Respiratory Review of 2021
: **Bronchiectasis**

한림의대 호흡기내과
최하영

Agenda

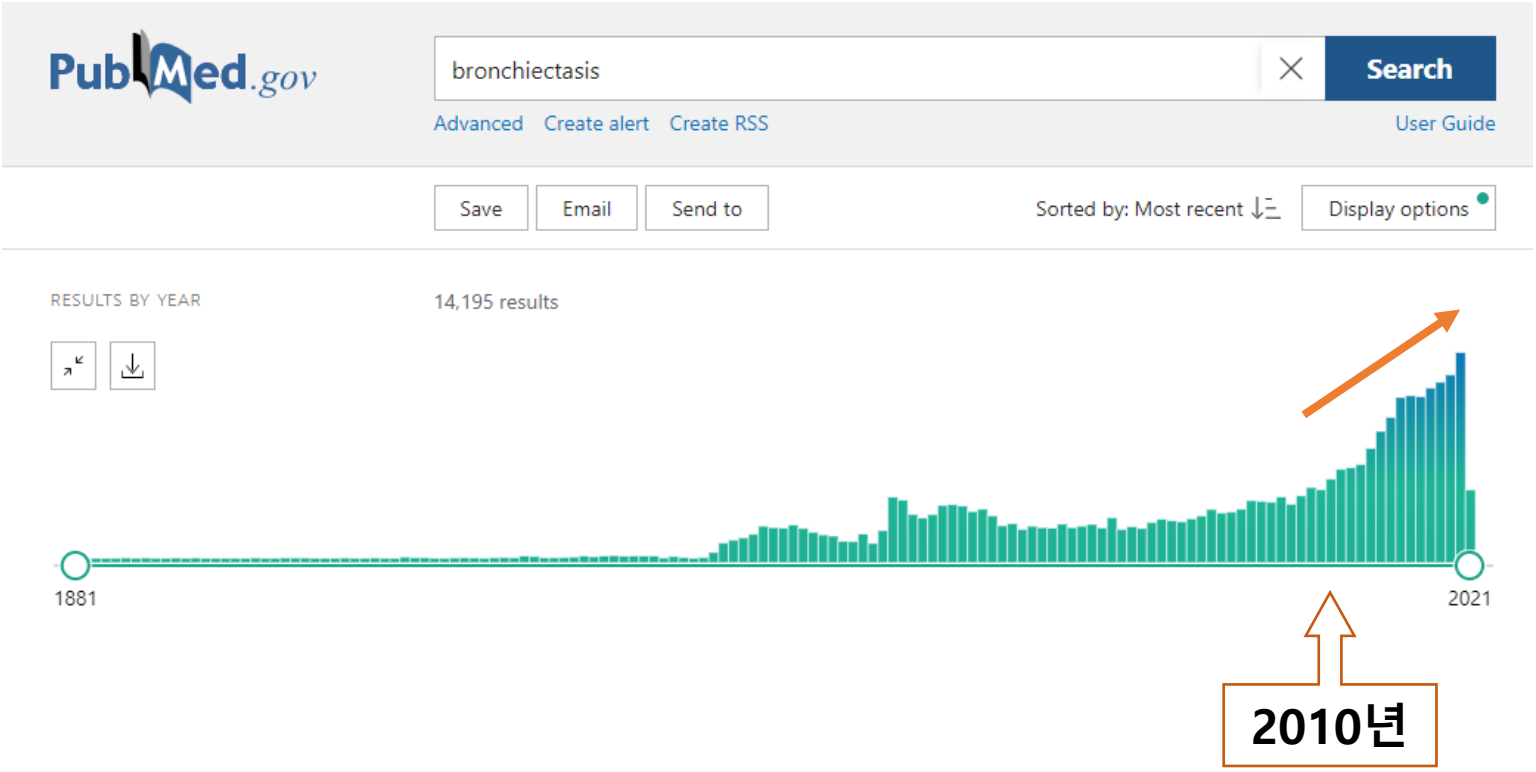
- Background

- Mucus hyperconcetration and Daily symptoms
- Neutrophilic inflammation
- Eosinophilic inflammation

Story begins…

- Bronchiectasis was first described in 1820

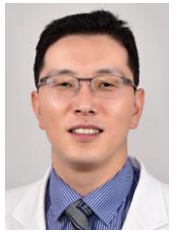
Dr. Laennec



Epidemiologic study to Cohort study

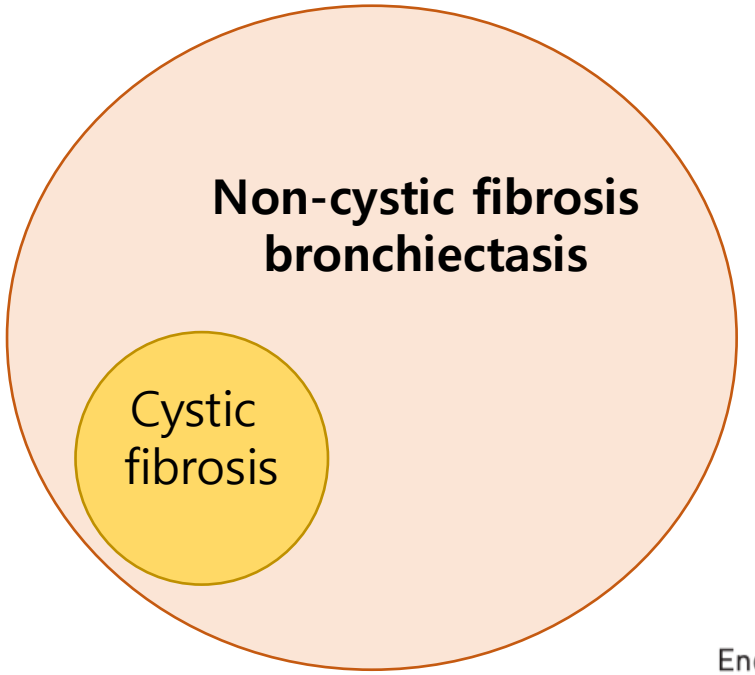
- **Epidemiologic study**
  - Prevalence
  - Disease burden – healthcare use and mortality
  - **Korean study (2019~)**

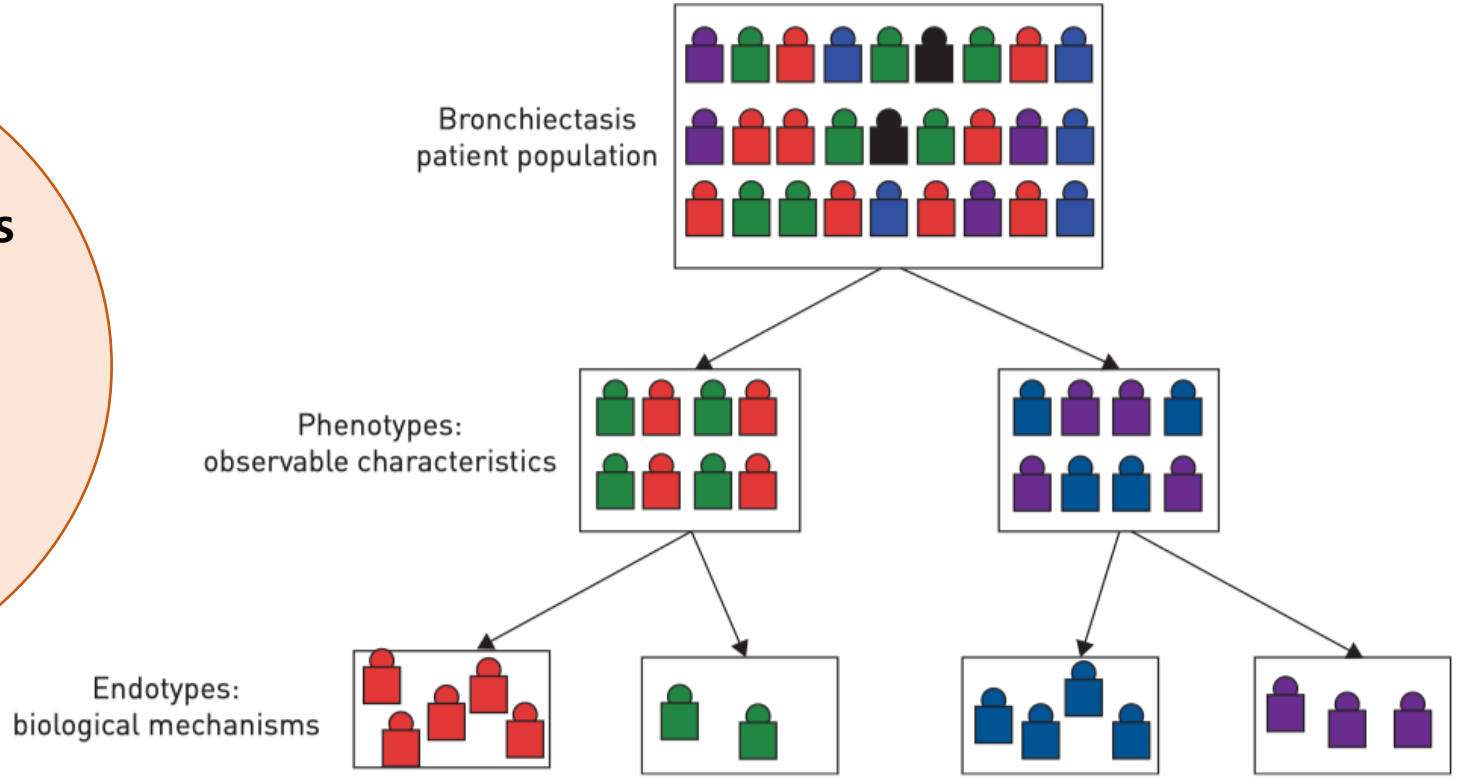
- **Cohort study**
  - EMBARC
  - Australian Bronchiectasis Registry
  - EMBARC-India
  - **KMBARC (2018~)**
  - US Bronchiectasis Research Registry



Lee H, et al. *Respirology* 2021 (in press)

Beyond Non-cystic fibrosis bronchiectasis





- Post-TB
- ABPA

…

- neutrophilic
- eosinophilic

…

ERS monograph Bronchiectasis

Agenda

- Background

- Mucus hyperconcetration and Daily symptoms [2]
- Neutrophilic inflammation [2]
- Eosinophilic inflammation [2]

Agenda

- Background

- **Mucus hyperconcetration and Daily symptoms [2]**
- Neutrophilic inflammation [2]
- Eosinophilic inflammation [2]

ORIGINAL ARTICLE

Airway Mucus Hyperconcentration in Non–Cystic Fibrosis Bronchiectasis

Kathryn A. Ramsey[1,2], Alice C. H. Chen[3,4], Giorgia Radicioni[1], Rohan Lourie[3,5], Megan Martin[6], Amy Broomfield[5], Yong H. Sheng[3], Sumaira Z. Hasnain[3], Graham Radford-Smith[7], Lisa A. Simms[8], Lucy Burr[3,6], David J. Thornton[9], Simon D. Bowler[6], Stephanie Livengood[1], Agathe Ceppe[1], Michael R. Knowles[1], Peadar G. Noone, Sr.[1], Scott H. Donaldson[1], David B. Hill[1,10], Camille Ehre[1], Brian Button[1], Neil E. Alexis[11], Mehmet Kesimer[1]*, Richard C. Boucher[1]*, and Michael A. McGuckin[3,12]*

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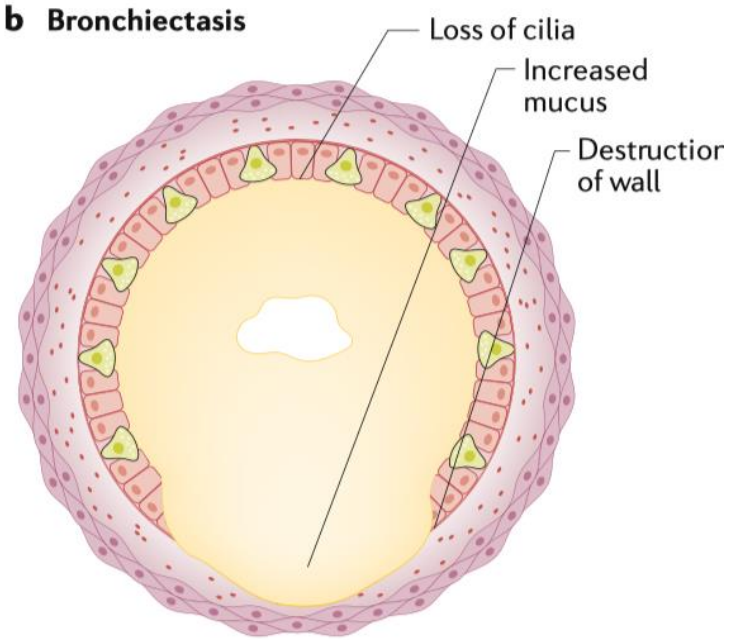
Am J Respir Crit Care Med 2020 Mar;201:661–670

