Dissecting bronchiectasis heterogeneity for personalized treatment

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양범희

Agenda

- Bronchiectasis heterogenicity
- Personalized medicine and appropriately targeting treatment
  - Targeting the neutrophil
  - Targeting the eosinophil
  - Immunomodulatory drugs
  - Targeting mucociliary clearance and cough
  - Multi-omics, and the microbiome
- Summary

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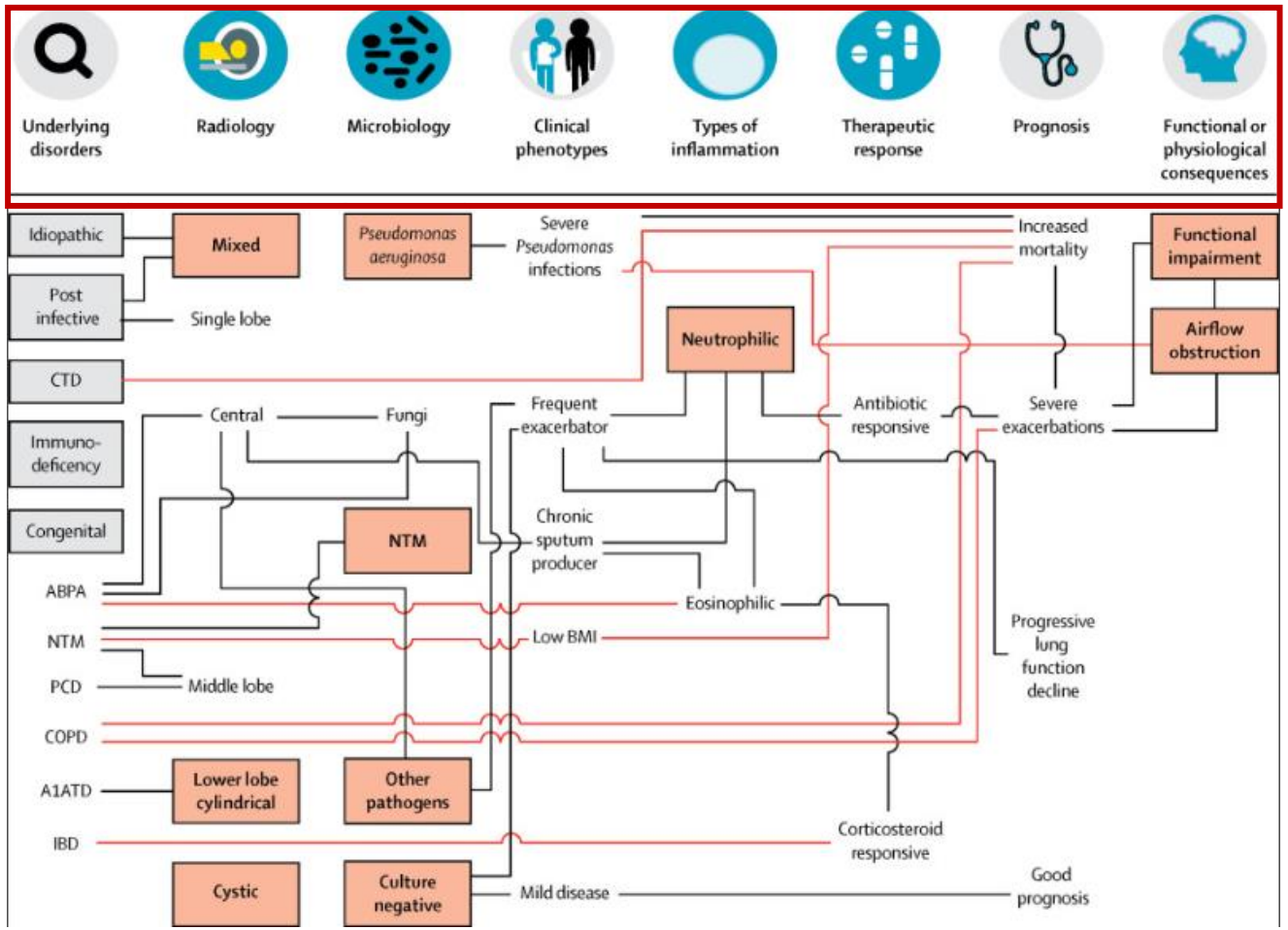
Heterogenous disease

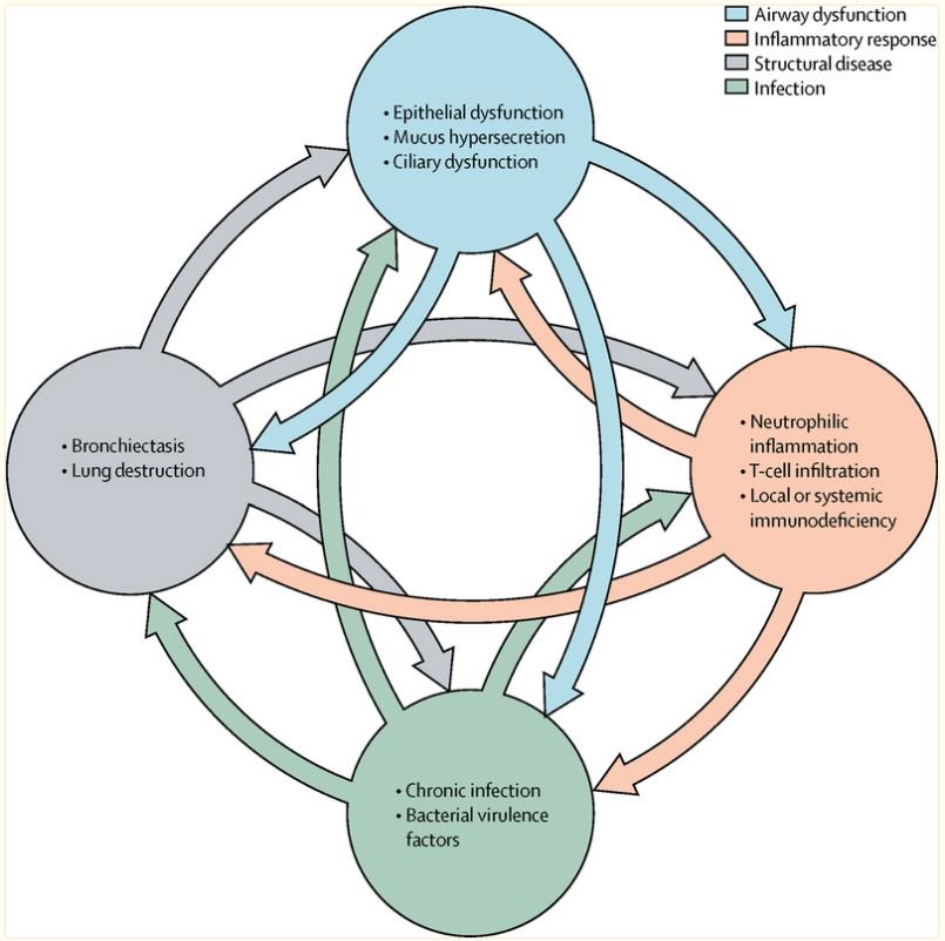
- **Geographic and ethnic variation** has been noted in the characteristics of patients with bronchiectasis.
  - Post-infectious-related disease has high prevalence in Asia
  - Bronchiectasis is common in indigenous populations in the Pacific region
  - Non-tuberculous mycobacteria is a great burden in North America
  - Idiopathic disease is predominant across Europe.

Important it is to learn about geographic and ethnic variations on patients' characteristics
Improve understanding of patients' subtypes and the clinical heterogeneity

Breathe (Sheff). 2016 Sep;12(3):222-235.

Heterogenous disease





Lancet Respir Med . 2022 Mar;10(3):298-306.
Lancet. 2018 Sep 8; 392(10150): 880–890.

