Insights into inflammation in Bronchiectasis: Precision endotyping and Implications for therapy

Hye Young Hong, MD.
Division of Pulmonology and Critical Medicine
Department of Internal Medicine,
Yonsei University College of Medicine

Table of Contents

- Pathophysiology of Bronchiectasis
- Endotyping of Bronchiectasis
- Treatment for Bronchiectasis: Precision Medicine

Rethinking bronchiectasis as an inflammatory disease

Merete B Long, Sanjay H Chotirmall, Michal Shteinberg, James D Chalmers

Background

- **Whitwell (1952)** "A Study of the Pathology and Pathogenesis of Bronchiectasis"
- First systematic pathological study using resected lung specimens (200 surgical specimen)
- Key Findings:
  - Rt.<Lt. (Lt. lower lobe- Lt. posterobasal segment/Lingular)
  - Bronchial wall thickening → loss of bronchiolar connections → complete blind-ending bronch
  - Saccular bronchiectasis was almost always associated with prior infections (pneumonia, measles…)

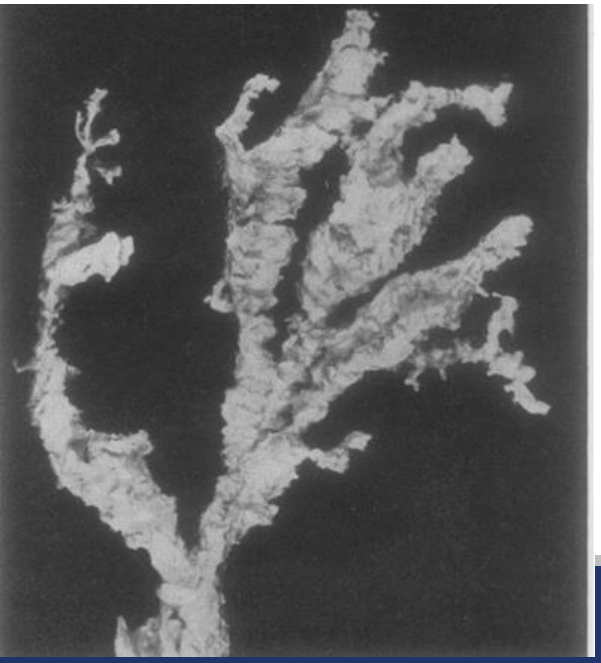


TABLE I

LOBAR DISTRIBUTION OF SPECIMENS

	No.	%
Left lung	19	9·5
Left upper lobe	6	3
Lingula	5	2·5
Left lower lobe	64	32
Base of left lower lobe	2	1
Left lower lobe and lingula	50	25
Base of left lower lobe and lingula	2	1
Total left lower lobe involvement	137	68·5
Total left-sided involvement	148	74
Right lung	3	1·5
Right upper lobe	6	3
Right middle lobe	10	5
Right lower lobe	14	7
Base of right lower lobe	2	1
Right middle lobe and right lower lobe	14	7
Right middle lobe and base of right lower lobe	1	0·5
Right lower lobe and anterior segment right upper lobe	1	0·5
Right lower lobe, right middle lobe, and anterior segment right upper lobe	1	0·5
Total right lower lobe involvement	36	18
Total right-sided involvement	52	26

SEGMENTAL SITE OF LESIONS IN 109 LEFT LOWER LOBES

Segment	Normal	Diseased
Apical	78	31
Anterior basal	30	79
Middle basal	10	99
Posterior basal	4	105

WHITWELL F. Thorax. 1952 Sep;7(3):213-39.

Bronchiectasis = Consequence of repeated infection?

- Management: long-term antibiotics, acute antibiotics during exacerbations

	EMBARC cohort (n=16 963)	UK (n=8163)	Southern Europe (n=4295)	Northern and western Europe (n=3444)	Central and eastern Europe (n=1061)
Inhaled corticosteroid	8700 (51·3%)	4796 (58·8%)	1779 (41·4%)	1630 (47·3%)	395 (37·2%)
LABA	8632 (50·9%)	4311 (52·8%)	2104 (49·0%)	1764 (51·2%)	453 (42·7%)
LAMA	4707 (27·7%)	2231 (27·3%)	1278 (29·8%)	911 (26·5%)	287 (27·0%)
LTRA	1007 (5·9%)	665 (8·1%)	135 (3·1%)	169 (4·9%)	38 (3·6%)
Theophylline	483 (2·8%)	298 (3·7%)	53 (1·2%)	70 (2·0%)	62 (5·8%)
Antibiotic treatments					
Inhaled antibiotic	1310 (7·7%)	620 (7·6%)	365 (8·5%)	306 (8·9%)	19 (1·8%)
Macrolide	2940 (17·3%)	1615 (19·8%)	475 (11·1%)	840 (24·4%)	10 (0·9%)
Other oral antibiotic prophylaxis	794 (4·7%)	574 (7·0%)	99 (2·3%)	101 (2·9%)	20 (1·9%)
Cyclical antibiotics	604 (3·6%)	297 (3·6%)	127 (3·0%)	116 (3·4%)	64 (6·0%)
Mucoactive drugs					
Carbocisteine or N-acetylcysteine	2910 (17·2%)	2389 (29·3%)	208 (4·8%)	256 (7·4%)	57 (5·4%)
Hypertonic saline	1454 (8·6%)	537 (6·6%)	224 (5·2%)	662 (19·2%)	31 (2·9%)
Isotonic saline	872 (5·1%)	356 (4·4%)	92 (2·1%)	373 (10·8%)	51 (4·8%)
Mannitol	4 (0%)	2 (0·0%)	0 (0%)	2 (0·1%)	0 (0%)
DNAse	75 (0·4%)	36 (0·4%)	19 (0·4%)	12 (0·3%)	8 (0·8%)
Sodium hyaluronate	24 (0·1%)	2 (0·0%)	16 (0·4%)	5 (0·1%)	1 (0·1%)

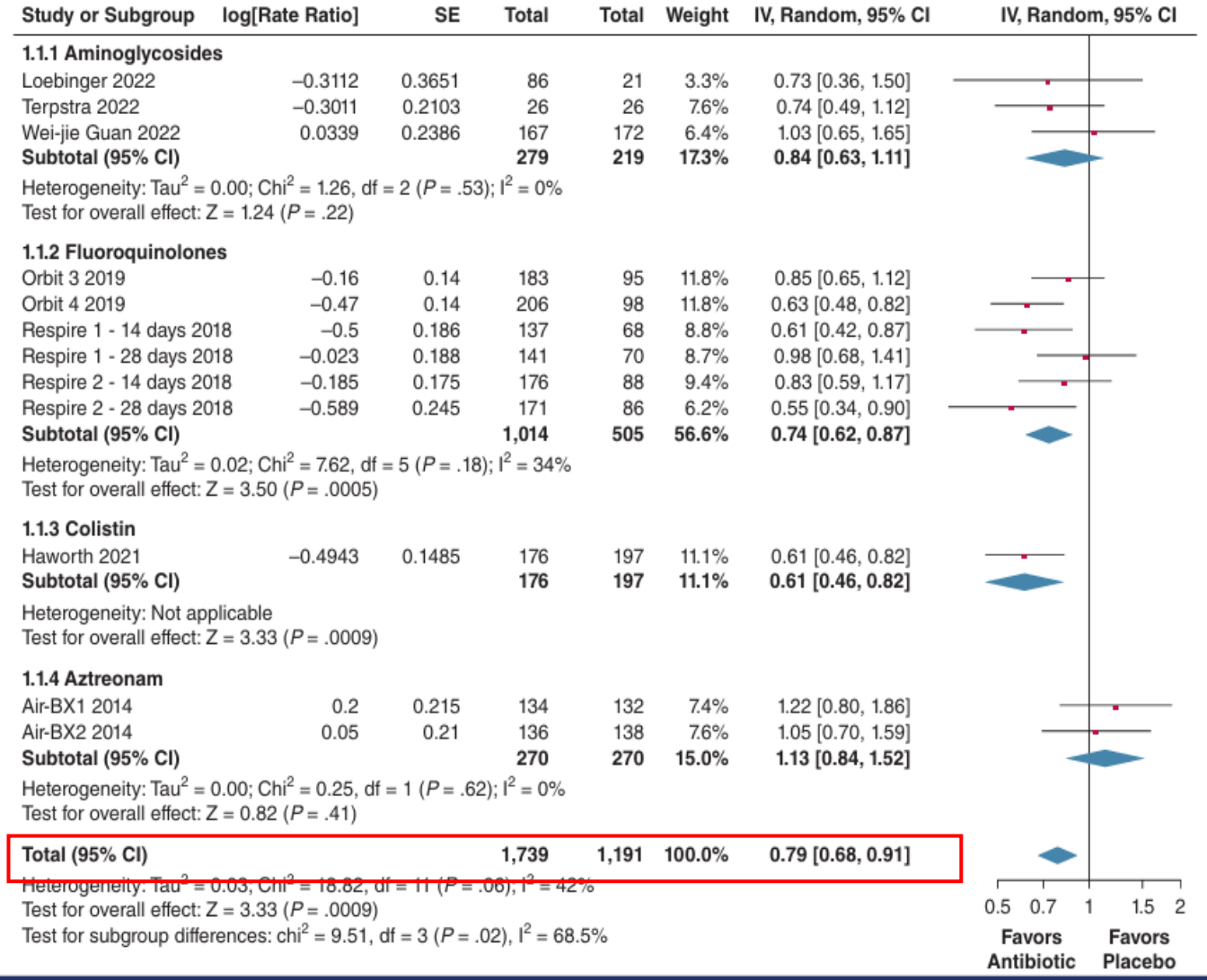
Data are n (%). LABA=long-acting beta agonist. LAMA=long-acting muscarinic antagonist. LTRA=leukotriene receptor antagonist.

TABLE 6 | Therapies Reported for Patients With Bronchiectasis[a]

Therapy	Data Available (No.)	Overall (N = 1,826)	NTM (n = 1,158)	No NTM (n = 668)	*P* Value[b] NTM vs No NTM
Antibiotic use, No. (%)					
Antibiotics for acute exacerbations only	1,764	727 (41)	402 (36)	325 (50)	< .01
Any suppressive antibiotic	1,775	694 (39)	491 (43)	203 (32)	< .01
Rotating oral suppressive antibiotics	1,771	125 (7)	64 (6)	61 (9)	< .01
Inhaled suppressive antibiotics	1,759	178 (10)	113 (10)	65 (10)	.98
Use of other therapies, No. (%)					
Inhaled steroid	1,794	696 (39)	403 (35)	293 (45)	< .01
Any oral steroid	1,789	237 (13)	112 (10)	125 (19)	< .01
Inhaled bronchodilator	1,798	1,098 (61)	638 (56)	460 (70)	< .01
Medication for gastric acid suppression	1,786	667 (37)	432 (38)	235 (36)	.43
Mucus-active agent	1,784	424 (24)	252 (22)	172 (26)	.04
Measures to improve bronchial hygiene, No. (%)					
Yes	1,730	965 (56)	642 (59)	323 (50)	< .01
Chest percussion/postural drainage	1,711	279 (16)	200 (19)	79 (12)	< .01
Flutter or positive expiratory pressure valve	1,719	825 (48)	568 (52)	257 (40)	< .01
High-frequency chest oscillation	1,716	252 (15)	142 (13)	110 (17)	.02

Chalmers JD et al, Lancet Respir Med. 2023 Jul;11(7):637-649.
Aksamit TR et al, Chest. 2017 May;151(5):982-992

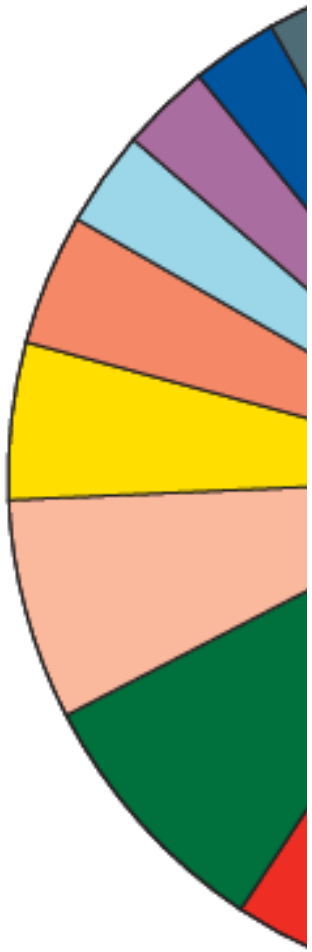
Bronchiectasis = Consequence of repeated infection?



Study or Subgroup	log[Rate Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI
1.1.1 Aminoglycosides						
Loebinger 2022	−0.3112	0.3651	86	21	3.3%	0.73 [0.36, 1.50]
Terpstra 2022	−0.3011	0.2103	26	26	7.6%	0.74 [0.49, 1.12]
Wei-jie Guan 2022	0.0339	0.2386	167	172	6.4%	1.03 [0.65, 1.65]
Subtotal (95% CI)			**279**	**219**	**17.3%**	**0.84 [0.63, 1.11]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.26$, df = 2 ($P = .53$); $I^2 = 0\%$						
Test for overall effect: Z = 1.24 ($P = .22$)						
1.1.2 Fluoroquinolones						
Orbit 3 2019	−0.16	0.14	183	95	11.8%	0.85 [0.65, 1.12]
Orbit 4 2019	−0.47	0.14	206	98	11.8%	0.63 [0.48, 0.82]
Respire 1 - 14 days 2018	−0.5	0.186	137	68	8.8%	0.61 [0.42, 0.87]
Respire 1 - 28 days 2018	−0.023	0.188	141	70	8.7%	0.98 [0.68, 1.41]
Respire 2 - 14 days 2018	−0.185	0.175	176	88	9.4%	0.83 [0.59, 1.17]
Respire 2 - 28 days 2018	−0.589	0.245	171	86	6.2%	0.55 [0.34, 0.90]
Subtotal (95% CI)			**1,014**	**505**	**56.6%**	**0.74 [0.62, 0.87]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.62$, df = 5 ($P = .18$); $I^2 = 34\%$						
Test for overall effect: Z = 3.50 ($P = .0005$)						
1.1.3 Colistin						
Haworth 2021	−0.4943	0.1485	176	197	11.1%	0.61 [0.46, 0.82]
Subtotal (95% CI)			**176**	**197**	**11.1%**	**0.61 [0.46, 0.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.33 ($P = .0009$)						
1.1.4 Aztreonam						
Air-BX1 2014	0.2	0.215	134	132	7.4%	1.22 [0.80, 1.86]
Air-BX2 2014	0.05	0.21	136	138	7.6%	1.05 [0.70, 1.59]
Subtotal (95% CI)			**270**	**270**	**15.0%**	**1.13 [0.84, 1.52]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 ($P = .62$); $I^2 = 0\%$						
Test for overall effect: Z = 0.82 ($P = .41$)						
Total (95% CI)			**1,739**	**1,191**	**100.0%**	**0.79 [0.68, 0.91]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 18.82$, df = 11 ($P = .06$); $I^2 = 42\%$						
Test for overall effect: Z = 3.33 ($P = .0009$)						
Test for subgroup differences: $chi^2 = 9.51$, df = 3 ($P = .02$), $I^2 = 68.5\%$						

- 20 RCTs of inhaled antibiotics (3458 patients)
- Reduced bacterial load
  - Mean reduction: -2.2log CFU/g sputum
- Small improvement QoL
  - QoL-B: +2.37 points (below MCID 8)
  - SGRQ: -3.13 points (below MCID 4)
- No consistent FEV_1 change

Cordeiro R et al. Chest. 2024 Jul;166(1):61-80.