Non-cystic fibrosis bronchiectasis

- Airway dilatation
- Persistent purulent sputum
- Episodic exacerbation

→ **<u>hypersecretory diseases?</u>** 👧♂

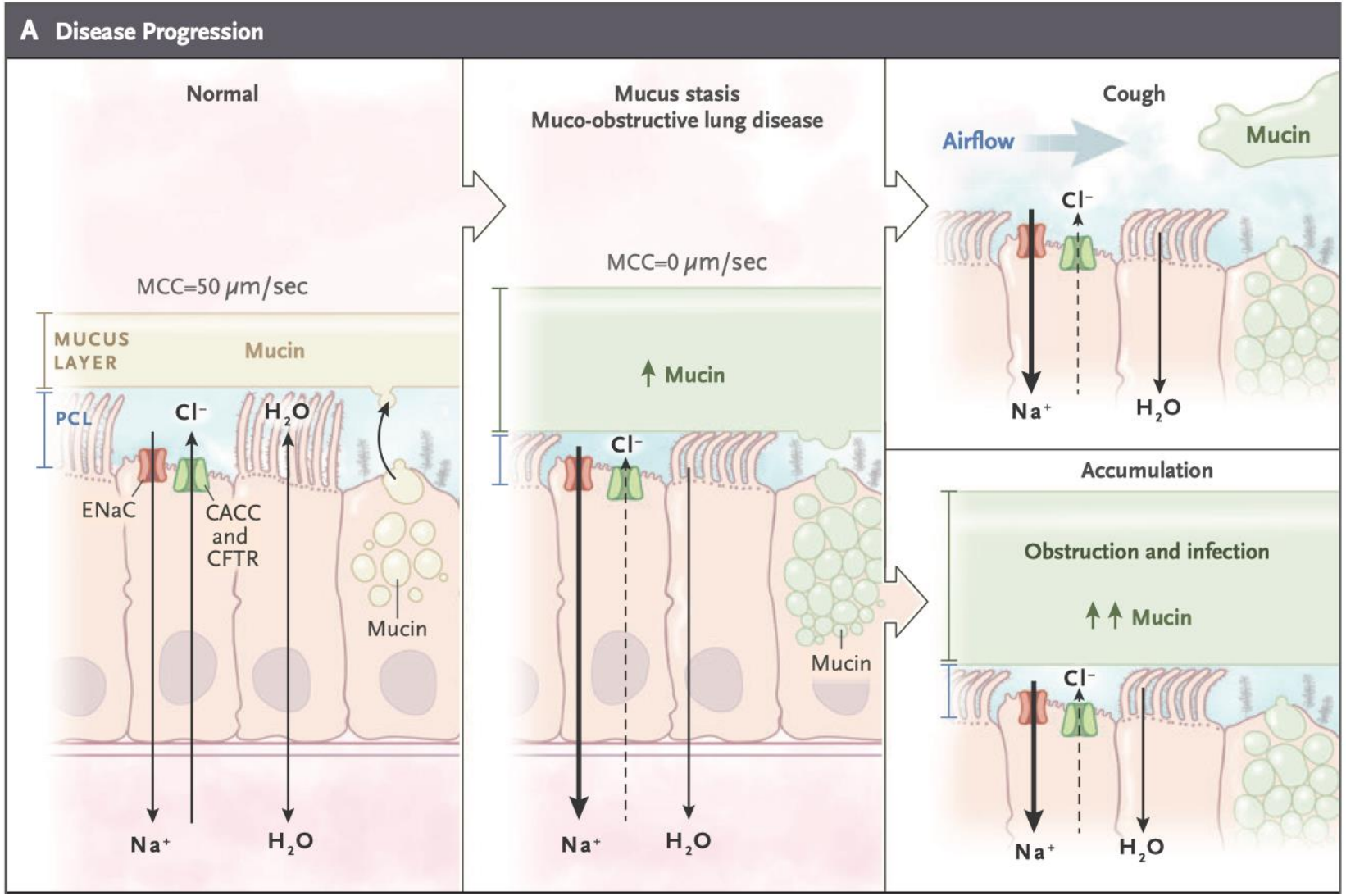


Nat Rev Dis Primers 2018;4:45
N Engl J Med 2019;380:1941

Muco-Obstructive Lung Disease

Mucus layer

Preciliary layer



N Engl J Med 2019;380:1941

Objectives

1. Investigate **mucus concentration** in Bronchiectasis vs Healthy subjects

2. Explore relationship between **mucus concentration** and **bronchiectasis severity**

Methods – study population

- Subjects from BLESS study (Australia)
  - BLESS Bronchiectasis (n = 99)
  - Healthy control subjects (n = 20)

- Replication cohort (North Carolina, USA)
  - UNC Bronchiectasis (n = 15)
  - Healthy control subjects (n = 15)

Methods – sputum collection and measurement

- BLESS cohort: HS-induced sputum
- UNC cohort: HS-induced and spontaneous sputum

- Mucus parameters
  - **Mucus concentration**
    - index of hydration (dry-to-wet ratio)
  - Sputum total mucin concentrations
  - Absolute concentrations of MUC5AC, MUC5B
  - Biophysical properties
  - Gene expression

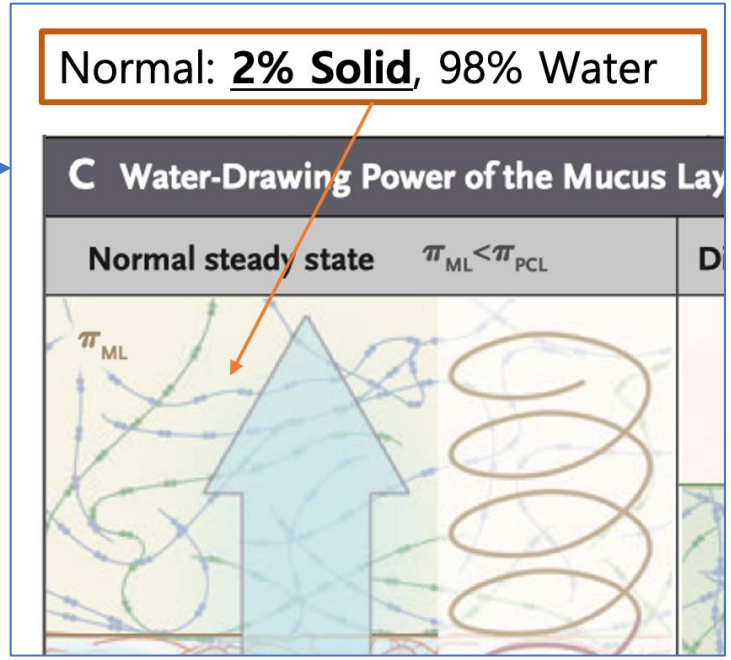


Figure 1. Biochemical properties of induced sputum

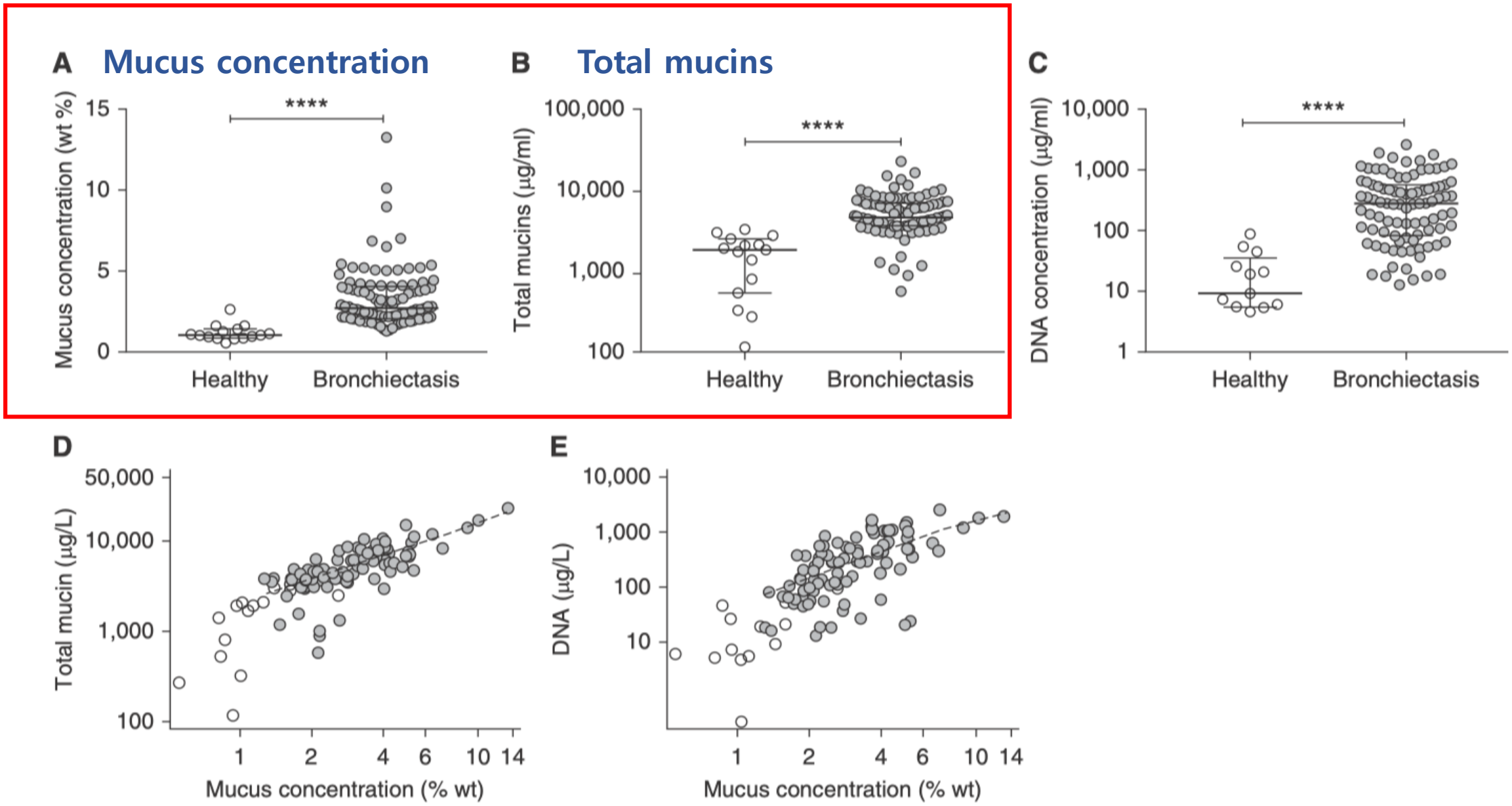
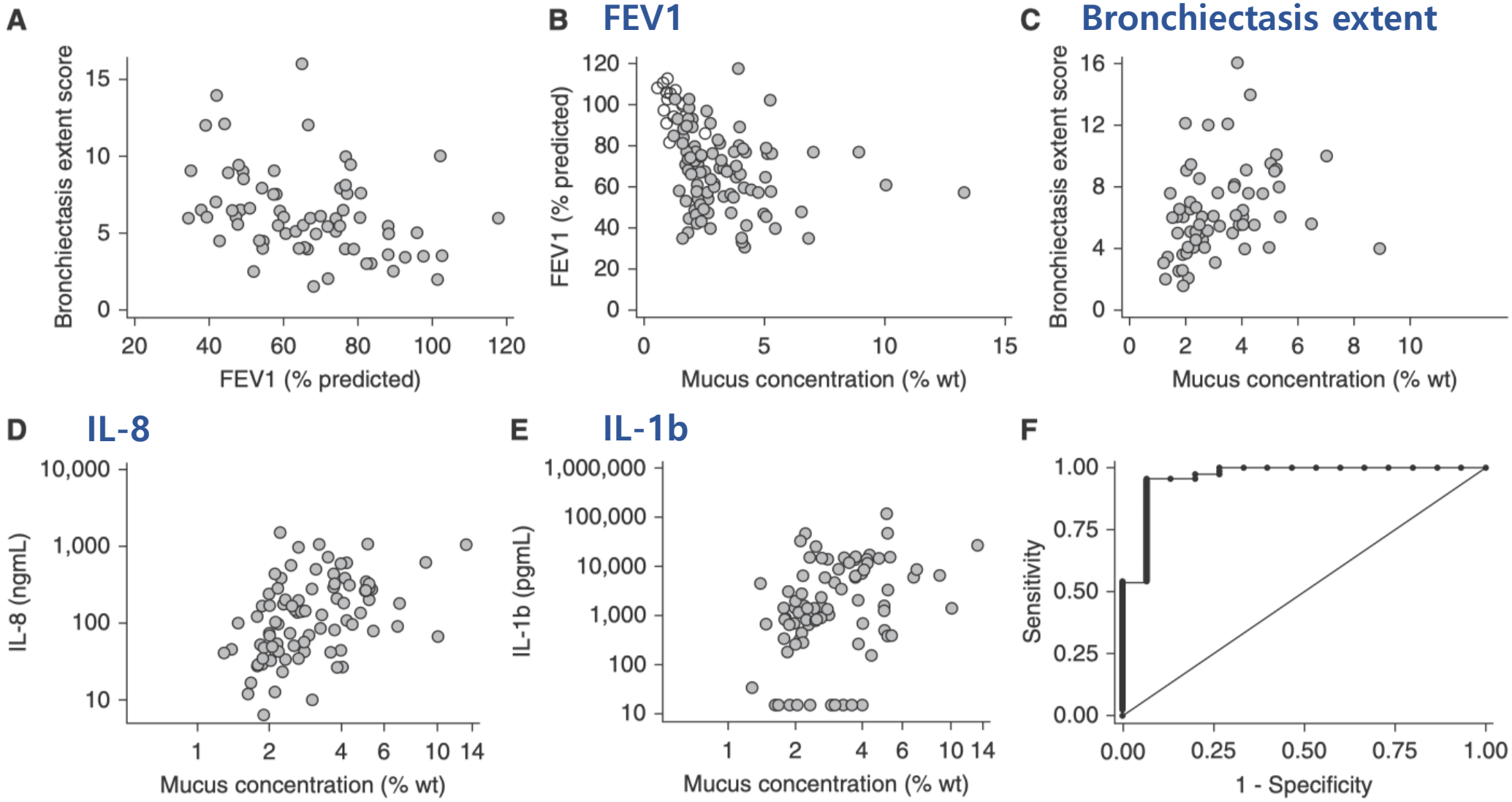


Figure 5. Association between mucus percent solids and clinical outcomes



Ability of mucus concentration to diagnose NCFB (**AUROC = 0.9603**)

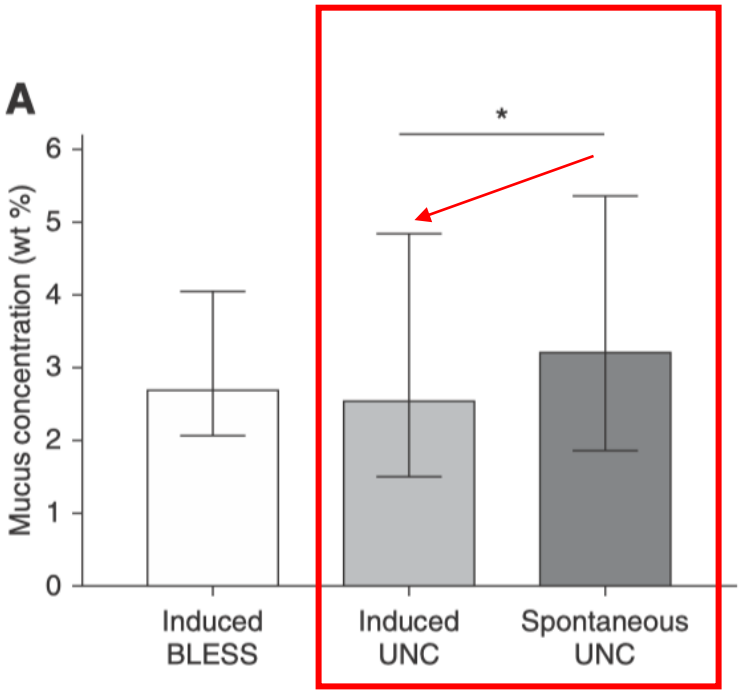
Summary

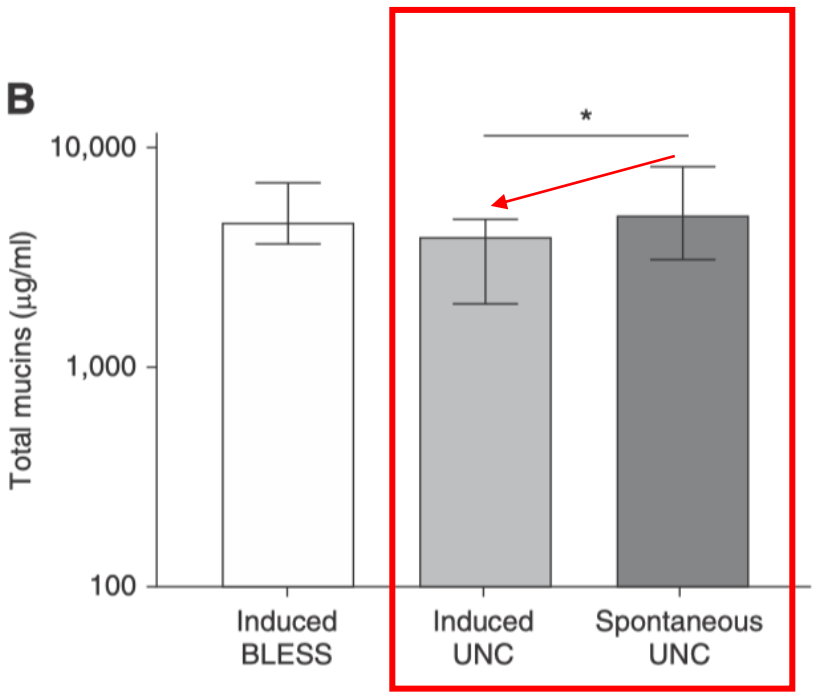
- **NCFB sputum** vs Healthy subject sputum
  - ↑ mucus concentrations
  - excellent biomarker for the presence of NCFB