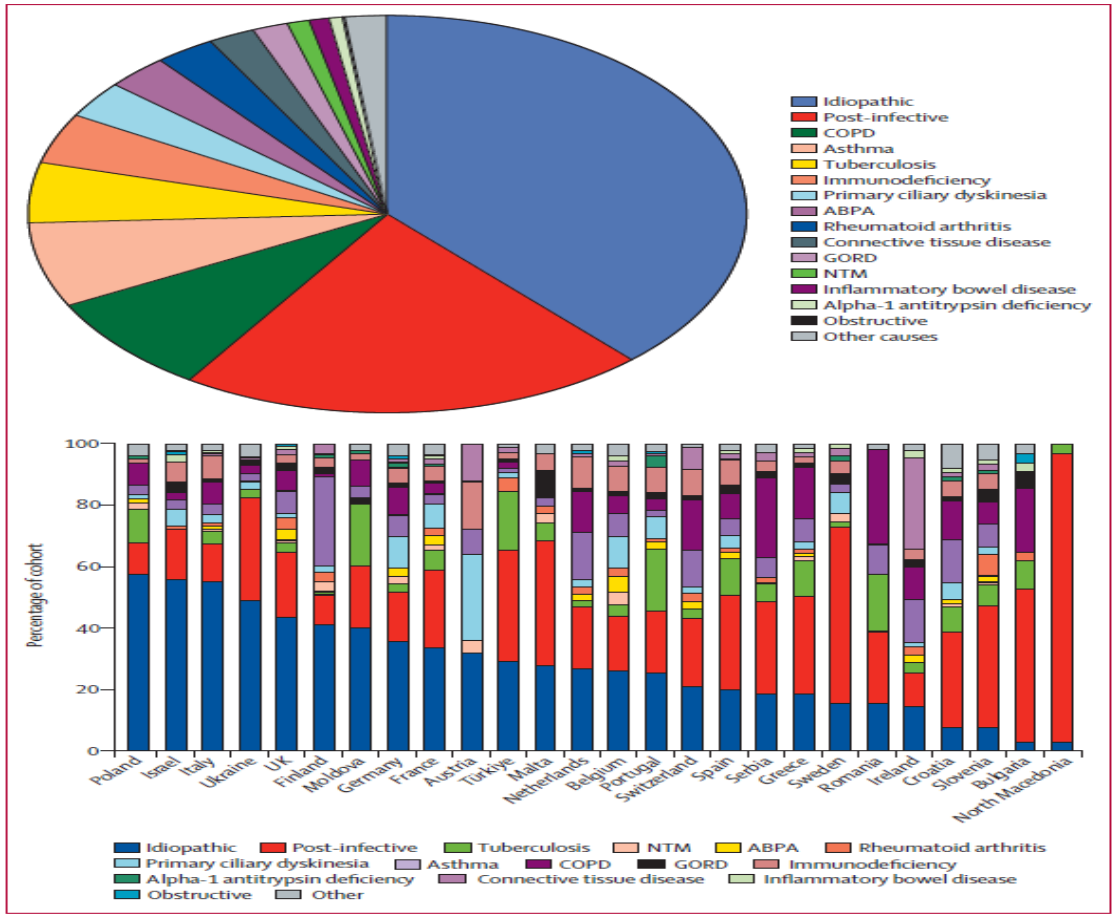
Geographic variation

	Korea (*n* = 598)	Australia (*n* = 653)	Europe[a] (*n* = 2596)	India[a] (*n* = 2195)
Age, years	66 (60–72)	73 (64–79)	67 (57–74)	56 (41–66)
Men	264 (44.1)	195 (29.9)	1010 (38.9)	1249 (56.9)
BMI, kg/m^2	22.9 (20.7–25.4)	25.0 (21.5–29.0)	24.8 (21.8–28.1)	21.5 (18.5–24.5)
Aetiology of bronchiectasis (top five in orders)				
First	Idiopathic (41%)	Idiopathic (29%)	Idiopathic (42%)	TB (36%)
Second	TB (20%)	Post-infective (27%)	Post-infective (17%)	Post-infective (22%)
Third	Post-infective (20%)	NTM (7%)	COPD (9%)	Idiopathic (21%)
Fourth	Asthma (5%)	PCD (4%)	Asthma (6%)	ABPA (9%)
Fifth	NTM (4%)	ABPA (4%)	Connective tissue diseases (6%)	COPD (5%)
Treatment				
Long-term antibiotics	23 (3.9)	205 (31.4)	503 (19.4)	271 (12.3)
Inhaled antibiotics	0	27 (4.1)	166 (6.4)	79 (3.6)

Heterogenous disease
Significant differences in the etiology, comorbidities and treatment of bronchiectasis among the different countries and regions

Respirology. 2021;26:618–620.

Bronchiectasis in Europe



- **Describe the clinical characteristics of bronchiectasis**
  - Four regions
    - **UK**
      Northern and western Europe
      Southern Europe
      Central and eastern Europe

Lancet Respir Med . 2023 Jul;11(7):637-649.

Microbiology of bronchiectasis in the EMBARC cohort

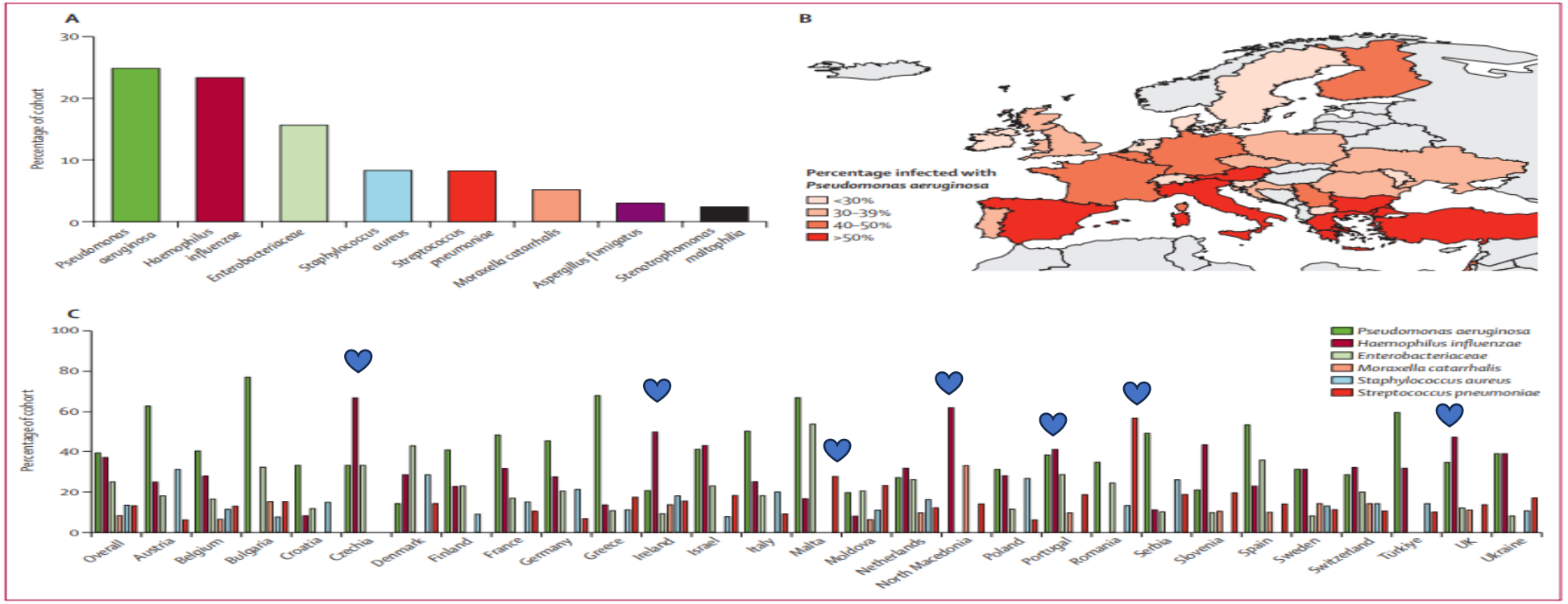


Figure 2: **Microbiology of bronchiectasis in the EMBARC cohort**
(A) Microbiology of the overall EMBARC cohort (n=16 963) showing the percentage of patients who isolated the most common pathogens; this analysis includes any isolation of the pathogen in either a sample taken when stable or at exacerbation (any sample). (B) Percentage of patients in different countries isolating *Pseudomonas aeruginosa* in any sample over the previous 1 year; the denominators are patients isolating at least one pathogenic microorganism during the previous year. (C) Percentage of patients in different countries from whom any one of the six most common pathogens or groups of pathogens was isolated from any sample over preceding 1 year; the denominators are patients from whom least one pathogenic microorganism was isolated from any sputum sample during the previous year.

Lancet Respir Med . 2023 Jul;11(7):637-649.