Potential aetiological entry points

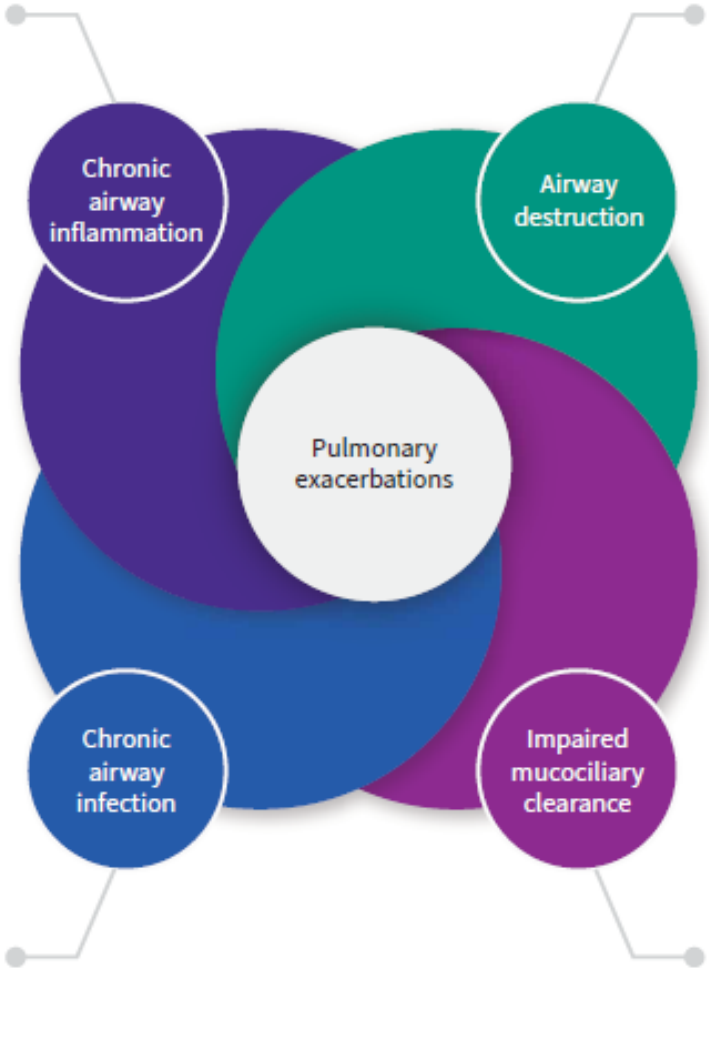
Connective tissue disease
ABPA
IBD
COPD

Chronic airway inflammation
Chronic airway inflammation is primarily driven by neutrophils, which are recruited to infection sites and release potent proteases that contribute to airway damage

Chronic airway infection
Abnormal mucus clearance leads to chronic airway infection, which in turn contributes to inflammation, lung damage and tissue remodelling

NTM
Immunodeficiency-related infections
Tuberculosis

Potential aetiological entry points



Potential aetiological entry points

Tracheobronchomegaly
Other congenital syndromes
Fibrosis causing traction

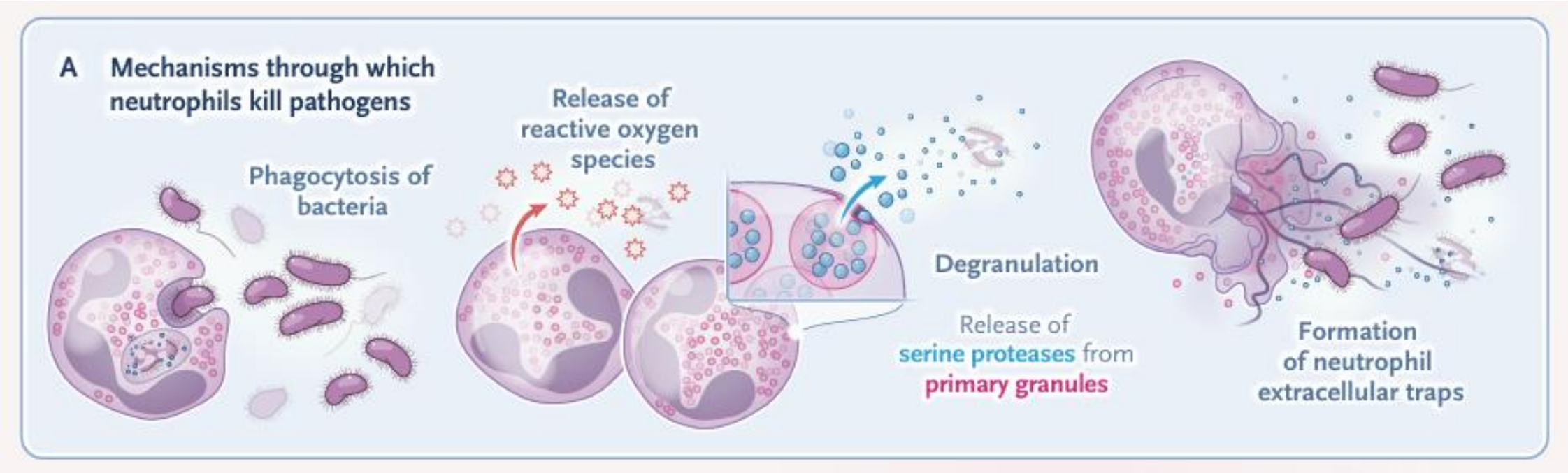
Airway destruction
Bronchial dilation, bronchial wall thickening, mucus plugging and emphysema are structural changes associated with bronchiectasis

Impaired mucociliary clearance
Impaired mucociliary clearance and epithelial dysfunction contribute to chronic infection and inflammation, as pathogens trapped in mucus cannot be efficiently removed from the lungs

Cystic fibrosis
Primary ciliary dyskinesia

Potential aetiological entry points

Chalmers JD et al. Lancet Respir Med. 2023 Jul;11(7):637-649.
Chalmers JD et al. Am J Respir Crit Care Med. 2017 May 15;195(10):1384-1393.



Neutrophil Serine Protease

- Neutrophil Elastase (NE)
- Proteinase 3 (PR3)
- Catepsin G (CatG)

Hill AT. N Engl J Med. 2025 Apr 24;392(16):1649-1652
Chalmers JD et al. ERJ Open Res. 2023 Jun 26;9(3):00633-2022.

Beyond Infection

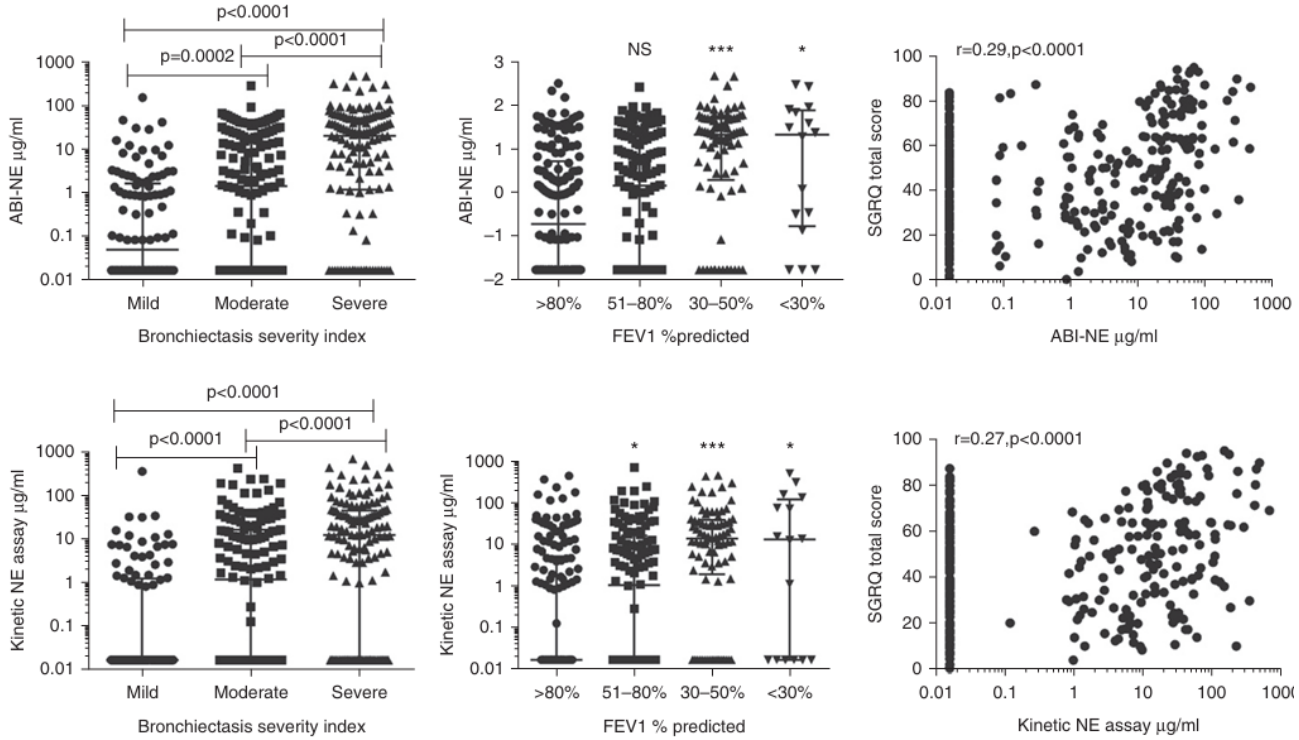
Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis

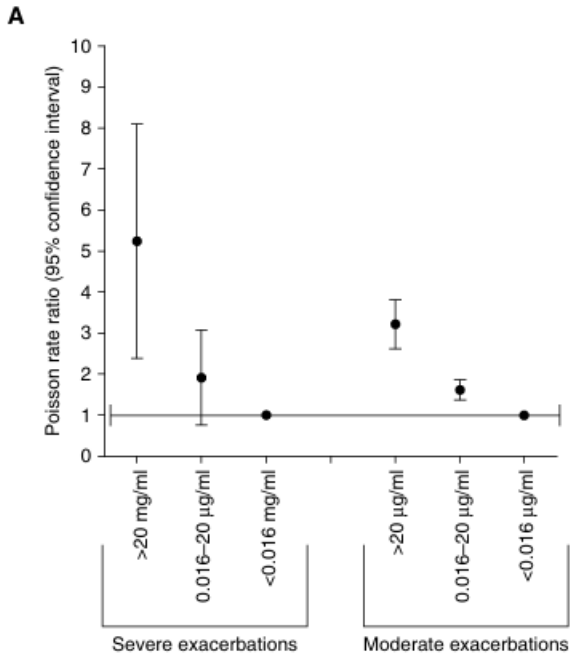
James D. Chalmers[1,2], Kelly L. Moffitt[3], Guillermo Suarez-Cuartin[4], Oriol Sibila[4], Simon Finch[1], Elizabeth Furrie[2], Alison Dicker[1,2], Karolina Wrobel[2], J. Stuart Elborn[5,6], Brian Walker[3], S. Lorraine Martin[3], Sara E. Marshall[2], Jeffrey T.-J. Huang[2*], and Thomas C. Fardon[1*]

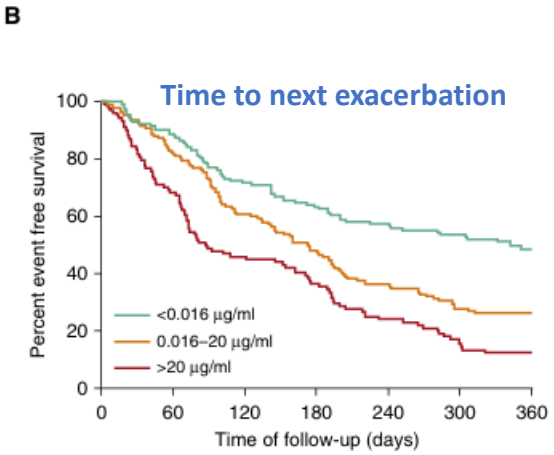
- Design: Single-center, prospective cohort study (TAYBRIDGE registry, Dundee, UK)
- Population: 433 patients with HRCT-confirmed bronchiectasis (381 sputum)
- Follow-up: 3 years
- Key Methods
  - Sputum NE activity measured with two assays (ABI-NE immunoassay, kinetic assay)
    - Cut off: <0.016μg/mL(low), 0.016-20, >20μg/mL(high)
  - Circulating desmosine (cDES) measured in serum
  - Clinical assessments: BSI, Reiff radiology score, SGRQ, spirometry, exacerbation history
  - Substudy (n=26): measured NE before, during, and after exacerbations

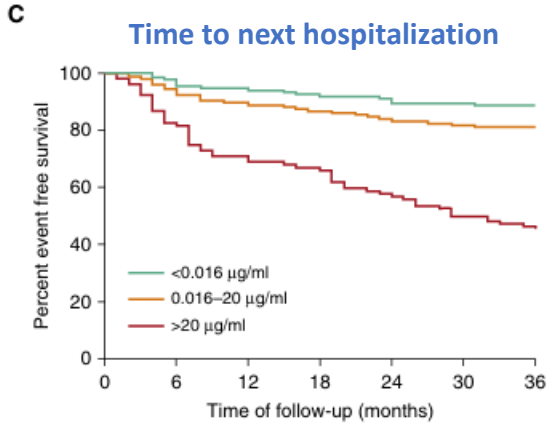
Chalmers JD et al. Am J Respir Crit Care Med. 2017 May 15;195(10):1384-1393.

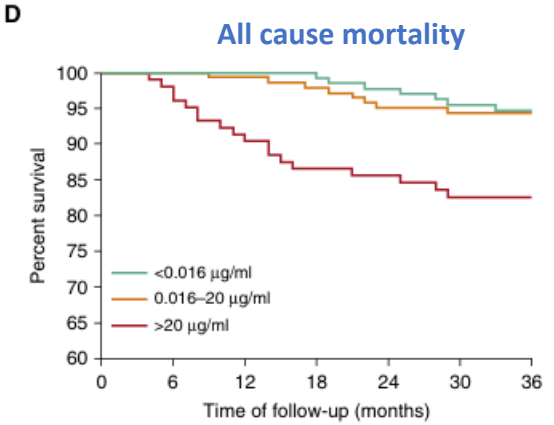
Beyond Infection











Sputum NE activity is associated with the future risk of exacerbations, including severe exacerbations and lung function decline

Chalmers JD et al. Am J Respir Crit Care Med. 2017 May 15;195(10):1384-1393.

Beyond Infection

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

- Sputum from mild (n=20) vs severe (n=20) bronchiectasis from Dundee University
- Discovery: Sputum proteomics → NET-associated proteins linked to BSI
- Hypothesis: NETs would be associated with bronchiectasis severity and outcomes
- Prospective cohorts (TAYBRIDGE/BRIDGE): sputum NETs (immunoassay)
- Primary Outcomes
  - Time to first severe exacerbation
  - All-cause mortality
- AE sub-study: paired sputum Day 1 vs Day 14 after systemic antibiotics

Keir HR et al. Lancet Respir Med. 2021 Aug;9(8):873-884.

