.267–4.005)	0.962	1.064 (0.425–2.665)	0.895

[a] *Cox proportional hazards model.*

AECOPD, acute exacerbations of chronic obstructive pulmonary disease.

Cui et al. Front. Med. 8:653777.

Blood eosinophil in AE: different stability 1Y F/U

Cui *et al. Respir Res* (2021) 22:301
https://doi.org/10.1186/s12931-021-01888-5

Respiratory Research

RESEARCH **Open Access**

Stability of blood eosinophils in acute exacerbation of chronic obstructive pulmonary disease and its relationship to clinical outcomes: a prospective cohort study

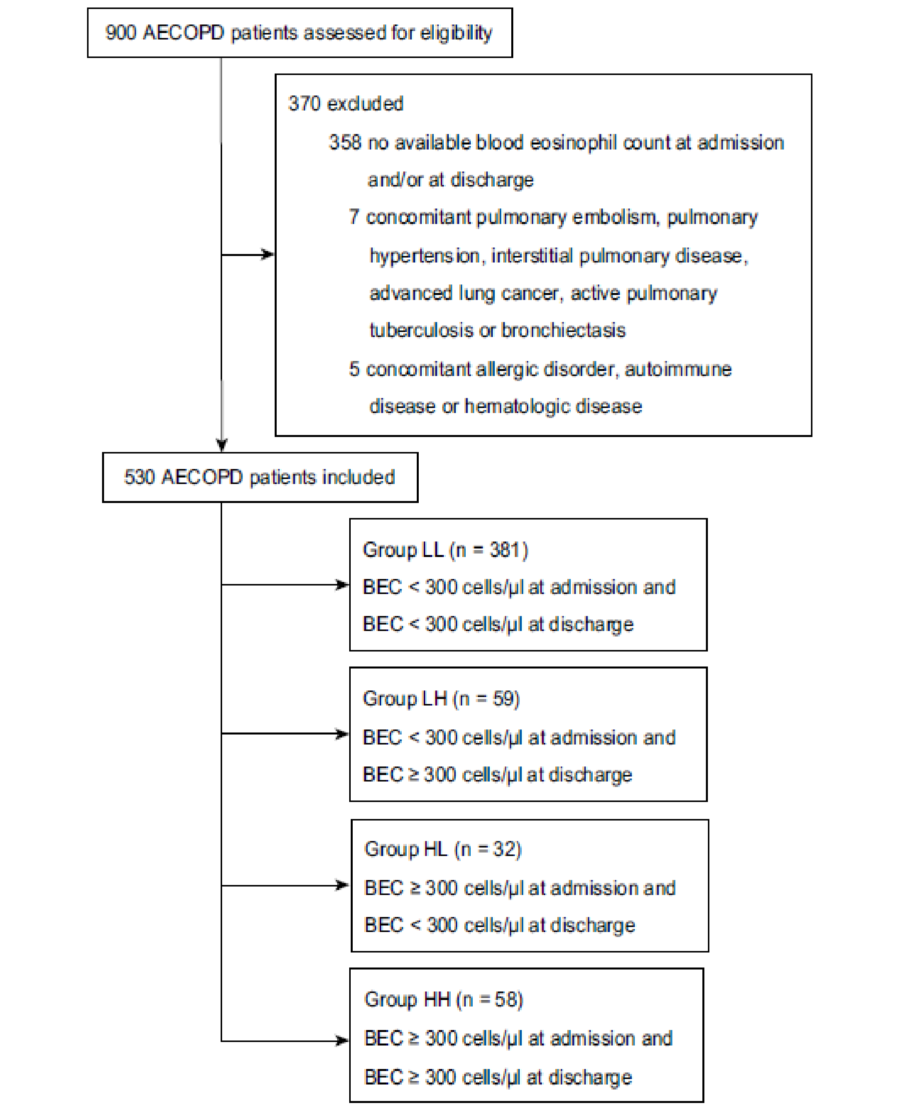


Fig. 1 Flowchart of eligible study population. *AECOPD* acute exacerbations of chronic obstructive pulmonary disease, *BEC* blood eosinophil count

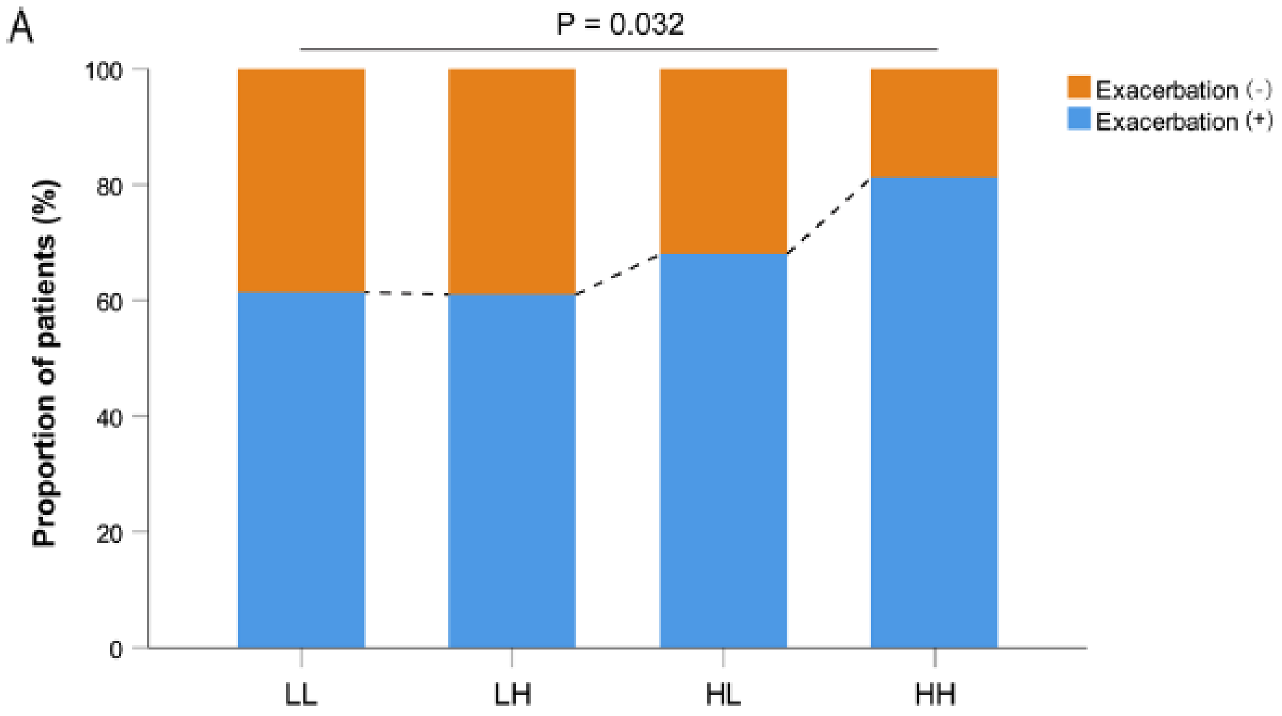
Cui et al. Respir Res (2021) 22:301

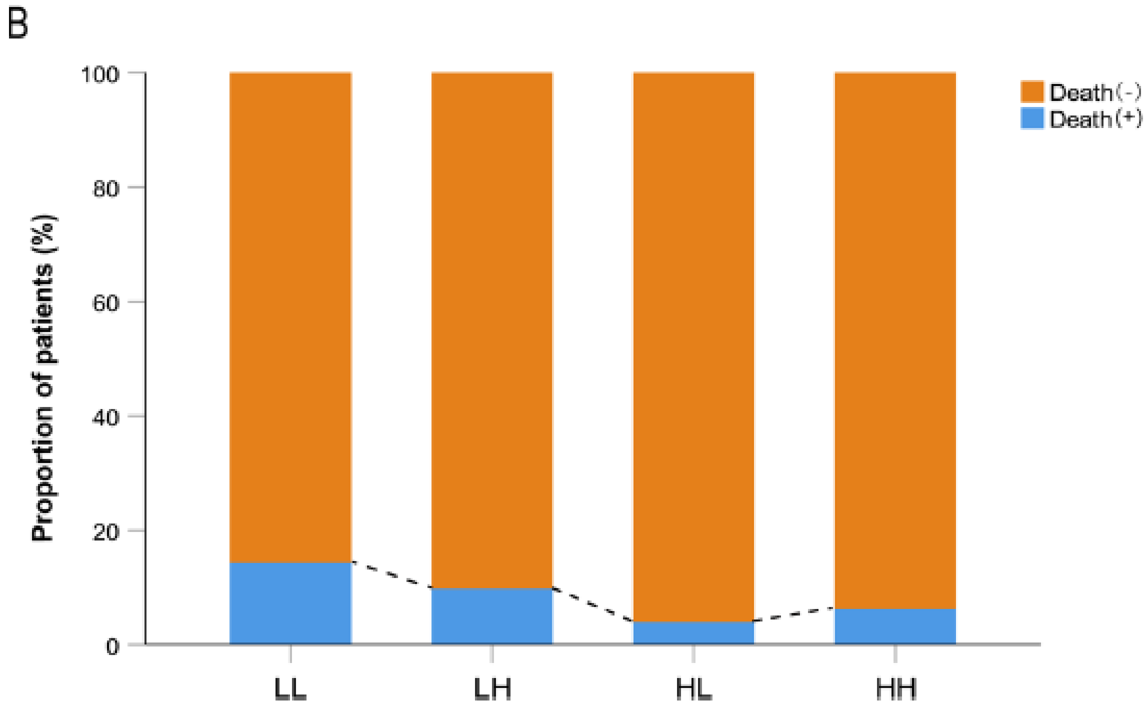
Blood eosinophil in AE: different stability 1Y F/U

LL: Adm (BEC <300) + D/C (BEC <300)
LH: Adm (BEC <300) + D/C (BEC >300)
HL: Adm (BEC >300) + D/C (BEC <300)
HH: Adm (BEC >300) + D/C (BEC >300)
*BEC: blood eosinophil count

AE proportion, p = 0.032

Mortality: not significant

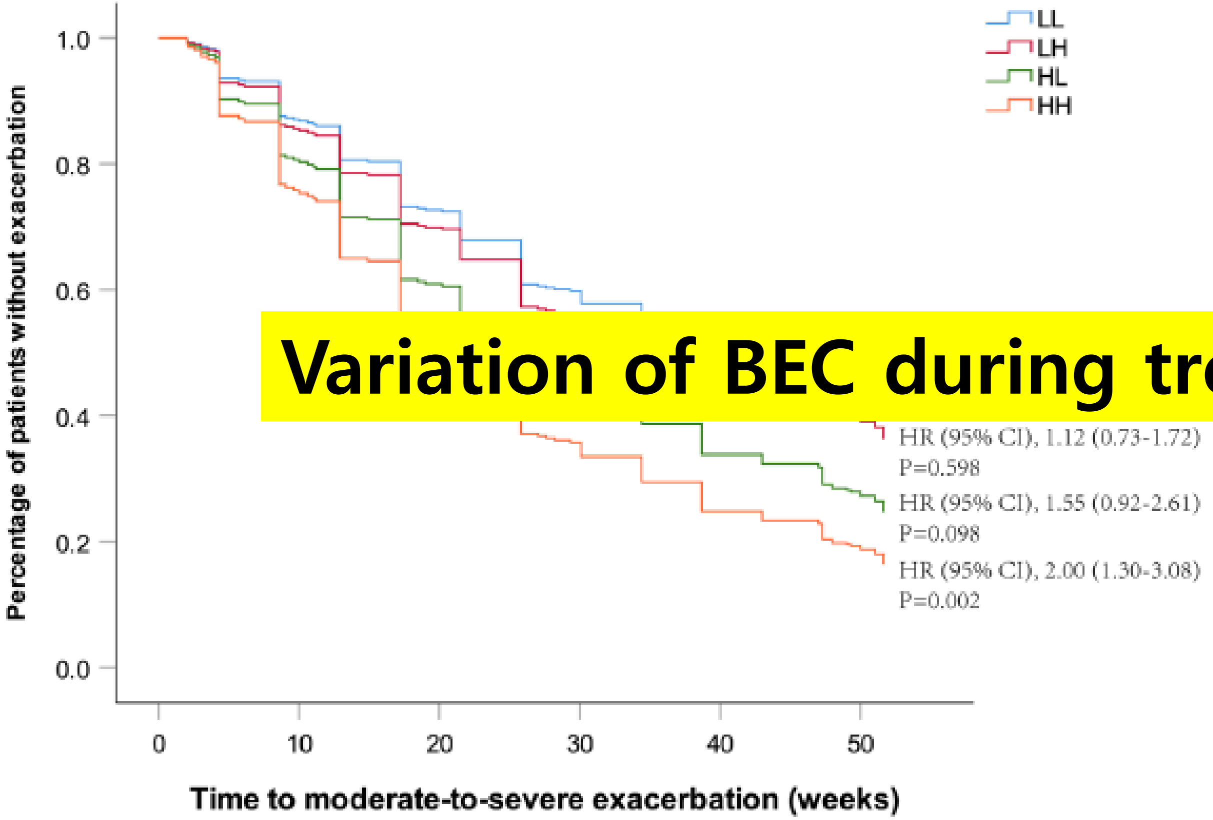




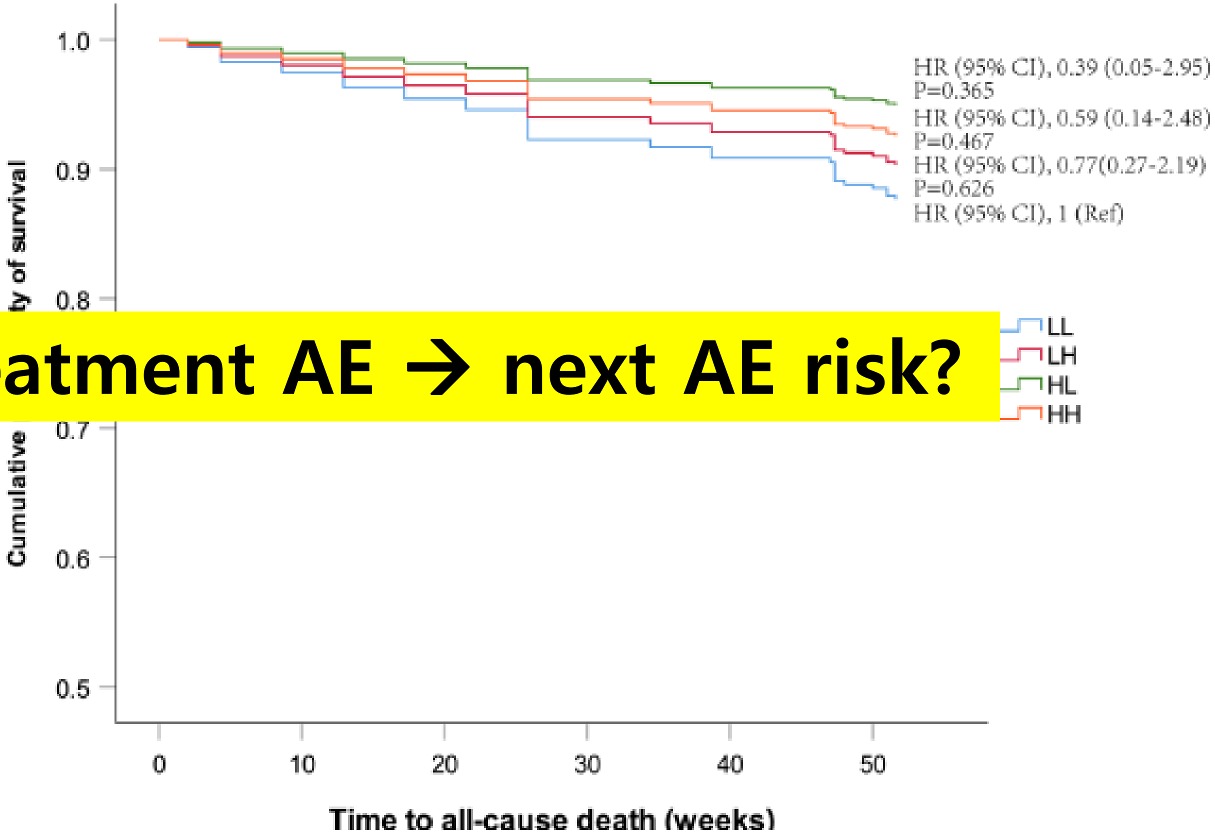
Cui et al. Respir Res (2021) 22:301

Blood eosinophil in AE: different stability 1Y F/U

Time-to first mod-sev AE



All cause survival



Variation of BEC during treatment AE → next AE risk?