- **Mucus concentration in NCFB**
  - produce mucostatis and reductions in FEV1
  - modest biomarker for NCFB disease extent/progression

Comment

- **Rehydration of NCFB airways**
  - may be a **rational therapeutic strategy**





Mucus concentration

Total mucins

ORIGINAL ARTICLE

Relationship between Symptoms, Exacerbations, and Treatment Response in Bronchiectasis

Yong-hua Gao[1,2], Hani Abo Leyah[2], Simon Finch[2], Mike Lonergan[2], Stefano Aliberti[3], Anthony De Soyza[4], Thomas C. Fardon[2], Gregory Tino[5], and James D. Chalmers[2]

[1]Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China; [2]Scottish Centre for Respiratory Medicine, University of Dundee, Dundee, United Kingdom; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [4]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and [5]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Am J Respir Crit Care Med 2020 Jun;201:1499–1507

Bronchiectasis exacerbations

- Definition:
  - **≥3 of symptoms for 48 hours**
    - Cough ↑
    - Sputum volume ↑
    - Sputum purulence
    - Dyspnea ↑
  - **Physicians's decision to prescribe antibiotics**

- Inhaled antibiotics to reduce exacerbation frequency
  - **<u>NO significant impact on daily symptoms</u>**

Eur Respir J 2017;49:1700051

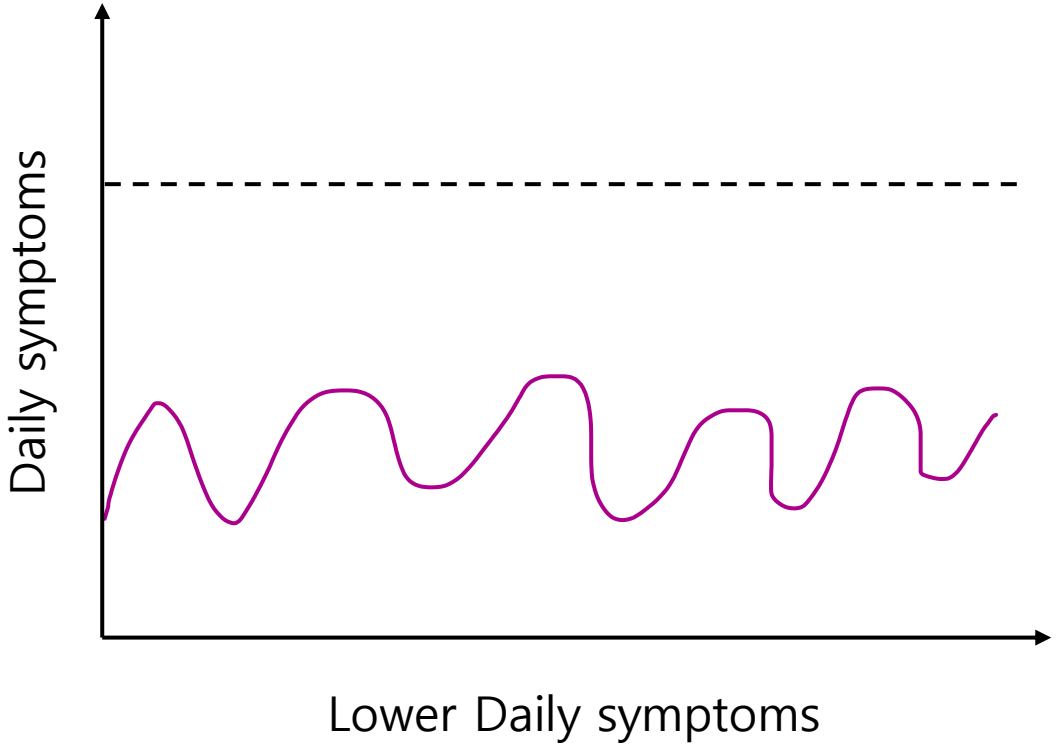
Bronchiectasis guidelines

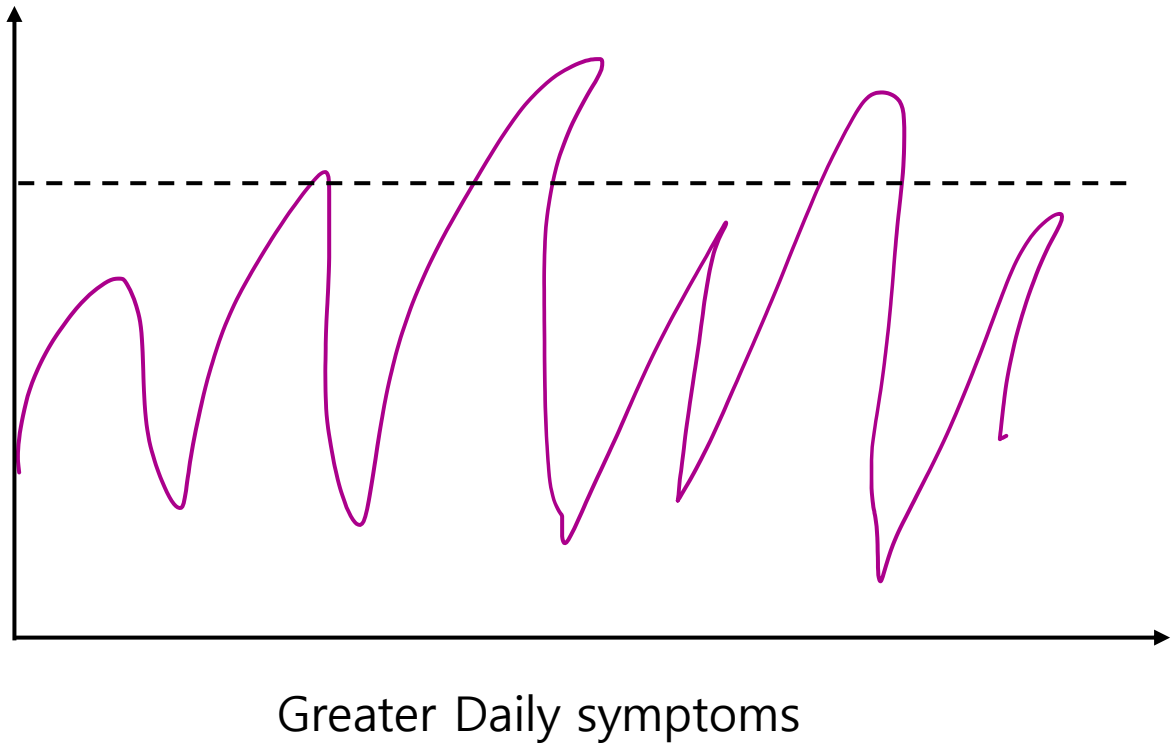
- Two separate objectives

1. **Control daily symptoms**
   - Airway clearance technique
   - Mucoactive agents – mucolytics
   - Nebulized hypertonic saline

2. **Prevent exacerbations**
   - Inhaled antibiotics
   - Macrolide

Threshold concept of exacerbation





Two hypothesis

- Patients with greater symptoms would be at high risk of exacerbations
- Highly symptomatic patients: treatment aimed at reducing daily symptoms would also reduce exacerbations

Methods

- 1st hypothesis
  - **Scotland observational NCFB cohort** 2012–2016 (n = 333)
  - Symptom burden according to SGRQ
    - >70: high
    - 40–70: moderate
    - <40: low

- 2nd hypothesis
  - **Dry powder mannitol RCT** → *Post hoc* analysis (n = 461)
  - 1:1 to 52-week treatment with inhaled mannitol 400mg or low-dose control twice per day
  - Failed to reduce exacerbation frequency

Thorax 2014;69:1073–1079

Observational study (1st hypothesis)

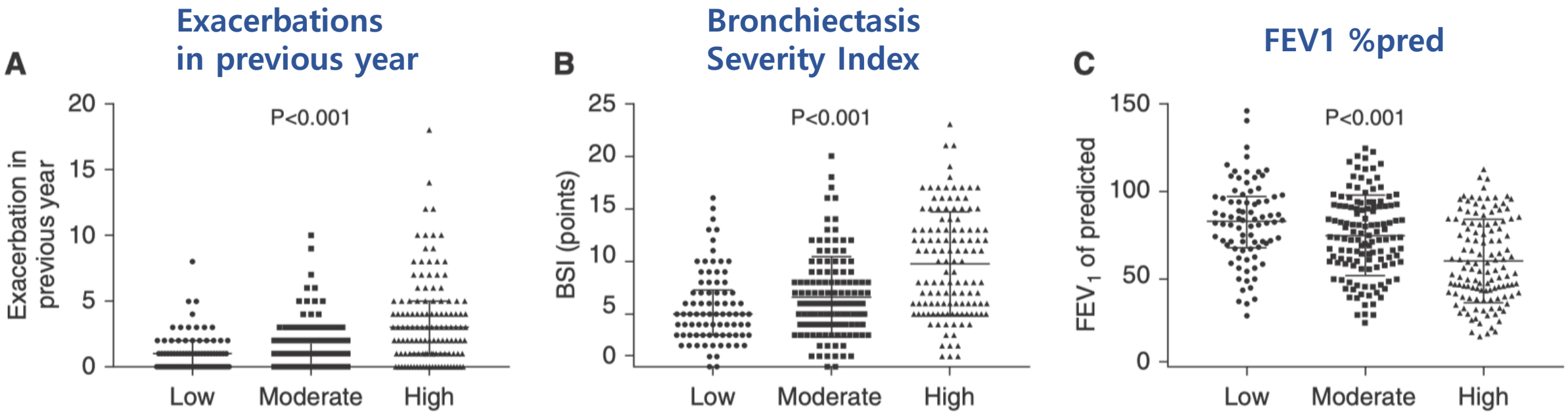


Figure 1. Association of low (St. George's Respiratory Questionnaire [SGRQ] symptom score, <40 points), moderate (SGRQ symptom score, 40–70 points), and high (SGRQ symptom score, >70 points) symptom burden with the number of exacerbations in the previous year (*A*), Bronchiectasis Severity Index (BSI) (*B*), and FEV_1 (*C*). *P* value is derived from comparison of all groups (Kruskal-Wallis test for *A–C*). The bars represent median and interquartile range.

Table 2. Relationship between baseline SGRQ and exacerbations

SGRQ Symptom Score	Exacerbations (Any)		Hospitalizations		Time to First Exacerbation	
	Rate Ratio (95% CI)	*P* Value	Rate Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Uncategorized score (unadjusted)	1.15 (1.09–1.21)	<0.001	1.27 (1.15–1.39)	<0.001	1.07 (1.01–1.13)	0.02
Uncategorized score (adjusted)*	1.10 (1.03–1.17)	0.005	1.19 (1.02–1.35)	0.03	1.04 (0.997–1.10)	0.27
Categorized score (unadjusted)						
Low (<40)	1	—	1	—	1	—
Moderate (40–70)	1.07 (0.73–1.58)	0.72	3.53 (1.31–9.54)	0.01	0.96 (0.66–1.38)	0.3
High (>70)	2.33 (1.61–3.37)	<0.001	6.88 (2.59–17.73)	<0.001	1.41 (0.99–2.02)	0.06
Categorized score (adjusted)*						
Low (<40)	1	—	1	—	1	—
Moderate (40–70)	1.01 (0.66–1.54)	0.96	2.29 (0.77–6.83)	0.14	0.96 (0.65–1.43)	0.84
High (>70)	1.74 (1.12–2.72)	0.01	3.28 (1.09–9.88)	0.04	1.16 (0.76–1.77)	0.49

- Adjusted for age, BMI, smoking, FEV1 %pred, *P. aeruginosa* isolation, *H. influenzae* isolation, *M. catarrhalis* isolation, idopathic bronchiectasis, post-infective bronchiectasis, and radiologic score

- **Not influence by disease severity**
  - BSI ($P_{interaction}$ = 0.25)
  - FEV1 %pred ($P_{interaction}$ = 0.62)

Mannitol study (2nd hypothesis)

- Original study
  - Inhaled mannitol vs Control
  - **Primary endpoint:** exacerbation frequency
  - **Secondary endpoint:** time to first exacerbation