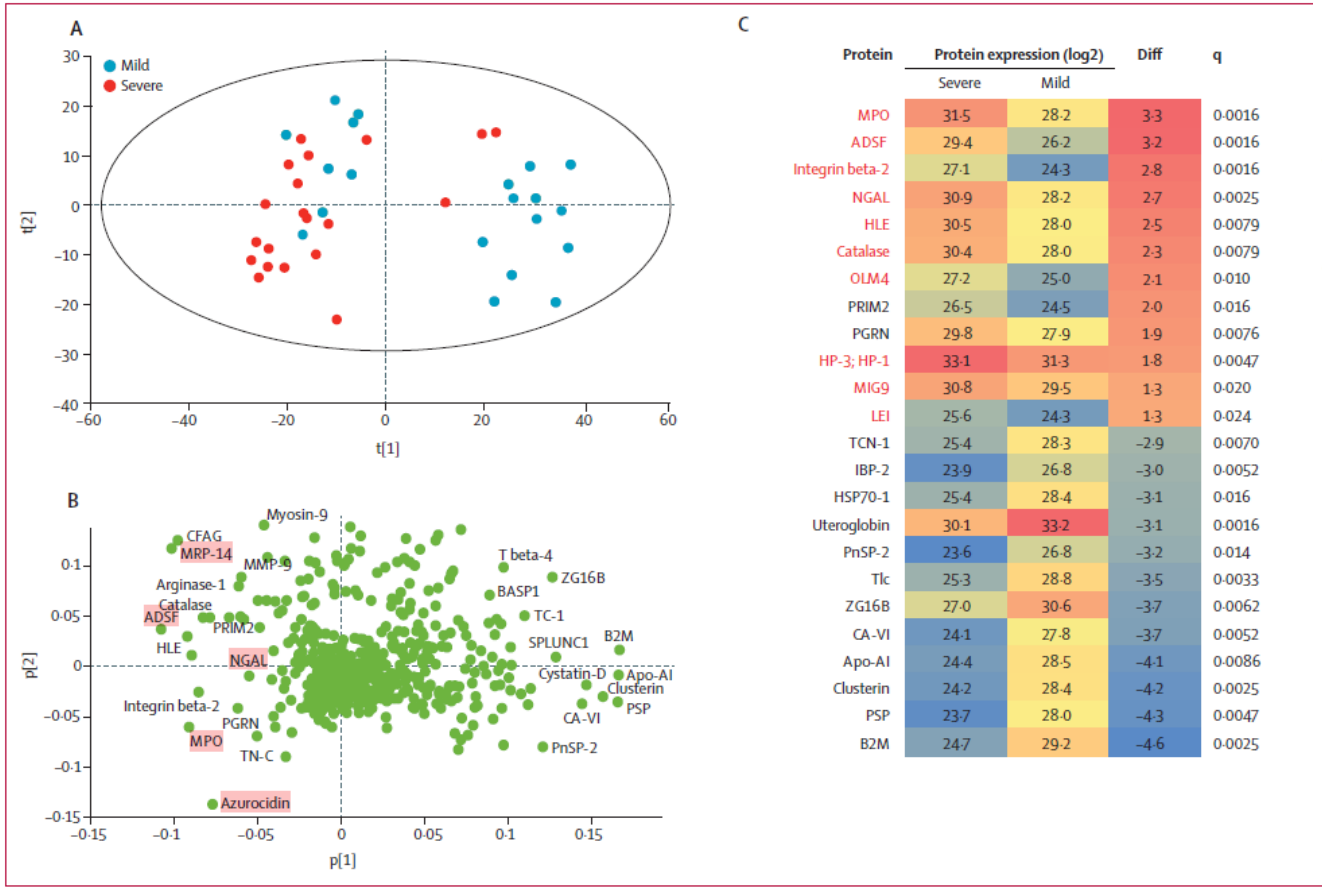
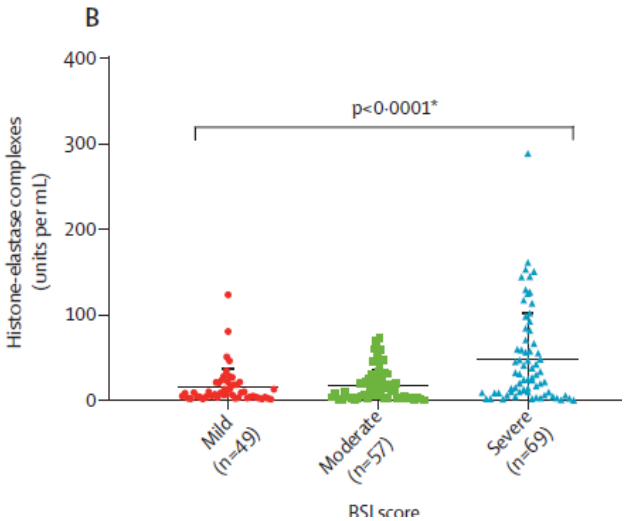
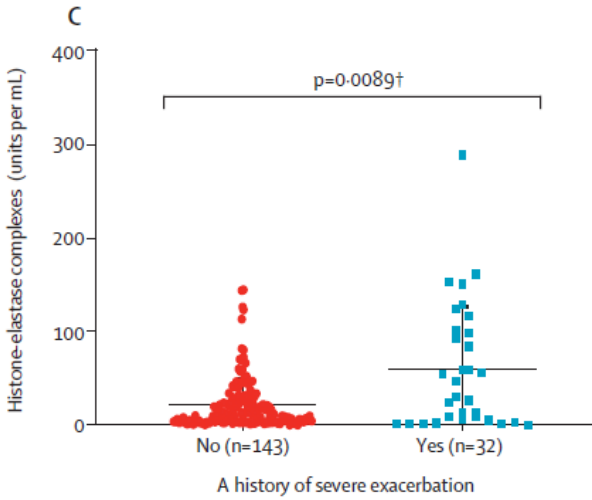
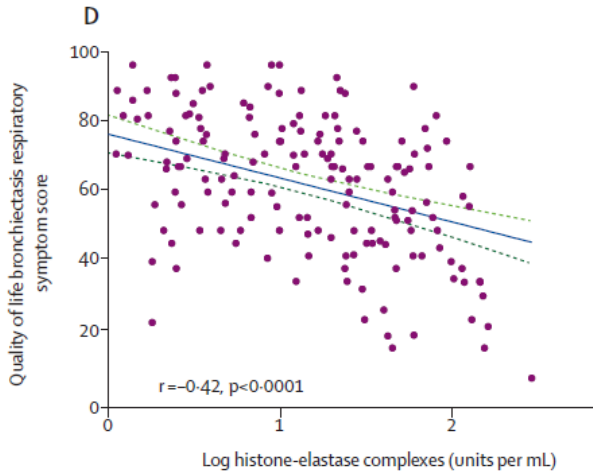
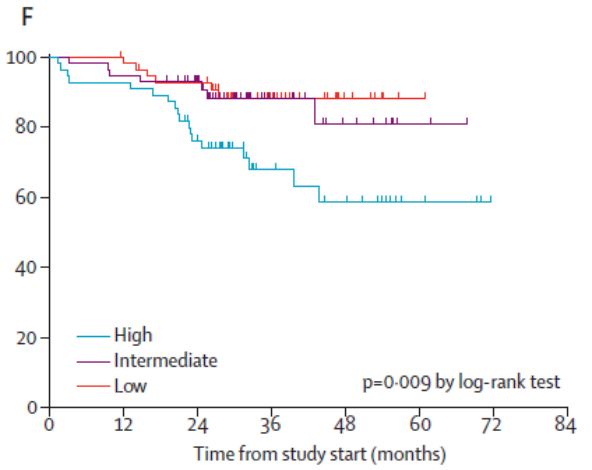


Figure 1: **Proteomics of patients with mild and severe bronchiectasis**









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)

Keir HR et al. Lancet Respir Med. 2021 Aug;9(8):873-884.

Eosinophilic inflammation

Characterization of Eosinophilic Bronchiectasis
A European Multicohort Study

Amelia Shoemark[1,2], Michal Shteinberg[3], Anthony De Soyza[4,5], Charles S. Haworth[6,7], Hollian Richardson[1], Yonghua Gao[8], Lidia Perea[9], Alison J. Dicker[1], Pieter C. Goeminne[10], Erin Cant[1], Eva Polverino[11,12], Josje Altenburg[13], Holly R. Keir[1], Michael R. Loebinger[2], Francesco Blasi[14,15], Tobias Welte[16], Oriol Sibila[9], Stefano Aliberti[17,18], and James D. Chalmers[1]

- **EMBARC cohort (except asthma)**

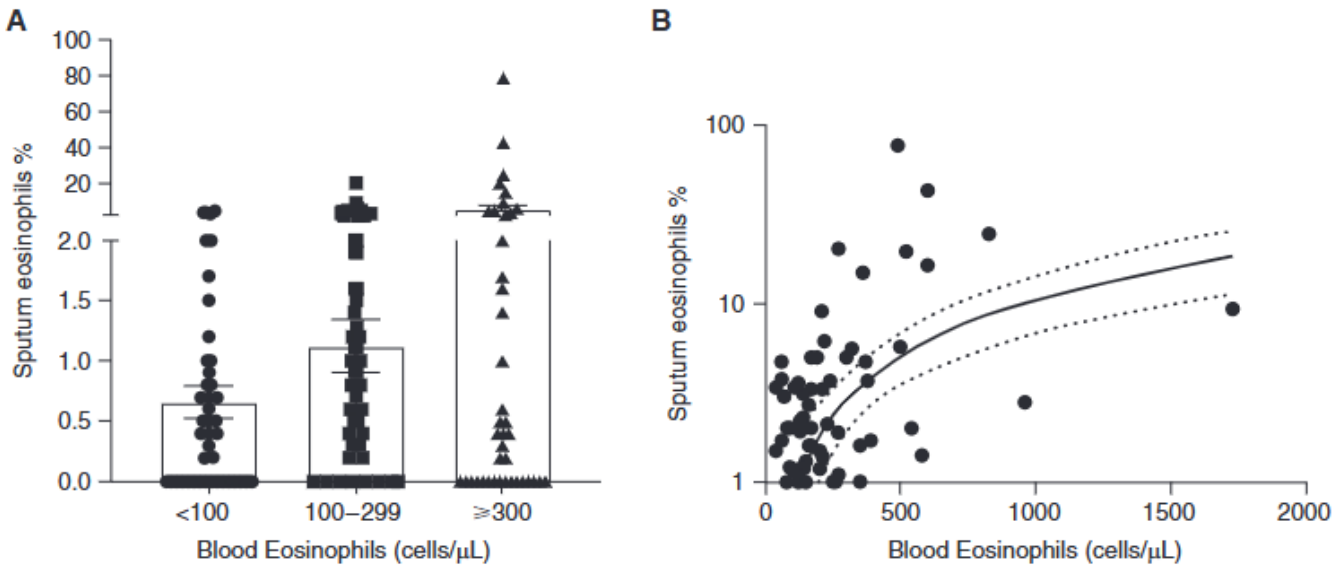
Table 1. Characteristics of Patients across Five European Cohorts, Stratified by Blood Eosinophil Count

Characteristics	Blood Eosinophil Counts			*P* Value
	<100 Cells/μl	100–299 Cells/μl	⩾300 Cells/μl	
No. of subjects	218	518	215	
Age, yr	66.8 (15.3)	66.0 (14.4)	65.1 (16.1)	0.53
Sex, F, *n* (%)	125 (57.3%)	270 (52.1%)	106 (49.3%)	0.23
BMI, kg/m^2	24.5 (5.5)	25.4 (5.4)	26.4 (5.9)	0.013
Etiology, *n* (%)				
Idiopathic	106 (48.6%)	246 (47.5%)	102 (47.4%)	—
Postinfective	32 (14.7%)	109 (21.0%)	34 (15.8%)	—
TB	5 (2.3%)	18 (3.5%)	7 (3.3%)	—
Immunodeficiency	8 (3.7%)	17 (3.3%)	12 (5.6%)	—
CTD	14 (6.4%)	9 (1.7%)	2 (0.9%)	—
COPD	16 (7.3%)	29 (5.6%)	21 (9.8%)	—
NTM	2 (0.9%)	4 (0.8%)	0 (0%)	—
PCD	7 (3.2%)	8 (1.5%)	5 (2.3%)	—
Others	28 (12.8%)	78 (15.1%)	32 (14.9%)	—
BSI, median (IQR)	8 (5–11)	6 (4–9)	6 (4–9)	<0.0001
mMRC dyspnea score, median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	0.071
FEV_1, L	1.64 (0.69)	1.93 (0.84)	1.92 (0.78)	0.003
FEV_1% predicted	73.2 (26.8)	78.1 (26.1)	77.9 (25.9)	0.061
Pseudomonas aeruginosa, *n* (%)	32 (14.7%)	80 (15.4%)	42 (19.5%)	0.3
NTM infection, *n* (%)	13 (6.0%)	25 (4.8%)	15 (7.0%)	0.08
Inhaled corticosteroid use, *n* (%)	124 (56.4%)	214 (41.2%)	94 (43.6%)	0.0004
Eosinophil count, cells/μl, median (IQR)	60 (20–90)	170 (120–200)	400 (310–540)	<0.0001

22.6%

Shoemark A et al. Am J Respir Crit Care Med. 2022 Apr 15;205(8):894-902.

Eosinophilic inflammation



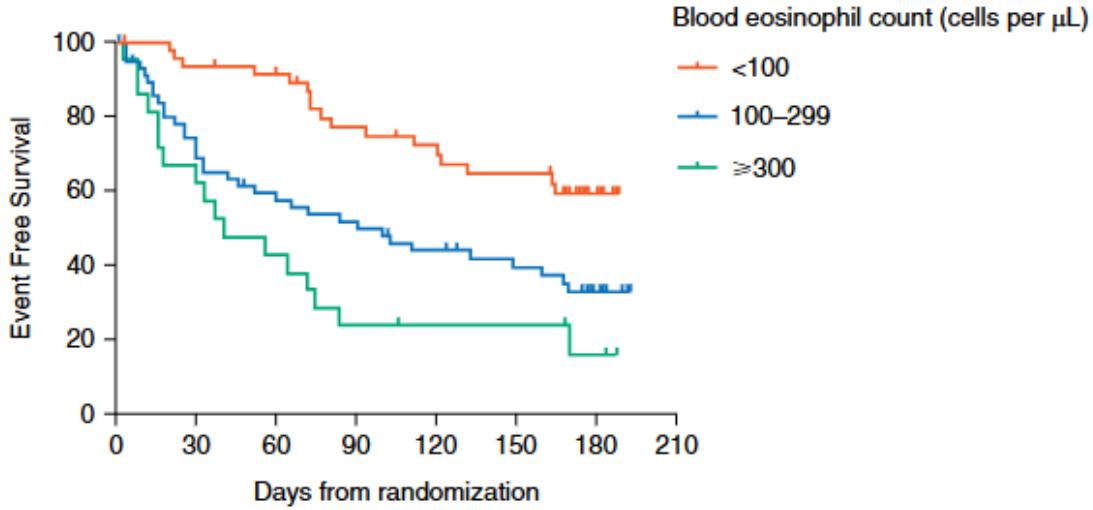


Figure 5. Kaplan-Meier survival curve showing the percentage of exacerbation event–free survival from randomization.

Shoemark A et al. Am J Respir Crit Care Med. 2022 Apr 15;205(8):894-902.