AE HR (HH vs. LL): 2.00 (95% CI 1.30-3.08), p = 0.002

Gradually changed, but not statistical difference

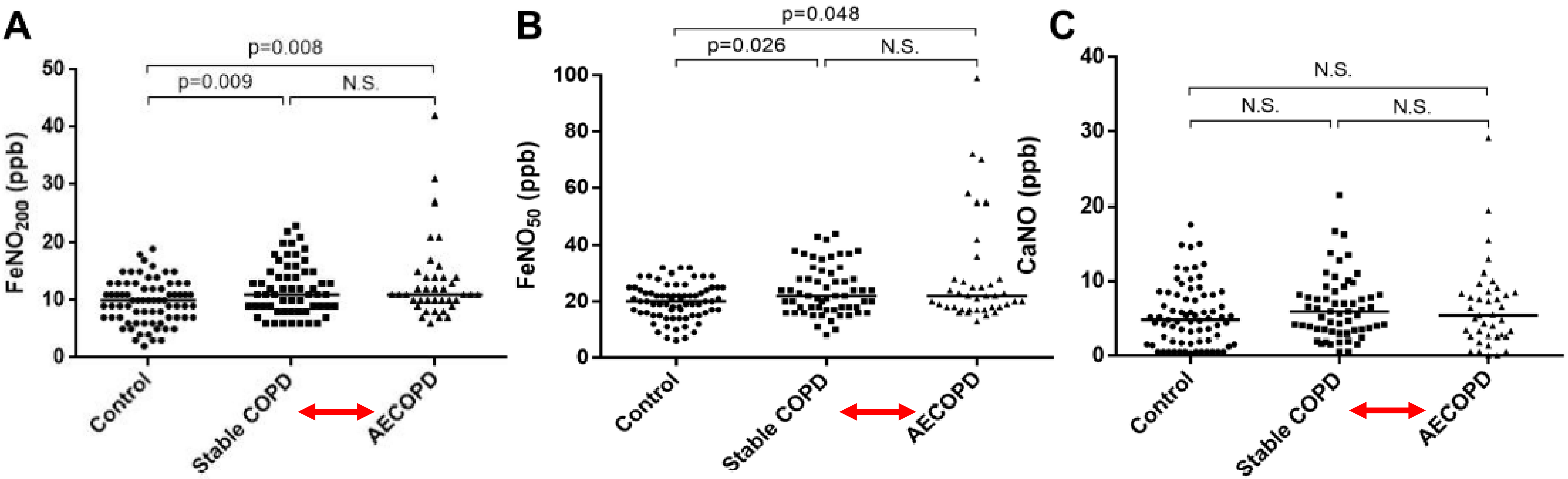
Cui et al. Respir Res (2021) 22:301

AECOPD classification – FeNO

AECOPD classification: FeNO

International Journal of General Medicine
Dovepress
open access to scientific and medical research
Open Access Full Text Article
ORIGINAL RESEARCH

Clinical Utility of Central and Peripheral Airway Nitric Oxide in Aging Patients with Stable and Acute Exacerbated Chronic Obstructive Pulmonary Disease



Int J Gen Med. 2021; 14: 571–580.

AECOPD classification: FeNO by different COPD phenotype

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2018, VOL. 15, NO. 4, 369–376
https://doi.org/10.1080/15412555.2018.1482532

Taylor & Francis
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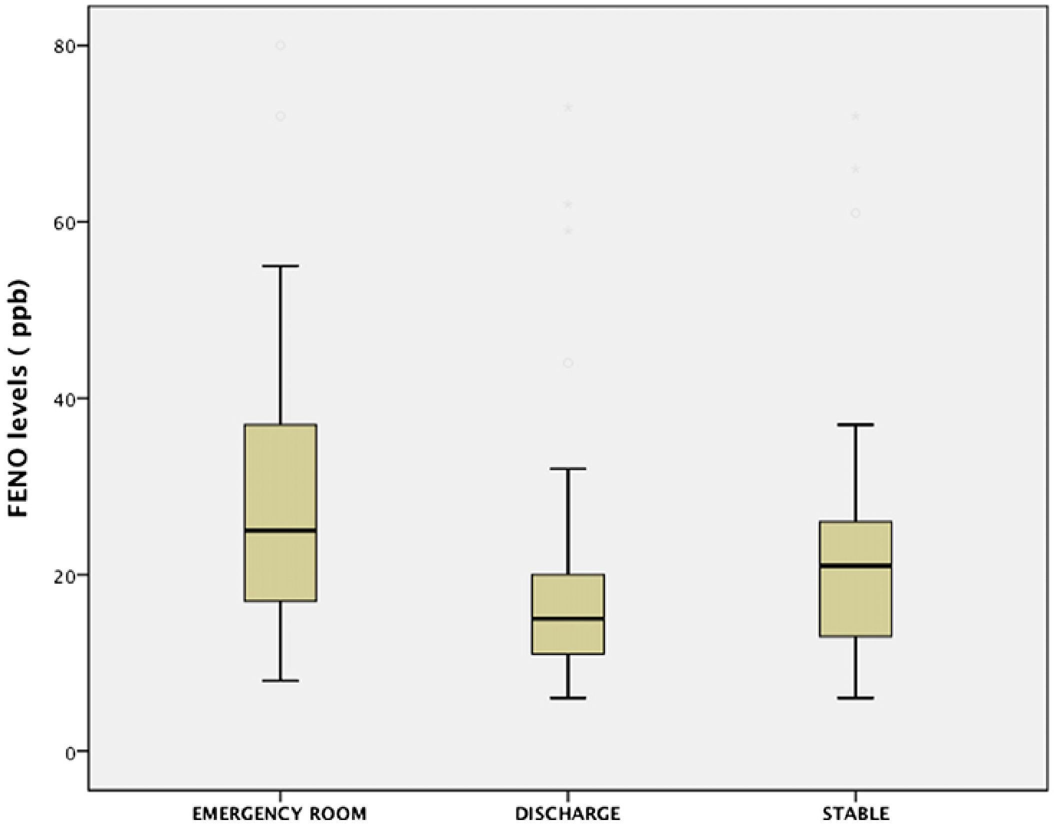
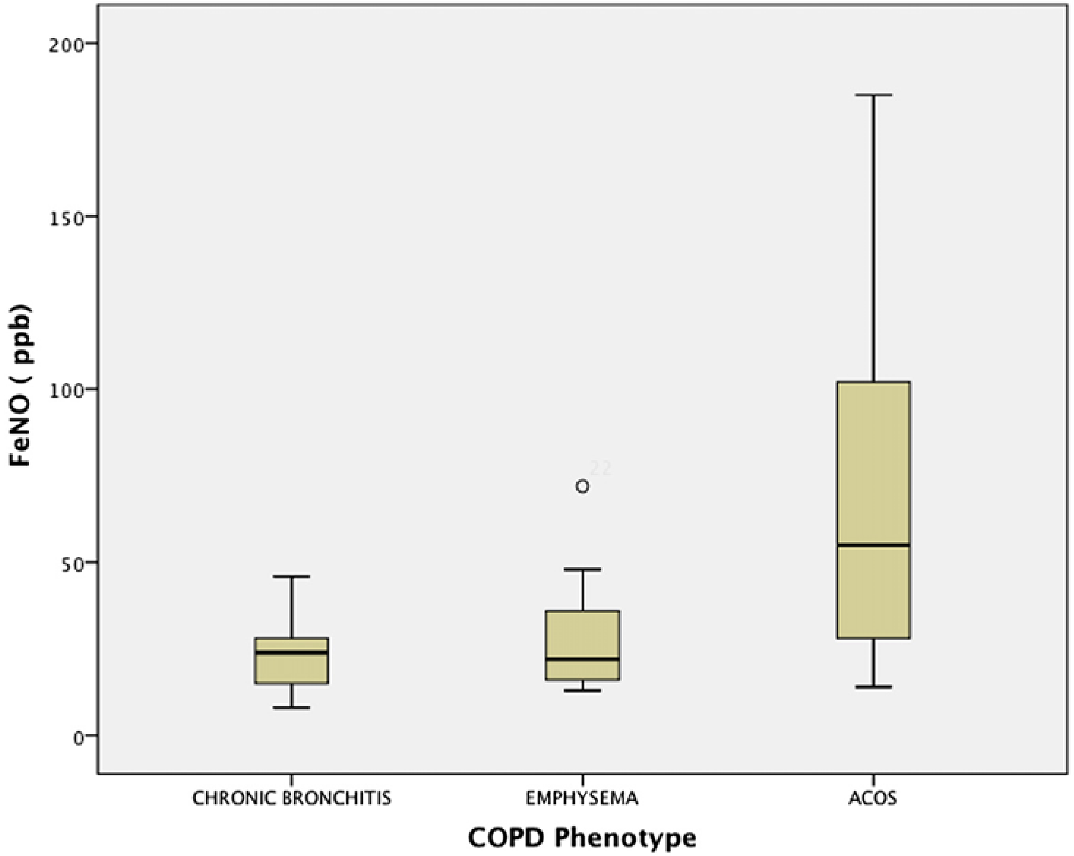
Value of Exhaled Nitric Oxide (FeNO) And Eosinophilia During the Exacerbations of Chronic Obstructive Pulmonary Disease Requiring Hospital Admission

Maria Teresa Río Ramírez[a], María Antonia Juretschke Moragues[a], Rocío Fernández González[b], Virginia Álvarez Rodríguez[c], Elena Aznar Andrés[c], Juan Pedro Zabaleta Camino[c], Rodolfo Romero Pareja[c], and





RAMIREZ ET AL. COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2018, VOL. 15, NO. 4, 369–376

Summary - 1

- Heterogeneity of AECOPD
  - 1st step of understanding personalized management
  - Various definition
  - Various phenotype
    - Etiology (bacteria, virus, environmental), Inflammation (neutrophilic, eosinophilic), comorbidities etc.
  - 4 categories: bacteria-, viral-, eosinophilic-, pauci-inflammatory-
  - Sputum color: Greenish, Yellowish ↔ Whitish-Grey
  - Sputum purulence: Purulent ↔ Mucoid
  - Sputum microbiome
    - Status AE: diversity, composition
    - + affected by time, medication, inflammatory endotype
  - Blood Eosinophil
    - Baseline level in stable COPD, Stability during AE
  - FeNO: not different? Different by phenotype of COPD such as ACO?

AECOPD Management

Management of AECOPD

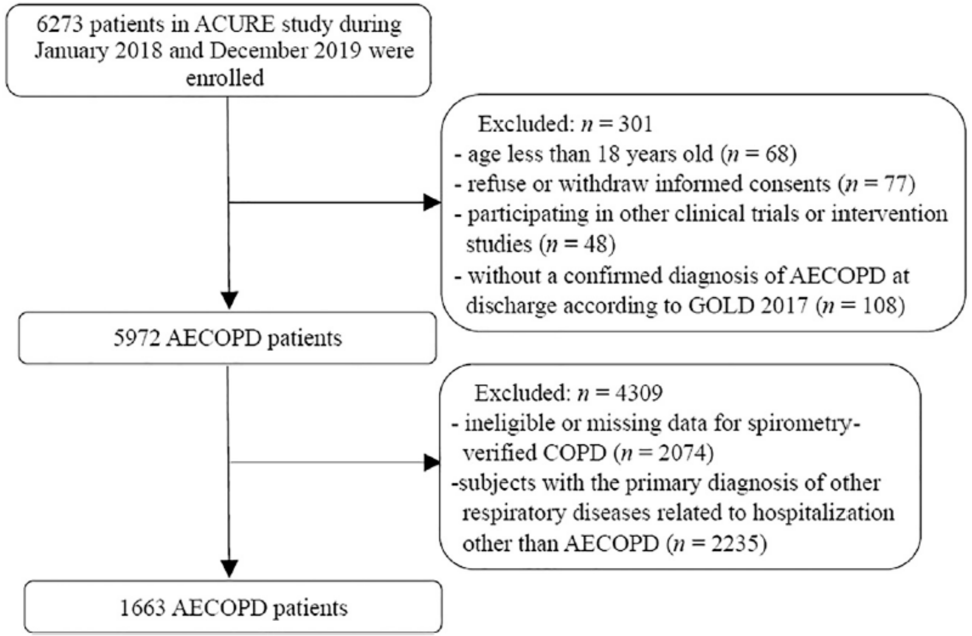
- **Keys of AECOPD**
  - Bronchodilator
  - **Systemic corticosteroid**
  - **Antibiotics**

AECOPD management - Antibiotics

Real-world antibiotics use in AECOPD

frontiers in Pharmacology
ORIGINAL RESEARCH
published: 25 May 2021
doi: 10.3389/fphar.2021.649884

Real-world antibiotic use in treating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in China: Evidence from the ACURE study



Characteristics	Overall (n=1434)
Types of antibiotic use	
Monotherapy	1102 (76.8)
Combination therapy with ≥2 antibiotics	332 (23.2)
Duration of antibiotic use, days (n=1400)	9.0 (7.0 – 11.0)
Routes of antibiotic use	
Oral	18 (1.3)
Intravenous	1400 (97.6)
Oral + intravenous	15 (1.0)
Oral + nebulized	1 (0.1)

Percentage of real-world antibiotics use = 1434/1663 (86.2%)

Ma et al. Front. Pharmacol. 12:649884.

Different effect of antibiotics on AECOPD

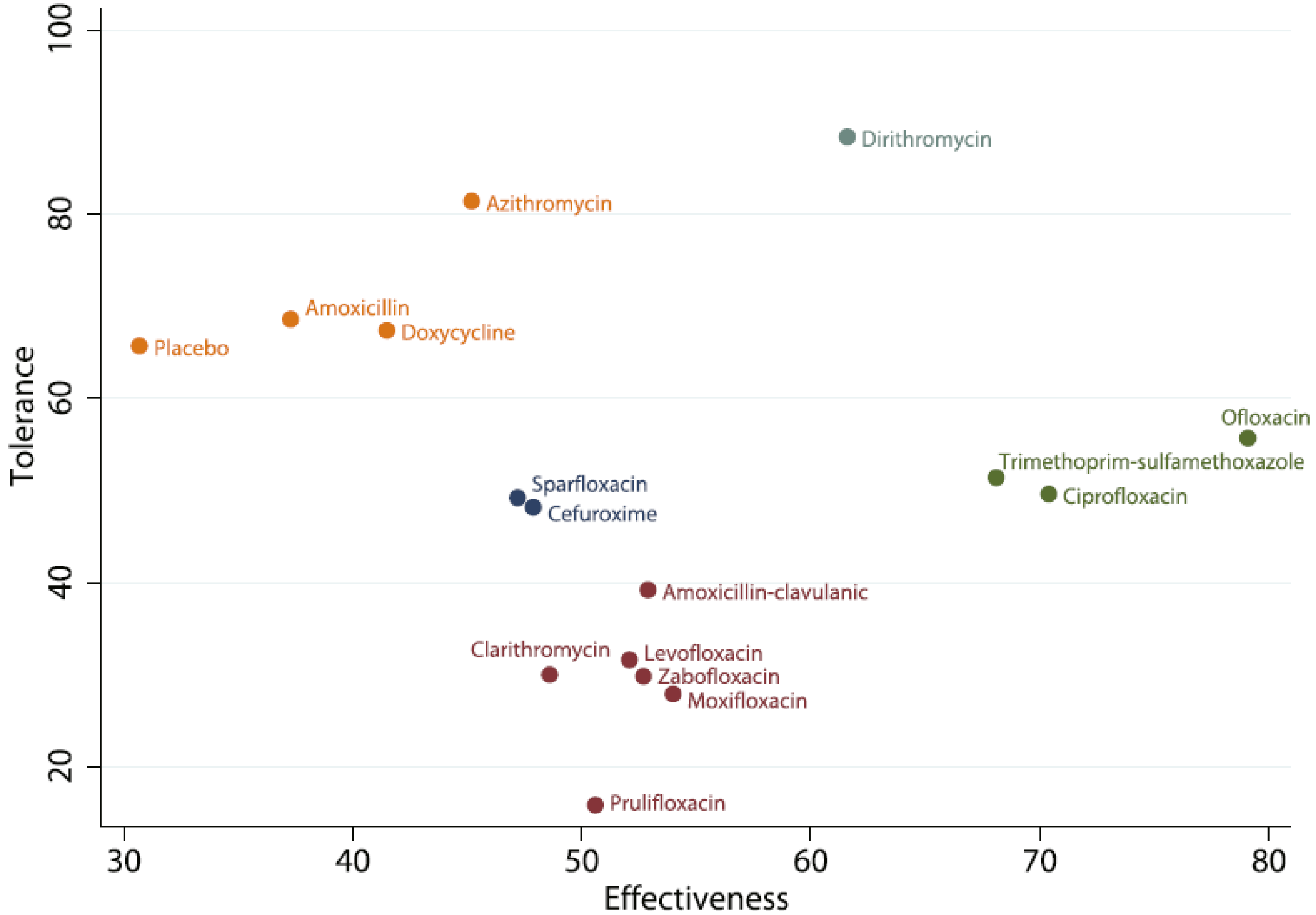
Zhang *et al. BMC Pulmonary Medicine*
DOI 10.1186/s12890-017-0541-0

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

CrossMark

Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: a network meta-analysis



Different effect on different antibiotics

Zhang et al. BMC Pulmonary Medicine DOI 10.1186/s12890-017-0541-0

Antibiotics resistance in COPD: systematic review

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2021, VOL. 18, NO. 6, 672–682
https://doi.org/10.1080/15412555.2021.2000957

Routledge
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REVIEW

Prevalence, Pattern, Risks Factors and Consequences of Antibiotic Resistance in COPD: A Systematic Review

Daniel Smith[a], Arran Gill[b], Lewis Hall[a] and Alice M. Turner[c,d]