Figure 2. Relationship between baseline SGRQ and exacerbations

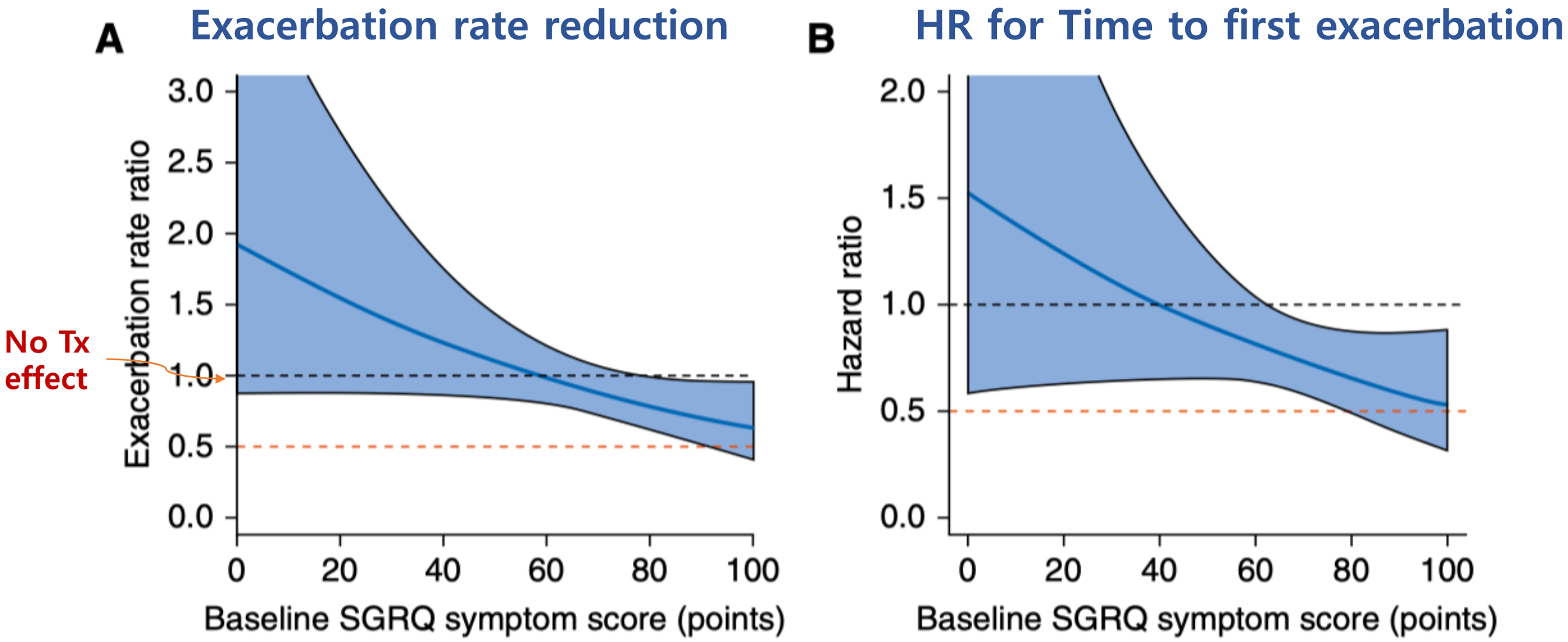
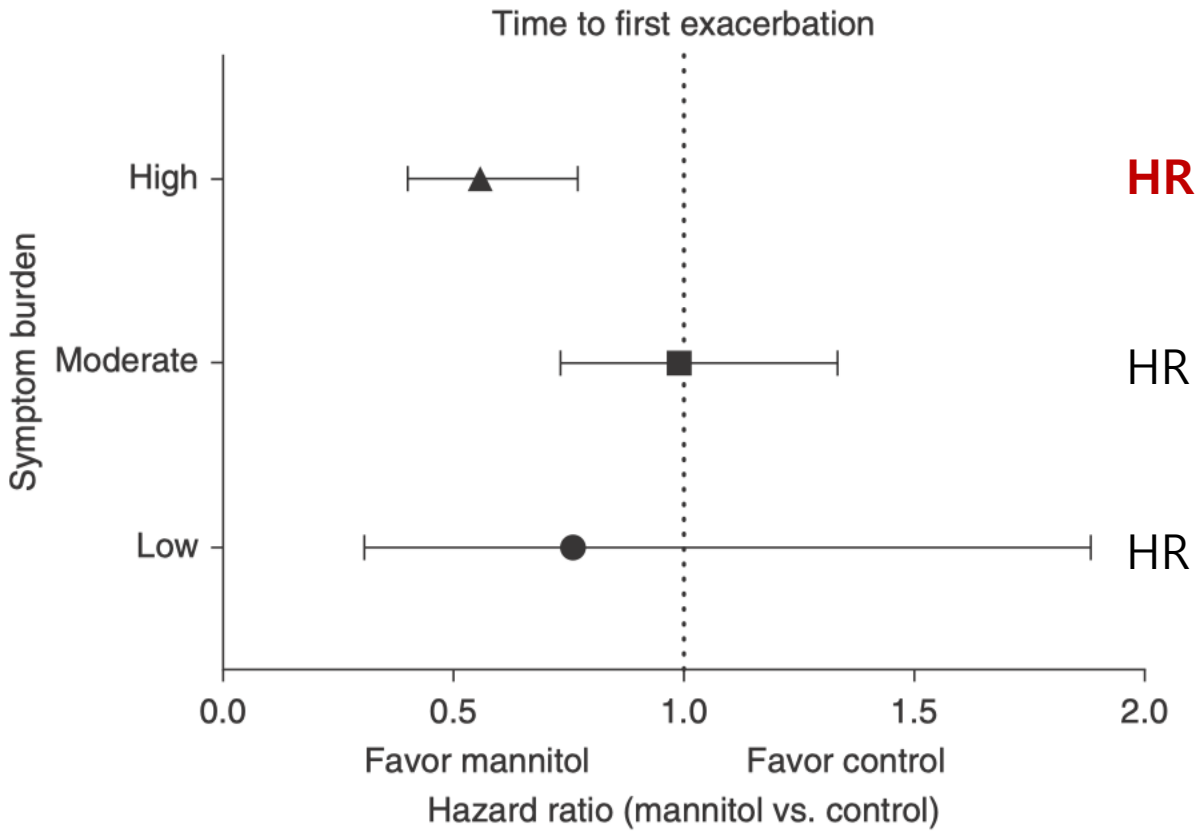


Figure 3. Hazard ratios for first exacerbations in NCFB divided according to symptoms burden



HR (95% CI), 0.56 (0.40–0.77); *P* < 0.001

HR (95% CI), 0.99 (0.73–1.34); *P* = 0.94

HR (95% CI), 0.76 (0.31–1.88); *P* = 0.55

Summary

- Patients with a **high burden of symptoms** are at **higher risk of exacerbations**
  - even after adjustment for underlying severity of bronchiectasis
- Benefit with inhaled mannitol was **only evident** in patients with **high symptom burden**

Comment

- Treatable traits concept

1. **Low symptom burden** with **frequent exacerbation**
   - airway clearance plus
   - antiinfective therapy or antiinflammatory therapy

2. **High symptom burden**
   - airway clearance and mucoactive drugs
   - **may be effective to prevent exacerbations**
   - contibuting to antibiotic stewardship

Agenda

- Background

- Mucus hyperconcetration and Daily symptoms [2]
- **Neutrophilic inflammation [2]**
- Eosinophilic inflammation [2]

Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study

Holly R Keir, Amelia Shoemark, Alison J Dicker, Lidia Perea, Jennifer Pollock, Yan Hui Giam, Guillermo Suarez-Cuartin, Megan L Crichton, Mike Lonergan, Martina Oriano, Erin Cant, Gisli G Einarsson, Elizabeth Furrie, J Stuart Elborn, Christopher J Fong, Simon Finch, Geraint B Rogers, Francesco Blasi, Oriol Sibila, Stefano Aliberti, Jodie L Simpson, Jeffrey T J Huang, James D Chalmers

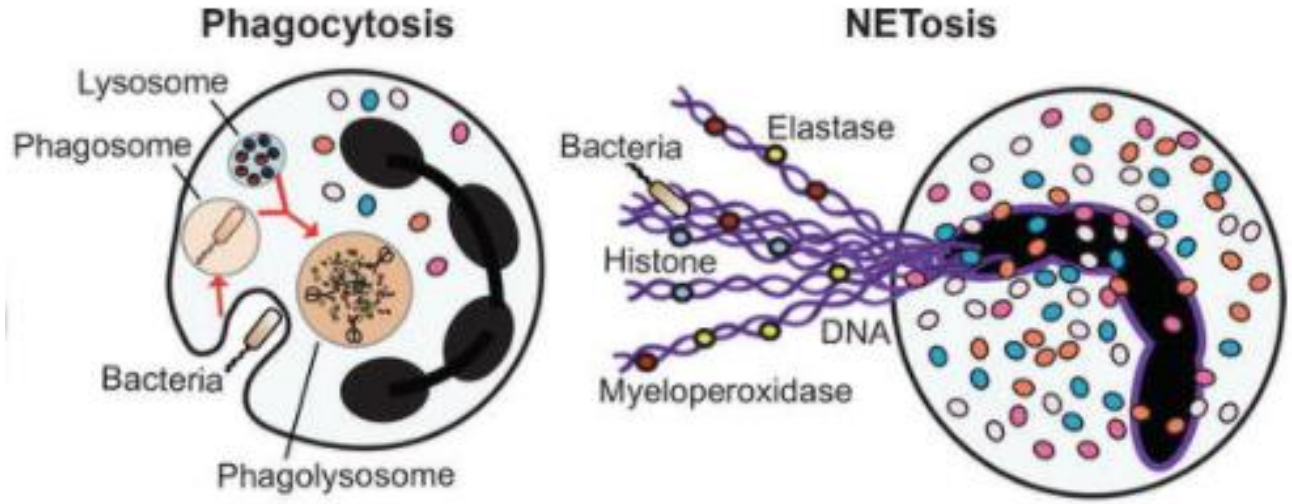
Lancet Respir Med 2021 Feb; Online ahead of print.

Neutrophilic inflammation in bronchiectasis

- **Pathophysiologic hallmark**
  - Airway infection
  - Tissue damage
  - Mucociliary dysfunction

Neutophilic extracellular trap (NET)

- **NET formation (NETosis)**
  - **meshwork** of extracellular fibers
    (chromatin DNA, histones, and bactericidal proteins)
  - immobilize and disarm pathogens
  - **not effective to *Pseudomonas* and *Heamophilus***



The Immune System 4th Ed.

Objectives

- Investigate the **association of NETs with**
  - Bronchiectasis severity
  - Bacterial infection
  - Mortality

- Evaluate **whether NETs proteins can be reduced through**
  - Anbiotics
  - Macrolide therapy

Methods

	Primary studies	Validation studies
Airway inflammation will be different between severe and mild bronchiectasis	Sputum proteomics study of patients with 20 severe *vs* 20 mild disease	NA
NETs will be associated with severe bronchiectasis and are predictive of poor outcomes	Observation cohort study of 175 patients from the UK	Observation cohort study of 275 patients from Italy, Spain, and the UK
Antibiotic treatment for 14 days will result in beneficial changes to the lung proteome including reduced NETs	Sputum proteomics study of 20 patients admitted to hospital for exacerbations of bronchiectasis treated with intravenous antibiotics in Dundee, UK	Observational cohort study of 20 patients admitted to hospital for exacerbations of bronchiectasis treated with intravenous antibiotics in Dundee, UK
Macrolide treatment will reduce sputum NETs	Cohort study of patients with bronchiectasis *P aeruginosa* infection treated with (n=26) or without azithromycin (n=26)	Post-hoc analysis of randomised controlled trial in poorly controlled asthma in 47 patients (AMAZES)

Figure 1. Proteomics of patients with mild and severe bronchiectasis

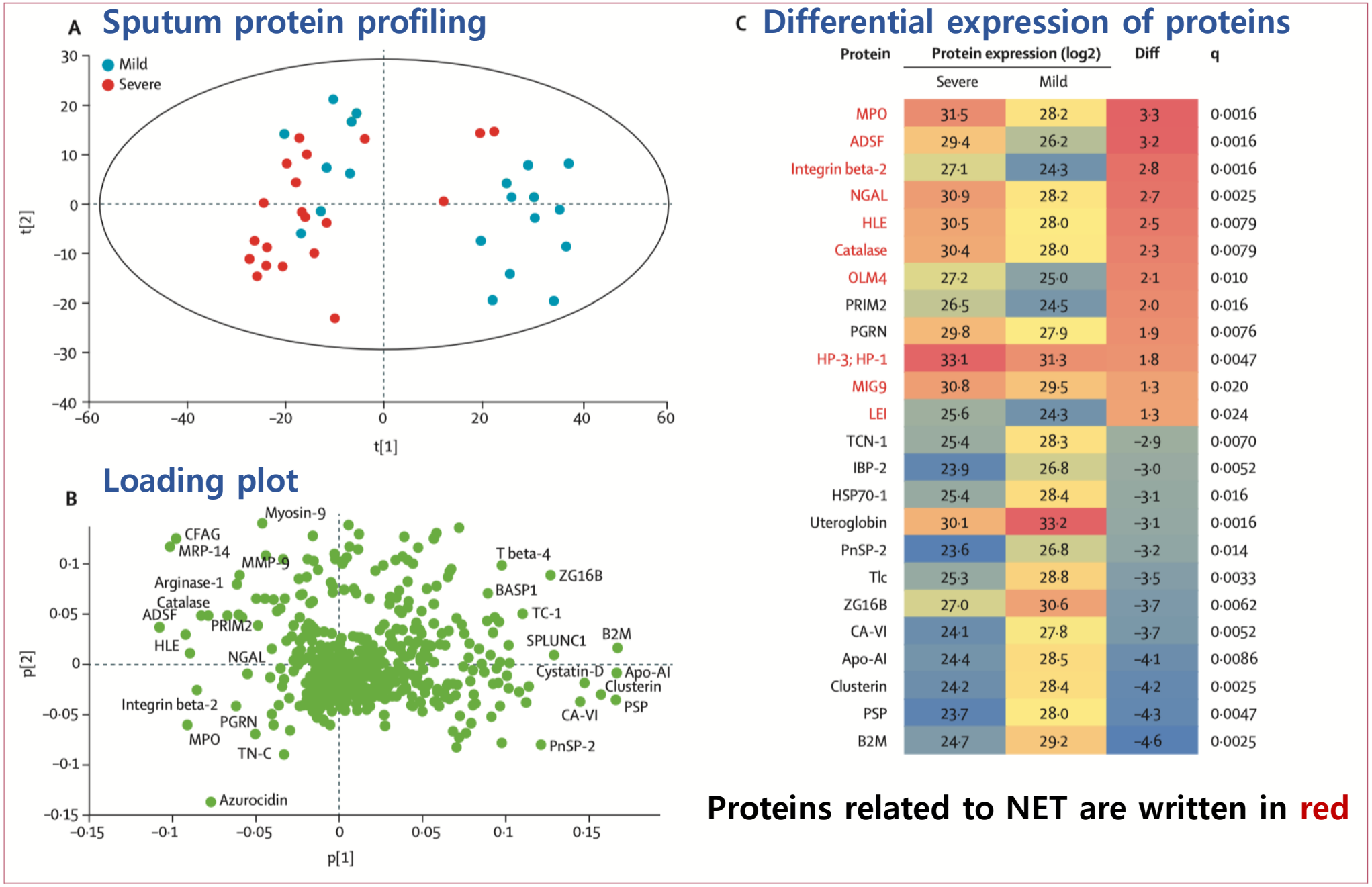
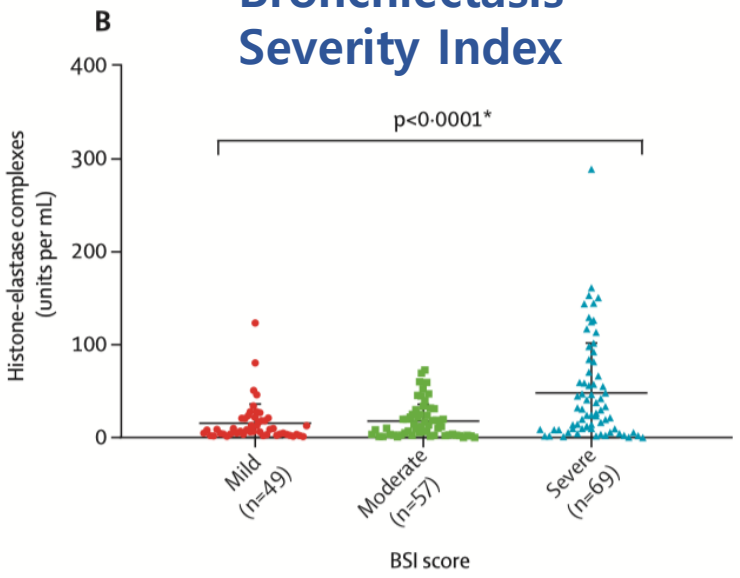
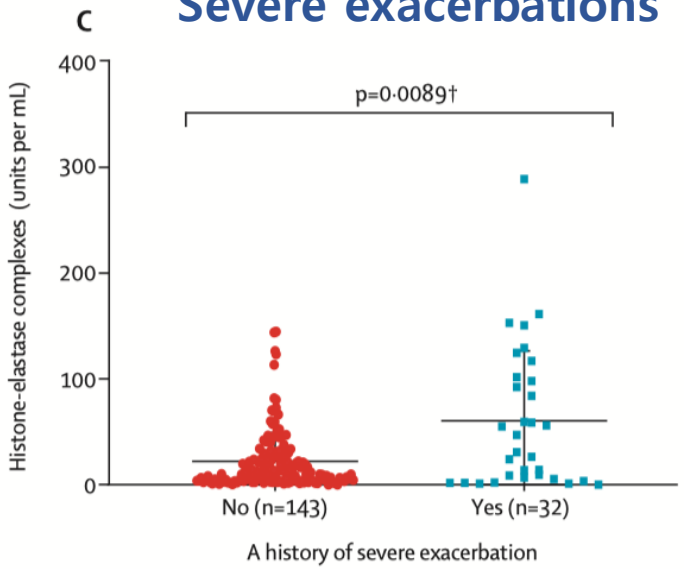