Severity of disease and exacerbations

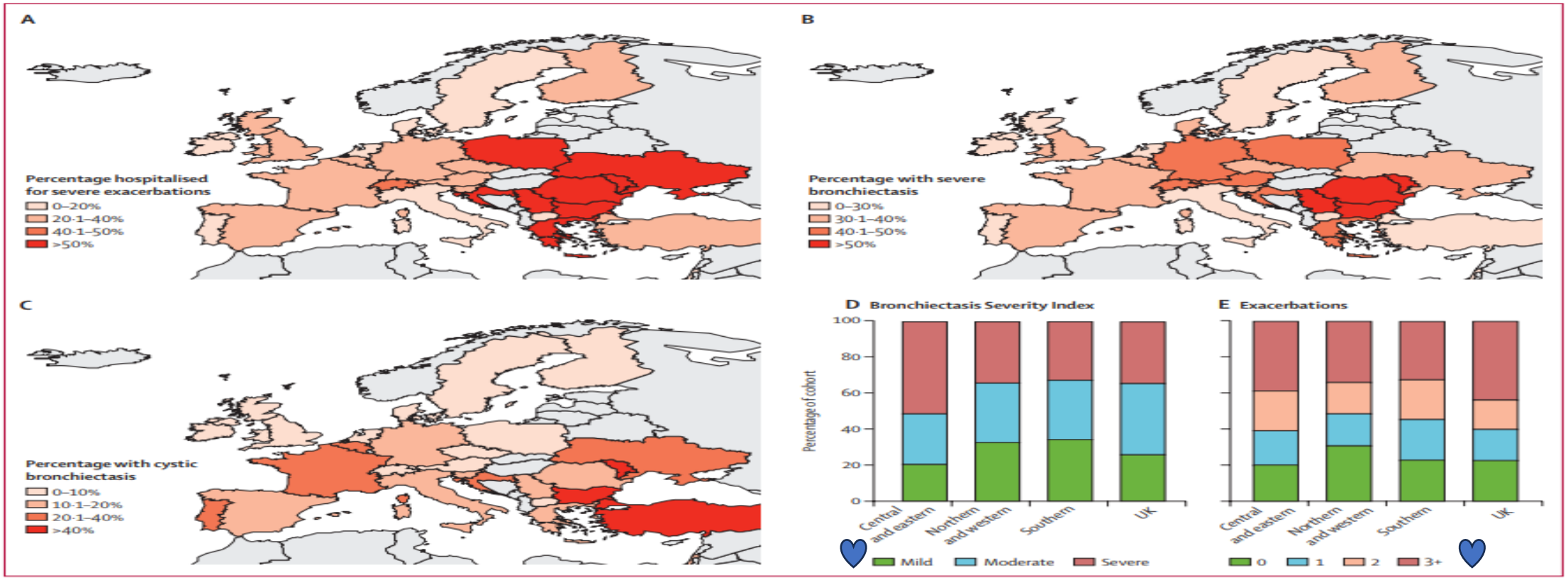


Figure 3: Severity of disease and exacerbations of bronchiectasis across Europe

Across Europe with the causes, severity, microbiology, and treatment being highly dependent on the region and patient characteristics

Lancet Respir Med . 2023 Jul;11(7):637-649.

Summary

- **Cohort studies in various countries**

Bronchiectasis
➡ Heterogenous disease

- **Clinical guidelines** for bronchiectasis in individual countries need to address these issues **based on epidemiological data** because they may vary from country to country

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Algorithm for the Treatment

Table 3. Algorithm for the Treatment of Bronchiectasis.*

Goal	Action	Outcome Measurement
All patients		
Patient education	Basic disease education, CT image review, provision of patient-friendly educational materials	Patient understands options for diagnosis and treatment
General health care	Vaccinations, nutritional support, smoking cessation	Pneumococcal, influenza, and Covid-19 vaccines; maintaining healthy weight; lung-function improvement
Address treatable causes		
Obstructed airway	Bronchoscopy	Removal of foreign body or tumor
Cystic fibrosis	CFTR modulators	Improvement in lung function, overall health
Immunoglobulin deficiency	Immunoglobulin replacement	Reduction in infectious exacerbations
Recurrent aspiration	Aspiration precautions	Reduction in exacerbations
Esophageal dysfunction	Aspiration precautions	Reduction in exacerbations
Allergic bronchopulmonary aspergillosis	Systemic glucocorticoids, antifungal therapy	Improved bronchiectasis
Airway clearance therapy	Exercise, huff coughing, active cycle of breathing techniques, autogenic drainage, slow expiration with ELTGOL	Improved endurance, improved mucus clearance, reduced cough

N Engl J Med 2022; 387:533-545

Algorithm for the Treatment

Targeted patients		
Airway clearance techniques for bothersome symptoms and exacerbations	Oscillatory positive-expiratory-pressure devices, high-frequency chest-wall oscillation devices, pulmonary rehabilitation, hypertonic sodium chloride nebulization	Improved mucus clearance, reduced cough, reduction in exacerbations
Oral antibiotics for maintenance in patients with ≥3 exacerbations per year	Long-term macrolide treatment, azithromycin (500 mg three times per wk or 250 mg daily)	Reduction in exacerbations; need to monitor for adverse effects, including antibiotic resistance, gastrointestinal effects, hearing loss, cardiac electrophysiological derangements, and drug–drug interactions
Nebulized antibiotics for maintenance in patients with ≥3 exacerbations per year	Inhaled aminoglycosides (tobramycin, gentamicin, amikacin), inhaled fluoroquinolones (ciprofloxacin, levofloxacin), inhaled aztreonam, inhaled colistin	Reduction in exacerbations; need to monitor because none of these drugs have been approved by regulatory authorities for this use; clinical trials have shown mixed results
Eradication of specific organisms, targeted to new growth of *P. aeruginosa*	Antibiotics targeted to known pathogen; intravenous antibiotic for 2 wk, plus nebulized antibiotic for 3 mo	Eradication for ≥6–12 mo
Surgical therapy	Resection of most involved section of lobe or lobes, lung transplantation	Reduction of infectious or inflammatory burden, treatment of advanced disease with poor prognosis

N Engl J Med 2022; 387:533-545

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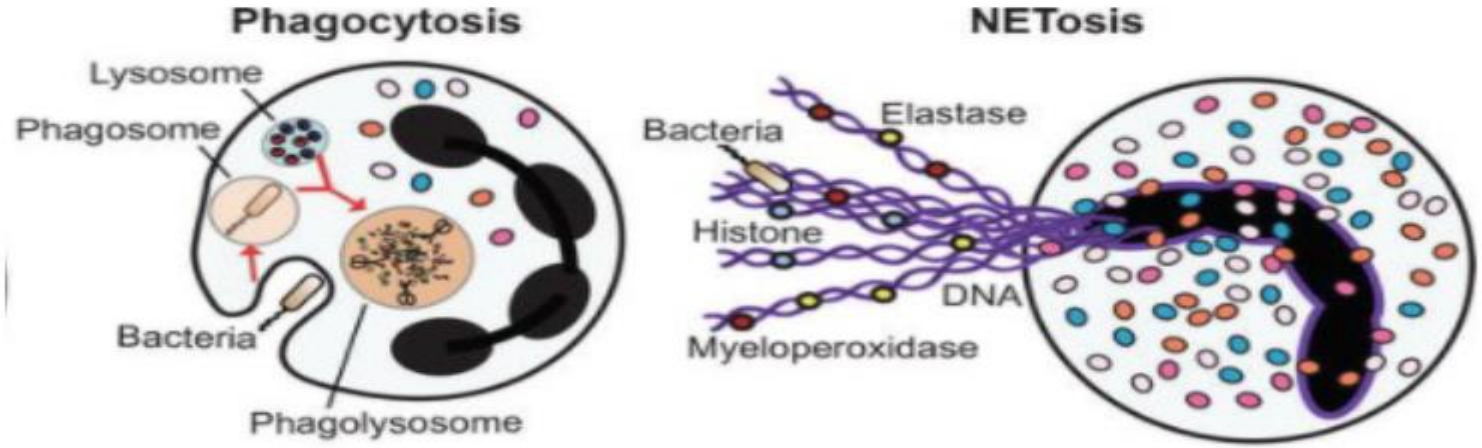
Targeting the neutrophil

- **Neutrophils are the dominant inflammatory cell** in the airway of most individuals with bronchiectasis.

- Patients have amplified numbers of neutrophils and other inflammatory cells compared with healthy controls,
  - **Neutrophil elastase**
  - **Myeloperoxidase**
  - **Matrix metalloproteinases**
  - **Cathepsins**
  - Aantimicrobial peptides (eg, LL-37)
  - Neutrophil-derived DNA.