Endotyping

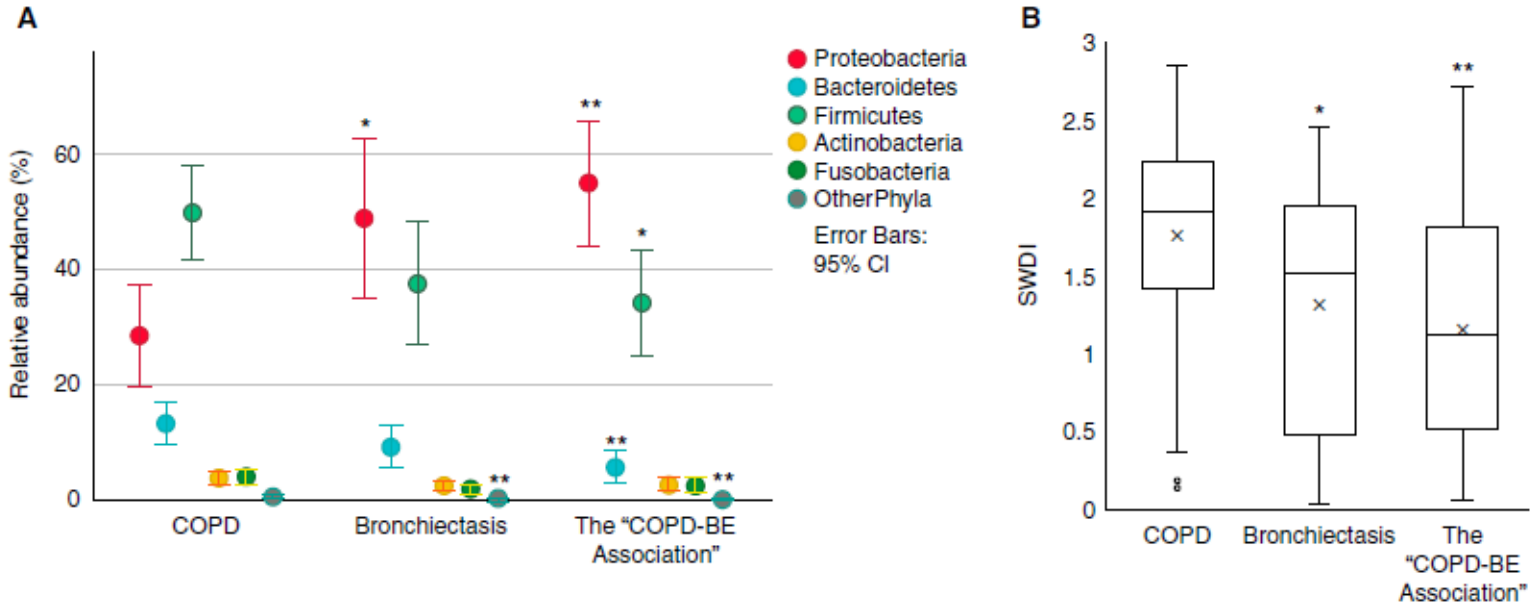
Endotyping Chronic Obstructive Pulmonary Disease, Bronchiectasis, and the "Chronic Obstructive Pulmonary Disease–Bronchiectasis Association"

Jeffrey T.-J. Huang[1], Erin Cant[2], Holly R. Keir[2], Alun K. Barton[1], Elena Kuzmanova[1], Morven Shuttleworth[2], Jennifer Pollock[2], Simon Finch[2], Eva Polverino[3], Mathieu Bottier[2], Alison J. Dicker[1], Amelia Shoemark[2], and James D. Chalmers[2]

- Design: Observational, multi-cohort study
- Population:
  - COPD (≥40 years, ≥10 pack-year smoking, FEV1/FVC <70%): 40
  - Bronchiectasis (CT-confirmed, symptomatic, non-CF, non-fibrosis): 30
  - COPD–bronchiectasis overlap (meeting criteria for both diseases): 48
- Hypothesis: COPD–bronchiectasis association has a distinct pathobiology that is different from COPD and more similar to bronchiectasis
- Procedures
  - Sputum sampling at stable state (≥4 weeks free from antibiotics/oral steroids)
  - Microbiome analysis: 16S rRNA sequencing
  - Proteomics: Label-free protein profiling of sputum supernatant
  - Targeted assays in validation cohort: NE, mucins (MUC5AC/MUC5B), cytokines, bacterial cultures

Huang JT et al, Am J Respir Crit Care Med. 2022 Aug 15;206(4):417-426.

Endotyping



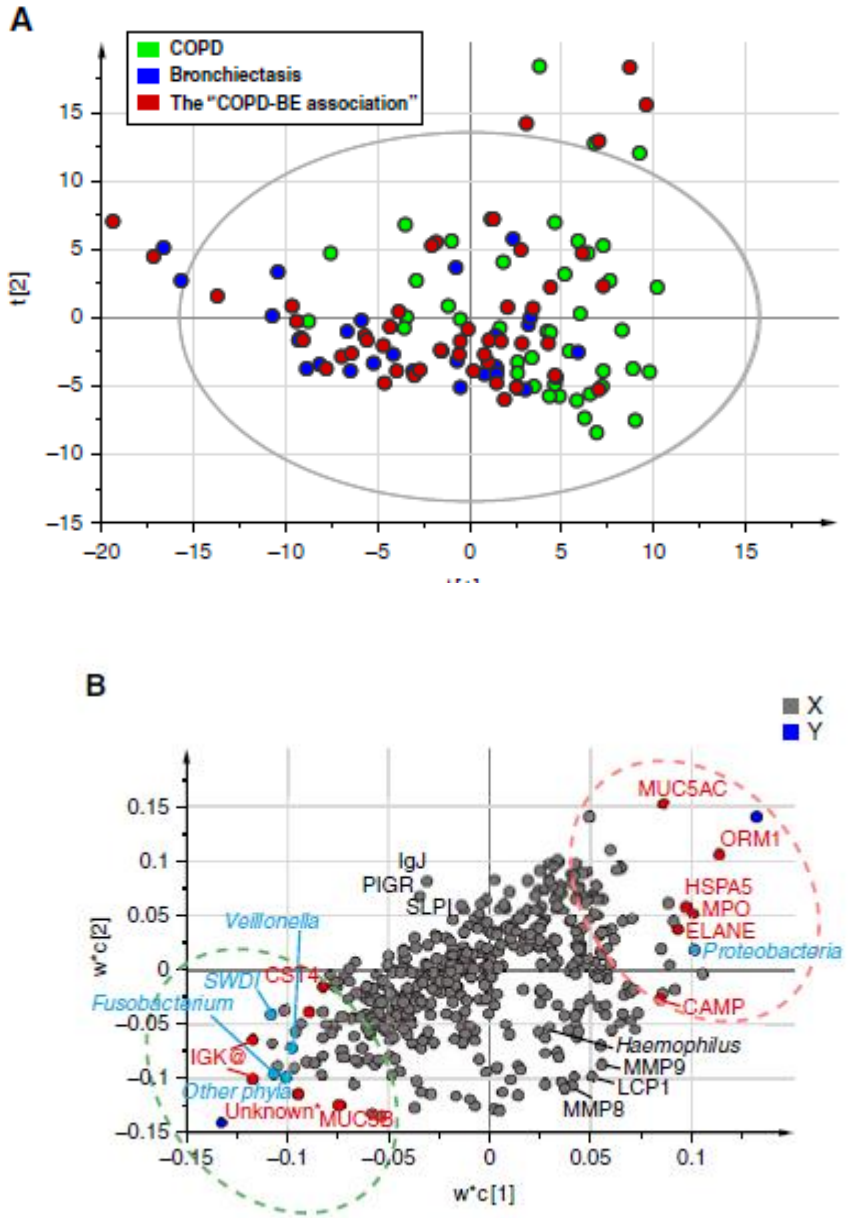


Figure 1. Relative abundance of lung microbiota at the (*A*) phylum level and (*B*) Shannon-Wiener Diversity Index in chronic obstructive pulmonary disease (COPD), bronchiectasis, and the COPD-BE association. **P* < 0.05 and ***P* < 0.01. CI = confidence interval; COPD-BE = COPD–bronchiectasis.

Huang JT et al, Am J Respir Crit Care Med. 2022 Aug 15;206(4):417-426.

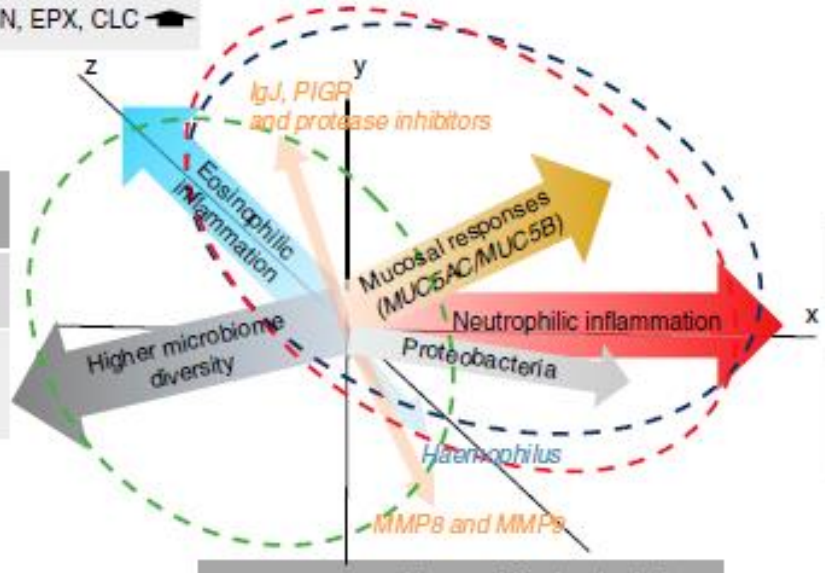
Endotyping

- Diverse/Protective
- Haemophilus-Proteolytic
- Infected, Epithelial-Response
- Proteobacteria-Neutrophilic
- Th2-High

	Diverse/Th2 endotype
Microbiome	SWDI % of Firmicutes ↑
Proteome	IL-4, IL-5, GSN, EPX, CLC ↑

	Infected/epithelial response endotype
Microbiome	SWDI ↑
Proteome	MUC5AC/MUC5B, ↑ SLPI, IgJ, PIGR ↑

COPD
Bronchiectasis
The "COPD-BE association"



	Diverse/protective endotype
Microbiome	SWDI % of Firmicutes ↑
Proteome	MUC5AC/MUC5B ↓ Protease inhibitors ↑ and Immunoglobulins ↑

	Proteobacteria/neutrophilic endotype
Microbiome	% of *Proteobacteria* ↑
Proteome	Neutrophil degranulation (ELANE, MPO, CAMP, etc.) ↑ MUC5AC/MUC5B ↑

	Haemophilus/proteolytic endotype
Microbiome	*Haemophilus* ↑
Proteome	MMP8 and MMP9 ↑ MUC5AC/MUC5B ↓

COPD–bronchiectasis overlap is characterized by neutrophilic inflammation, resembling bronchiectasis endotypes

Huang JT et al, Am J Respir Crit Care Med. 2022 Aug 15;206(4):417-426.

Endotyping

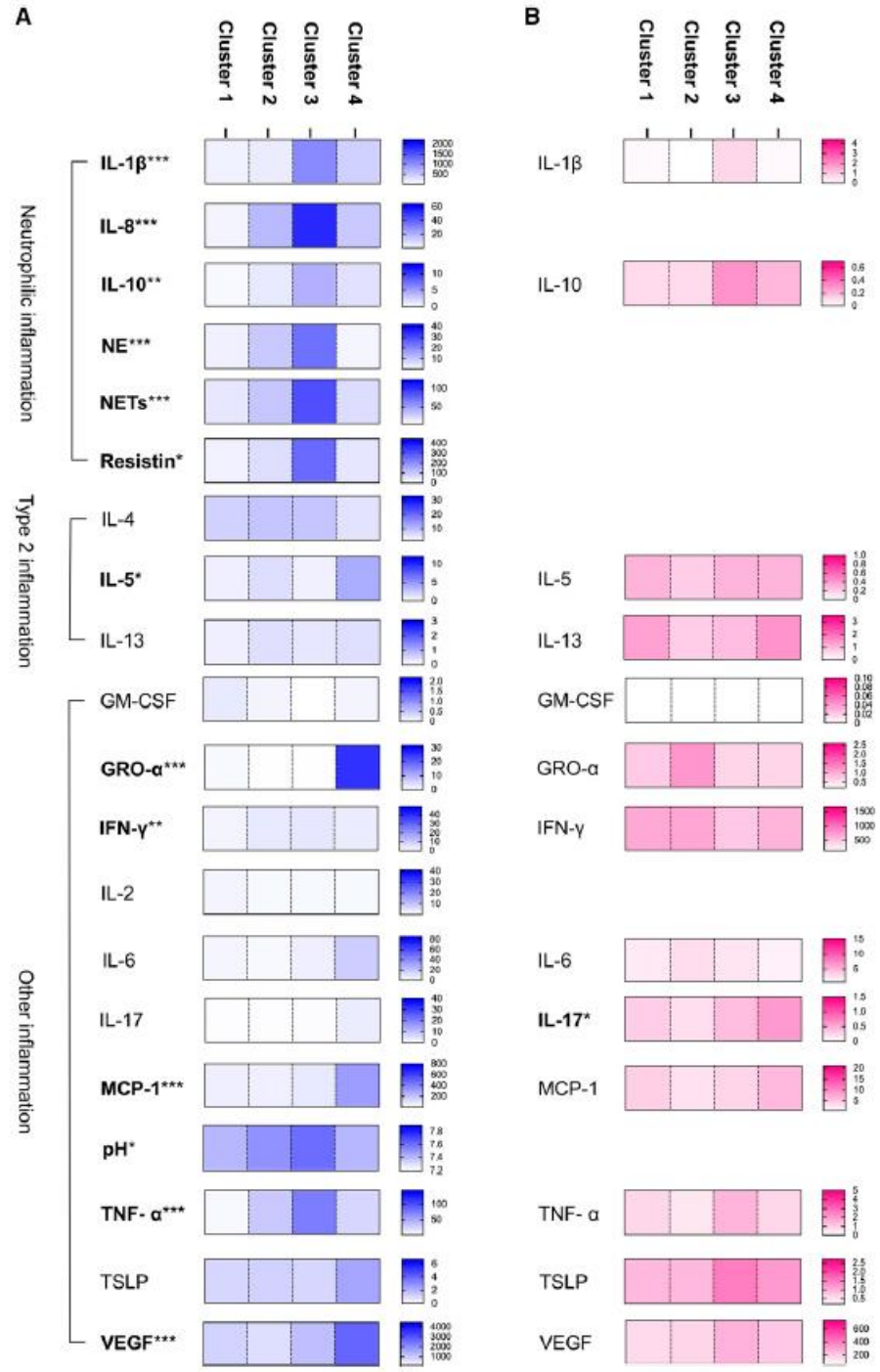
Inflammatory Molecular Endotypes in Bronchiectasis: A European Multicenter Cohort Study