Microorganism Author, year	State	Penicillin	Ampicillin[p]/ Amoxicillin [x]		Co-amoxiclav		Tetracycline [t]/ Doxycycline [d]		Quinolones, Ciprofloxacin [c]/ Levofloxacin [l]		Macrolides[x], Azithromycin[a]/ Erythromycin[e]/ Clarithromycin [c]		Cefuroxime	
		Resistance rate (number of samples resistant/number of samples tested, %)												
H. influenzae														
Median, range (%)			**39.7**	**20.4–73.3**	**1.85**	**0–40**	**0.5**	**0.2–6.7**	**0**	**0–0**	**4**	**0–46.7**	**0.2**	**0–0.5**
Maddi et al. [55]	Stable		11/15 [p] 8/15 [x]	(73.3) (53.3)	6/15	(40)	1/15 [t]	(6.7)	0/15[c,l]	(0)	3/15[a] 7/15[e] 4/15[c]	(20) (46.7) (26.7)		
Pettigrew et al. [56]	Mixed								0/100[c,l]	(0)	1/100[a]	(1)		
Pfaller et al. [57]	AE		–/– [p]	(26)	–/–	(0)	–/– [t]	(0.2)	–/–[c,l]	(0)	–/–[a] –/–[c]	(1) (7)	–/–	(0.2)
Pfaller et al. [58]	AE		–/– [p]	(20.4)	–/–	(3.7)	–/– [d]	(0.5)	–/–[c,l]	(0)	–/–[c]	(0) (7.3)	–/–	(0.5)
Querol-Ribelles et al. [59]	AE				–/–	(0)			–/–[c,l]	(0)	–/–[a] –/–[c]	(0) (0.6)	–/–	(0)

D.Smith et al. Journal of Chronic Obstructive Pulmonary Disease 2021, VOL. 18, NO. 6, 672–682

Antibiotics resistance in COPD: systematic review

Resistance rate (number of samples resistant/number of samples tested, %)

Microorganism Author, year	State	Penicillin		Ampicillin[p]/ Amoxicillin [x]		Co-amoxiclav		Tetracycline [t]/ Doxycycline [d]		Quinolones, Ciprofloxacin [c]/ Levofloxacin [l]		Macrolides[x], Azithromycin[a]/ Erythromycin[e]/ Clarithromycin [c]		Cefuroxime		Piperacillin/ Tazobactam		Colistin	
P. aeruginosa																			
Median, range (%)										**51.3**	**50–52.6**					**19.2**	**19.2–19.2**	**2.6**	**2.6–2.6**
Gallego et al. [60]	Mixed									41/78[c]	(52.6)					15/78	(19.2)	2/78	(2.6)
										39/78[l]	(50)								
S. pneumoniae																			
Median, range (%)		**11.3**	**3–15**	**1.2**	**1.2–1.2**	**1.2**	**1.1–3**	**22.1**	**20.2–24**	**1**	**0–4.2**	**33.1**	**24–35**	**16.9**	**13.6–20.2**				
Desai et al. [27]	Mixed	6/75	(8)									18/75[e]	(24)						
Pfaller et al. [57]	AE	-/-	(15)			–/–	(3)	-/- [t]	(24)	–/–[l]	(1)	–/–[e]	(35)						
Pfaller et al. [58]	AE	13/89	(14.6)			1/89	(1.1)	18/89[t]	(20.2)	0/89[l]	(0)	29/89 [e]	(32.6)	18/89	(20.2)				
Querol-Ribelles et al. [59]	AE	–/–	(3)	–/– [x]	(1.2)	–/–	(1.2)			–/–[l]	(4.2)	–/–[a,c]	(33.1)		(13.6)				
												–/–[e]	(34.3)						
M. catarrhalis																			
Median, range (%)		**93**	**93–93**	**90.4**	**90.4–90.4**	**0**	**0–0**	**0.5**	**0.3–0.7**	**0**	**0–0**	**2**	**0–3.7**	**0**	**0–0**				
Pfaller et al. [57]	AE		(93)			0/323	(0)	1/323[t]	(0.3)	0/323[c,l]	(0)	–/–[e]	(2)	0/323	(0)				
Pfaller et al. [58]	AE			–/– [p]	(90.4)	–/–	(0)	-/- [t]	(0.7)	–/–[c,l]	(0)	–/–[e]	(3.7)	–/–	(0)				
Querol-Ribelles et al. [59]	AE					–/–	(0)			[c,l]	(0)	–/–[a,c]	(0)	–/–	(0)				

Higher % of AMR (antimicrobial resistance rate) in non-hospitalized patients (AECOPD)

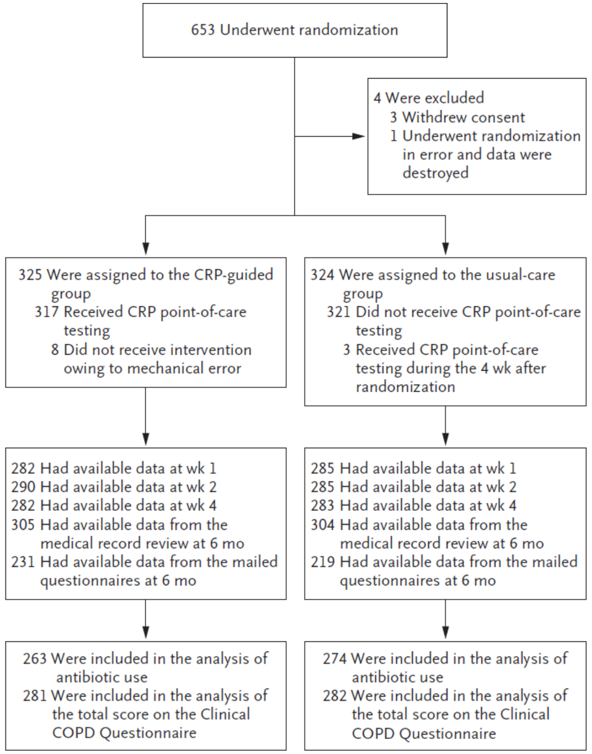
→ Need of proper guidance

D.Smith et al. Journal of Chronic Obstructive Pulmonary Disease 2021, VOL. 18, NO. 6, 672–682

Antibiotics guidance by point-of-CRP

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 11, 2019 VOL. 381 NO. 2

C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations



- For primary clinic patients
- Not enough clinical features for AECOPD

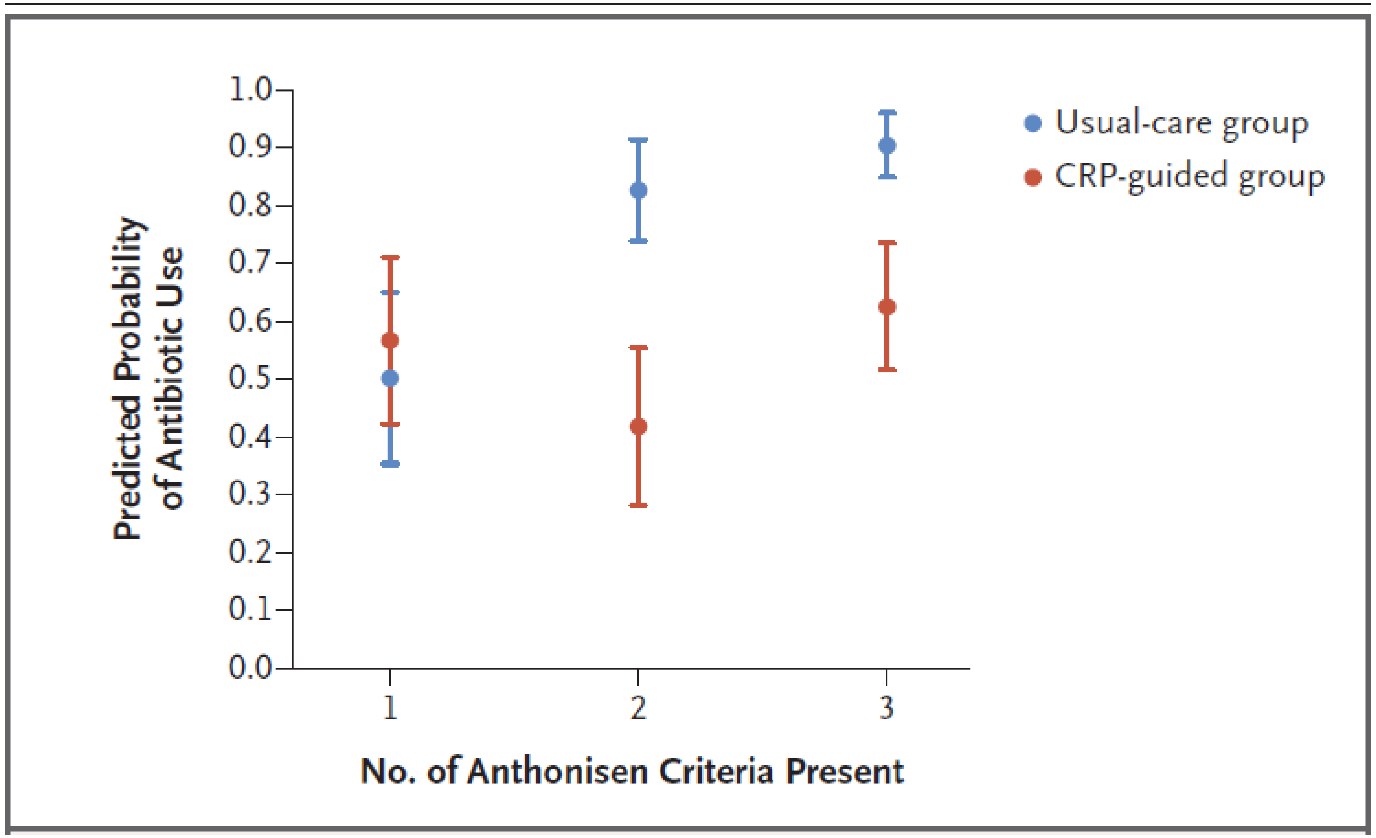
  (e.g. the Anthonisen criteria) → Point-of-care testing of CRP
- CRP guidance in this study
  - < 20 : antibiotics unlikely
  - 20-40 : may be beneficial → consider Antibiotics

    (if purulent sputum, underlying disease, AE severity)
  - > 40 : likely to beneficial → prescribe Antibiotics

    (unless lower risk, unlikely to bacterial infection, or non-severe)

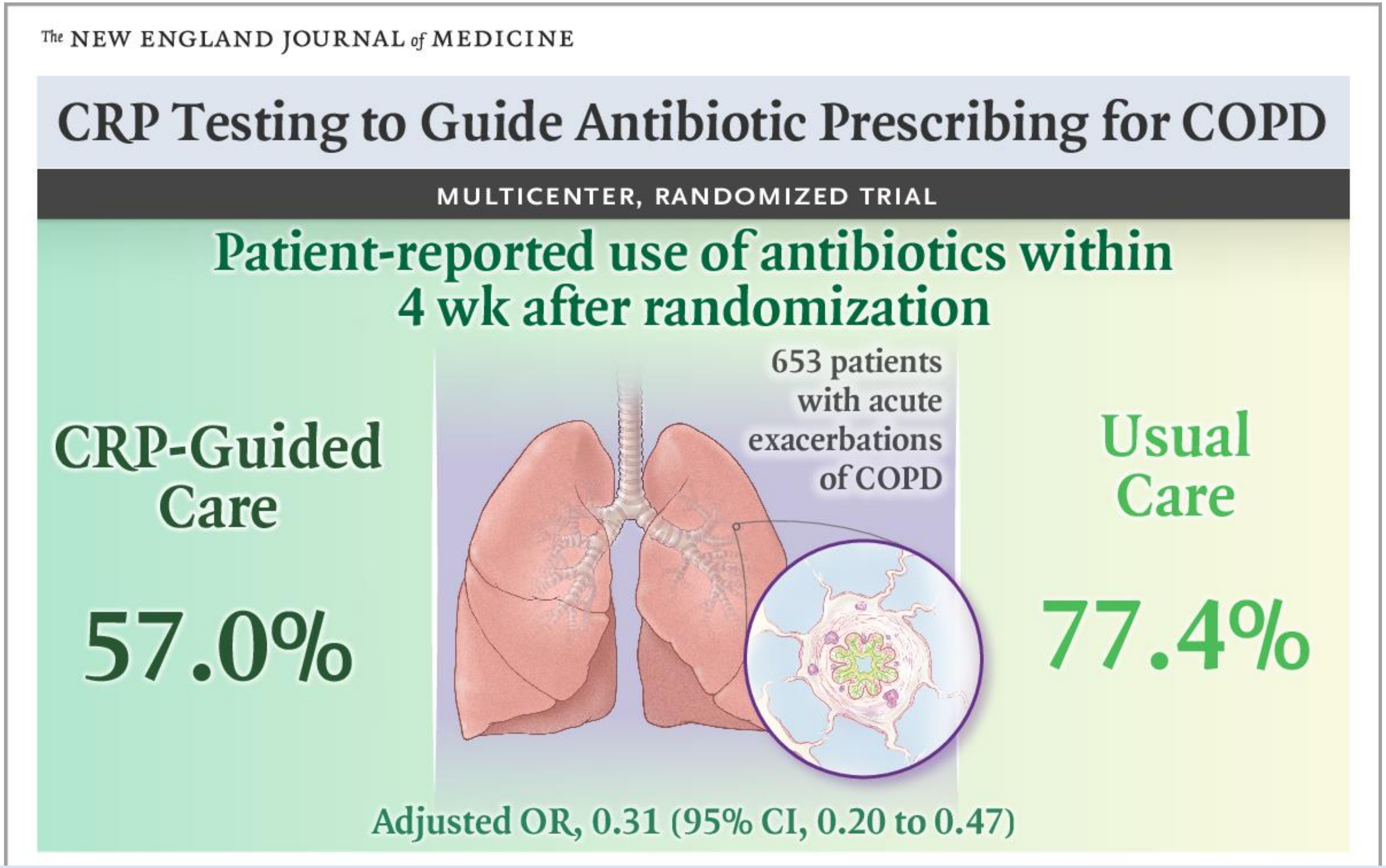
Butler et al. N Engl J Med 2019;381:111-20.

Antibiotics guidance by point-of-CRP



Butler et al. N Engl J Med 2019;381:111-20.

Antibiotics guidance by point-of-CRP



Lower antibiotics use than conventional group in point-of-CRP group with no inferiority of clinical outcomes

Butler et al. N Engl J Med 2019;381:111-20.

Antibiotics guidance by Procalcitonin

CrossMark

Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis

Alexander G. Mathioudakis[1], Victoria Chatzimavridou-Grigoriadou[2], Alexandru Corlateanu[3] and Jørgen Vestbo[1]

Antibiotics Cut-off Procalcitonin level: 0.25ug/L

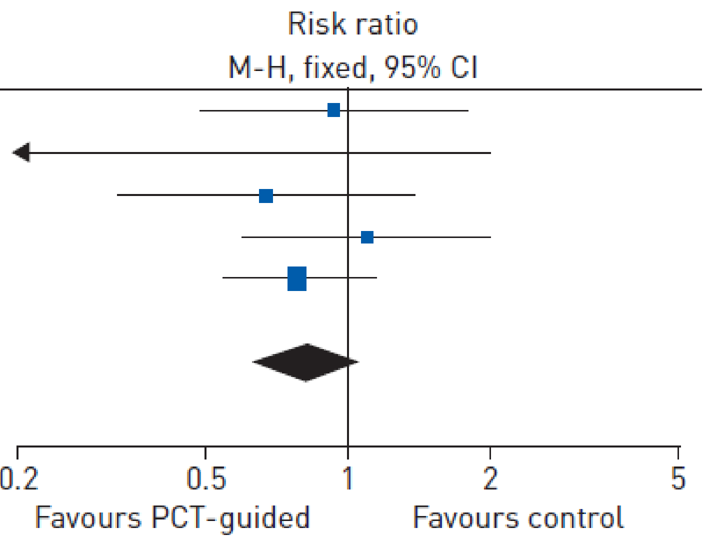
Treatment failure: symptom deterioration, non-improvement, ICU admission, death within 4 wks

a)

First author, year [ref.]	PCT-guided events/total	Standard care events/total	Weight %	Risk ratio M-H, fixed, 95% CI
Corti, 2016 [19]	14/62	14/58	16.0	0.94 (0.49–1.79)
Nangia, 2012 [21]	0/50	4/50	5.0	0.11 (0.01–2.01)
Schuetz, 2009 [24]	11/115	16/113	17.9	0.68 (0.33–1.39)
Stolz, 2007 [13]	18/102	17/106	18.5	1.10 (0.60–2.01)
Verduri, 2015 [14]	30/88	39/90	42.7	0.79 (0.54–1.14)
Total events/total (95% CI)	73/417	90/417	100	0.81 (0.62–1.06)

Heterogeneity: Chi-squared=3.23, df=4 (p=0.52); I^2=0%

Test for overall effect: Z=1.51 (p=0.13)