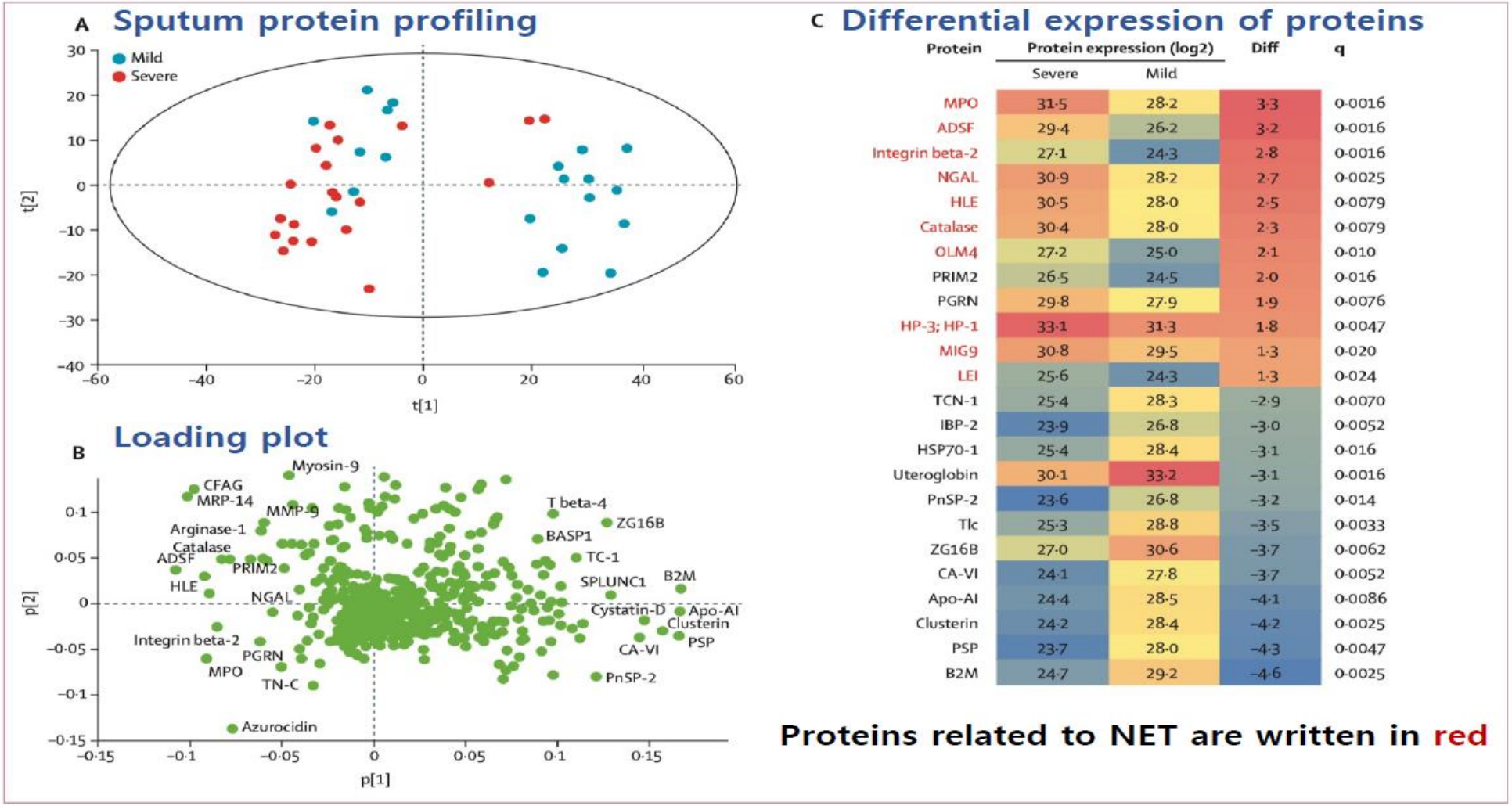
Targeting the neutrophil

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



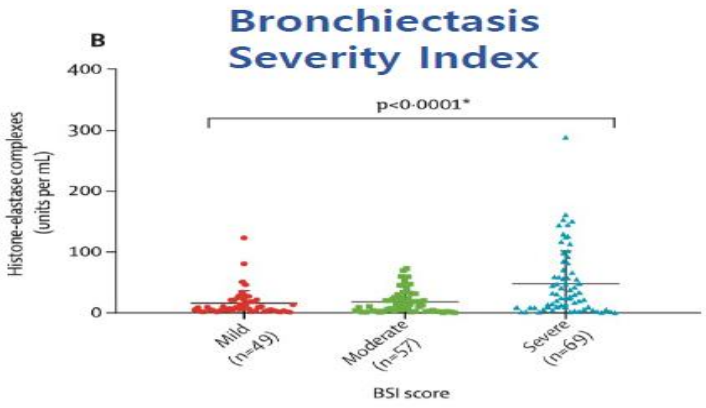
The Immune System 4th Ed

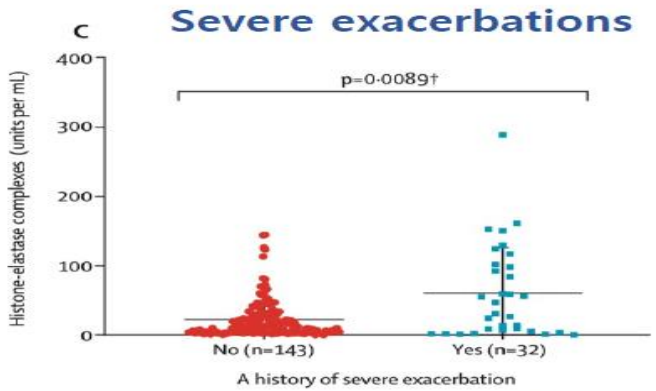
Proteomics of patients with mild and severe bronchiectasis

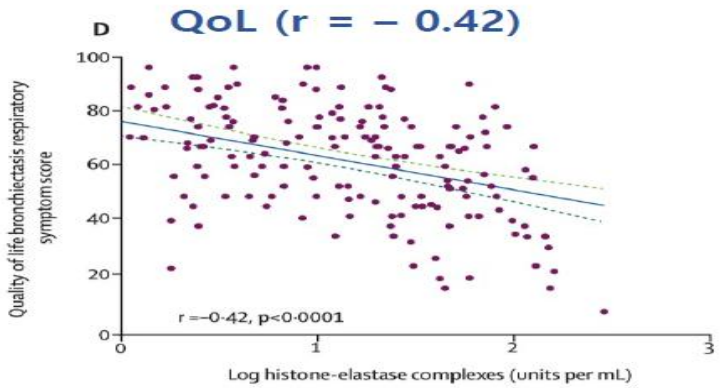


Lancet Respir Med. 2021 Aug;9(8):873-884.