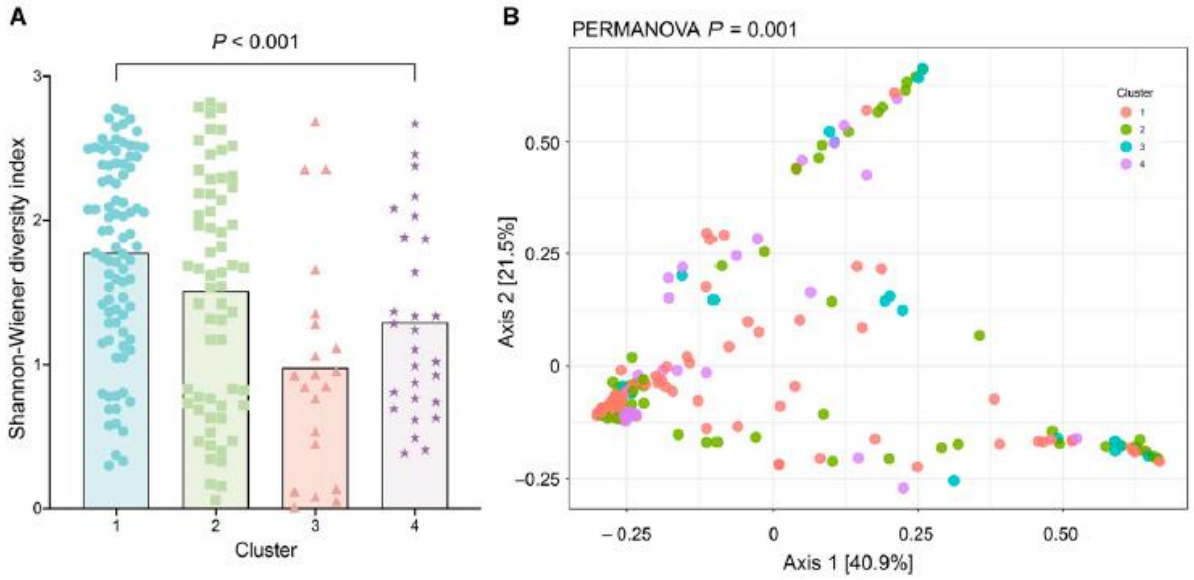
Hayoung Choi[1,3], Soorack Ryu[4], Holly R. Keir[1], Yan Hui Giam[1], Alison J. Dicker[1], Lidia Perea[1], Hollian Richardson[1], Jeffrey T. J. Huang[2], Erin Cant[1], Francesco Blasi[5,6], Jennifer Pollock[1], Michal Shteinberg[7], Simon Finch[1], Stefano Aliberti[8,9], Oriol Sibila[10], Amelia Shoemark[1], and James D. Chalmers[1]

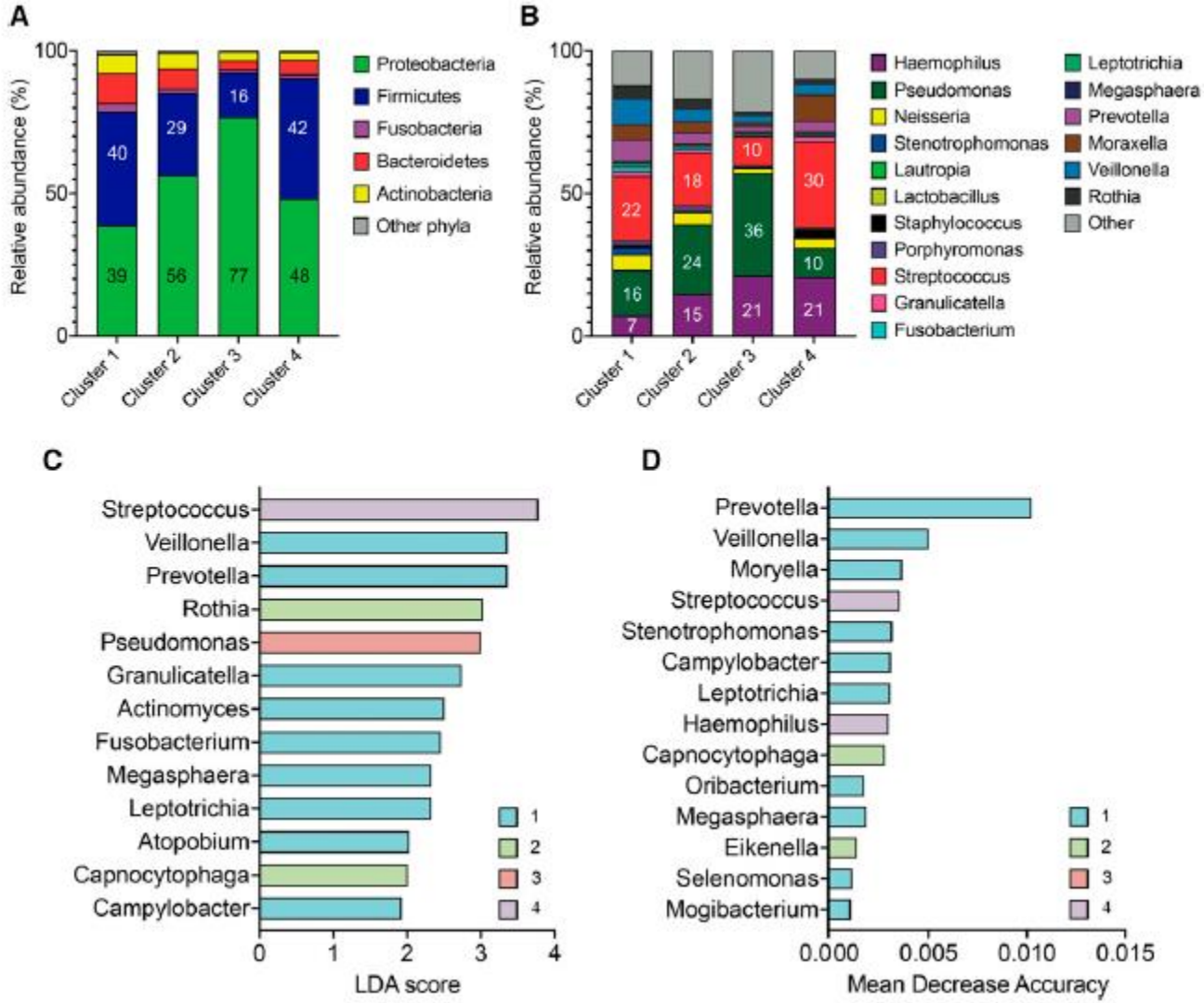
- EMBARC–BRIDGE Study (prospective observational cohort)
- Study population: Patients with stable bronchiectasis confirmed by CT
  + clinical features (cough, sputum, recurrent chest infections)
- Hypothesis: Distinct inflammatory endotypes exist in bronchiectasis
- Clinical data: demographics, smoking history, lung function, exacerbations, BSI
- Inflammatory markers:
  - Sputum: 20 markers (e.g., GM-CSF, IL-1β, IL-6, IL-8, neutrophil elastase, NETs)
  - Serum: 13 markers (e.g., GM-CSF, IL-6, IL-10, VEGF)
- Microbiome: Sputum 16S rRNA sequencing; assessed α-diversity and β-diversity

Choi H et al. Am J Respir Crit Care Med. 2023 Dec 1;208(11):1166-1176.

Characteristic	Total (n = 199; 100%)	Cluster 1: Milder Neutrophilic (n = 88; 44.2%)	Cluster 2: Mixed-Neutrophilic and Type 2 (n = 62; 31.2%)	Cluster 3: Most Severe Neutrophilic (n = 21; 10.6%)	Cluster 4: Mixed-Epithelial and Type 2 (n = 28; 14.0%)	P Value
Age, yr, median (IQR)	69 (61–77)	70 (62–77)	68 (62–78)	67 (61–76)	67 (62–76)	0.91
Female, *n* (%)	109 (54.8)	54 (61.4)	31 (50.0)	10 (47.6)	14 (50.0)	0.42
Inhaled corticosteroid use, *n* (%)	113 (56.8)	48 (54.6)	39 (62.9)	12 (57.1)	14 (50.0)	0.65
Oral antibiotic use, *n* (%)	46 (23.1)	25 (28.4)	11 (17.7)	6 (28.6)	4 (14.3)	0.27
Inhaled antibiotic use, *n* (%)	25 (12.6)	12 (13.6)	6 (9.7)	6 (28.6)	1 (3.6)	0.070
MRC dyspnea scale, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (2–3)	2 (2–4)	0.19
Smoking status, *n* (%)						
Never smoker	117 (58.8)	53 (60.2)	35 (56.5)	14 (66.7)	15 (53.6)	0.91
Ex-smoker	72 (36.2)	32 (36.4)	23 (37.1)	6 (28.6)	11 (39.3)	
Current smoker	10 (5.0)	3 (3.4)	4 (6.4)	1 (4.7)	2 (7.1)	
Smoking pack-years, *n* (%)						
<10	12 (6.0)	6 (6.8)	4 (6.5)	0 (0)	2 (7.1)	0.34
10–20	19 (9.5)	9 (10.2)	5 (8.1)	3 (14.3)	2 (7.1)	
21–40	24 (12.1)	8 (9.1)	6 (9.7)	3 (14.3)	7 (25.0)	
⩾40	15 (7.5)	8 (9.1)	5 (8.1)	0 (0)	2 (7.1)	
Not reported	12 (6.0)	4 (4.5)	7 (11.3)	1 (4.7)	0 (0)	
Exacerbation frequency, median (IQR)	2 (1–3)	2 (1–3)	3 (1–4)	2 (1–2)	2 (1–3)	0.035
Exacerbation group, *n* (%)						
0	31 (15.6)	15 (17.1)	6 (9.7)	3 (14.3)	7 (25.0)	0.17
1	46 (23.1)	19 (21.6)	13 (21.0)	7 (33.3)	7 (25.0)	
2	40 (20.1)	17 (19.3)	10 (16.1)	7 (33.3)	6 (21.4)	
⩾3	84 (41.2)	37 (42.0)	33 (53.2)	4 (19.1)	8 (28.6)	
History of hospitalization, *n* (%)	26 (13.1)	10 (11.4)	7 (11.3)	4 (19.1)	5 (17.9)	0.59
FEV_1, % predicted, *n* (%)						
⩾80	61 (30.7)	32 (36.4)	14 (22.6)	6 (28.6)	9 (32.1)	0.49
50–79	100 (50.3)	41 (46.6)	36 (58.1)	9 (42.9)	14 (50.0)	
30–49	31 (15.6)	11 (12.5)	11 (17.7)	4 (19.1)	5 (17.9)	
<30	7 (3.4)	4 (4.5)	1 (1.6)	2 (9.4)	0 (0)	
BSI, median (IQR)	7 (4–10)	7 (4–10)	8 (5–11)	8 (4–12)	5 (4–8)	0.15
BSI group, *n* (%)						
Mild	55 (27.6)	25 (28.4)	13 (21.0)	6 (28.6)	11 (39.3)	0.46
Moderate	71 (35.7)	32 (36.4)	22 (35.5)	6 (28.6)	11 (39.3)	
Severe	73 (36.7)	31 (35.2)	27 (43.5)	9 (42.8)	6 (21.4)	







Endotype → Distinct airway microbiome

Choi H et al. Am J Respir Crit Care Med. 2023 Dec 1;208(11):1166-1176.

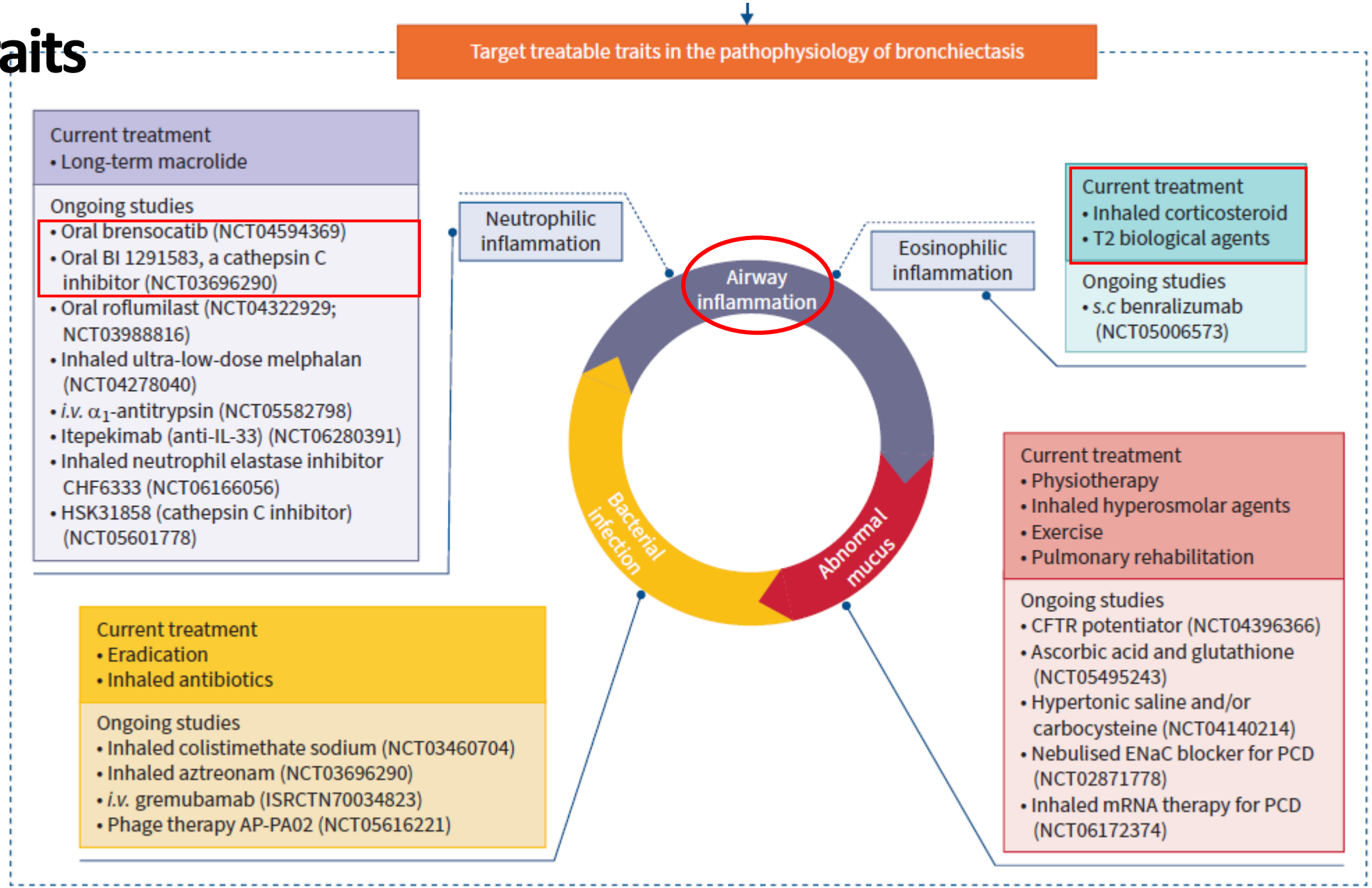
Table 3. Unadjusted and Adjusted Incident Rate Ratios for Exacerbation Frequency over a 12-Month Follow-Up according to Inflammatory Clusters

Cluster	Exacerbation		Severe Exacerbation	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Unadjusted analysis				
1	1.0 (Reference)		1.0 (Reference)	
2	1.53 (1.19–1.97)	0.001	2.53 (1.25–5.14)	0.010
3	1.46 (1.02–2.09)	0.039	3.21 (1.35–7.61)	0.008
4	1.15 (0.80–1.64)	0.45	1.12 (0.36–3.47)	0.84
Adjusted analysis*				
1	1.0 (Reference)	—	1.0 (Reference)	—
2	1.49 (1.16–1.92)	0.002	2.46 (1.21–5.00)	0.013
3	1.61 (1.12–2.32)	0.010	2.81 (1.18–6.68)	0.019
4	1.28 (0.89–1.83)	0.19	0.99 (0.32–3.07)	0.99

Definition of abbreviations: CI = confidence interval; IRR = incident rate ratio.
*Adjusted for prior exacerbation history (exacerbation analysis) and prior severe exacerbation (severe exacerbation analysis).