Figure 2. Validating the association between NET concentration and BE outcomes

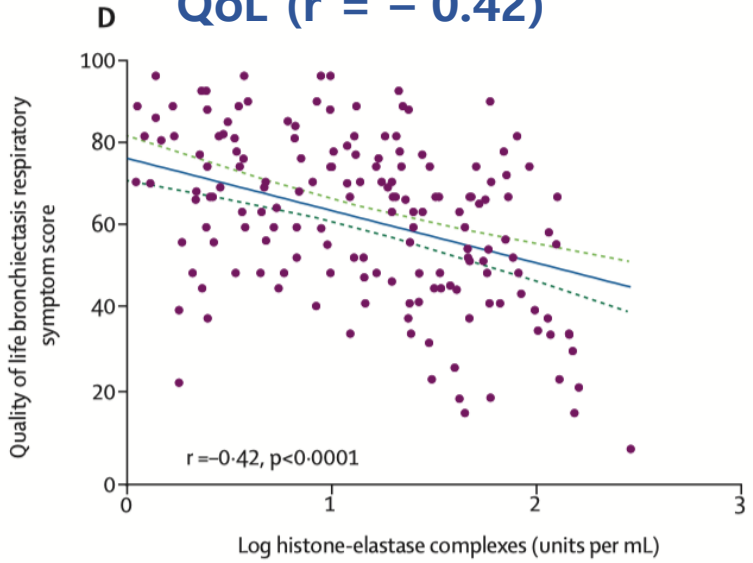
Bronchiectasis Severity Index



Severe exacerbations



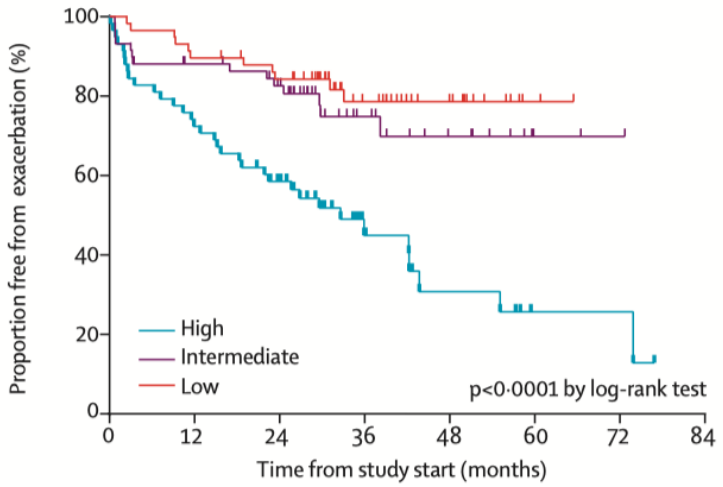
QoL (r = – 0.42)



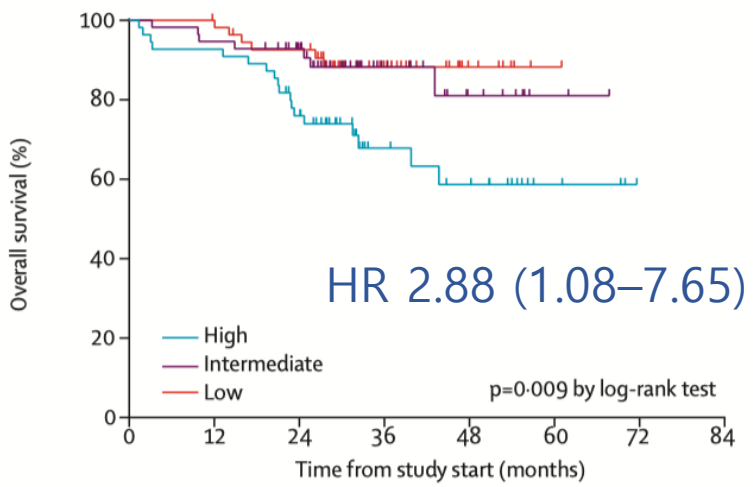
NET concentration

- Low
- Intermediate
- High

Time to first exacerbation



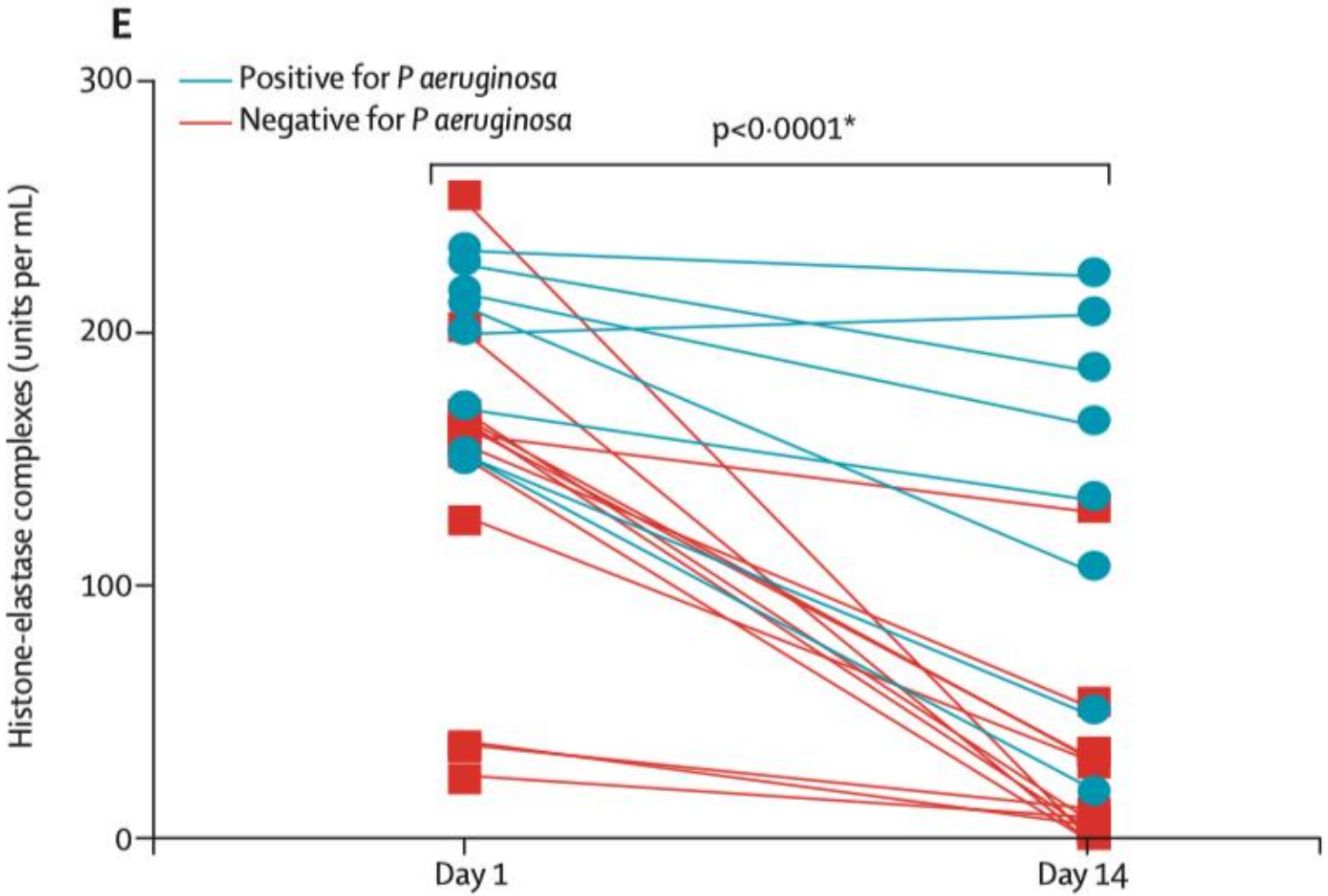
Mortality



Number at risk (number censored)								
High	58 (0)	43 (0)	31 (4)	12 (18)	7 (20)	3 (23)	3 (23)	0 (24)
Intermediate	59 (0)	50 (3)	44 (6)	18 (29)	10 (36)	3 (43)	2 (44)	0 (45)
Low	58 (0)	53 (0)	48 (2)	25 (23)	14 (34)	3 (45)	1 (47)	0 (47)

58 (0)	55 (0)	48 (24)	19 (26)	14 (34)	7 (37)	4 (40)	0 (40)
59 (0)	57 (0)	53 (4)	21 (33)	12 (41)	4 (49)	2 (51)	0 (52)
58 (0)	58 (0)	53 (2)	27 (26)	14 (39)	3 (50)	1 (52)	0 (52)

Figure 3. Antibiotic responses and *Pseudomonas aeruginosa* status

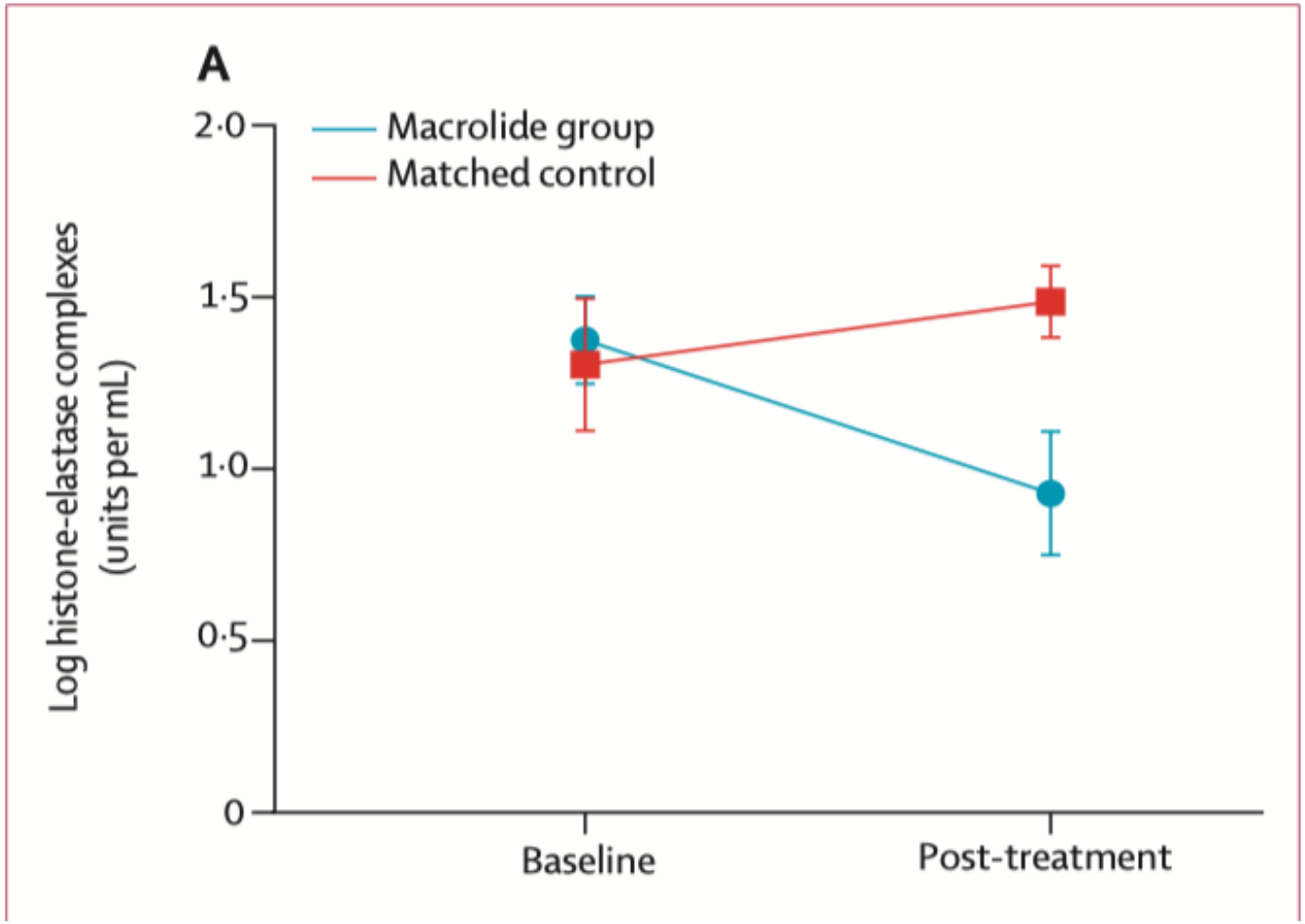


Sputum NET concentration during 2 week-course of antibiotics

Figure 4. Changes in NET concentrations in response to long-term macrolide therapy

UK bronchiectasis cohort (n = 52)

- *Pseudomonas* infection treated with macrolide (n = 26) vs not treated (n =26)
- AZIT 250mg three times per week for 1 year



Summary

- **NETs** identified as a **key marker of disease severity and treatment response** in bronchiectasis
  - support the concept of targeting neutrophilic inflammation
  - theoretically reduce a broad range of neutrophil and downstream inflammatory mediators without compromising bacterial clearance

  - ➢ Novel treatment (DPP-1 inhibitor)
  - ➢ Macrolide

Comment

- **Long-term macrolide** for bronchiectasis treatment
  - reduce **exacerbation frequency** (adjusted IRR **0.49**)
  - reduce **time to first exacerbation** (adjusted HR **0.46**)

Pseudomonas aeruginosa infection	..	..	0·47
Yes	0·36 (0·19–0·69)	0·0017	..
No	0·47 (0·34–0·65)	<0·0001	..