Eur Respir Rev 2017; 26: 160073

Antibiotics guidance by Procalcitonin

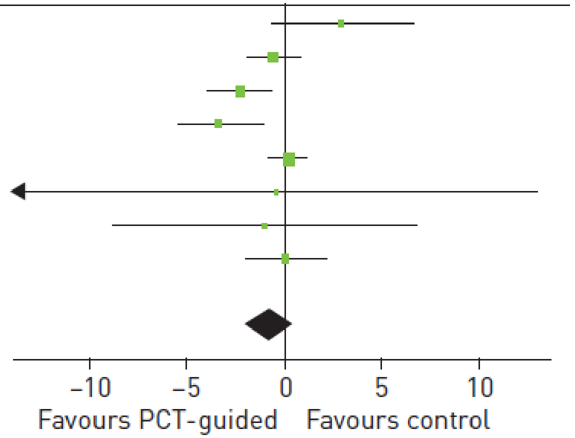
Hospital LOS

b)

First author, year [ref.]	PCT-guided Mean±SD	PCT-guided Total	Standard care Mean±SD	Standard care Total	Weight %	Mean difference IV, random, 95% CI
Christ Crain, 2004 [22]	13.7±7.3	29	10.8±7	31	7.7	2.90 (−0.72–6.52)
Corti, 2016 [19]	4.5±2.96	62	5.1±4.44	58	19.9	−0.60 (−1.96–0.76)
Kristoffersen, 2009 [23]	4.8±2.8368	28	7.1±3.6057	32	17.8	−2.30 (−3.93–−0.67
Liu, 2015 [20]	16.06±4.73	52	19.41±6.74	56	14.1	−3.35 (−5.53–−1.17)
Nangia, 2012 [21]	7.5±2.5	50	7.3±2.3	50	22.9	0.20 (−0.74–1.14)
Schuetz, 2009 [24]	8.8±51.23	115	9.2±51.23	113	0.8	−0.40 (−13.70–12.90)
Stolz, 2007 [13]	9±30.547	102	10±25.9622	106	2.2	−1.00 (−8.72–6.72)
Verduri, 2015 [14]	5±7.0795	88	5±7.1618	90	14.7	0.00 (−2.09–2.09)
Total (95% CI)		526		536	100.0	−0.76 (−1.95–0.43)

Heterogeneity: τ^2=1.37, Chi-squared=16.93, df=7 (p=0.02); I^2=59%

Test for overall effect: Z=1.25 (p=0.21)



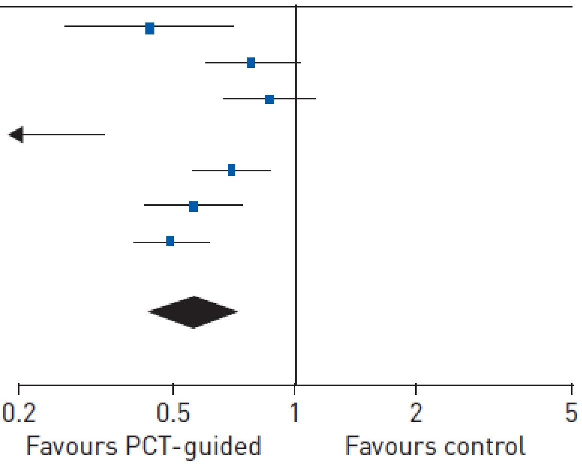
Antibiotics exposure

c)

First author, year [ref.]	PCT-guided events/total	Standard care events/total	Weight %	Risk ratio M-H, random, 95% CI
Christ Crain, 2004 [22]	11/29	27/31	11.4	0.44 (0.27–0.71)
Corti, 2016 [19]	36/62	43/58	15.5	0.78 (0.60–1.02)
Kristoffersen, 2009 [23]	26/38	41/42	15.5	0.87 (0.67–1.12)
Nangia, 2012 [21]	9/50	50/50	9.9	0.19 (0.11–0.33)
Schuetz, 2009 [24]	56/115	79/113	16.1	0.70 (0.56–0.87)
Stolz, 2007 [13]	41/102	76/106	15.4	0.56 (0.43–0.73)
Verduri, 2015 [14]	43/88	90/90	16.3	0.49 (0.40–0.61)
Total events/total (95% CI)	222/484	406/500	100.0	0.56 (0.43–0.73)

Heterogeneity: τ^2=0.10, Chi-squared=36.55,df=6 (p<0.00001); I^2=84%

Test for overall effect: Z=4.25 (p<0.0001)



Eur Respir Rev 2017; 26: 160073

Antibiotics guidance by Procalcitonin

Overall mortality at longest f/u

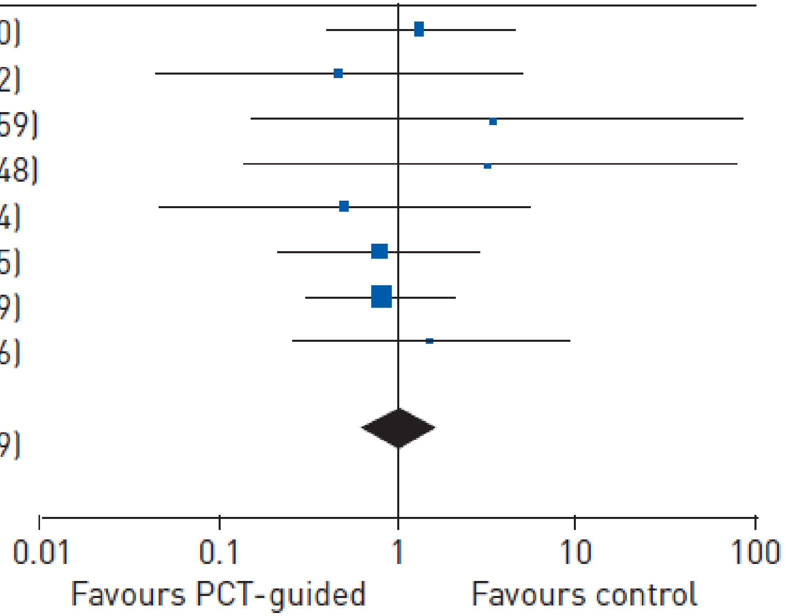
d)

First author, year [ref.]	PCT-guided events/total	Standard care events/total	Weight %	Risk ratio M-H, fixed, 95% CI
Christ Crain, 2004 [22]	5/29	4/31	15.6	1.34 (0.40–4.50)
Corti, 2016 [19]	1/62	2/58	8.4	0.47 (0.04–5.02)
Kristoffersen, 2009 [23]	1/28	0/32	1.9	3.41 (0.14–80.59)
Liu, 2015 [20]	1/52	0/56	1.9	3.23 (0.13–77.48)
Nangia, 2012 [21]	1/50	2/50	8.1	0.50 (0.05–5.34)
Schuetz, 2009 [24]	4/115	5/113	20.4	0.79 (0.22–2.85)
Stolz, 2007 [13]	7/102	9/106	35.7	0.81 (0.31–2.09)
Verduri, 2015 [14]	3/88	2/90	8.0	1.53 (0.26–8.96)
Total events/total (95% CI)	23/526	24/536	100.0	0.99 (0.58–1.69)

Heterogeneity: Chi-squared=2.59, df=7 (p=0.92); I^2=0%

Test for overall effect: Z=0.05 (p=0.96)

Risk ratio M-H, fixed, 95% CI



Probable benefit of PCT-guided treatment → need of validation in proper setting

Eur Respir Rev 2017; 26: 160073

Preventive antibiotics or antiviral therapy

Brennan *et al. Respiratory Research* (2022) 23:58
https://doi.org/10.1186/s12931-022-01947-5

Respiratory Research

REVIEW **Open Access**

Check for updates

Antimicrobial therapies for prevention of recurrent acute exacerbations of COPD (AECOPD): beyond the guidelines

Michelle Brennan[1*], M. J. McDonnell[1], M. J. Harrison[1], N. Duignan[1], A. O'Regan[1], D. M. Murphy[2], C. Ward[3] and R. M. Rutherford[1]

Brennan et al. Respiratory Research (2022) 23:58

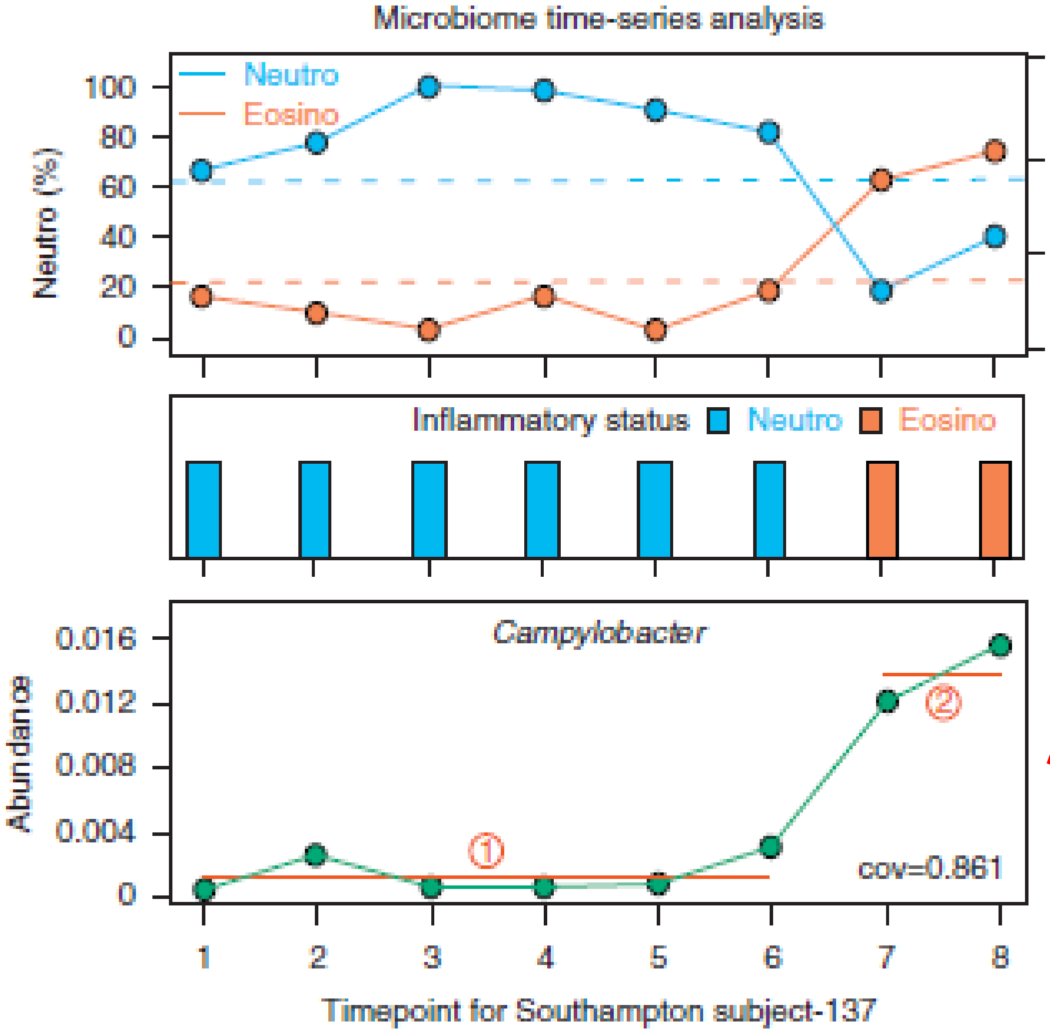
Preventive antibiotics or antiviral therapy

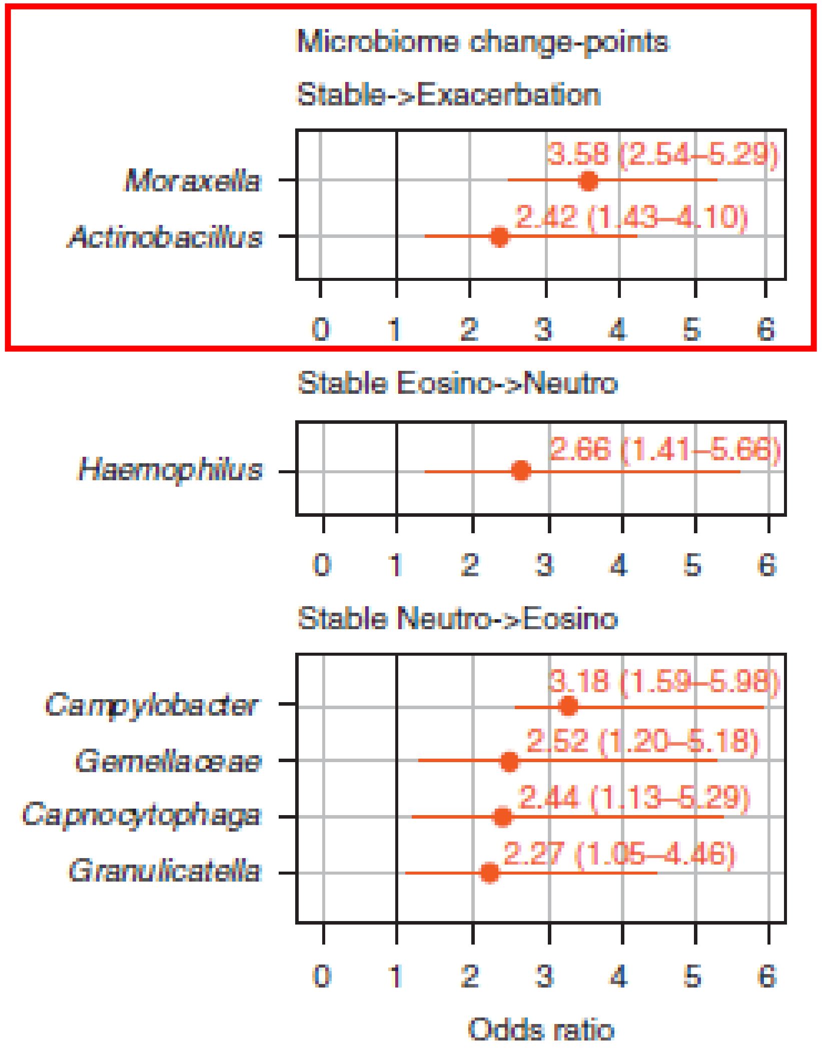
Table 1 Co-factors in acute exacerbations of COPD

Reduced mucociliary clearance	GORD	Airway colonization	Immune deficiency	Aspiration	GOLD D treatment
Direct injury by tobacco smoke	Increased frequency of Hiatus Hernia [4] and GORD [6] leading to chemical, food and microbial aspiration	*H Influenzae* *S pneumonia* *M catarrhalis* *P aeruginosa*	Innate immunity impaired- shortening of cilia, squamous cell metaplasia, goblet-cell hyperplasia, loss of tight junction from toxic effects of smoking	Swallowing normally performed in exhalation. In COPD pts swallowing can be immediately before or after inspiration heightening aspiration -risk considerably [12]	•LAMA/LABA •ICS •Azithromycin •Roflumilast •Influenza Vacc •Pneumococcal Vacc •Pulmonary rehabilitation within 6 weeks of hospital discharge for AECOPD
Chronic airway inflammation ± bronchiectasis		*Adenovirus* *Influenza B* *Coronovirus* *Rhinovirus* *Influenza A* [6, 7]	Adaptive immunity- fewer CD4+T central memory cells and CD8+T effector memory cells [8]		
Recent exacerbation					
Airways obstruction					
Dynamic expiratory coll					
↑Mucus tenacity					
Expiratory muscle weakness—sarcopenia, altered pulmonary dynamics					

- Recurrent AECOPD despite of following guided-therapy → lack of data
- Preventive antibiotics?
- Antiviral therapy or targeted vaccination

What about probiotics?





Wang et al. Am J Respir Crit Care Med Vol 203, Iss 12, pp 1488–1502, Jun 15, 2021

What about probiotics?