Choi H et al. Am J Respir Crit Care Med. 2023 Dec 1;208(11):1166-1176.

Treatable traits



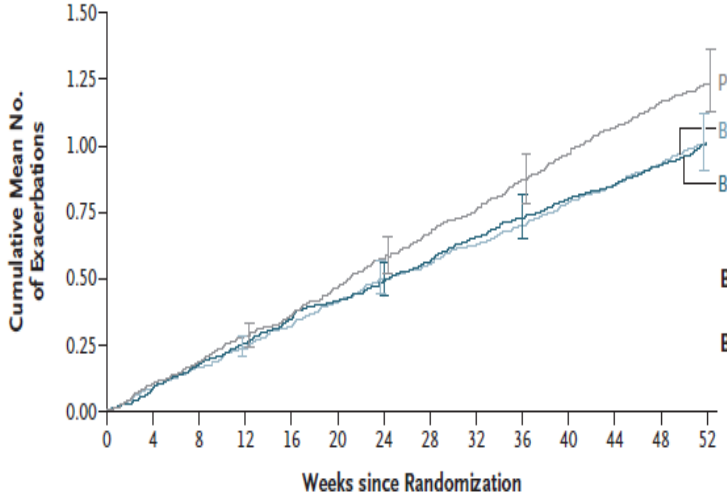
Choi H et al. Eur Respir J. 2024 Jun 28;63(6):2400518.

Neutrophilic inflammation – ASPEN (Brensocatib)

- Dipeptidyl peptidase-1 (DPP-1) activates neutrophil serine proteases (NSPs)
  (neutrophil elastase, proteinase-3, cathepsin G)
- **Brensocatib** is an oral, reversible DPP-1 inhibitor
  Reduces neutrophil protease activation, aiming to decrease airway inflammation and exacerbations
- **Patients:** CT-confirmed non-CF bronchiectasis and ≥2 exacerbations in the prior year
  Excluded current smokers and COPD
- **Intervention:** Brensocatib 10 mg, 25 mg, or placebo once daily for 52 weeks.
- **Primary endpoint:** Annualized rate of pulmonary exacerbations
- **Key secondary endpoints:** Time to first exacerbation, proportion of exacerbation-free patients, FEV_1 decline, severe exacerbations, and quality of life (QOL-B)

Chalmers JD et al. N Engl J Med. 2025 Apr 24;392(16):1569-1581.

A Exacerbations over the 52-Wk Treatment Period

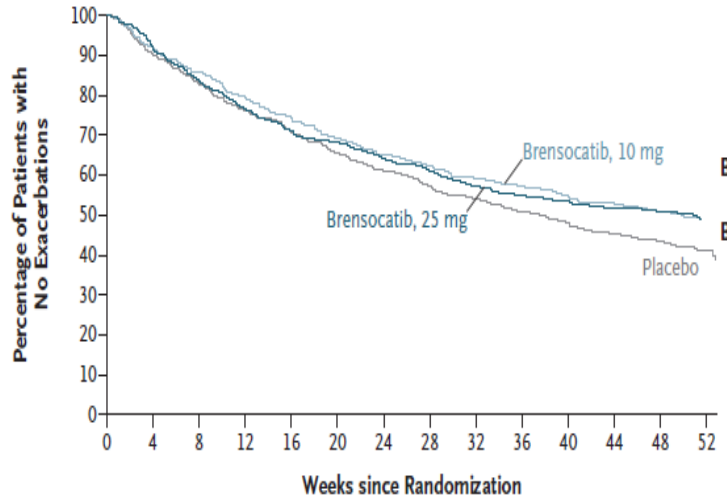


	Rate Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	0.79 (0.68 to 0.92)	0.004
Brensocatib, 25 mg (N=575)	0.81 (0.69 to 0.94)	0.005
Placebo (N=563)	—	—

No. at Risk

Brensocatib, 10 mg	583	582	582	576	570	565	564	555	546	540	533	529	522	516
Brensocatib, 25 mg	575	572	568	566	563	552	550	543	540	537	528	523	520	515
Placebo	563	562	556	551	547	544	539	534	529	522	519	509	507	499

B Time to the First Pulmonary Exacerbation

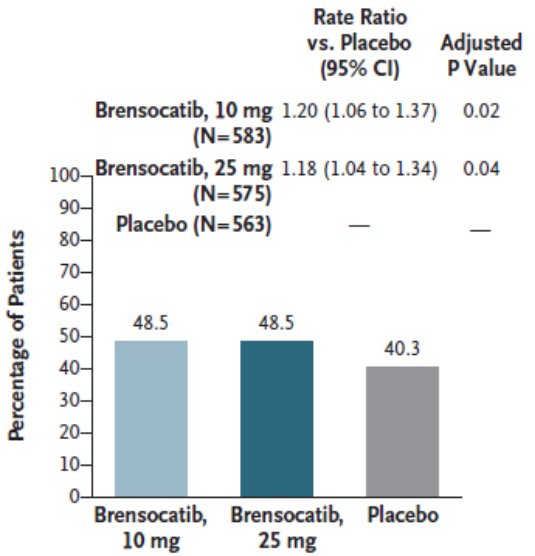


	Hazard Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	0.81 (0.70 to 0.95)	0.02
Brensocatib, 25 mg (N=575)	0.83 (0.70 to 0.97)	0.04
Placebo (N=563)	—	—

No. at Risk

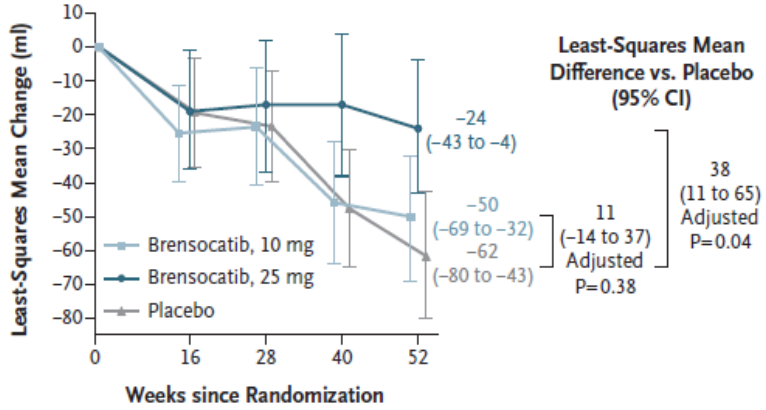
Brensocatib, 10 mg	583	537	498	459	427	393	367	346	322	310	292	280	265	183
Brensocatib, 25 mg	575	526	475	433	400	380	357	337	313	296	282	270	264	169
Placebo	563	506	461	417	386	354	328	303	281	261	245	228	217	154

C Exacerbation-free during the Treatment Period



	Rate Ratio vs. Placebo (95% CI)	Adjusted P Value
Brensocatib, 10 mg (N=583)	1.20 (1.06 to 1.37)	0.02
Brensocatib, 25 mg (N=575)	1.18 (1.04 to 1.34)	0.04
Placebo (N=563)	—	—

D Change in Postbronchodilator FEV_1 from Baseline



No. with Data

Brensocatib, 10 mg	579	545	529	513	475
Brensocatib, 25 mg	571	529	523	494	487
Placebo	563	522	513	494	468

- **Annualized exacerbation rate↓**
- Time to first exacerbation
  - HR: 0.81 (10 mg) and 0.83 (25 mg) vs placebo (p = 0.02 and 0.04)
- Exacerbation-free patients at 52 weeks
  - Placebo: 40.3%
  - Brensocatib (both doses): 48.5%
- **Lung function (FEV_1)**
  - Brensocatib 25 mg slowed decline: +38 mL vs placebo (p = 0.04)
  - 10 mg: no significant difference
- **Safety**: Overall adverse events: similar between groups

Chalmers JD et al. N Engl J Med. 2025 Apr 24;392(16):1569-1581.

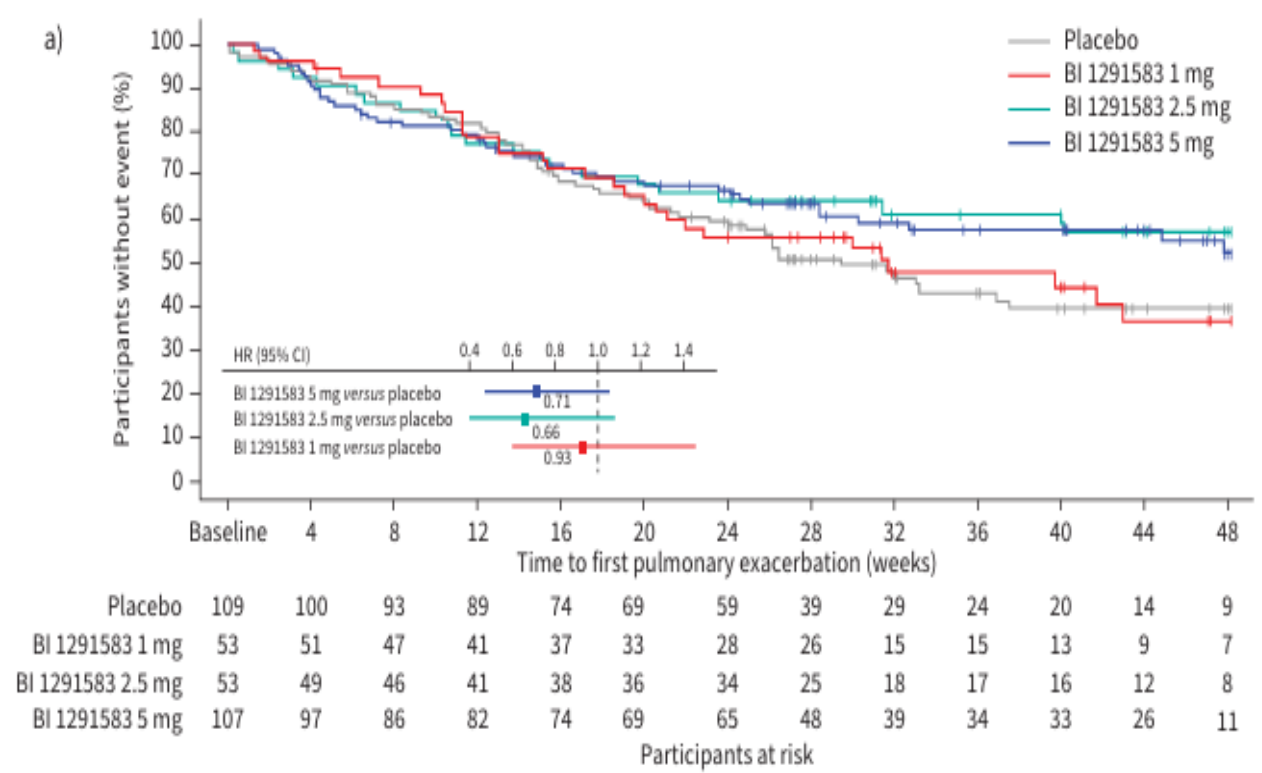
Neutrophilic inflammation – AIRLEAF (BI 1291583)

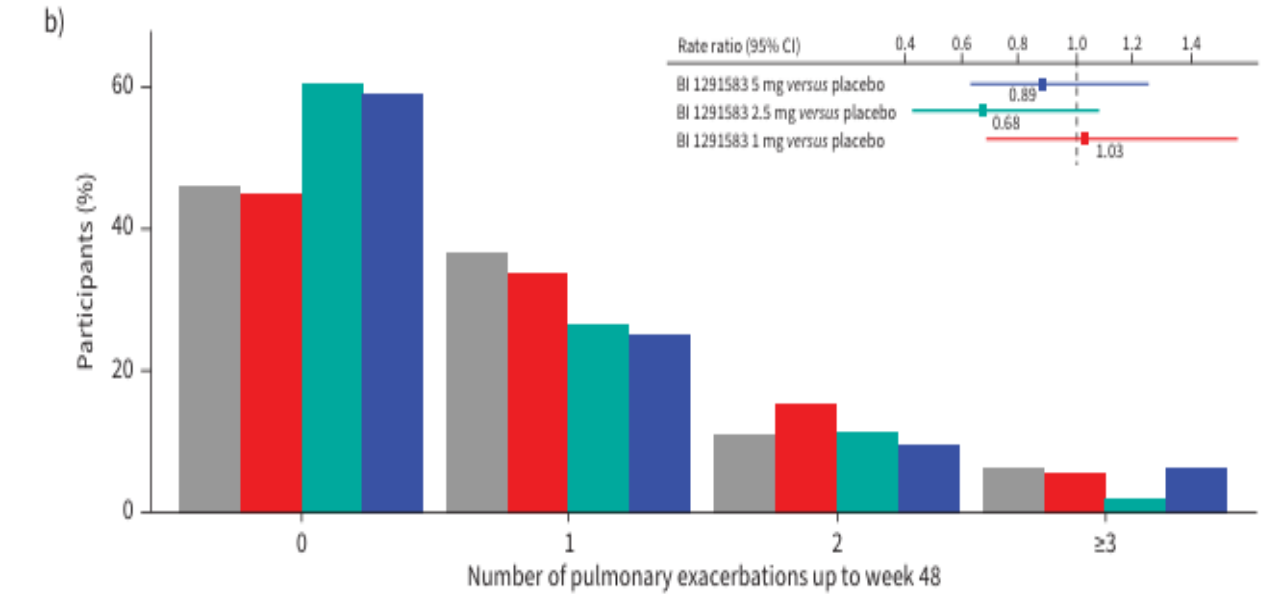
- BI 1291583: oral cathepsin-C/DPP1 inhibitor
- **Patients**: Adults with non-CF bronchiectasis, sputum-producing, with a recent history of exacerbation
- **Intervention**: BI 1291583 1 mg(N=53), 2.5 mg (N=53), or 5 mg (107) vs placebo (109),

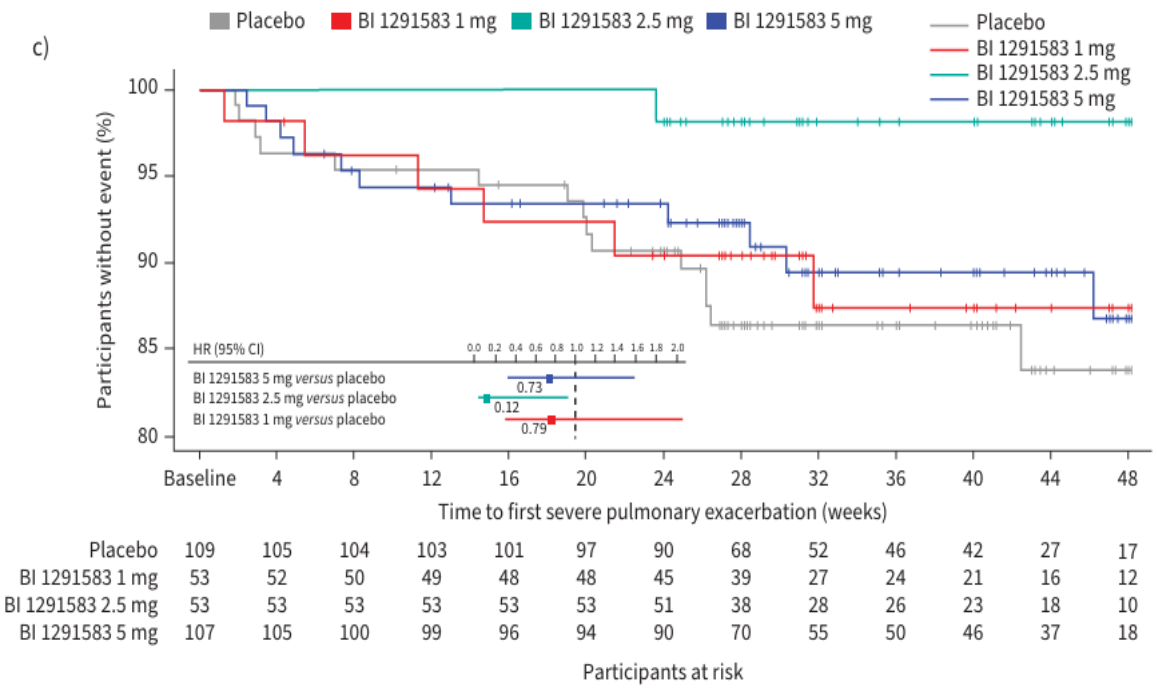
  24–48 weeks
- **Primary endpoint**: Time to first bronchiectasis exacerbation up to 48 weeks

  (5mg vs placebo)
- **Secondary endpoint**: Rate of exacerbation, Change of QOL-B, SGRQ, FEV_1

Chalmers JD et al. Eur Respir J. 2025 Jan 2;65(1):2401551.