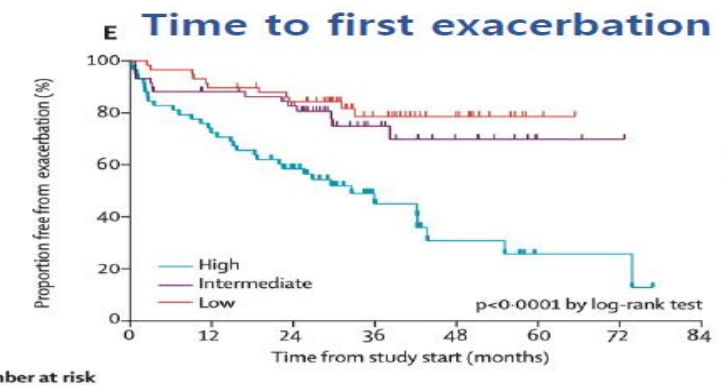
NET concentration and BE outcomes

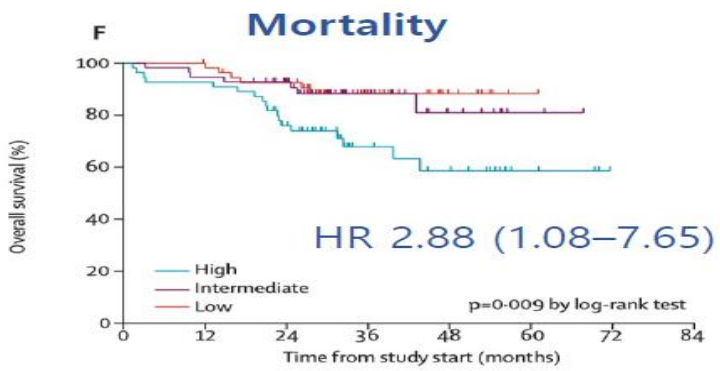






NET concentration
- Low
- Intermediate
- High





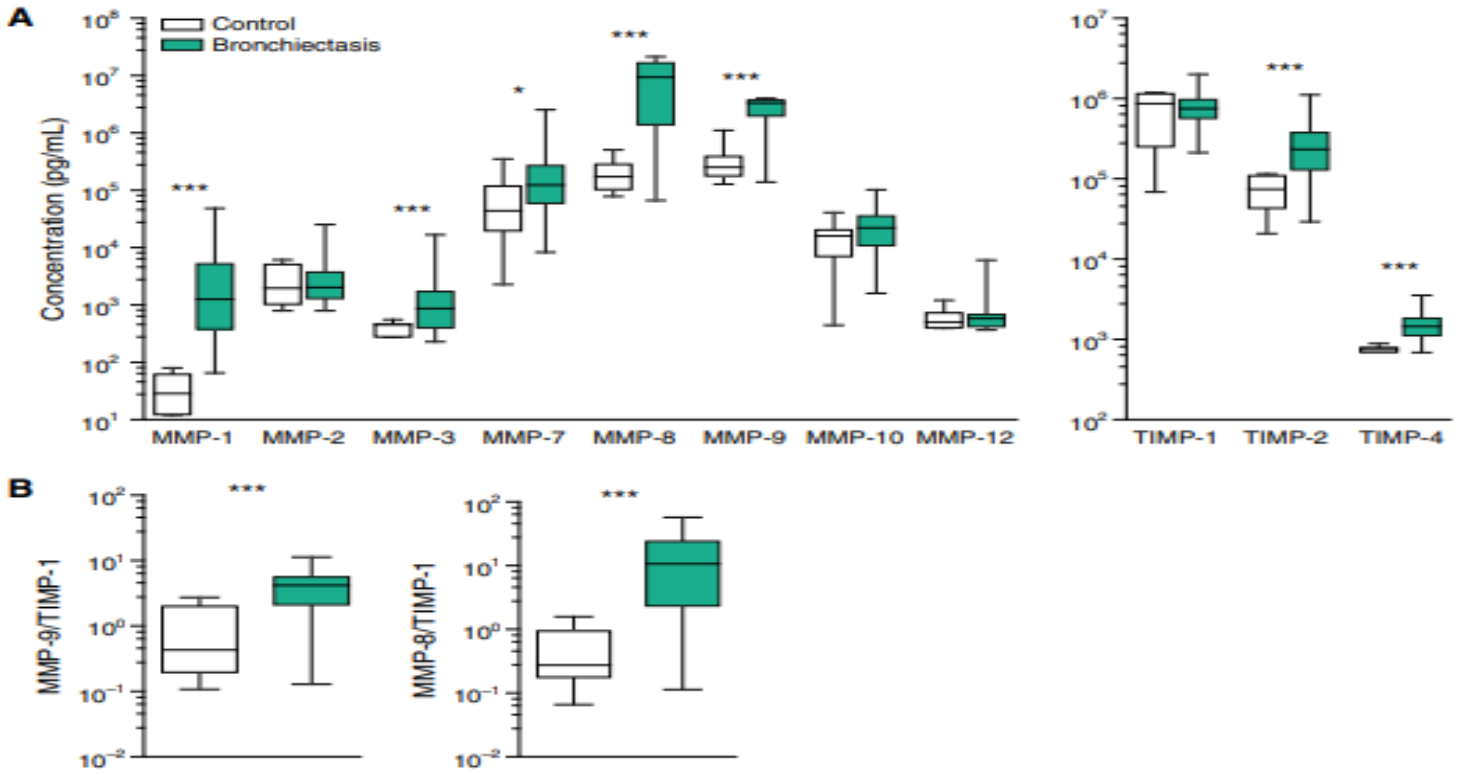
Number at risk (number censored)								
High	58 (0)	43 (0)	31 (4)	12 (18)	7 (20)	3 (23)	3 (23)	0 (24)
Intermediate	59 (0)	50 (3)	44 (6)	18 (29)	10 (36)	3 (43)	2 (44)	0 (45)
Low	58 (0)	53 (0)	48 (2)	25 (23)	14 (34)	3 (45)	1 (47)	0 (47)

	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)

NETs identified as a key marker of disease severity and treatment response in bronchiectasis.

Lancet Respir Med. 2021 Aug;9(8):873-884.

Matrix Metalloproteinases and Bronchiectasis

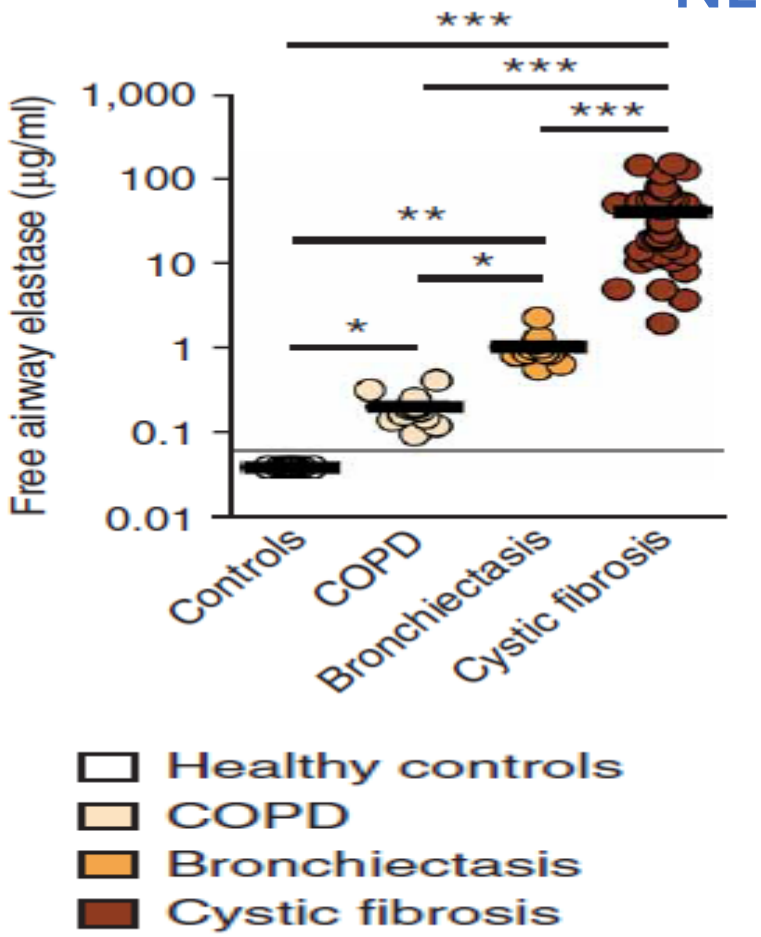


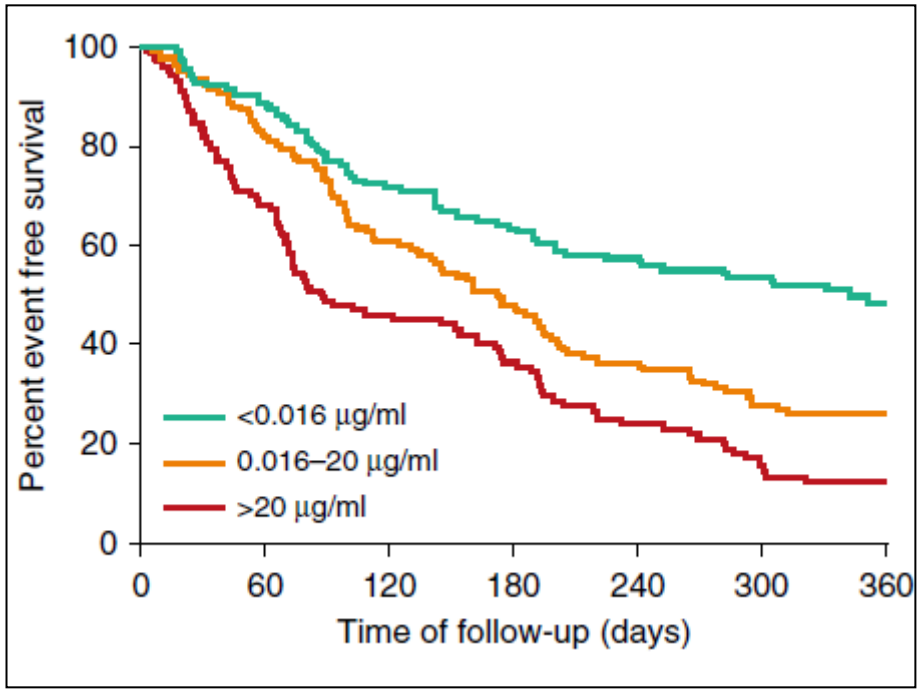
Increased MMP levels (particularly MMP-8 and MMP-1) and MMP/TIMP ratios in patients with bronchiectasis compared with healthy control subjects correlated with lower lung function and higher levels of inflammatory markers.

Lancet Respir Med. 2021 Aug;9(8):873-884.