International Journal of Chronic Obstructive Pulmonary Disease
Dovepress
open access to scientific and medical research

Open Access Full Text Article
STUDY PROTOCOL

Prevention of Acute Exacerbation in Subjects with Moderate-to-very Severe COPD by Modulating Lower Respiratory Microbiome: Protocol of a Prospective, Multicenter, Randomized Controlled Trial

Open access
Protocol

BMJ Open

Prediction of exacerbation frequency of AECOPD based on next-generation sequencing and its relationship with imbalance of lung and gut microbiota: a protocol of a prospective cohort study

Li Deng ,[1] Jiali Yan,[2] Huachong Xu,[1] Chunzhen Huang,[3] Yiwen Lv,[1] Qianxin Wu,[1] Yinji Xu,[2,3] Xiaoyin Chen[1]

Int J Chron Obstruct Pulmon Dis. 2020; 15: 2985–2990
BMJ Open 2021;11:e047202. doi:10.1136/bmjopen-2020-047202

Antibiotics guidance: GOLD guideline

CRP

- "Data has indicated that antibiotics usage can be safely reduced from 77.4% to 47.7% when CRP is low"

Procalcitonin

- "We cannot recommend at this time the use of PCT-based protocols to make the decision on using antibiotics in patient with COPD exacerbation; however, confirmatory trials are required"

Summary

- "Antibiotics should be given to patients with exacerbations of COPD for 5-7 days"
  - Have three cardinal symptoms (increase in dyspnea, sputum volume, and sputum purulence
  - 2 of cardinal symptom + increased purulence
  - Mechanical ventilation (noninvasive or invasive)

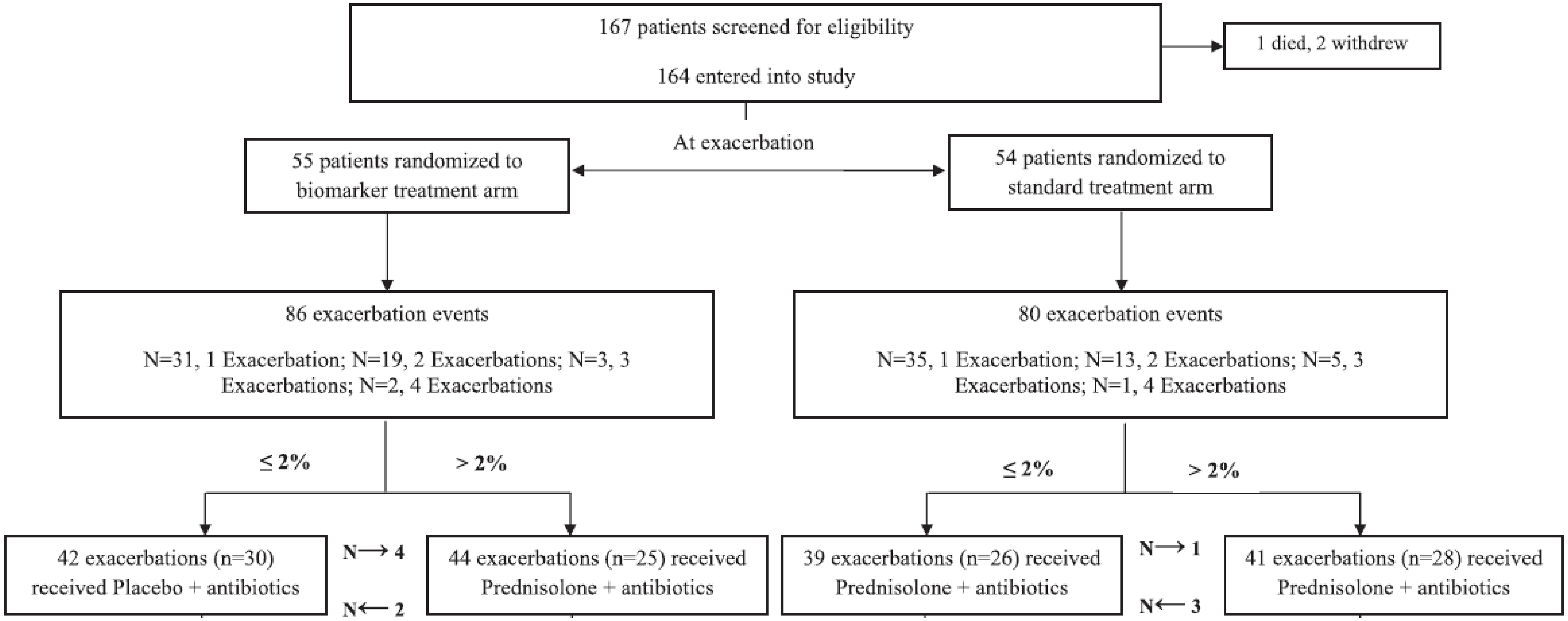
AECOPD management – systemic corticosteroid

Blood eosinophil guided: 2%

Blood Eosinophils to Direct Corticosteroid Treatment of Exacerbations of Chronic Obstructive Pulmonary Disease

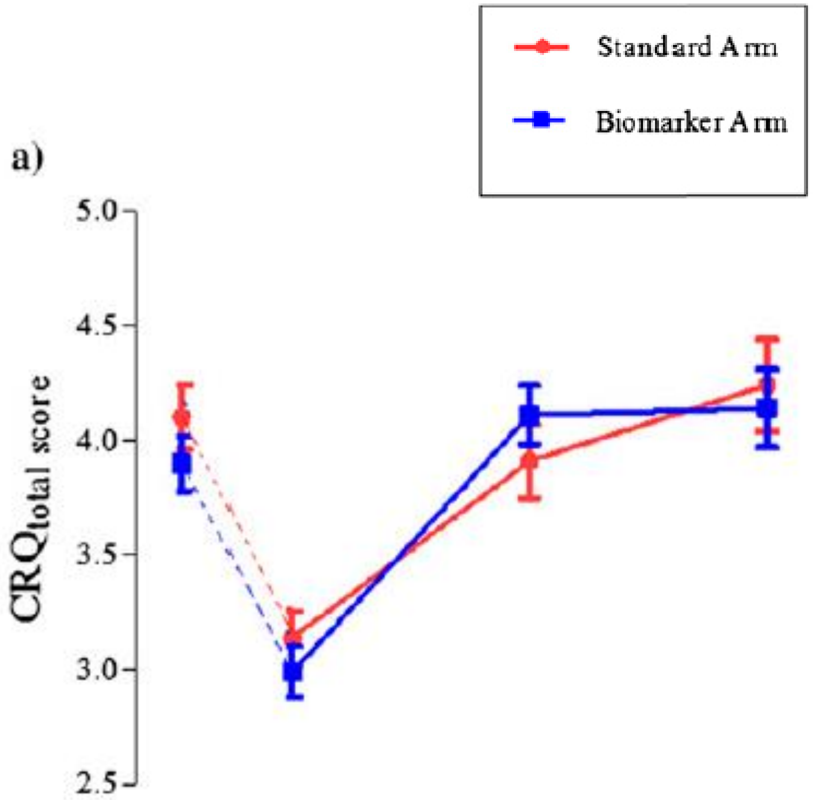
A Randomized Placebo-Controlled Trial

Mona Bafadhel[1], Susan McKenna[1], Sarah Terry[1], Vijay Mistry[1], Mitesh Pancholi[1], Per Venge[2], David A. Lomas[3], Michael R. Barer[1], Sebastian L. Johnston[4], Ian D. Pavord[1], and Christopher E. Brightling[1]

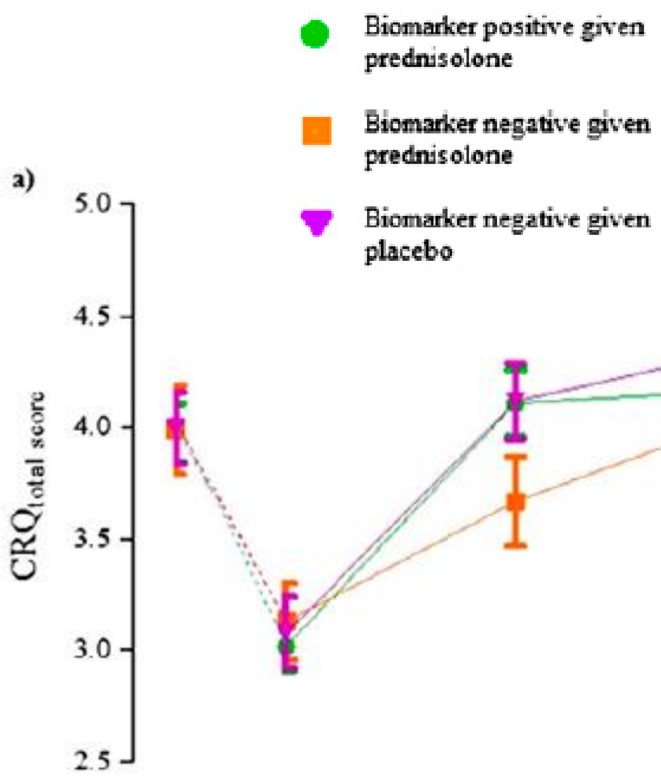


Bafadhel et al. Am J Respir Crit Care Med Vol 186, Iss. 1, pp 48–55, Jul 1, 2012

Blood eosinophil guided: 2%



Standard vs. biomarker
= 0.8 vs 1.1, p = 0.05



Biomarker-negative exacerbation
: mean difference 0.45, p = 0.04

Treatment failure in biomarker-negative AE: steroid (15%) vs placebo (2%) (p=0.04)

Bafadhel et al. Am J Respir Crit Care Med Vol 186, Iss. 1, pp 48–55, Jul 1, 2012

Blood eosinophil guided: 300 cells/mcl

THE LANCET
Respiratory Medicine

ARTICLES | VOLUME 7, ISSUE 8, P699-709, AUGUST 01, 2019

Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial

Blood eosinophil: 300

- Eosinophil-guided group (n=159) vs. Control group (n=159)
- Treatment failure at 30 days → Eosinophil-guided group; 42 (26%) vs Control group; 41 (26%), p=0.90
- 30 days mortality → Eosinophil-guided group; 6% vs Control group; 4%, p=0.43
- Median duration of systemic corticosteroid therapy

; Eosinophil-guided group (2 days (IQR 1·0 to 3·0)) vs. Control group (5 days (5·0 to 5·0)), p<0·0001.

Lancet Respir Med. 2019 Aug;7(8):699-709.

$FeNO_{200}$ > 10 ppb

FeNO at 50ml/s: $FeNO_{50}$
FeNO at 200ml/s: $FeNO_{200}$

Table 4 The Difference from Baseline in $FeNO_{50}$, CAT and Pulmonary Function Test

Variables	High $FeNO_{50}$	Low $FeNO_{50}$	P-value
$FeNO_{50}$	−24.00(−33.00,-2.00)	−1.50(−4.75,6.75)	0.018
CAT	−6.00(−9.00,-4.00)	−2.50(−4.00,0.50)	0.031
FEV1/FVC	6.48(−0.74,8.68)	2.44(−0.96,8.74)	0.286
FEV1% pred	2.70(−0.90,16.70)	6.35(−0.88,9.78)	0.340
FEV1	0.09(−0.05,0.28)	0.17(−0.05,0.26)	0.370
PEF	0.20(−0.42,1.40)	0.57(0.17,0.96)	0.676
PEF25	0.12(−0.15,0.72)	0.18(0.00,0.48)	0.906
PEF50	0.12(−0.06,0.43)	0.05(−0.02,0.23)	0.427
PEF75	0.06(0.01.0.18)	0.03(−0.01,009)	0.427

Notes: Data are presented as median (interquartile range); Kruskal–Wallis test for all other variables.

In AECOPD,

$FeNO_{50}$ > 25ppb (31%)
$FeNO_{200}$ > 10ppb (59%)

→Possibility of FeNO200 as treatment response marker of AECOPD

Table 5 The Difference from Baseline in $FeNO_{200}$, CAT and Pulmonary Function Test

Variables	High $FeNO_{200}$	Low $FeNO_{200}$	P-value
$FeNO_{200}$	−4.00(−6.00,1.00)	0.50(−0.75,4.00)	0.017
CAT	−4.00(−6.00,-3.00)	−1.00(−3.75,0.50)	0.031
FEV1/FVC	2.62(−1.99,7.83)	3.54(−0.17,13.76)	0.542
FEV1% pred	3.50(−2.30,11.40)	5.90(1.10,9.43)	0.803
FEV1	0.09(−0.04,0.24)	0.19(−0.05,0.31)	0.921
PEF	0.72(−0.05,1.09)	0.34(0.07,0.73)	0.176
PEF25	0.13(−0.10,0.50)	0.32(0.09,0.71)	0.611
PEF50	0.05(−0.03,0.25)	0.13(−0.02,0.28)	0.863
PEF75	0.02(−0.01,0.13)	0.04(0.00,0.10)	0.922

Notes: Data are presented as median (interquartile range); Kruskal–Wallis test for all other variables.

Int J Gen Med. 2021; 14: 571–580.

Systemic corticosteroid guidance: GOLD guideline

- Systemic corticosteroid in AECOPD
  - Proven Tx effect: improve FEV1, shorten recovery time, improve oxygenation, reduce early relapse, reduce Tx failure, reduce hospital LOS
  - 40mg/d for 5 days (longer → pneumonia, mortality)
  - Oral or IV
  - May be less effective in AECOPD with lower BEC
  - BEC guided Tx for shortening steroid: not fully evaluated
  - FeNO: lack of evidence for decision

AECOPD management – CHF as comorbid condition

CHF and COPD: common

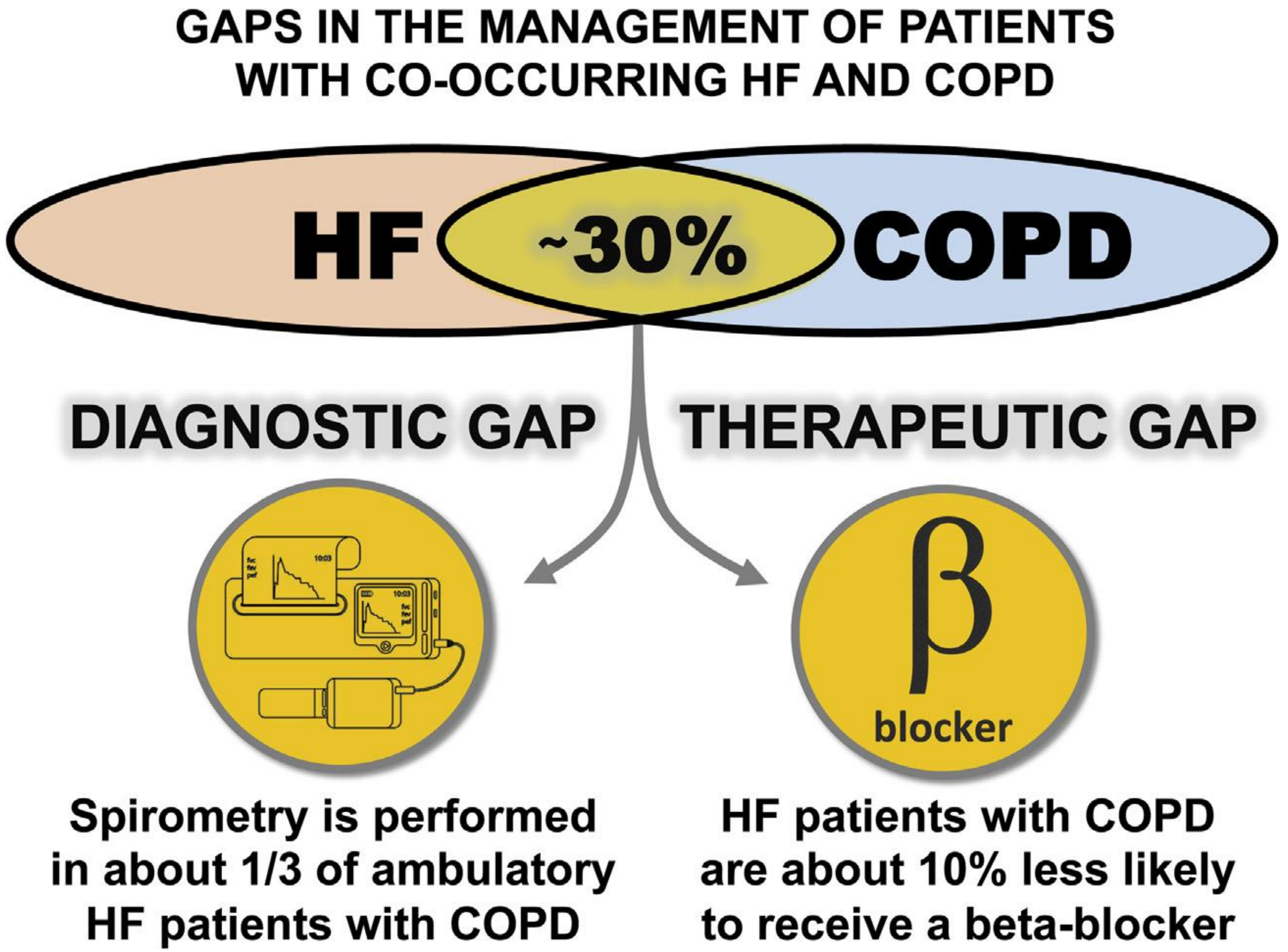
MINI-FOCUS ISSUE: HEART FAILURE AND PULMONARY CONDITIONS

STATE-OF-THE-ART REVIEW

Diagnostic and Therapeutic Gaps in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease

Marco Canepa, MD, PhD,[a,b,*] Frits M.E. Franssen, MD, PhD,[c,d,*] Horst Olschewski, MD,[e] Mitja Lainscak, MD, PhD,[f] Michael Böhm, MD,[g] Luigi Tavazzi, MD,[h] Stephan Rosenkranz, MD, PhD[i,j]

JACC: HEART FAILURE CME/MOC/ECME



Canepa et al. JACC: HEART FAILURE VOL. 7, NO. 10, 2019

CHF and COPD: common

		HF	COPD
STABLE	*Treatment based on the severity of each condition*	*LVEF, NYHA class, signs of congestion* **DIURETIC** **BETA-BLOCKER** **RAAS INHIBITORS**	*FEV_1, symptoms, exacerbation risk* **LAMA and/or LABA** **INHALED CORTICOSTEROIDS**
UNSTABLE	*The two conditions may or may not be related* *Differential diagnosis may be challenging* *Identification and treatment of the precipitants*	**HF WORSENING** **DIURETIC** Consider transitory intravenous Adequate oral dose to the lowest effective dose **BETA-BLOCKER** Withdraw only when needed (e.g. cardiogenic shock, inotropes) Consider brief dose reduction and titration when possible **RAAS INHIBITORS** No evidence for ARB better than ACEi in COPD patients	**COPD EXACERBATION** **BRONCHODILATORS** Short-acting beta2 agonists recommended as initial bronchodilators **SYSTEMIC CORTICOSTEROIDS** Add a 5-7 day course of oral corticosteroids when needed **ANTIBIOTICS** Add a 5-7 day course of antibiotics when needed (e.g. respiratory infections)

Canepa, M. et al. J Am Coll Cardiol HF. 2019;7(10):823-33.