HR=hazard ratio. BMI=body-mass index. SGRQ=St George's Respiratory Questionnaire.

Table 3: **Subgroup analysis of time to first bronchiectasis exacerbation**

- Change in future bronchiectasis guidelines?

Lancet Respir Med 2019;7:845

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

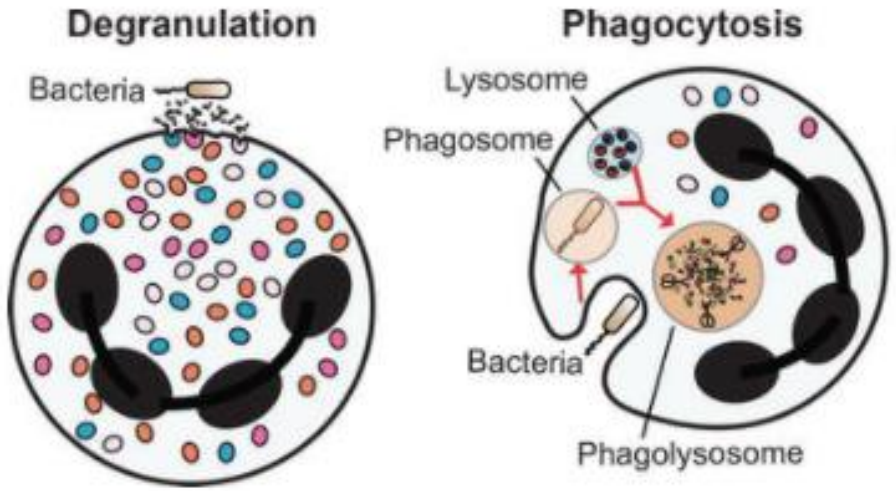
Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

James D. Chalmers, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., Mark L. Metersky, M.D., Michael R. Loebinger, B.M., B.Ch., Ph.D., Francesco Blasi, M.D., Ph.D., Oriol Sibila, M.D., Ph.D., Anne E. O'Donnell, M.D., Eugene J. Sullivan, M.D., Kevin C. Mange, M.D., M.S.C.E., Carlos Fernandez, M.D., M.P.H., Jun Zou, Ph.D., and Charles L. Daley, M.D., for the WILLOW Investigators*

N Engl J Med 2020 Nov;383:2127–2137

Neutrophil elastase

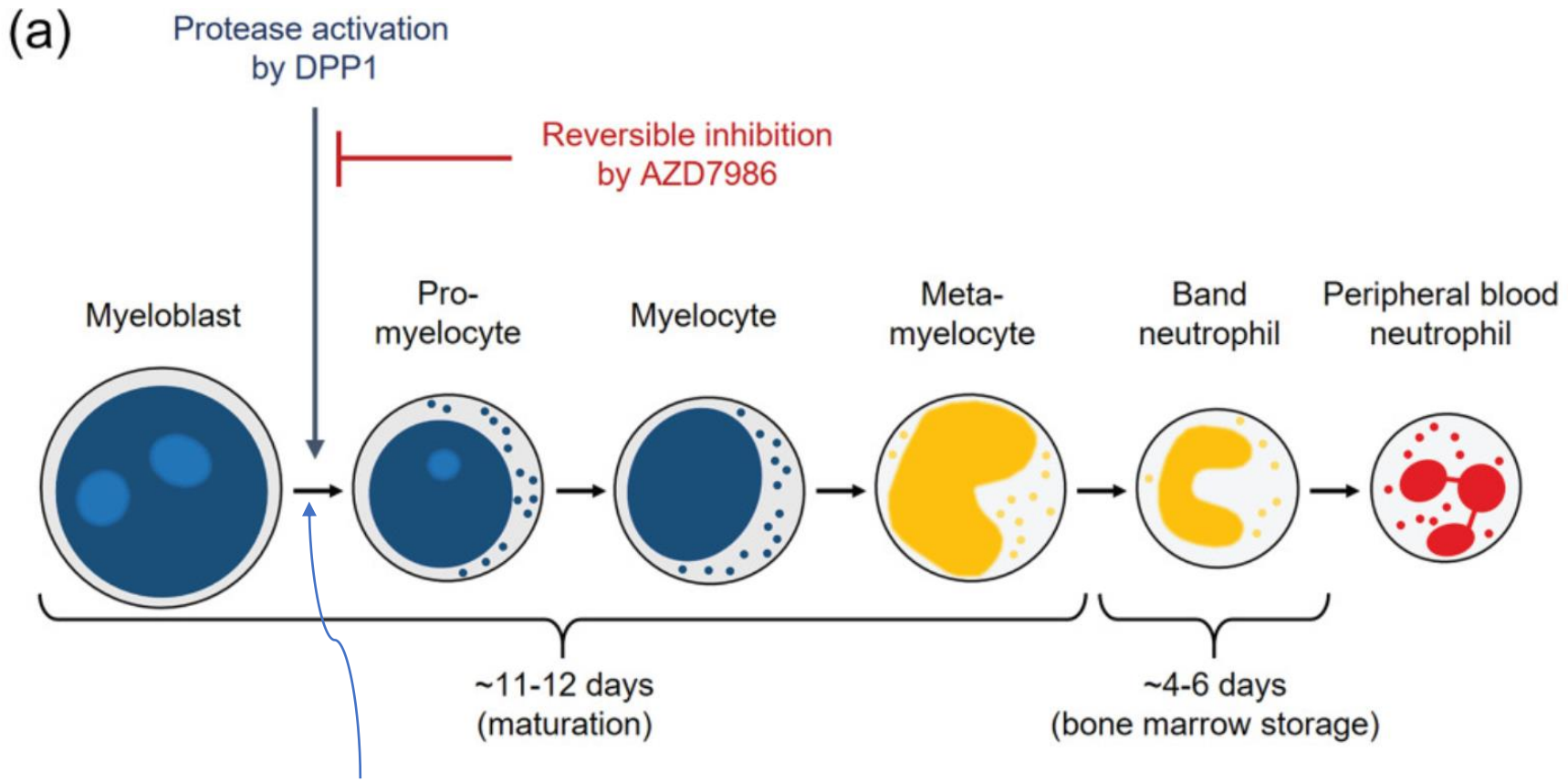
- released by activated neutrophils in bronchiectasis
- **impair phagocytosis** by cleavage of complement and Rc
  - activity correlates Ds severity, FEV1, radiologic extent and predict future exacerbations



ERS monograph Bronchiectasis

DPP-1 inhibitor?

- dipeptidyl peptidase 1 (DPP-1): **brensocatib**



Clin Pharmacol Ther 2018;104:1155–1164

Methods

- Double-blind, parallel group trial
  - 116 sites across 14 countries
- Inclusion
  - 18–85-year-old bronchiectasis patients
  - ≥2 documented exacerbation in the previous year
- Exclusion
  - CF, immunodeficiency, α1-antitrypsin deficiency
  - primary diagnosis of COPD or asthma
  - severe periodontitis

Methods

- **1:1:1 ratio**
  - Placebo (n = 87)
  - 10 mg of brensocatib (n = 82)
  - 25 mg of brensocatib (n = 87)

- Randomization was stratified according to
  - Long-term macrolide (≥6 months of treatment)
  - *Pseudomonas aeruginosa* infection

- Neutrophil elastase measured in sputum

Methods

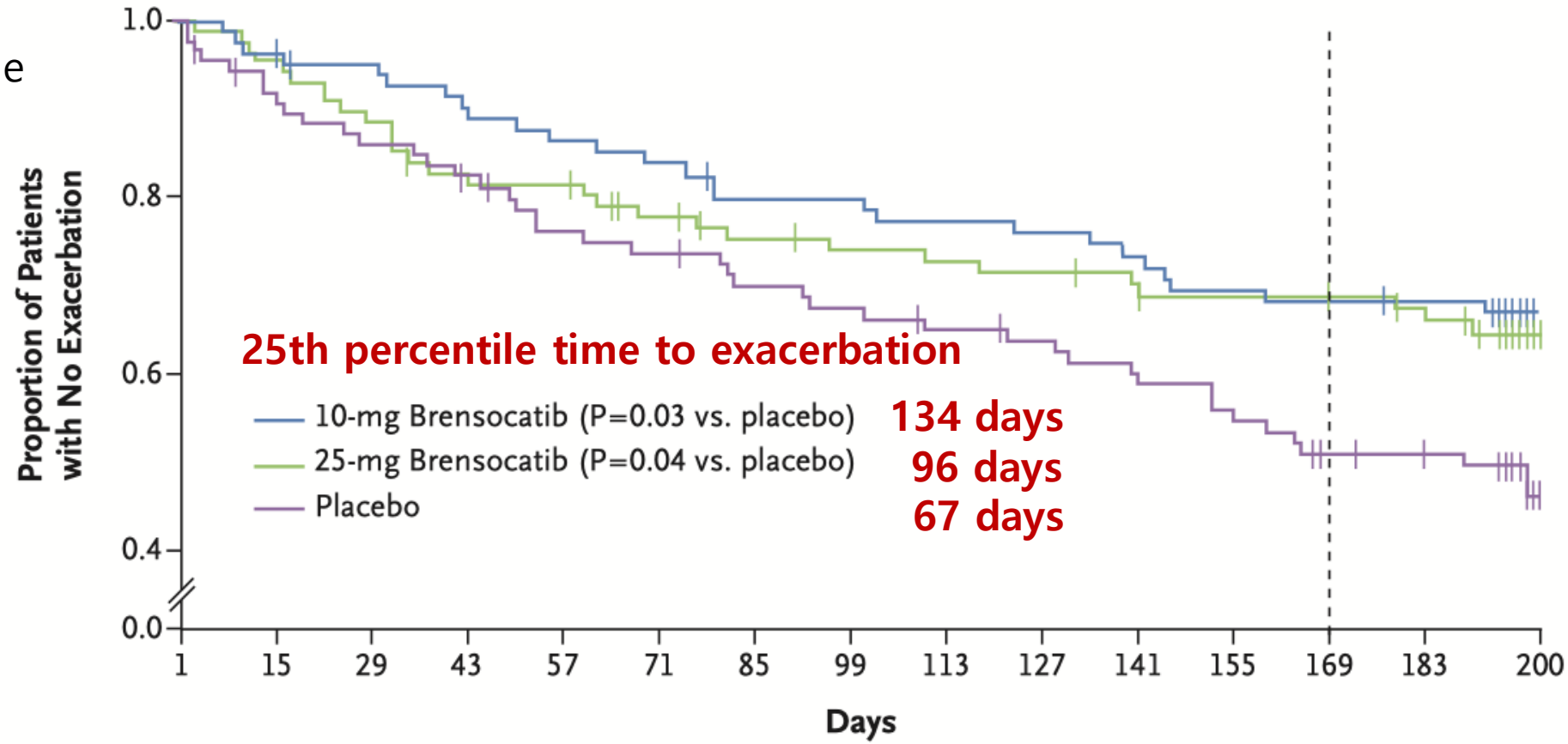
- Primary endpoint
  - **Time to the first exacerbation** during the 24-week treatment

- Secondary endpoints
  - **Exacerbation Rate**
  - Change in FEV1 %pred after bronchodilator use
  - Change in symptoms score on QOL-B
  - Change in concentration of active neutrophil elastase in sputum

Figure 1A. Time to first exacerbation (Intention-to-Treat Population)

Primary endpoint

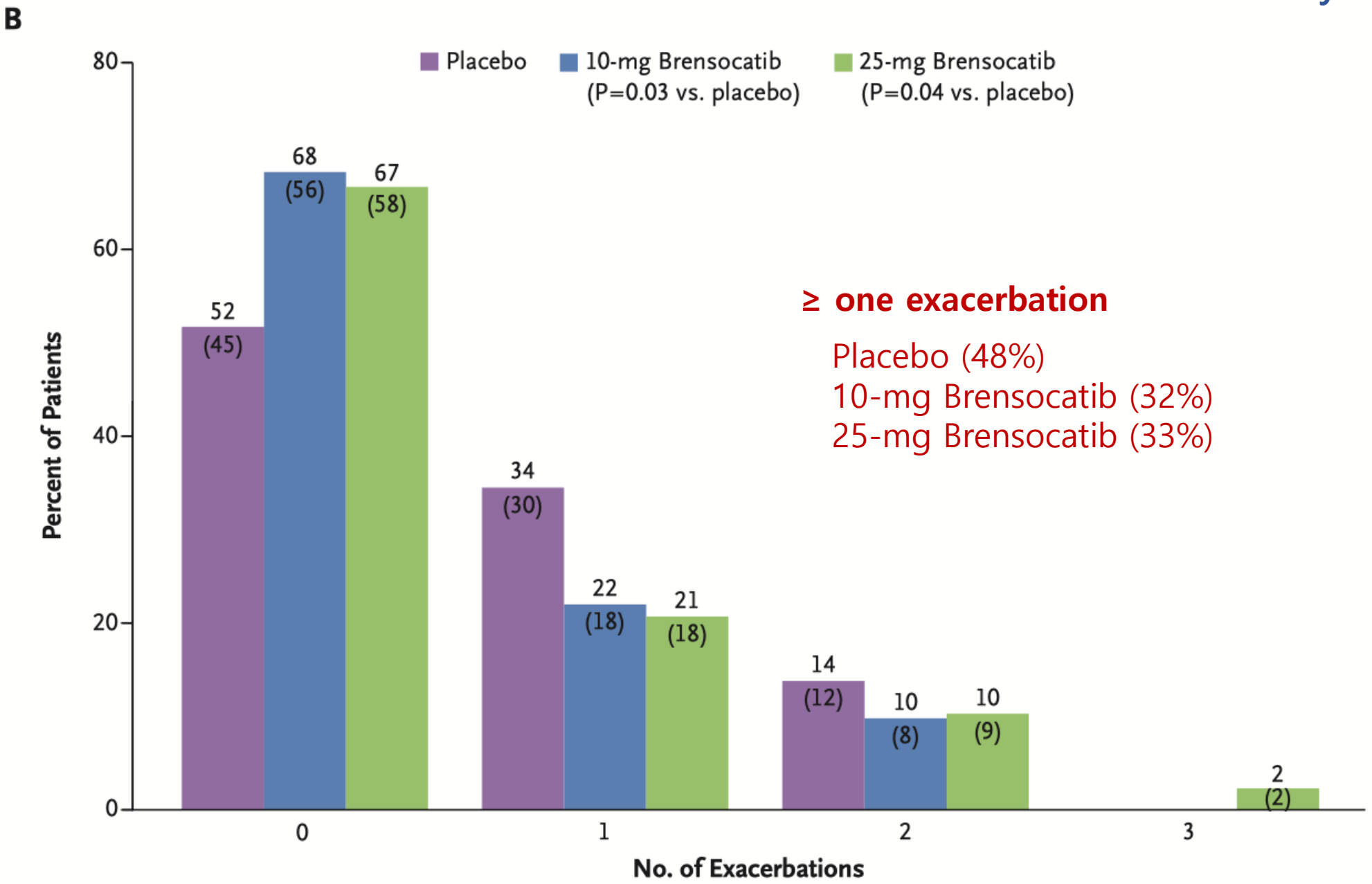
Placebo - median time to exacerbation = 189 days