Role of Neutrophil Elastase

NE activity in sputum



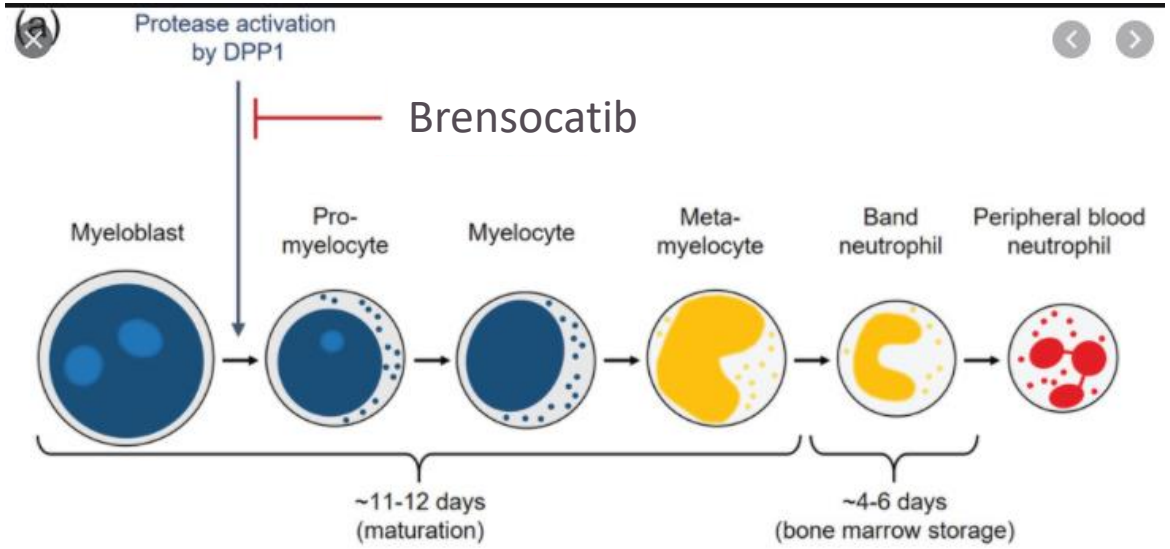


Time to next exacerbation. Elevated sputum NE activity associated with shorter time to next exacerbation

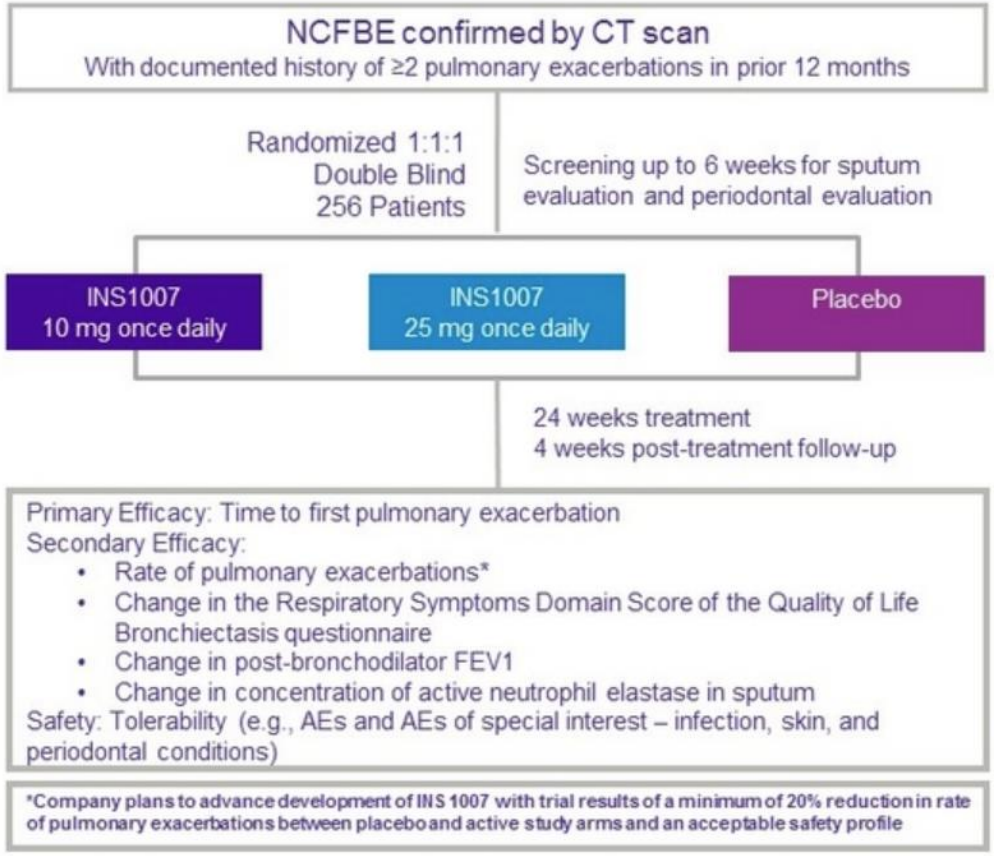
Single-center prospective cohort study, Dundee, Scotland:
381 bronchiectasis patients

Brensocatib

- Brensocatib
  - a small molecule, oral, **reversible inhibitor** of dipeptidyl peptidase I (DPP1), an enzyme responsible for activating neutrophil serine proteases (NSPs), such as **neutrophil elastase**, in neutrophils when they are formed in the bone marrow



Brensocatib



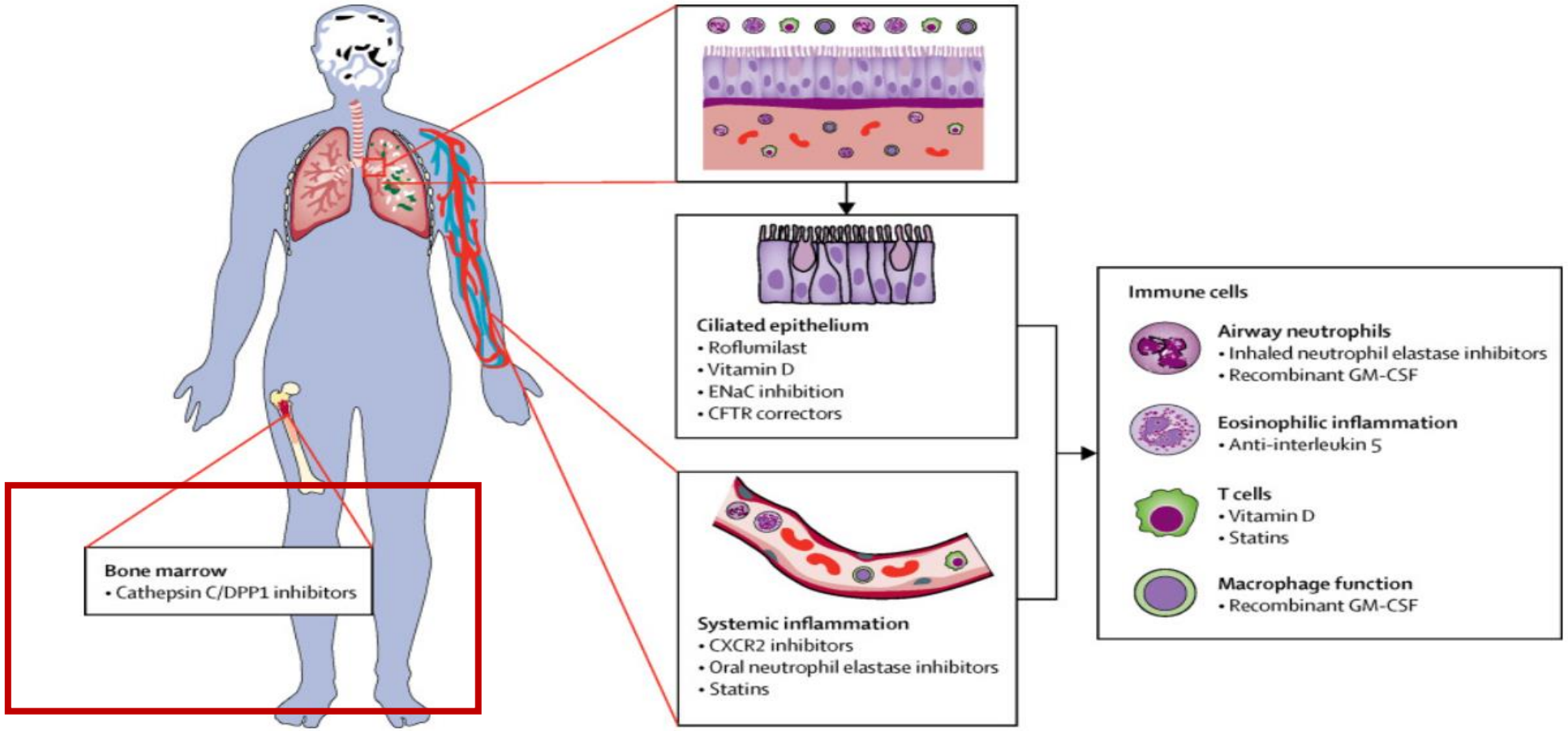
The WILLOW study met its primary endpoint, with brensocatib significantly prolonging time to first pulmonary exacerbation over the 24-week treatment period versus placebo (p=0.027 for the 10 mg group; p=0.044 for the 25 mg group). **The risk of exacerbation at any time** during the trial was reduced by **42%** for the 10 mg group versus placebo **(HR 0.58, p=0.029)** and by 38% for the 25 mg group versus placebo (HR 0.62, p=0.046).