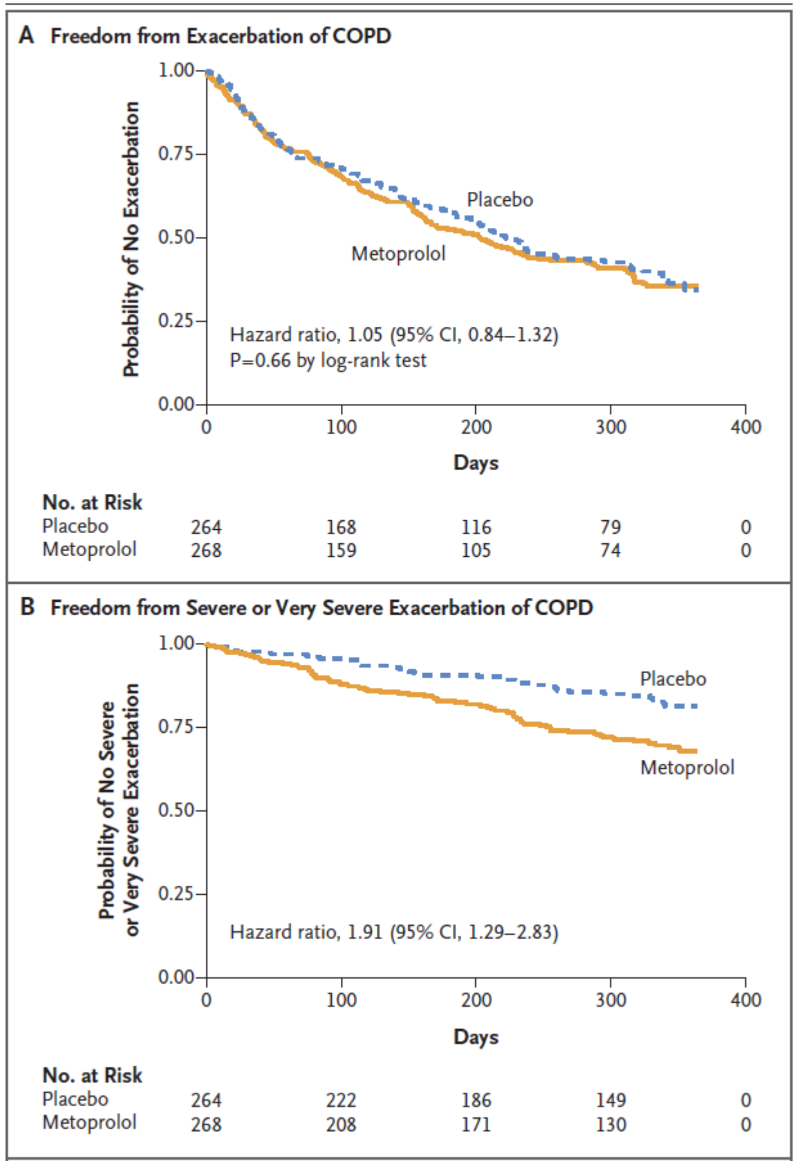
Canepa et al. JACC: HEART FAILURE VOL. 7, NO. 10, 2019

CHF and COPD: common

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD



Dransfield et al. N Engl J Med 2019;381:2304-14.

CHF and COPD: BNP

Høiseth et al. Respiratory Research 2012, 13:97
http://respiratory-research.com/content/13/1/97

RESPIRATORY RESEARCH

RESEARCH **Open Access**

NT-proBNP independently predicts long term mortality after acute exacerbation of COPD – a prospective cohort study

Arne Didrik Høiseth[1,3*], Torbjørn Omland[1], Tor-Arne Hagve[2], Pål H Brekke[1] and Vidar Søyseth[1]

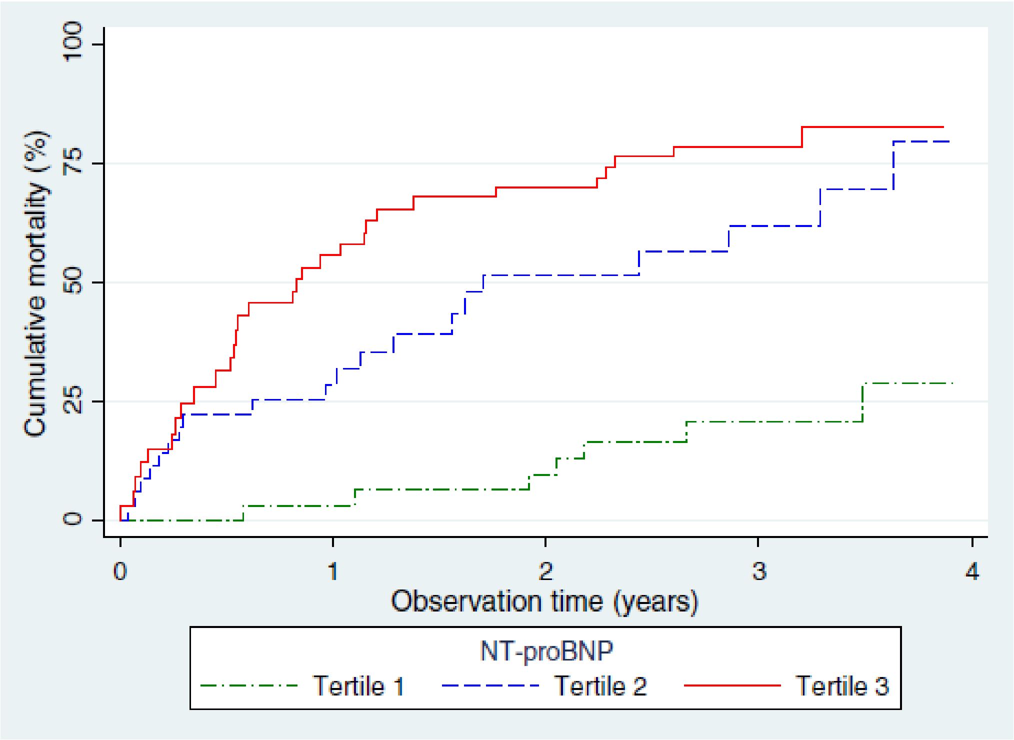


Figure 1 Mortality after acute exacerbation of COPD stratified by level of NT-proBNP. Based on 217 admissions and 57 mortalities in 99 patients.

Høiseth et al. Respiratory Research 2012, 13:97

CHF and COPD: Echo + Lung US

OPEN

EXPERT CONSENSUS DOCUMENT

Echocardiography and lung ultrasonography for the assessment and management of acute heart failure

Lung and pleural ultrasonography[37,38]				
Alternative diagnoses for patient's signs and symptoms?	Pneumothorax assessment	Anterior, upper chest on each hemithorax	Presence of lung sliding along pleural line rules out pneumothorax in the scanned chest zones	Sensitivity 91%, specificity 98% for detection of pneumothorax[136]
Evidence of pulmonary oedema?	Pulmonary oedema detection	Three or four anterior/lateral chest zones on each hemithorax	Three or more B-lines in two or more zones on each hemithorax considered diagnostic for AHF	Sensitivity 94%, specificity 92% for diagnosis of AHF in patients with dyspnoea in the ED[33,38]
Evidence of pleural effusions?	Pleural effusion detection	Posterior axillary line on both hemithoraces	Echo-free space above the diaphragm	Sensitivity 79–84%, specificity 83–98% for diagnosis of AHF in patients with dyspnoea in the ED[44,45]

Nat Rev Cardiol 14, 427–440 (2017).

CHF and COPD: Lung US as decision maker

Pre-hospital LUS in COPD

- Severe dyspnea patient who has COPD or HF in Vicenza, Italy
- Case-Control study
- Pre-ho
- LUS: W

Conclusion

- More appropriate pharmacologic therapy (p=0.01)
- Appropriate CPAP in COPD (p=0.011)
- In A-profile, LUS guided Tx vs. Control → Lower PCO_2 52.23 vs. 42.62mmHg, p=0.049

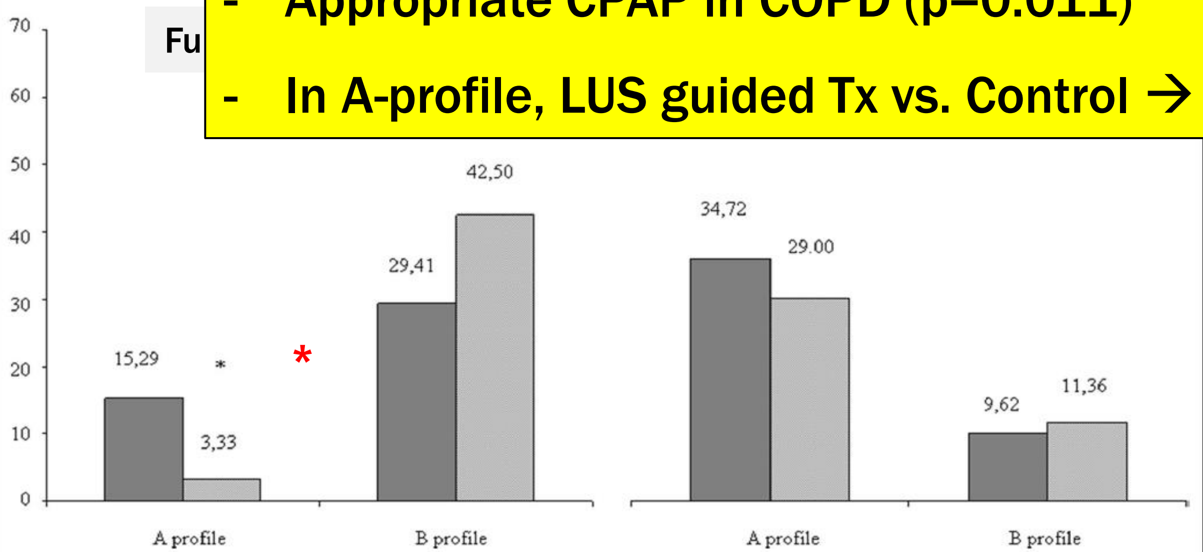


Fig. 1 Pharmacological therapy in the two study groups splitted by lung profile

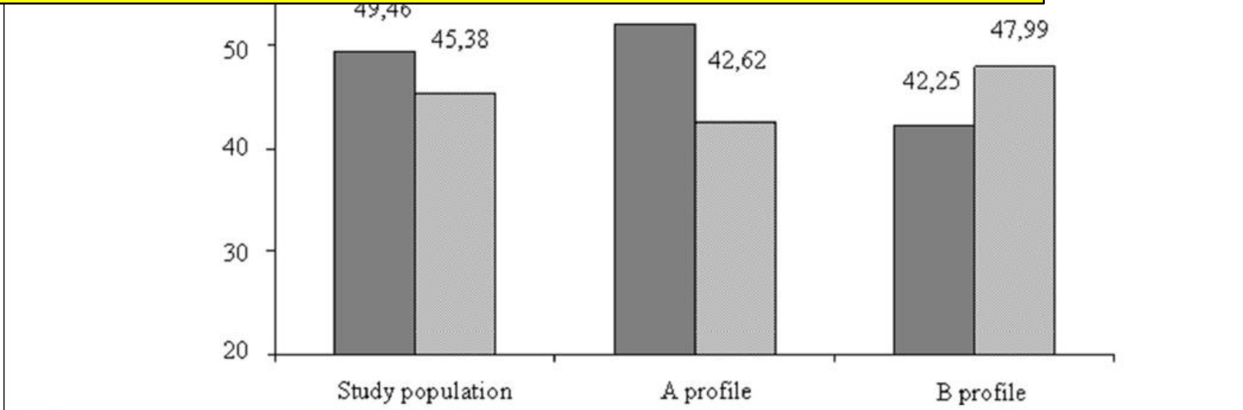
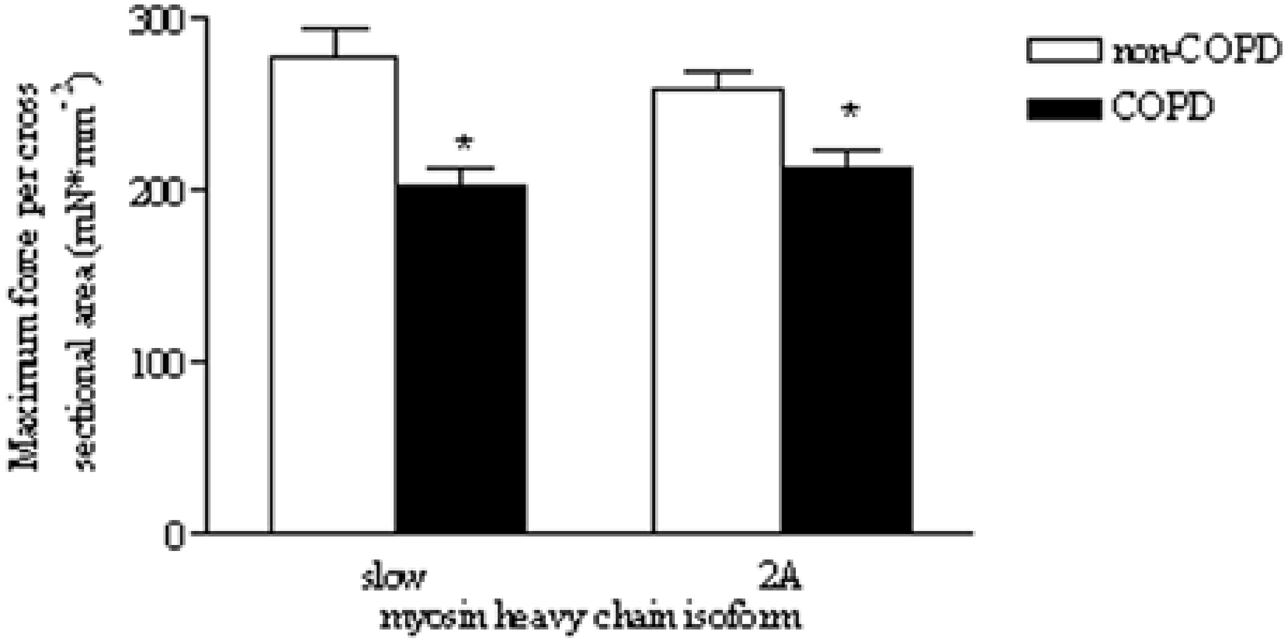


Fig. 2 PCO_2 concentration in the two study groups splitted by lung profile

Zanatta et al. Crit Ultrasound J (2018) 10:22

AECOPD management – DD as comorbid condition

Diaphragm muscle adaptation in COPD



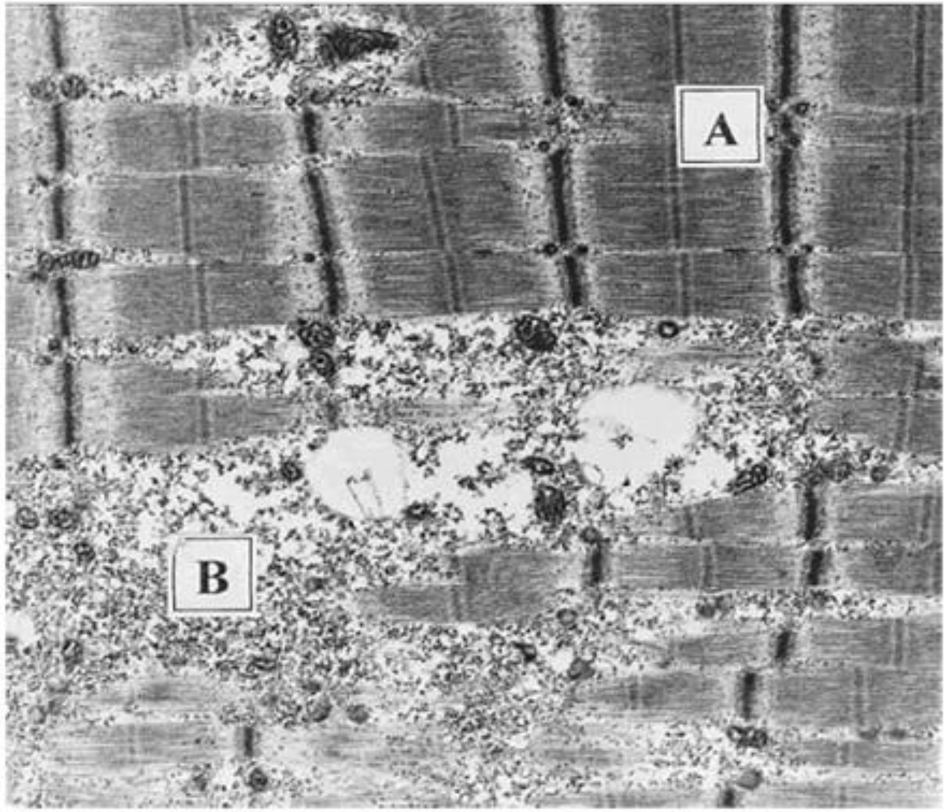


Figure 5
Electronmicroscopic photograph showing areas of normal (A) and disrupted (B) sarcomeres in a diaphragm sample from a patient with moderate-severe COPD. Note the disruption and even absence of A- and I-bands. Reproduced from Orozco-levi et al. [20] with permission.