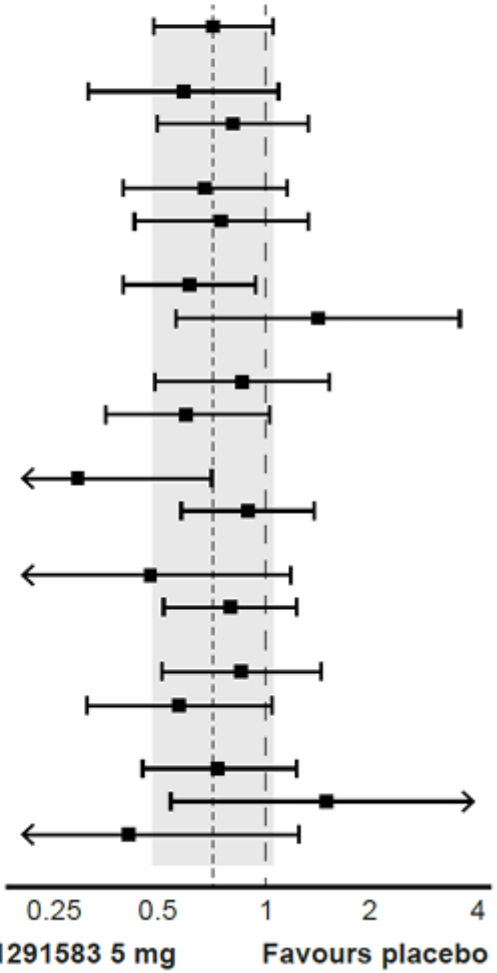


- Significant **dose-dependent benefit** for time to first pulmonary exacerbation (Emax model, p=0.0448)
- **Primary comparison** (5 mg vs placebo): HR 0.71
  95% CI 0.48–1.05; *p*=0.0857
- **SGRQ** Total responders (≥4-point improvement at wk 24):
  2.5 mg: 62.7%
- **QoL-B** (≥8-point improvement at wk 24): 5 mg (47.5%)
- **FEV_1 change**: 2.5 mg: +52.4 mL (wk 24), +78.4 mL (wk 36), +47.7 mL (wk 48)

Chalmers JD et al. Eur Respir J. 2025 Jan 2;65(1):2401551.

Supplementary figure S2. Forest plot of subgroup analyses for the primary endpoint (time to first pulmonary exacerbation up to Week 48) for BI 1291583 5 mg versus placebo

Parameter	Events/n		HR (95% CI)
	Placebo	BI 1291583 5 mg	
Overall model	59/109	44/107	0.71 (0.48–1.05)
Sex			
Male	24/42	17/43	0.58 (0.31–1.09)
Female	35/67	27/64	0.81 (0.49–1.34)
Age			
<65 years	31/54	23/55	0.67 (0.39–1.15)
≥65 years	28/55	21/52	0.75 (0.42–1.32)
Age			
<75 years	51/89	34/87	0.61 (0.39–0.94)
≥75 years	8/20	10/20	1.41 (0.56–3.59)
P. aeruginosa status			
Positive	24/37	23/38	0.86 (0.48–1.53)
Negative	35/72	21/69	0.60 (0.35–1.03)
Maintenance use of macrolides			
Yes	15/20	7/21	0.29 (0.12–0.72)
No	44/89	37/86	0.89 (0.57–1.38)
History of pulmonary exacerbations			
1	13/29	7/33	0.47 (0.19–1.19)
≥2	46/80	37/74	0.79 (0.51–1.23)
Aetiology			
Idiopathic or post-infectious	30/67	28/69	0.85 (0.50–1.43)
All other aetiologies	29/42	16/38	0.57 (0.31–1.04)
Geographical region			
Western Europe, North/South America, Other	41/71	27/57	0.74 (0.45–1.22)
Eastern Europe	5/19	13/37	1.50 (0.53–4.20)
Asia	13/19	4/13	0.40 (0.13–1.24)



Chalmers JD et al. Eur Respir J. 2025 Jan 2;65(1):2401551.

Eosinophilic inflammation

The U-Shaped Relationship Between Eosinophil Count and Bronchiectasis Severity

The Effect of Inhaled Corticosteroids

Miguel Ángel Martínez-García, MD; Raúl Méndez, MD; Casilda Olveira, MD; Rosa Girón, MD; Marta García-Clemente, MD; Luis Máiz, MD; Oriol Sibila, MD; Rafael Golpe, MD; Juan Luis Rodríguez-Hermosa, MD; Esther Barreiro, MD; Concepción Prados, MD; Juan Rodríguez-López, MD; Grace Oscullo, MD; Gonzalo Labarca, MD; and David de la Rosa, MD

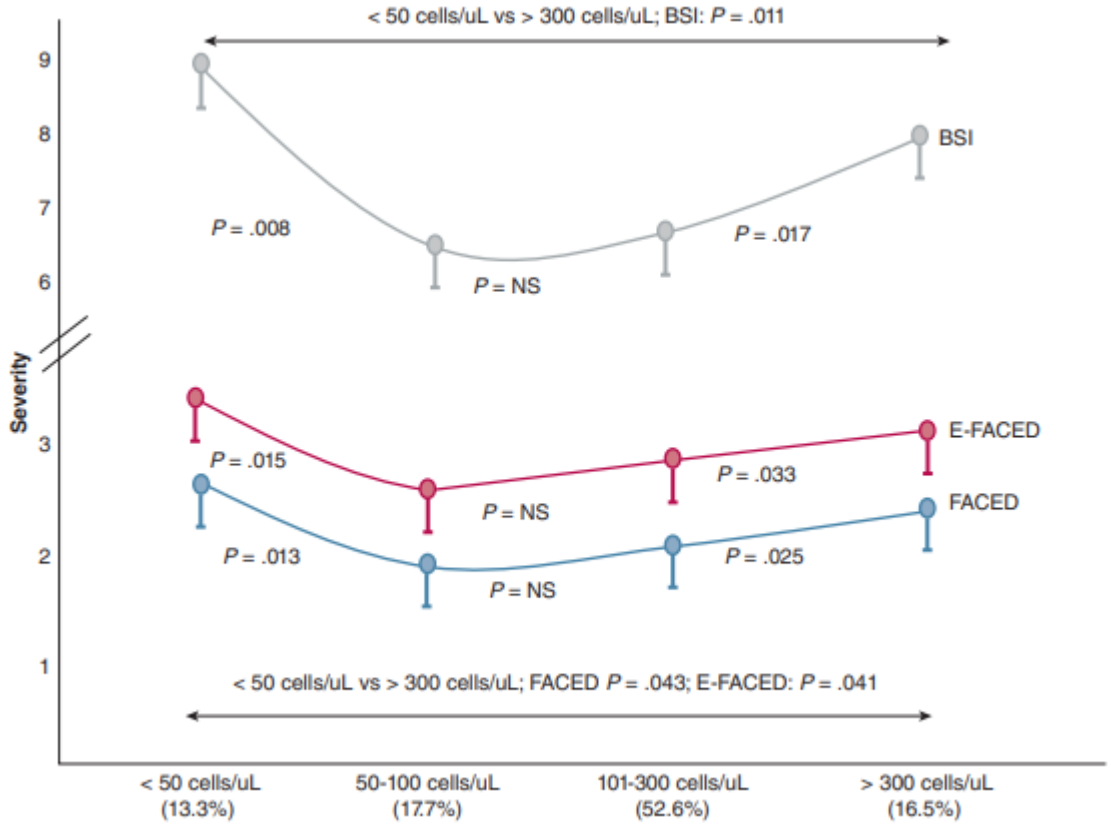
- A multicenter prospective observational study (Spanish Bronchiectasis Registry)
- Patients: Stable bronchiectasis patients confirmed by CT (928 pts)
- Patients group: Eosinopenic (<50), Low (51-100), Normal (101-300), Eosinophilic (>300)
- Clinical outcome: Severity, Number of exacerbation, Chronic infection, Effect of ICS

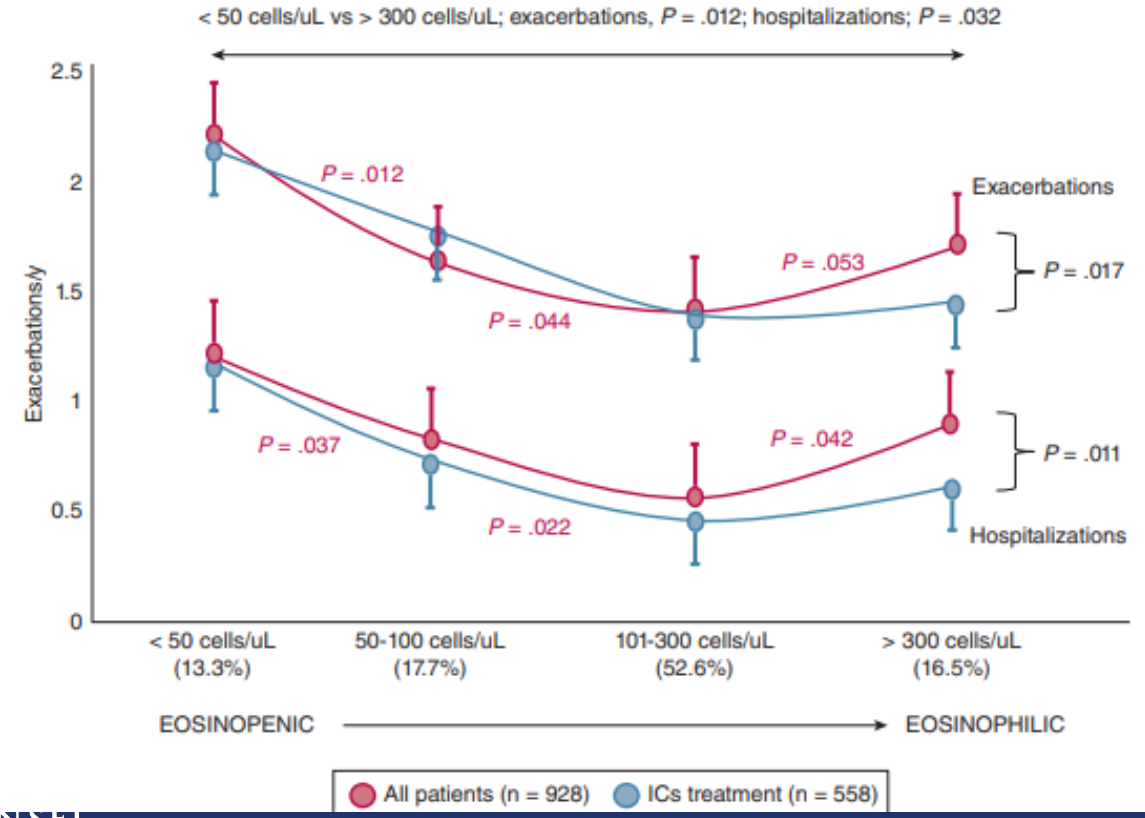
→BEC>300: 153 patients (16.5%)

Martínez-García MÁ et al. Chest. 2023 Sep;164(3):606-613.

Eosinophilic inflammation

- Both **eosinopenia (<50)** and **eosinophilia (>300)** were associated with **greater disease severity**
- Higher number (P=0.012) and severity (P=0.032) of exacerbations in eosinopenia
- Eosinophilic group (>300): ICS significantly reduced exacerbations





Martínez-García MÁ et al. Chest. 2023 Sep;164(3):606-613.