Cumulative No. of Events/ No. at Risk															
10-mg Brensocatib	0/82	3/79	4/76	9/72	11/69	13/66	16/62	16/62	18/60	19/59	21/57	24/54	25/53	25/52	26/4
25-mg Brensocatib	0/87	4/83	10/77	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/54	26/52	26/52	28/49	29/10
Placebo	0/87	8/78	12/73	15/69	20/63	22/61	25/57	27/55	29/52	30/50	34/47	37/44	40/38	40/37	42/5

Figure 1B. Patients with No, One, or More exacerbations (Intention-to-Treat Population)

Secondary endpoint



≥ one exacerbation

Placebo (48%)
10-mg Brensocatib (32%)
25-mg Brensocatib (33%)

Figure 2. Time to first exacerbation , According to subgroup

Study was not powered to detect differences on this end point

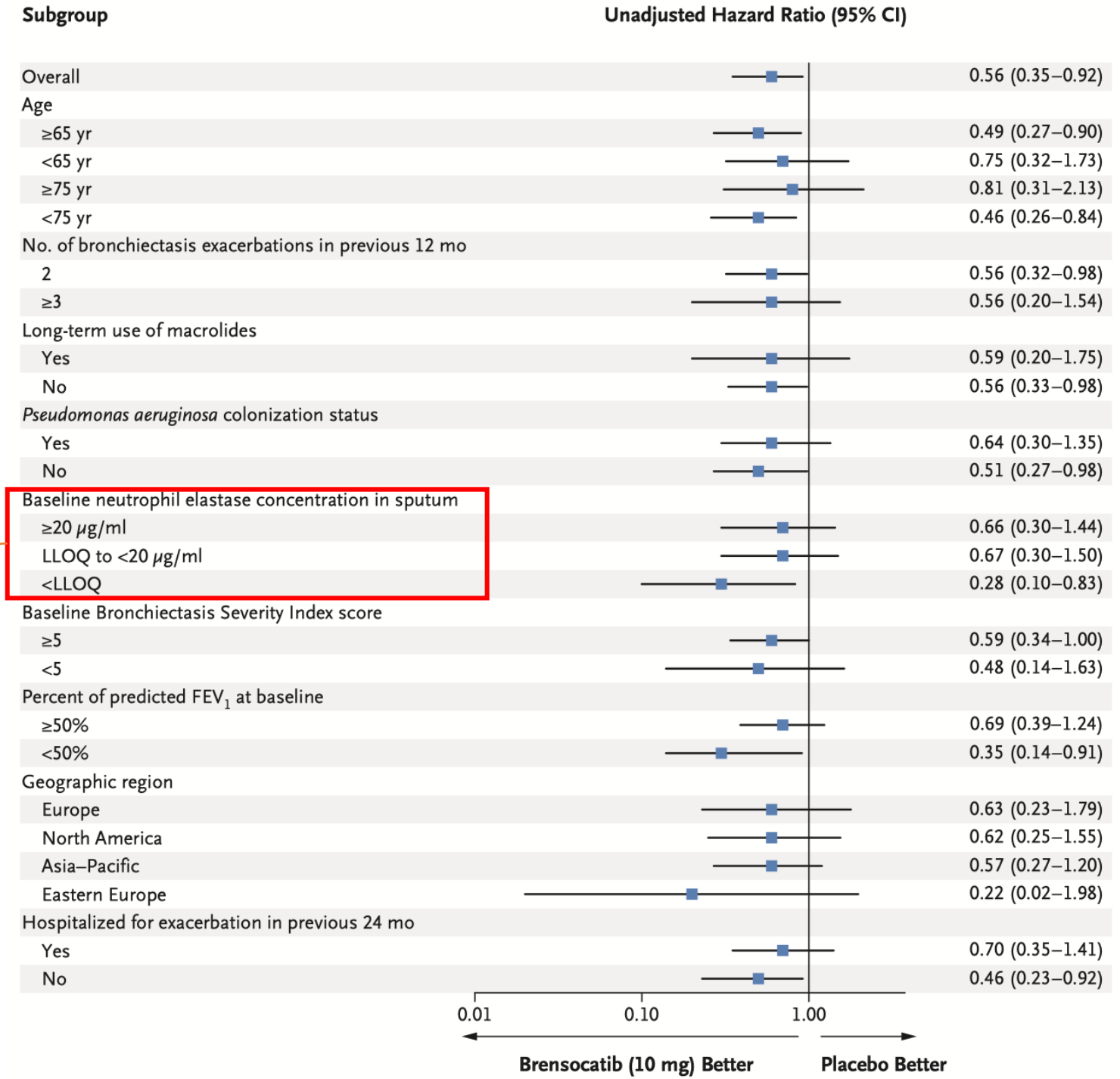
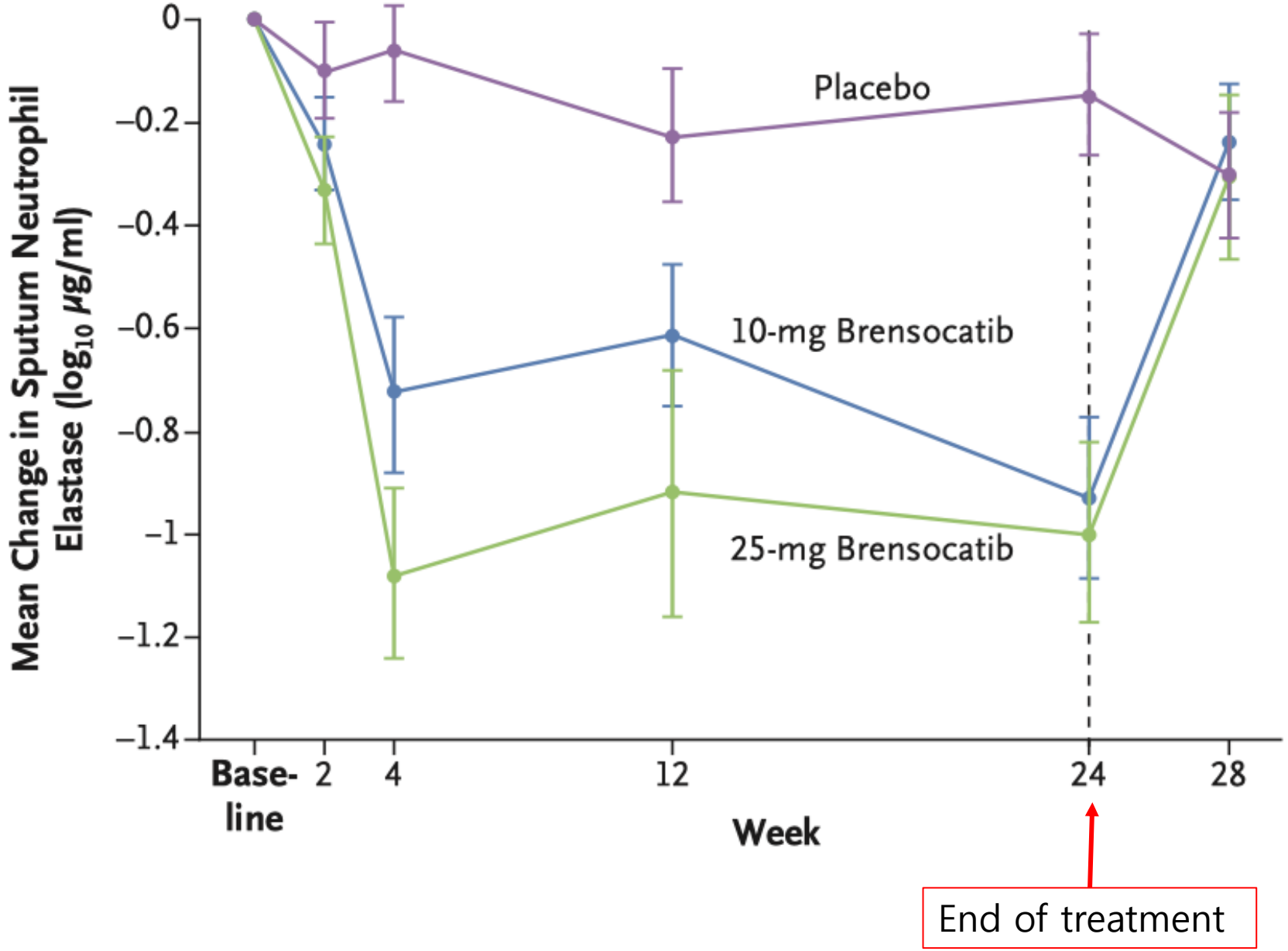


Figure 3. Mean change in sputum neutrophil elastase concentration

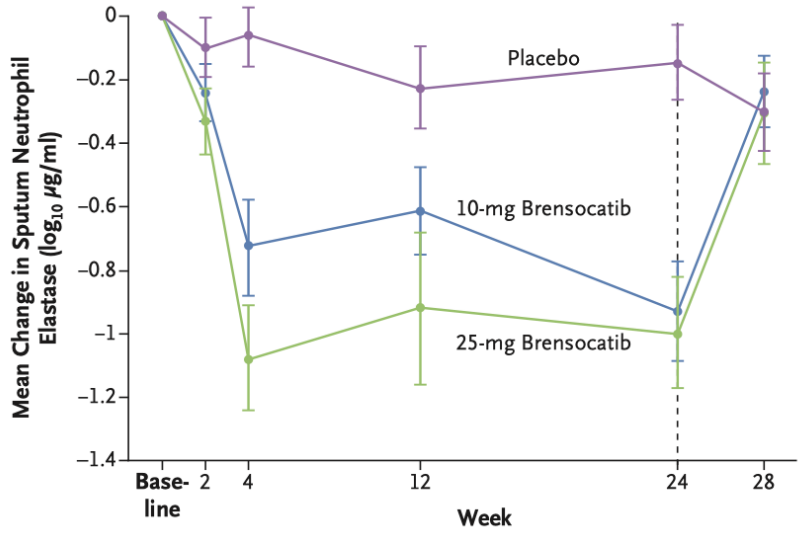


Summary

- Brensocatib
  - Prolonged time to the first exacerbation
  - Led to a lower frequency of exacerbation in bronchiectasis
- Potential clinical benefits of directly reducing neutrophilic inflammation in bronchiectasis

Comment

- Reduction in neutrophil recruitment (CXCR2 and LTB4 antagonist)
  - increased risk of infection
- **DPP-1 antagonism with brensocatib**
  - reduction in concentration of neutrophil elastase



- **A long-term study** is warranted

Agenda

- Background

- Mucus hyperconcetration and Daily symptoms [2]
- Neutrophilic inflammation [2]
- Eosinophilic inflammation [2]

AGORA
RESEARCH LETTER

Blood eosinophils predict inhaled fluticasone response in bronchiectasis

Eur Respir J 2020 Sep;56:2000453

Inhaled corticosteroid in bronchiectasis

- Eosinophilic inflammation
  - contribute to pathogenesis in ABPA or severe asthma-related BE
  - Increaseingly **identified as endotypes in BE**

- ICS in bronchiectasis – matter of debate
  - Guideline recommends only in specific comorbidities
    - ABPA, asthma, IBD, etc.
  - ~42% of BE patients receiving ICS
  - **Identification of specific BE population who respond to ICS** – key

Cochrane Database Syst Rev 2018;5:CD000996
Eur Respir J 2017;50:1700629

Hypothesis

- BE patients with a **high blood eosinophil count** can **benefit from ICS**
  - clinically meaningful improvement of QoL

Methods

- *Post hoc* analysis
  - RCT evaluating impact of ICS on QoL in bronchiectasis patients
  - Spanish study in 2006
  - Those with concomitant ABPA or asthma excluded + COPD excluded

- Original study design – stable bronchiectasis patients
  - 250 µg twice daily of **fluticasone propionate (FP)**
  - 500 µg twice daily of FP
  - Placebo

- Primary outcome
  - Clinically significant improvement in **SGRQ (≥4 points)**

Respir Med 2006;100:1623–1632

Methods

- Cut-off value of eosinophils in bronchiectasis?
  - **3% of eosinophil threshold** arbitrarily chosen
    - median value in cohort
  - **150 cells/µL cut-off** used for further analysis