Ottenheijm et al. Respiratory Research 2008, 9:12

DD and COPD: common, especially in severe AE

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Prevalence and outcomes of diaphragmatic dysfunction assessed by ultrasound technology during acute exacerbation of COPD: A pilot study

Federico ANTENORA,[1] Riccardo FANTINI,[1] Andrea IATTONI,[1] Ivana CASTANIERE,[1] Antonia SDANGANELLI,[1] Francesco LIVRIERI,[1] Roberto TONELLI,[1] Stefano ZONA,[2] Marco MONELLI,[1] Enrico M. CLINI[1,3] AND Alessandro MARCHIONI[1]

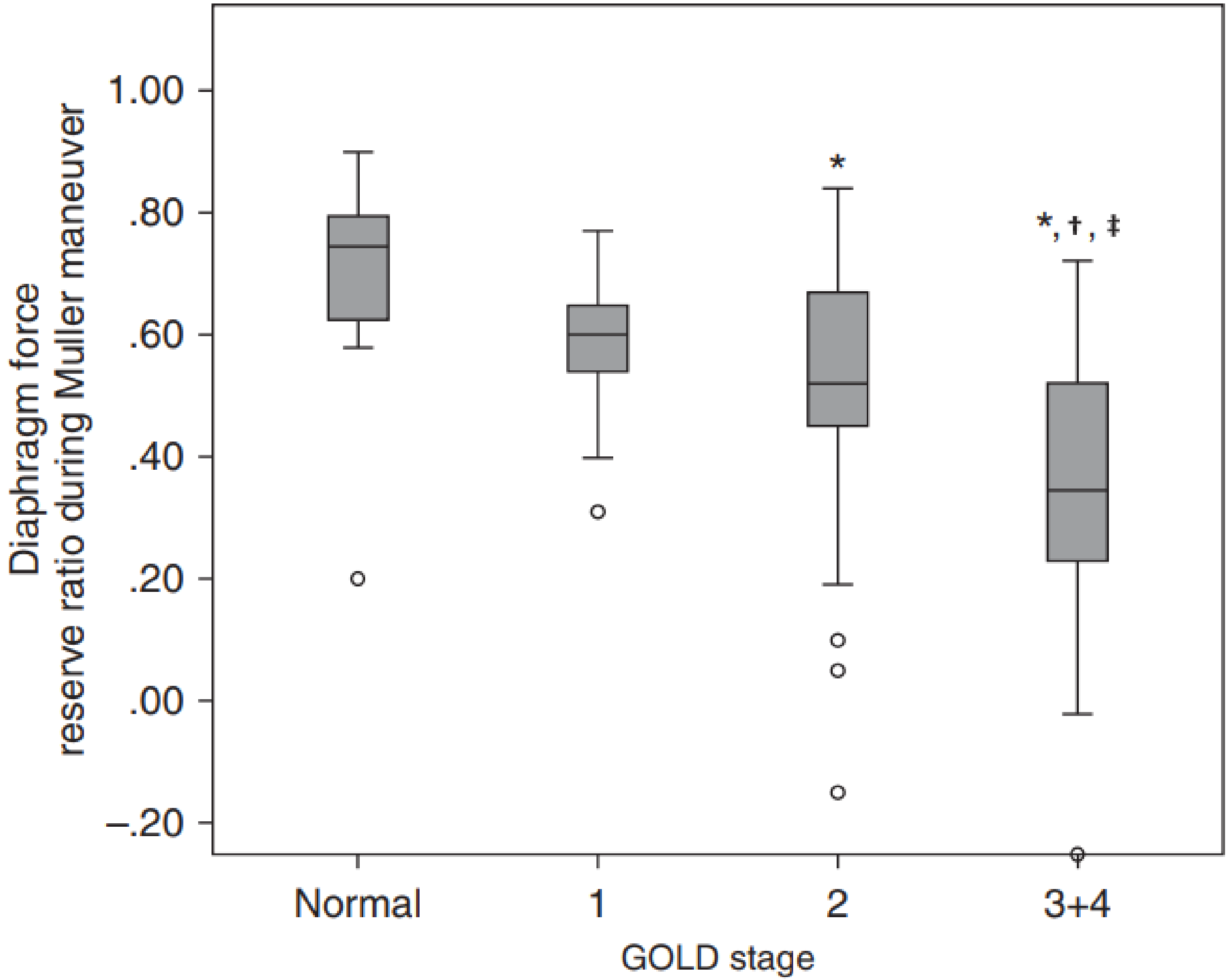
		Diaphragmatic status		
	Overall	DD+	DD−	*P*-value
Patients	41 (100)	10 (24.4)	31 (75.6)	
Age (years)	76	75	76	0.52
Male	26 (63.4)	7 (70)	19 (61.2)	0.47
Pneumonia	19 (46)	7 (70)	12 (38)	0.08
Sepsis	9 (22)	4 (40)	5 (16.1)	0.12
Diabetes	16 (39)	6 (60)	10 (34.5)	0.15
Use of steroids	15 (37.5)	8 (80)	7 (23.3)	0.002
GCS	14 (12–15)	14 (12–14)	14 (12–15)	0.13
APACHE II	20 (16–24)	22 (20–26)	19 (15–24)	0.18
SAPS II	41 (33–45)	44.5 (38–50)	40 (33–45)	0.39
PaO_2/FiO_2	163 (122–197.5)	182 (106–200)	146 (124–197)	0.7
pH	7.24 (7.21–7.30)	7.23 (7.22–7.27)	7.26 (7.19–7.31)	0.6
$PaCO_2$ (mm Hg)	85 (76.5–105)	90 (82–107)	84 (73–100)	0.2
Blood lactate (mg/dL)	6 (4–11)	4 (3–5)	7 (5–14)	0.02
Respiratory rate (bpm)	32 (28–35)	35 (32–35)	30 (28–35)	0.09

F.Antenora et al. Respirology. 2017 Feb;22(2):338-344

DD and COPD: measured by sono

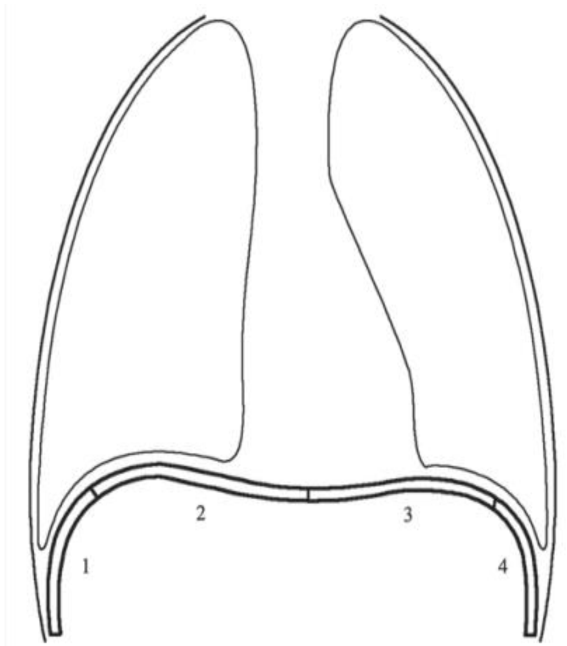
- Healthy vs COPD: Different status of stable condition of diaphragm muscle
- Different by COPD st

Variables	D Range)]	*P* Value
TFdi-tidal, %		0.002
TFdi-max, %		
Muller		0.006
Sniff test		0.104
DE-max, cm		
Muller		0.003
Sniff test		0.456
Diaphragm force reserve rati		
Muller		<0.001
Sniff test		<0.001

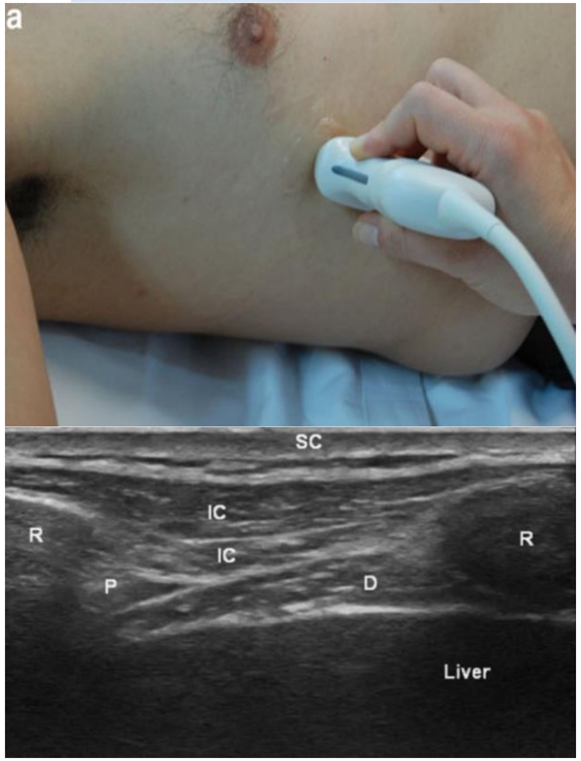


N.Rittayamia et al. AnnalsATS 2020;17:10

DD and COPD: measured by sono

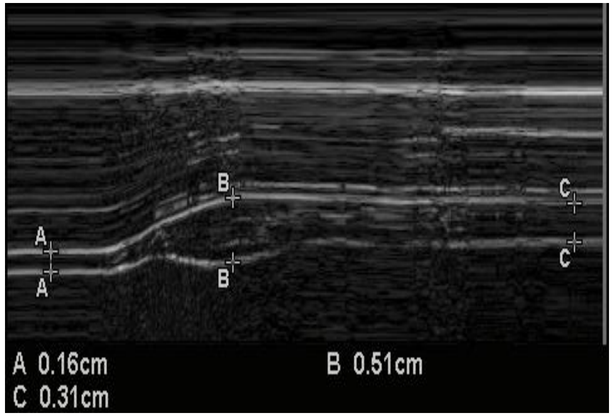


Diaphragm mass



Cut-off values: < 2mm

Diaphragm driving power

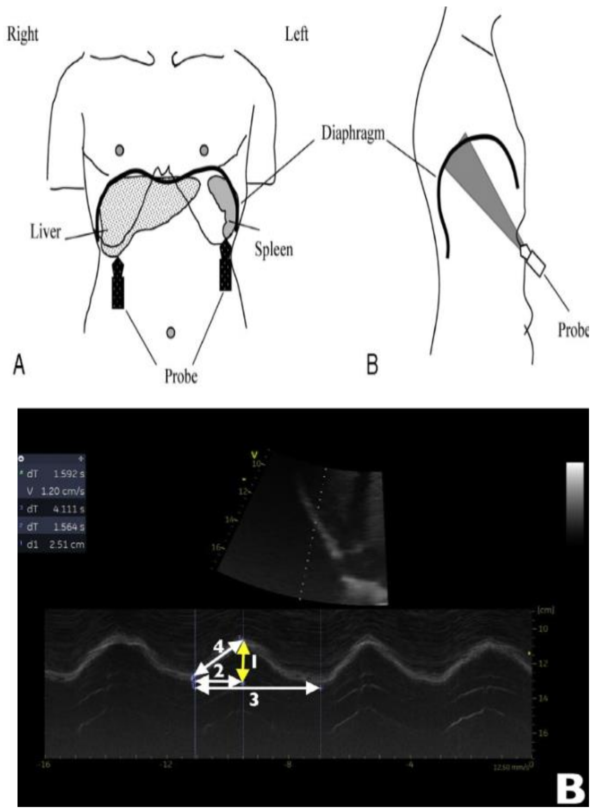


A) end-expiration
B) peak inspiratory muscle contraction

(B-A)/A = Diaphragm thickening fraction (TF)

Cut-off values: < 20%

Diaphragm mobility



Cut-off values: <50mm

DD and COPD: stable vs. AE

International Journal of Chronic Obstructive Pulmonary Disease | Dovepress
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Open Access Full Text Article | ORIGINAL RESEARCH

Diaphragm Ultrasound is an Imaging Biomarker that Distinguishes Exacerbation Status from Stable Chronic Obstructive Pulmonary Disease

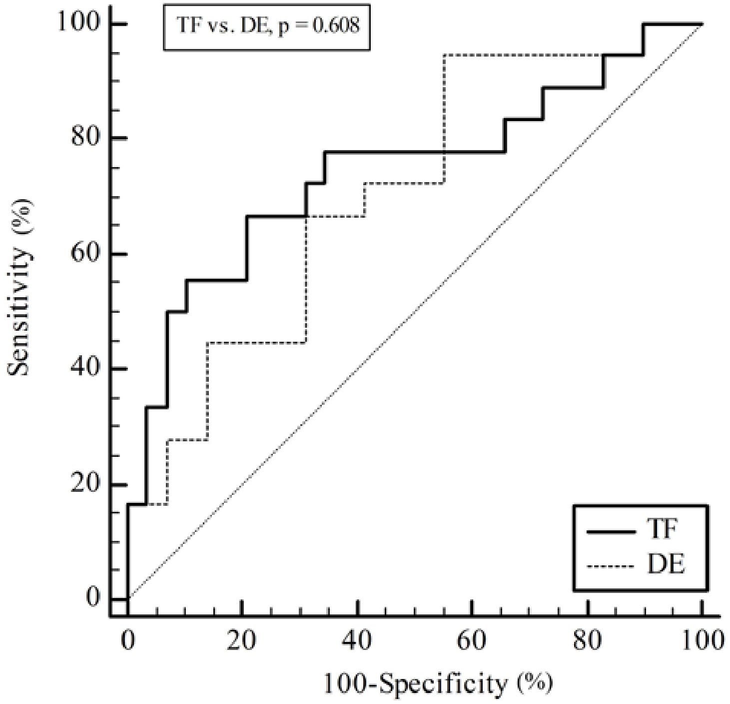


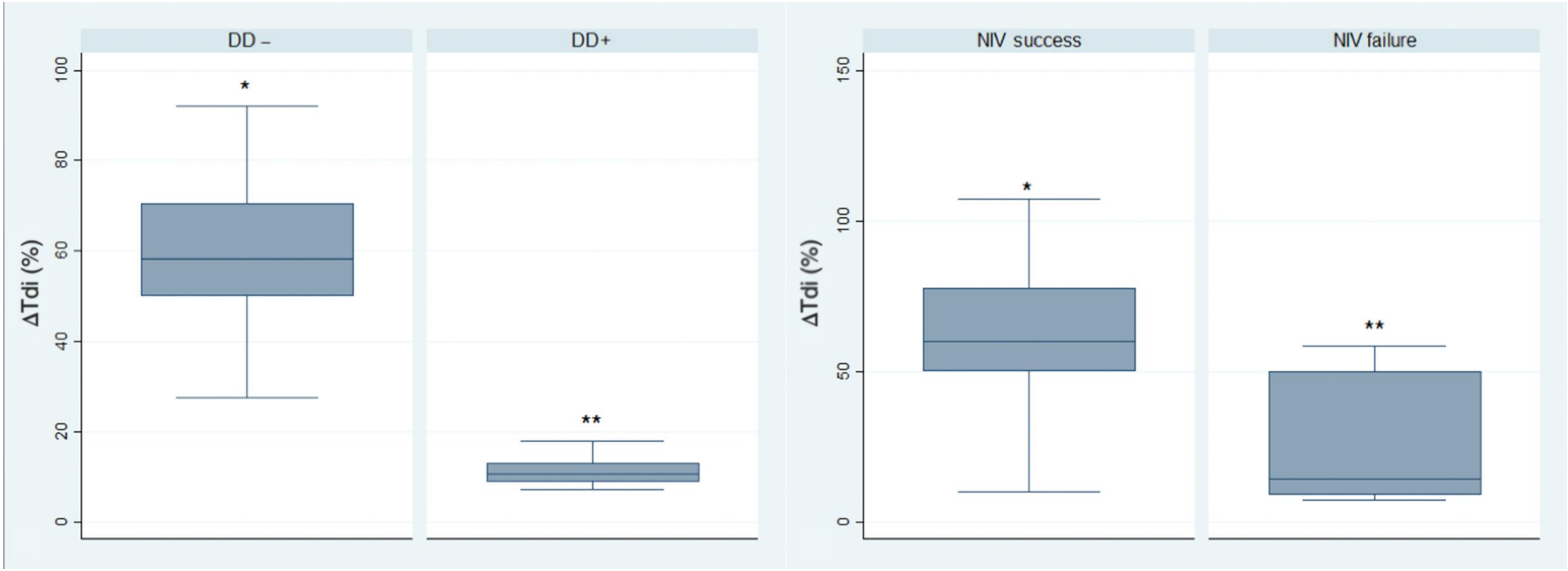
Table 4 Logistic Regression Analysis for Estimating Exacerbation of Chronic Obstructive Pulmonary Diseases

Model 1	Univariate		Multivariate	
	p-value	OR (95% CI)	*p*-value	OR (95% CI)
Age	0.722	0.99 (0.94–1.05)	0.682	0.98 (0.91–1.06)
Male sex	0.317	1.96 (0.53–7.28)	0.544	1.74 (0.29–10.34)
mCCI	0.049	1.62 (1.00–2.62)	0.157	1.73 (0.81–3.70)
BMI	0.007	0.80 (0.68–0.94)	0.002	0.70 (0.56–0.88)
Low TF_{max}	0.006	5.57 (1.64–18.94)	0.014	8.40 (1.55–45.56)
Model 2	**Univariate**		**Multivariate**	
Age	0.722	0.99 (0.94–1.05)	0.233	0.95 (0.88–1.03)
Male sex	0.317	1.957 (0.53–7.28)	0.393	2.16 (0.37–12.67)
mCCI	0.049	1.62 (1.00–2.62)	0.032	2.68 (1.09–6.60)
BMI	0.007	0.80 (0.68–0.94)	0.022	0.79 (0.64–0.97)
Low DE_{max}	0.011	16.25 (1.92–137.78)	0.038	11.51 (1.15–115.56)

Abbreviations: mCCI, modified Charlson Comorbidity Index; BMI, body mass index; TF_{max}, diaphragm thickening fraction during maximal deep breathing; DE_{max}, diaphragm excursion during maximal deep breathing.