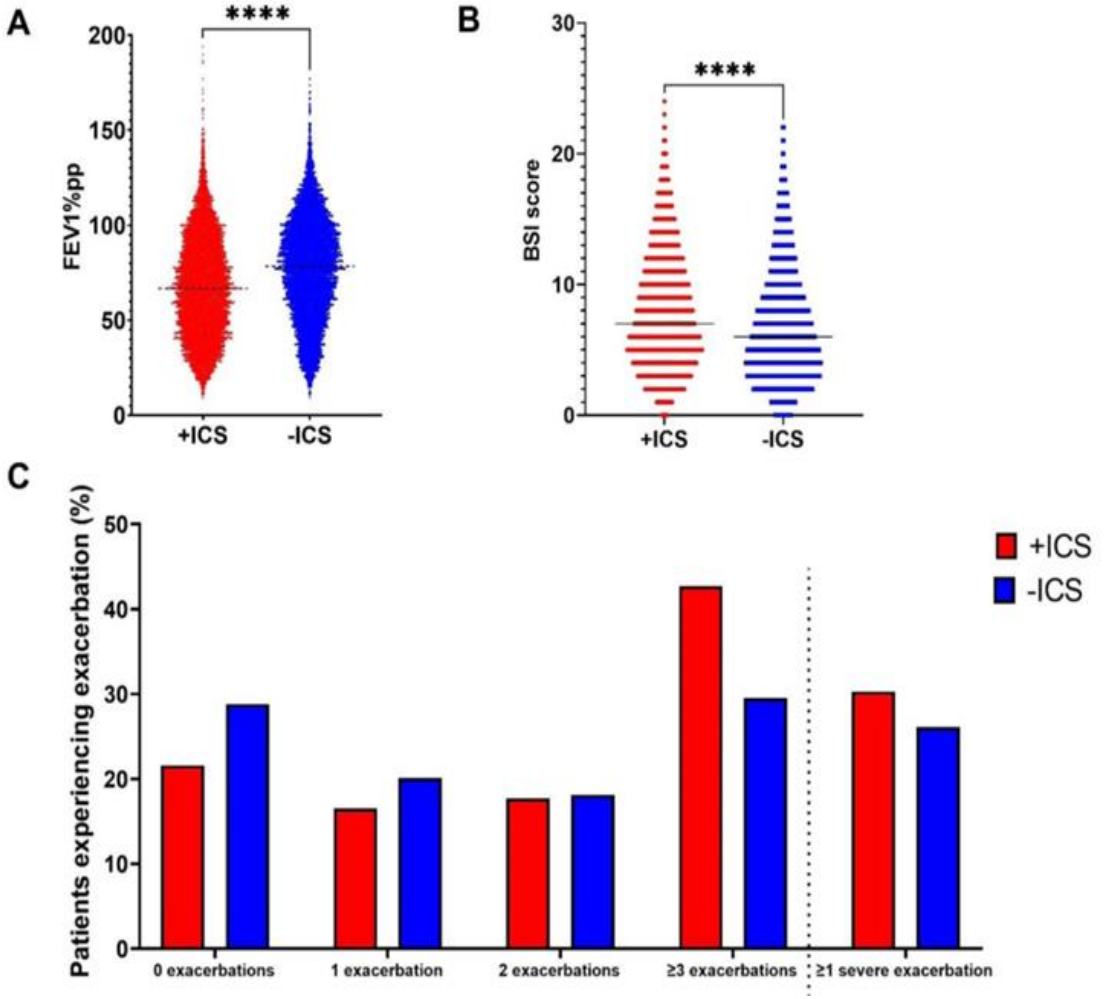
Eosinophilic inflammation

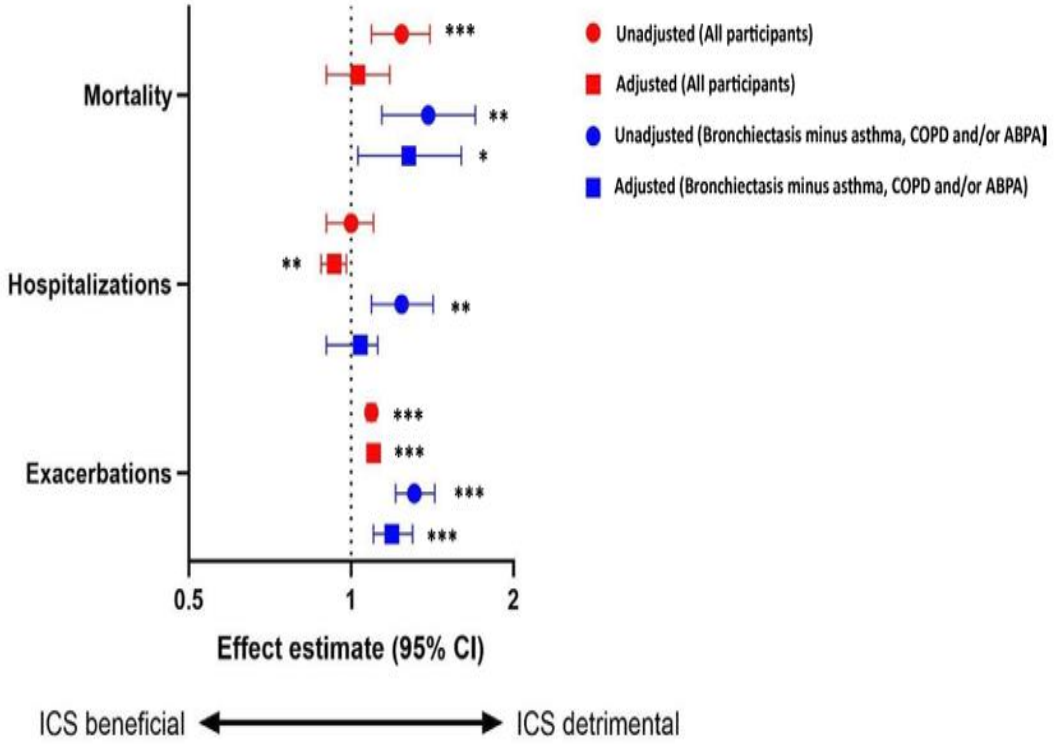
Original research

Use of inhaled corticosteroids in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC)

- Real-world use of inhaled corticosteroids (ICS) in bronchiectasis patients (19324 pts.)
- **Evaluate the association between ICS use and clinical outcomes in bronchiectasis**
  - Exacerbation rates
  - Hospitalizations
  - Mortality
- Overall, 52.3% (10,109/19,324) were on ICS at baseline
- Even after excluding patients with asthma, ABPA, and/or COPD: 32.7% (3,174/9,715)

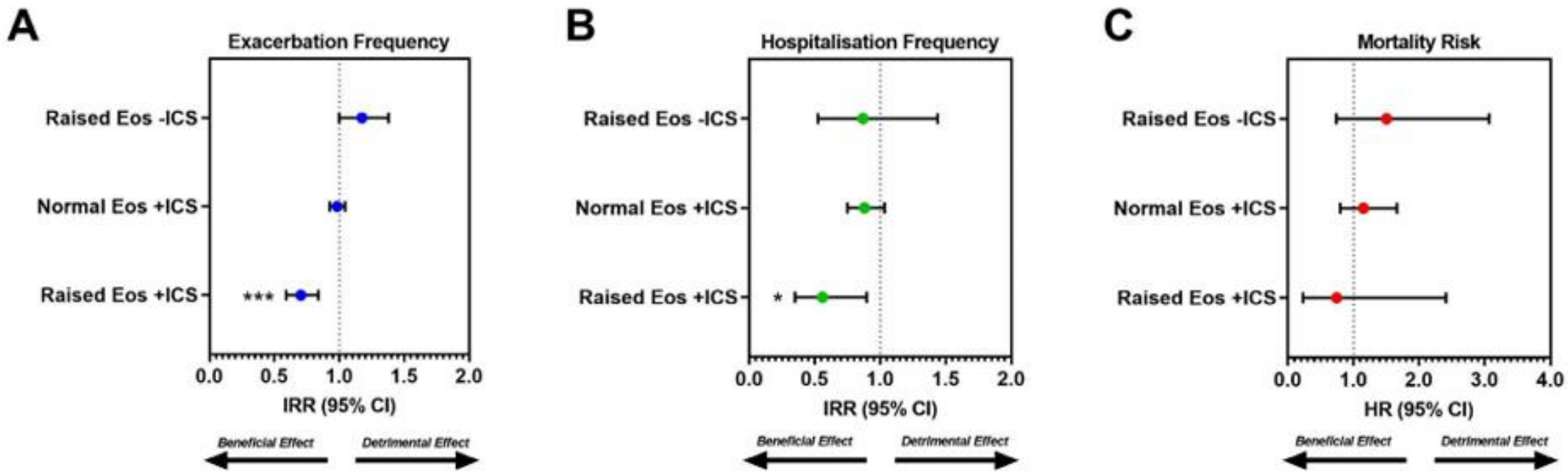
Pollock J et al. Thorax 2025;80:358-368.





- **ICS users** had more severe disease compared to non-users
  - **Worse lung function** (lower FEV_1)
  - **Higher Bronchiectasis Severity Index (BSI)**
  - **More frequent exacerbations** at baseline ($p < 0.0001$)

Pollock J et al. Thorax 2025;80:358-368..



Subgroup with elevated blood eosinophils (above upper limit of normal)

ICS use was associated with a significant reduction in exacerbation frequency—relative risk (RR) = 0.70 ($p < 0.001$)

Pollock J et al. Thorax 2025;80:358-368..

Eosinophilic inflammation – biologics

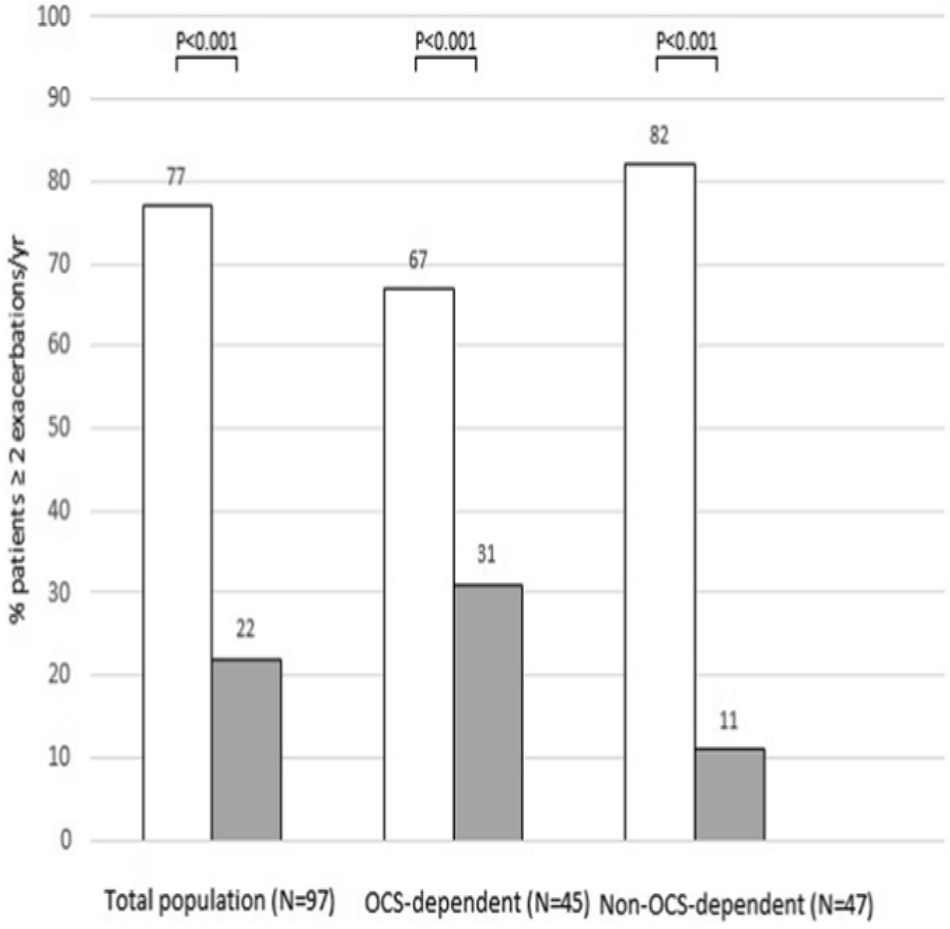
Original Article

Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis

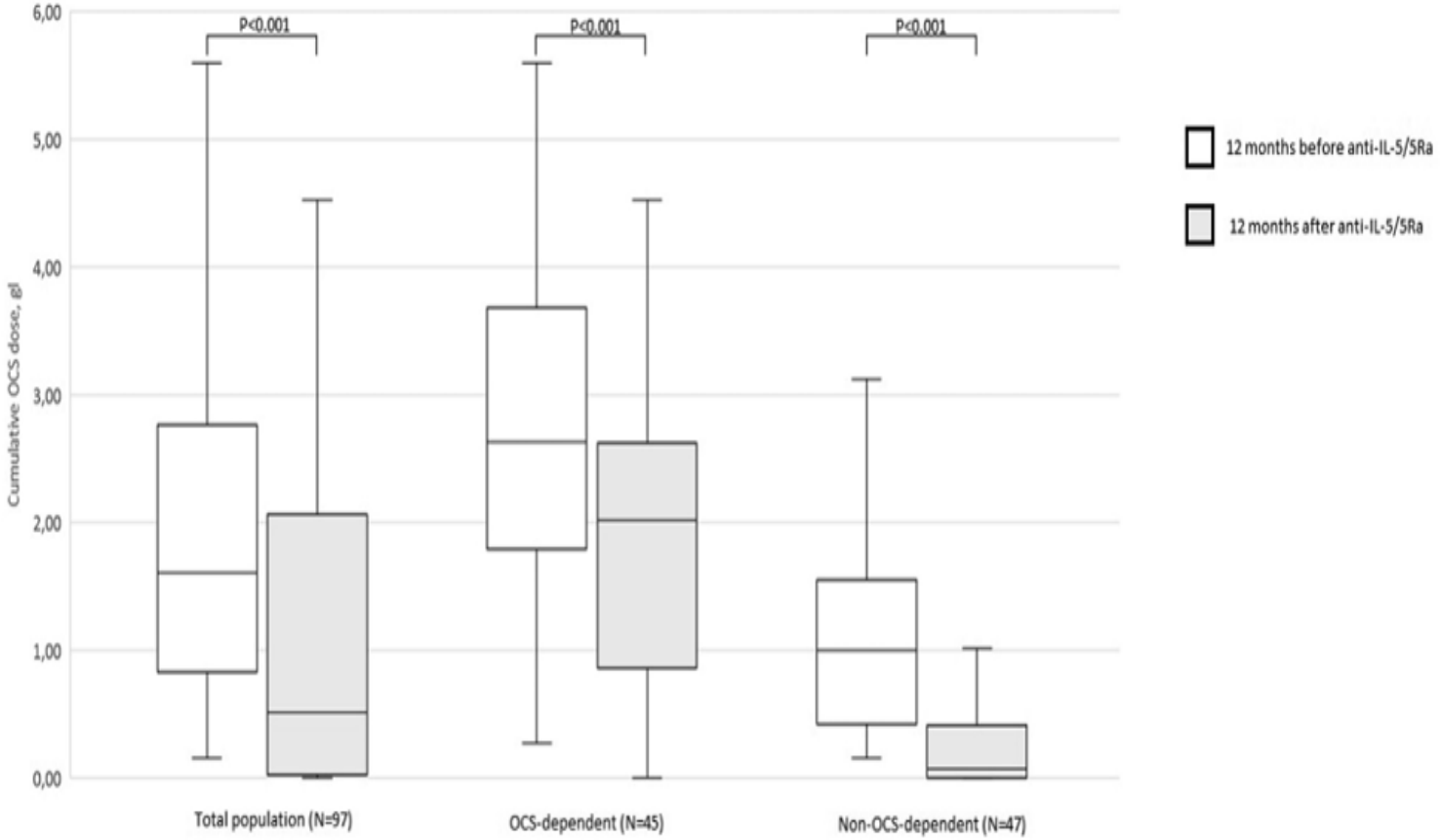
- Retrospective multicenter real-world study (Netherlands RAPSODI registry)
- Sample size: 97 patients with Severe eosinophilic asthma + CT-confirmed bronchiectasis
- Baseline characteristics:
  - Frequent exacerbations
  - Many on long-term oral corticosteroids (OCS)
  - Heterogeneous bronchiectasis severity
- Patients received IL-5/IL-5Rα biologics, Follow-up: ≥12 months
- Outcomes
  - Exacerbation frequency
  - OCS use and dosage
  - Lung function (FEV_1)
  - Safety

Bendien SA et al. J Allergy Clin Immunol Pract. 2023 Sep;11(9):2724-2731.

Eosinophilic inflammation – biologics



Exacerbations: ≥2/year fell from 77% → 22%



Maintenance OCS: 47% → 30% (P<0.001)
In OCS-dependent pts (N=45): daily dose 10 mg → 2.5 mg

Bendien SA et al. J Allergy Clin Immunol Pract. 2023 Sep;11(9):2724-2731.

Upcoming study

- Oral BI1291583 (AIRTIVITY trial, Phase3): CatC inhibitor 2.5mg vs. placebo
  Primary outcome: Annualized rate of pulmonary exacerbations up to week 76
- Oral HSK31858 (SAVE-BE trial, Phase2): DPP-1 inhibitor 20mg vs. 40mg vs. placebo
  Primary outcome: annualized exacerbation requency over 24 weeks
- IV α_1-antitrypsin (BATMAN trial): Prolastin-C 120mg/kg, weekly vs. 180mg/kg vs. placebo
  Change from baseline in sputum neutrophil elastase activity

- MAHALE study: A multicenter, Phase3 RCT, Non-CF bronchicatsis
  Benralizumab: 30mg every 4 weeks vs. Placebo at least 28 weeks and up to 52 weeks
  Annualized bronchiectasis exacerbations rate

Chalmers JD et al. N Engl J Med. 2025 Apr 24;392(16):1569-1581.

Summary

- Inflammation drives bronchiectasis
- From phenotypes to endotypes
- Endotyping guides prognosis and treatment
- Precision therapies are emerging
- Future = Precision medicine guided by biomarkers

Pollock J et al. Thorax 2025;80:358-368..

YONSEI UNIVERSITY
COLLEGE OF MEDICINE