Table 1. Baseline characteristics of the four study groups

Variable	N = 44			N = 42		
	LowEos group (Eos <3%)		p-value	HighEos group (Eos ⩾3%)		p-value
	FP+ n=28	FP- n=16		FP+ n=29	FP- n=13	
Age years	73 (68.5–78.0)	69.5 (68–75)	0.35	67 (63–73)	72 (66–75)	0.09
Males	20 (71.4)	8 (50.0)	0.16	18 (62.1)	9 (69.2)	0.65
BMI kg·m^{-2}	27.3 (25.0–29.6)	26.6 (26.0–29.0)	0.96	27.1 (25.5–29.1)	29.8 (28.3–31.3)	0.06
Aetiology						
Idiopathic	15 (53.6)	6 (37.5)	0.38	12 (41.4)	4 (30.8)	0.82
Post-infective	7 (25.0)	4 (25.0)		9 (31.0)	7 (53.9)	
Post-tuberculous	5 (17.9)	3 (18.8)		6 (20.7)	2 (15.4)	
Other	1 (3.6)	3 (18.9)		2 (7.0)		
Purulent sputum	10 (35.7)	7 (43.8)	0.60	9 (31.0)	3 (23.1)	0.72
BORG	3 (2–5)	3 (2.5–4.5)	0.97	3 (2–5)	3 (2–5)	0.92
COPD	5 (17.9)	3 (18.8)	1.00	10 (34.5)	4 (30.8)	1.00
FEV$_1$ mL	1260 (955–1630)	1310 (1120–1830)	0.53	1350 (1116–1670)	1250 (980–1600)	0.39
FEV$_1$ %	56 (41.5–77.5)	57.5 (50–72)	0.71	62 (42–70)	60 (51–85)	0.37
CRP	0.8 (0.2–1.2)	0.5 (0.2–1.0)	0.49	0.7 (0.5–1.1)	0.6 (0.3–1.1)	0.35
Sputum daily volume mL	10 (10–30)	17.5 (5–40)	0.65	20 (10–40)	10 (10–20)	0.43
Gram-positive PMM	6 (21.4)	0 (0.0)	0.07	3 (10.3)	1 (7.7)	1.00
mMRC basal						
0	2 (7.1)	3 (18.8)	0.56	1 (3.5)	1 (7.7)	0.58
1	6 (21.4)	1 (6.3)		7 (24.1)	5 (38.5)	
2	15 (53.6)	9 (56.3)		13 (44.8)	5 (38.5)	
3	4 (14.3)	3 (18.8)		8 (27.6)	2 (15.4)	
4	1 (3.6)	0 (0.0)				
Exacerbations post-randomisation	1 (0–2)	1 (0–1)	0.58	1 (0–1)	1 (1.0–1.5)	0.81
Baseline SGRQ	42.8 (31.6–55.4)	45.8 (36.2–60.6)	0.25	50.8 (33.9–61.5)	41.5 (25.2–51.5)	0.21

Table 1. Outcome data stratified by Eos% (<3% VS. ≥3%)

After six month-FP treatment

Variable	LowEos group (Eos <3%)		p-value	HighEos group (Eos ⩾3%)		p-value
	FP+ n=28	FP- n=16		FP+ n=29	FP- n=13	
Change SGRQ ⩾4 points	10 (37.0)	1 (6.7)	0.06	15 (51.7)	0 (0.0)	0.001
SGRQ total change*	+0.5 (+5.2 to −5.7)	+0.4 (+4.5 to −2.0)	0.42	−4.1 (+0.4 to −9.7)	+1.6 (+3.1 to +0.7)	0.002
FEV_1 at 6 months mL	1524±369.3	1476±607.0	0.86	1429±470.5	1404±212.0	0.90
FEV_1 at 6 months %	61.4±19.6	66.4±19.6	0.59	64.8±19.2	65.6±17.1	0.93
mMRC (3–4) at 3 months	5 (17.9)	2 (12.5)	1.0	0 (0.0)	3 (23.1)	0.03
Exacerbations at 6 months	12 (57.1)	3 (27.3)	0.15	7 (30.4)	6 (50.0)	0.29

Table 1. Outcome data stratified by Eos cell count (<150 VS. ≥150)

After six month-FP treatment

Variable	LowEos group (Eos <150 cells·μL^{-1}) FP+ n=13	FP- n=10	p-value	HighEos group (Eos ⩾ 150 cells·μL^{-1}) FP+ n=44	FP- n=19	p-value
Change SGRQ ⩾4 points	4 (33.3)	1 (11.1)	0.34	21 (47.7)	0 (0.0)	<0.0001
SGRQ total change*	−2.5 (−5.3 to +2.7)	−0.7 (−2.0 to +1.6)	0.54	−3.1 (−8.9 to +2.8)	+1.6 (0.4 to +4.2)	0.003
FEV1 at 6 months mL	1761.3±614.3	1260±538.7	0.14	1371.3±441.0	1610±393.4	0.21
FEV1 at 6 months %	68.4±19.6	58.5±15.3	0.33	61.4±20.3	72.6±18.5	0.21
MRC (3–4) at 3 months	3 (23.1)	1 (10.0)	0.60	2 (4.6)	4 (21.1)	0.06
Exacerbations at 6 months	7 (70.0)	3 (37.5)	0.34	12 (35.3)	6 (40.0)	0.75

Summary

- **6-month FP significantly improved QoL** in BE subgroup
  - **Eosinophil count ≥3% or 150 cells/μL**

- This successful outcome was not observed
  - Eosinophil count <3% or 150 cells/μL
  - Those not treated with FP

Systemic effects of fluticasone on blood eosinophils in bronchiectasis

To the Editor:

baseline and not during treatment with FP. This is pertinent as FP produces dose-dependent suppression of blood eosinophils due to systemic absorption from the lung. Hence, 1 mg of inhaled fluticasone in asthma patients is systemically equivalent to 5.3 mg of oral prednisolone for blood eosinophil suppression and 8.5 mg for cortisol suppression [2]. We would therefore be interested to know if similar

improvements in quality of life occur in bronchiectasis in relation to blood eosinophilia with other inhaled corticosteroids (ICS) that exhibit much less systemic glucocorticoid potency, such as budesonide or beclmomethasone [3]. Also, it would be interesting to know if patients with bronchiectasis who have

Eur Respir J 2020;56:2002005

Blood eosinophils do not predict inhaled budesonide response in bronchiectasis

From the authors:

TABLE 1 Changes in Saint George's Respiratory Questionnaire (SGRQ) comparing low (LowEos) and high eosinophil group patients (HighEos) (cut-off points of 3% and 150 cells·μL^{-1})

Variable (n=40)	LowEos Group (Eos <3%) n=23 (57.5%)	HighEos Group (Eos ⩾3%) n=17 (42.5%)	p-value	LowEos Group (Eos <150) n=26 (65%)	HighEos Group (Eos ⩾150) n=14 (35%)	p-value
Baseline SGRQ	38.4 (16.7 to 57.5)	38.9 (20.5 to 51.6)	0.847	37.7 (17.4 to 57.5)	39.4 (18.1 to 52.7)	0.885
Change SGRQ ⩾4 points %	36.4%	41.2%	0.509	36%	42.9%	0.466
SGRQ total change	−0.8 (−7.4 to 9.9)	−2.9 (−8.4 to 7.7)	0.489	−0.9 (−8.1 to 9.6)	−2.9 (−7.9 to 8.1)	0.408

Data are presented as median (interquartile range), unless otherwise stated.

Summary

- ***Hyposthesis-generating, not confirmative***

- **6-month FP significantly improved QoL** in BE subgroup
  - **Eosinophil count ≥3% or 150 cells/μL**
- This successful outcome was not observed
  - Eosinophil count <3% or 150 cells/μL
  - Those not treated with FP
- Pure bronchiectasis with neither asthma or COPD
- Lower exacerbation rate despite no statistical significance

AGORA
RESEARCH LETTER

Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series

Eur Respir J 2020 Jan;55:1901333

Methods – **Retrospective case series**

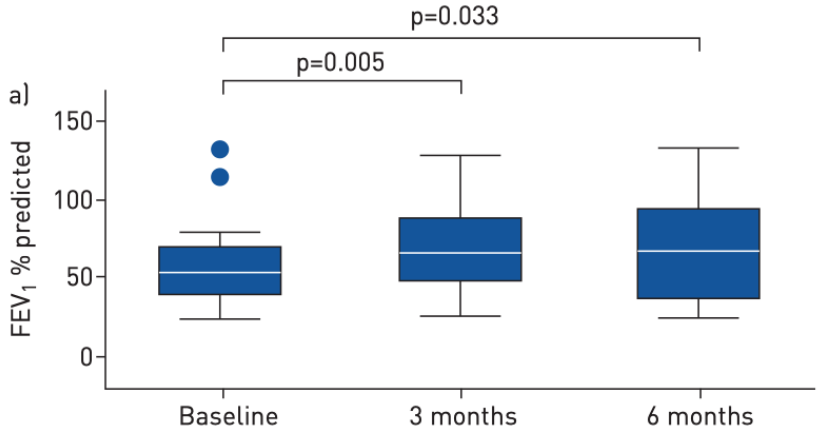
- Anti-eosinophilic therapy in refractory eosinophilic BE
  - Anti-IL5 (mepolizumab)
  - Anti-IL5α (benalizumab)

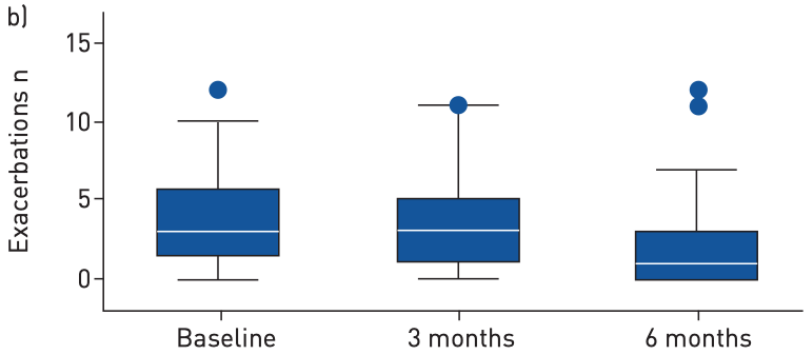
- Primary diagnosis of bronchiectasis with eosinophilic endotype (definition: eosinophilia ≥ 300 cells/µL at baseline or before initiation of long-term OCS therapy)

Methods

- 450 patients in regular FU at the Adult Bronchiectasis Clinic of the Hannover Medical School (2016–2018)
  - **21** received anti-IL5 or anti-IL5α therapy (mepolizumab in 12 and benalizumab in 9)
  - refractory disease despite optimized maintenance therapy
- Dose (licensed for use in severe eosinophilic asthma)
  - mepolizumab: 100mg every 4 weeks
  - benalizumab: 30mg every 4 weeks for 1st three doses, then every 8 weeks
- FU data obtained after 3 and 6 months of therapy

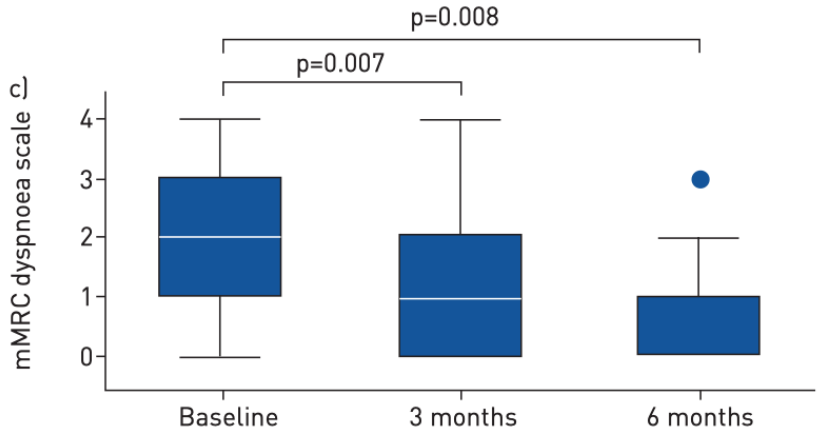
FEV1 %pred

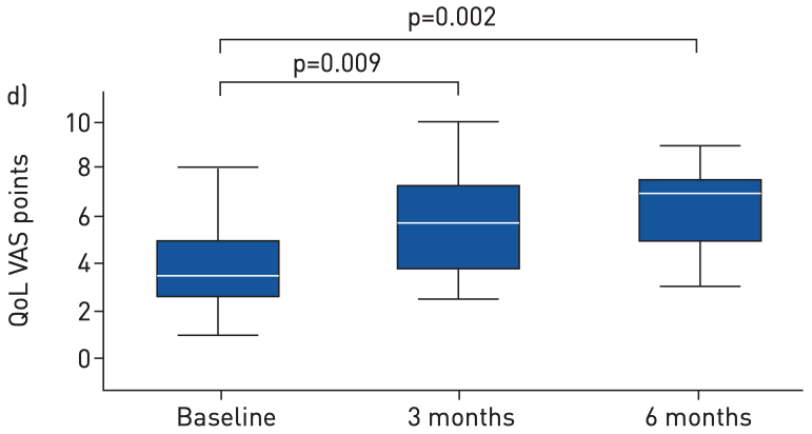




Exacerbations

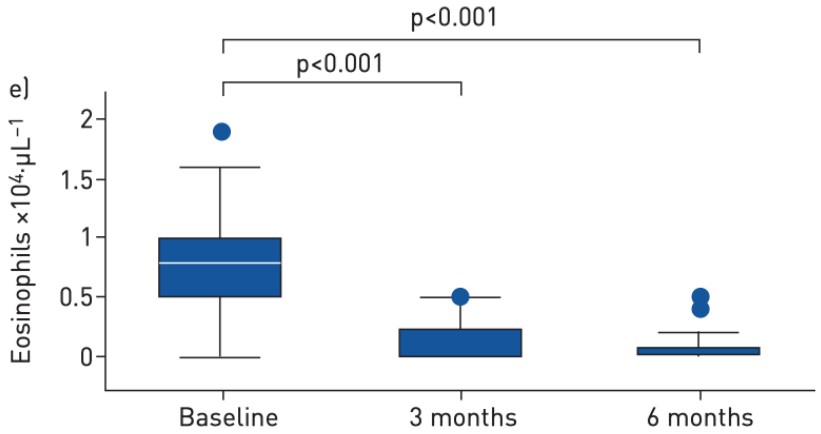
mMRC scale

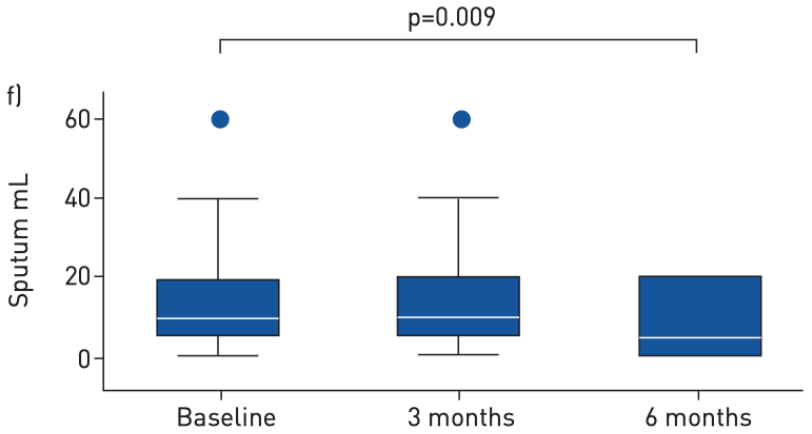




QoL VAS score

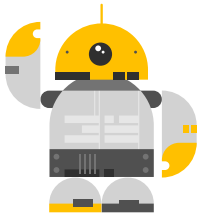
Eosinophil count





Sputum volume

Take home message



- Mucus Hyperconcentration
  - Beyond daily symptoms → Disease progression in BE
  - **Threshold** concept: highly symptomatic patients
- Neutrophilic inflammation
  - sputum **protemics**
  - targeted by existing (macrolide) and novel therapies (brensocatib)
- Eosinophilic inflammation
  - **eosinophilic endotypes** identified increasingly
  - **ICS responders** and **Biologics candidates** – future research needed

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