TJ An et al. Int J Chron Obstruct Pulmon Dis . 2022 Jan 4;17:3-12

DD and COPD in AE: NIV success rate



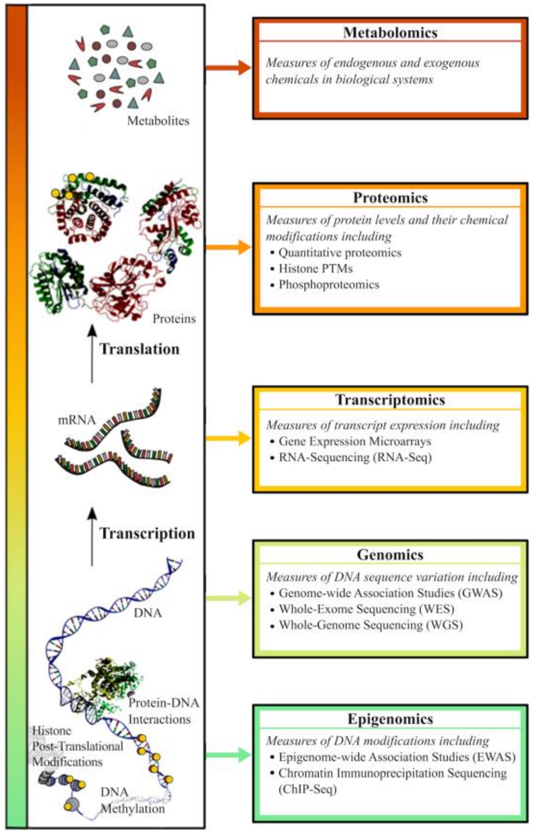
F.Antenora et al. Respirology. 2017 Feb;22(2):338-344

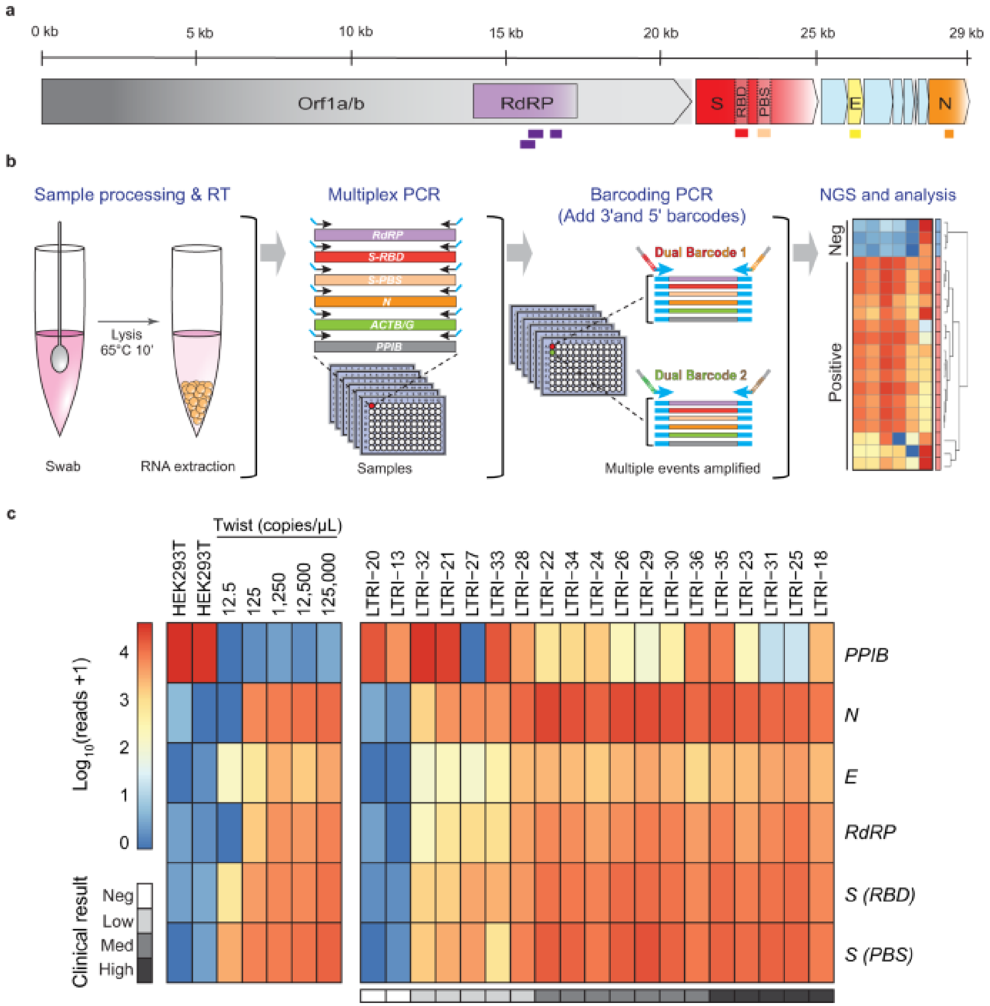
Summary - 2

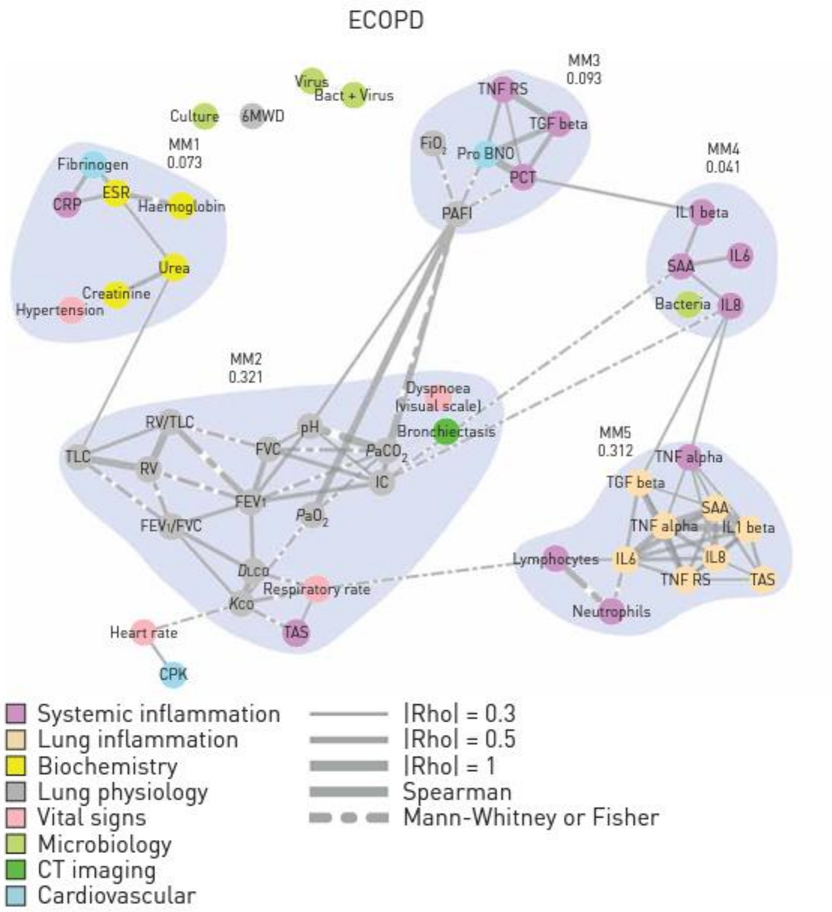
- Management of AECOPD
  - Antibiotics use
    - Consider community antimicrobial resistance
    - Indication of use in AECOPD: sputum purulence, cardinal symptom, severity of disease
    - Point-of-CRP, Procalcitonin
  - Corticosteroid use
    - Blood eosinophil count: lower is poor in response of AECOPD, not fully evaluated.
    - FeNO: lack of evidence, currently, FeNO 200
  - CHF: common, conflict response of medication, evaluation device
  - DD: common especially in severe AECOPD, evaluation device

Future of personalized medicine in AECOPD

Advance in data acquisition, analyses, and interpretation : multi-Omics, NGS, and multi-level network analyses

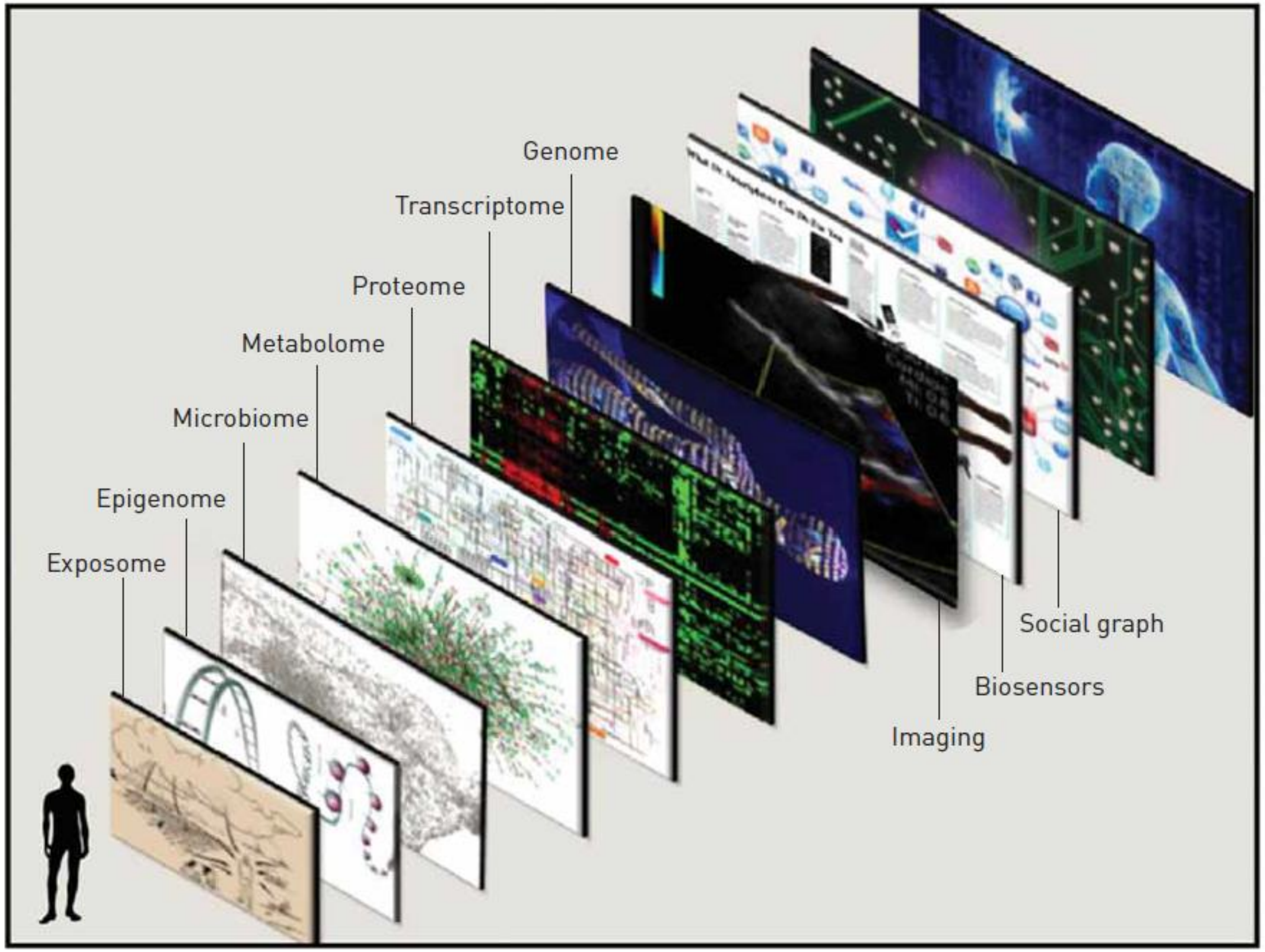






Kan et al. Respiratory Research (2017) 18:149
Nature Communications volume 12, Article number: 1405 (2021)
NOELL ET AL. Eur Respir J 2017; 50: 1700075

Personalized medicine in COPD



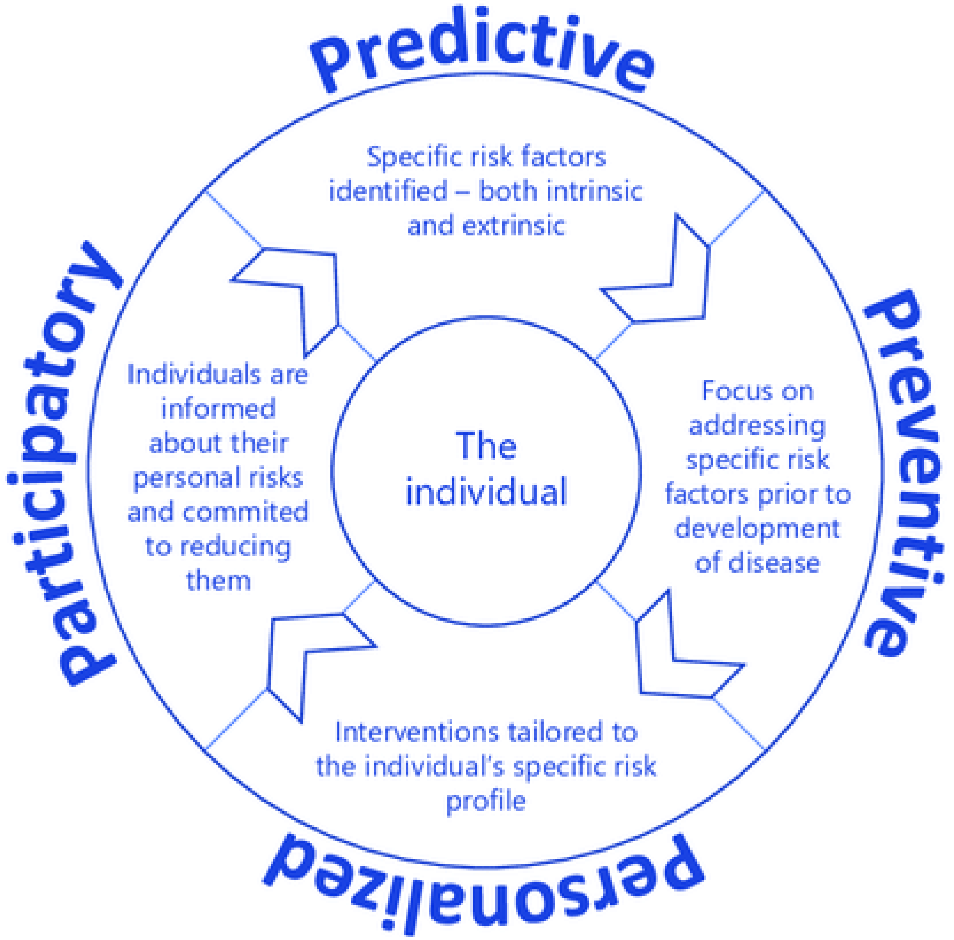
Noell et al. Eur Respir Rev 2018; 27: 170110

Take Home Messages

Take Home Messages

- Heterogeneity of AECOPD
  - Various phenotype
  - 4 categories: bacteria-, viral-, eosinophilic-, pauci-inflammatory-
    - Sputum color: Greenish, Yellowish ↔ Whitish-Grey
    - Sputum purulence: Purulent ↔ Mucoid
    - Sputum microbiome: diversity, composition, affected by time, medication, inflammatory endotype
    - Blood Eosinophil: Baseline level in stable COPD, Stability during AE
    - FeNO: FeNO 200, further study
- Management of AECOPD
  - Antibiotics use
    - Consider community antimicrobial resistance
    - Indication of use in AECOPD: sputum purulence, cardinal symptom, severity of disease
    - Point-of-CRP, Procalcitonin
  - Corticosteroid use
    - Blood eosinophil count: lower is poor in response of AECOPD, not fully evaluated.
  - Comorbidities: CHF, DD etc.
    - Ultrasound

P4: Predictive, Preventive, Personalized, Participatory



Are we ready? Not yet, but we are preparing it.

Everything comes to those who wait.

Thank you for your attention