42%

c.f.)Macrolide HR = **0.49 (0.36-0.66)**

Chalmers. N Engl J Med. 2020;383(22):2127-2137.

Novel treatment approaches



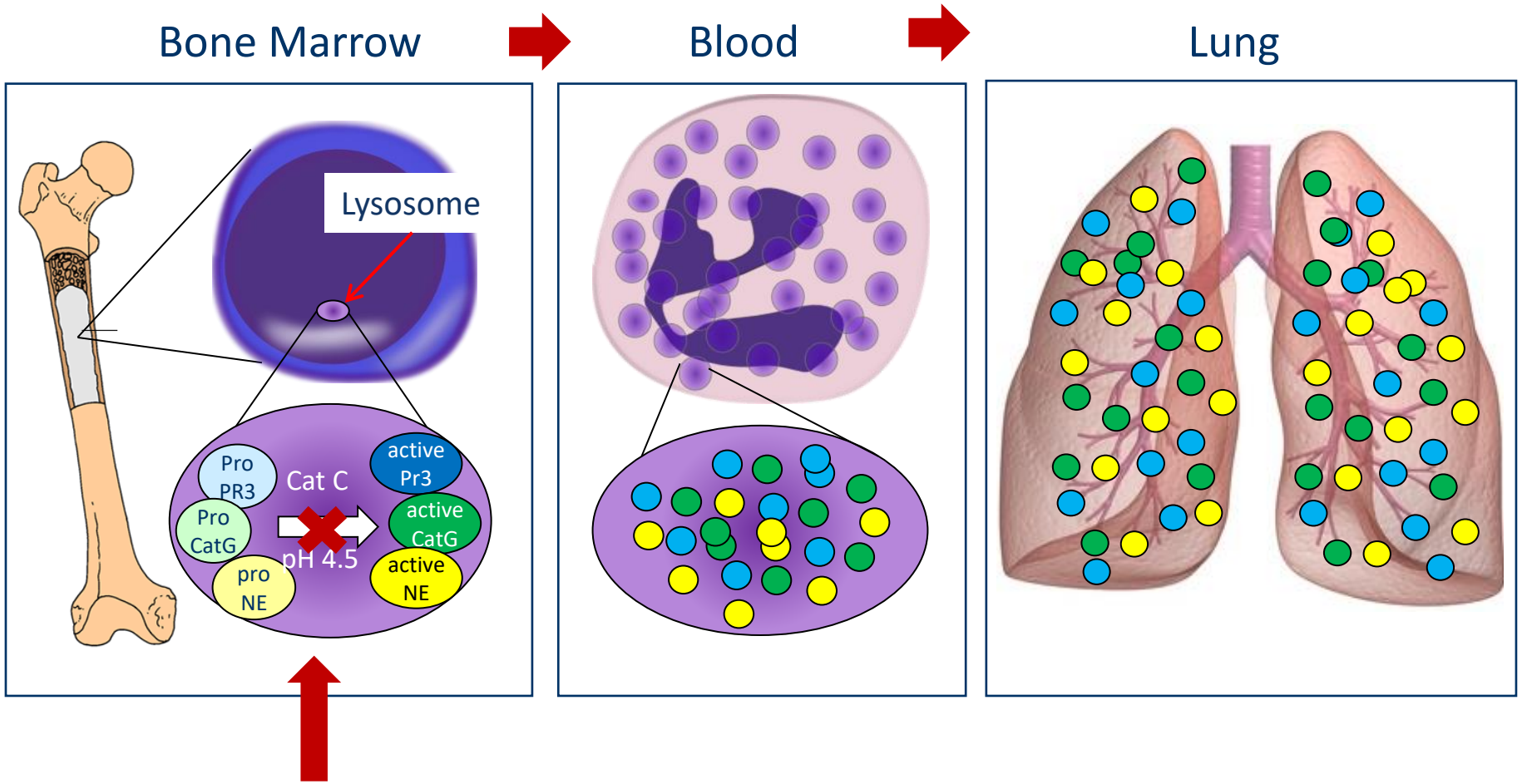
CathepsinC/DPP1 inhibitors

Lancet Respir Med. 2018 Sep;6(9):715-726.

Cathepsin C inhibition

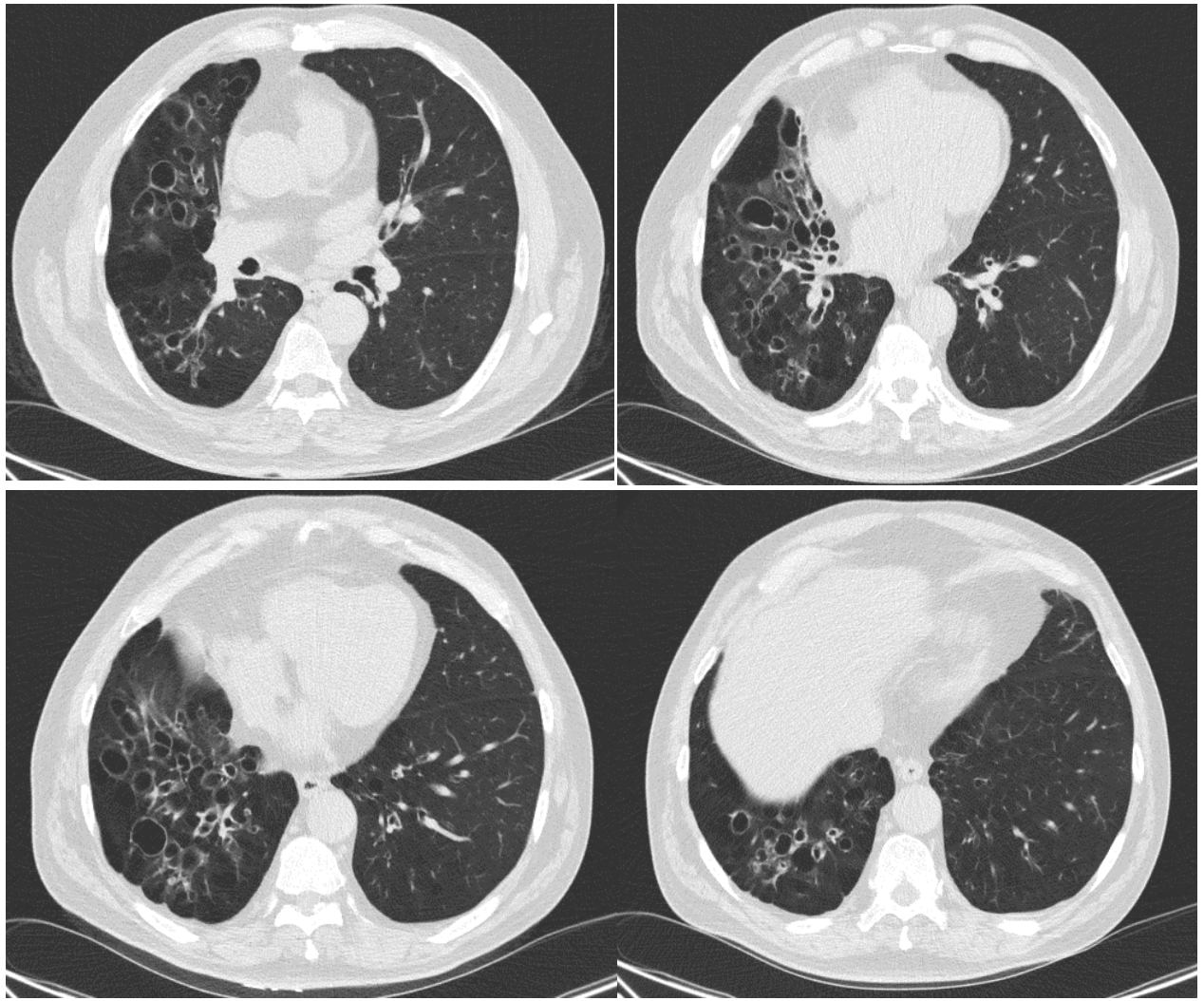
3 Neutrophil Serine Proteases are activated by the enzyme Cathepsin C:

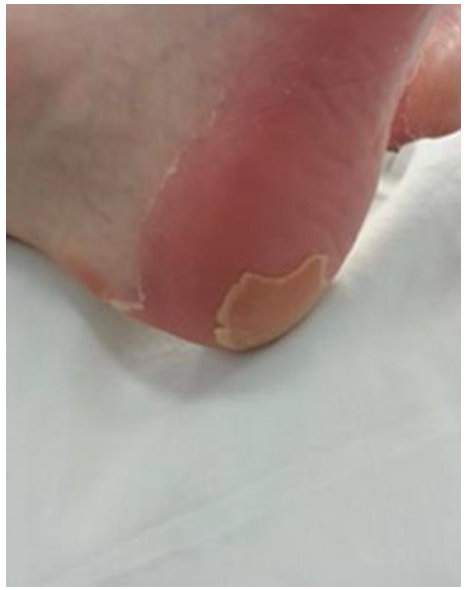
- = Neutrophile Elastase (NE)
- = Cathepsin G (CatG)
- = Proteinase 3 (PR3)



M/73

- PFT
  - FVC 2.46 L, 73%
  - FEV1 1.30L, 56%
  - FEV1/FVC 53%
- FENO 18
- Blood eosinophilia





Gene Expression Profiling in

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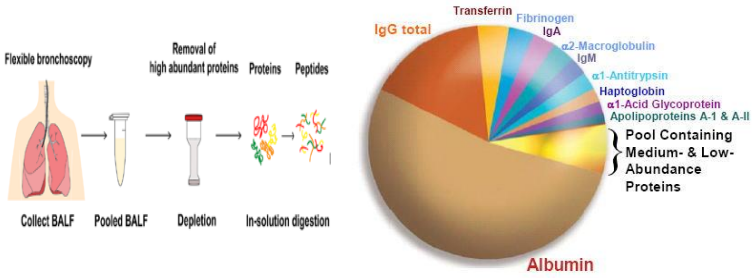
Department of Medicine, School of Medicine, and Department of Epider
Baltimore, Maryland

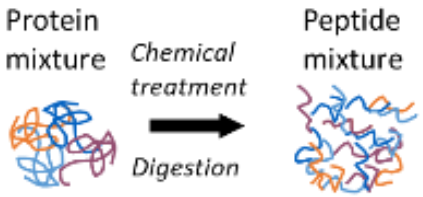
Asthma is a chronic inflammatory disease of the lungs, characterized by airway hyperreactivity, mucus hypersecretion, and airflow obstruction. Despite recent advances, the genetic regulation of asthma pathogenesis is still largely unknown. Gene expression profiling techniques are well suited to study complex diseases and hold substantial promise for identifying novel genes and pathways in asthma; however, relatively few studies have been completed in human asthma. The few studies that have been done have identified many novel candidate genes and pathways in asthma pathogenesis, including ALOX15 and serine proteinase inhibitors cathepsin C and G. The interpretation of results of these studies should be cautious, as limitations include small sample sizes and heterogeneity of study populations and tissues sampled. In the future, the promise of gene expression studies would be enhanced by the use of larger sample sizes and attempts to standardize phenotype, sample collection techniques, and analysis. As the field of expression profiling in asthma advances, we hope it will improve our understanding of critical questions about mechanisms involved in susceptibility to the disease, as well as help to personalize care by improving appropriate selection of patients for prevention and treatment strategies.

Proteomics in Korea

단백질 추출



Anderson, L., Mol Cell Proteomics,2003, 2, 1096



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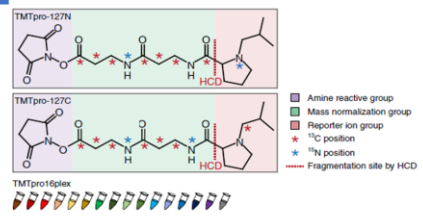
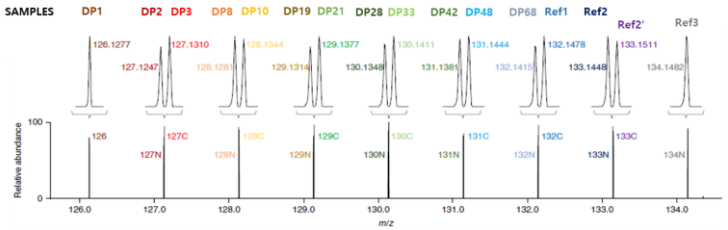
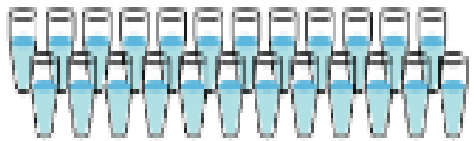
2	19026343	DP2	AE
3	19035480	DP3	stable
4	19080725	DP8	stable
5	19107819	DP10	AE
6	19197210	DP19	stable
7	19217287	DP21	AE
8	19280262	DP28	AE
9	19337775	DP33	AE
10	19423640	DP42	AE
11	19486174	DP48	stable
12	19689889	DP68	AE

(TMT-labeling) & 분획

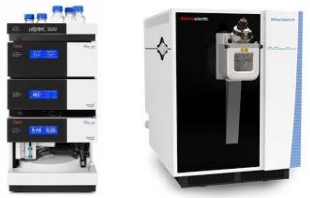


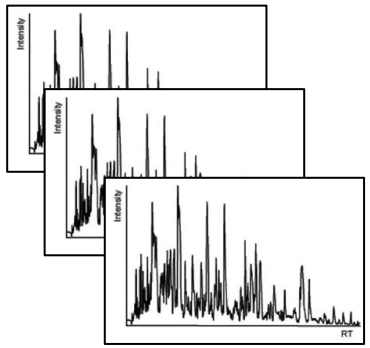


Basic- RPLC Fractions(10)

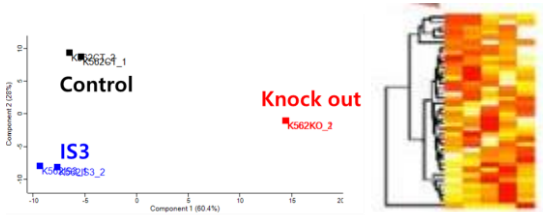


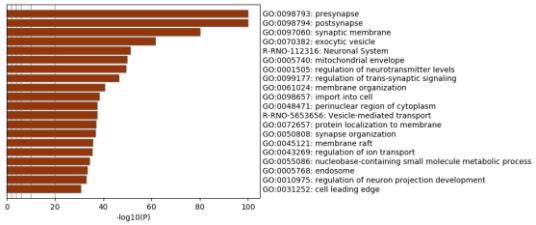
질량 분석

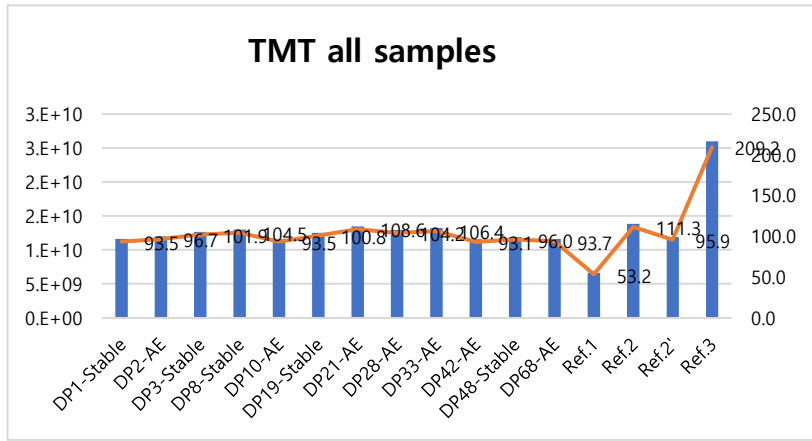




정성/정량분석

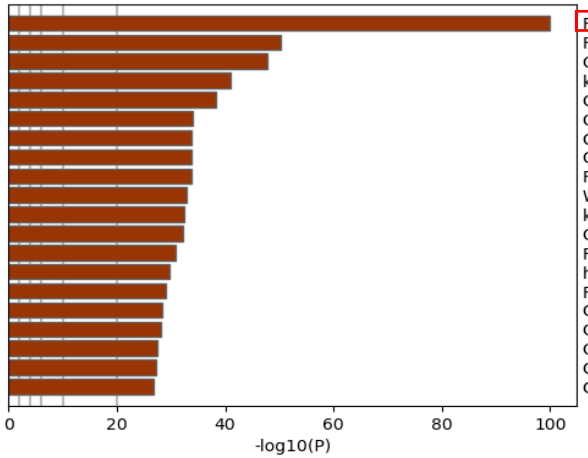






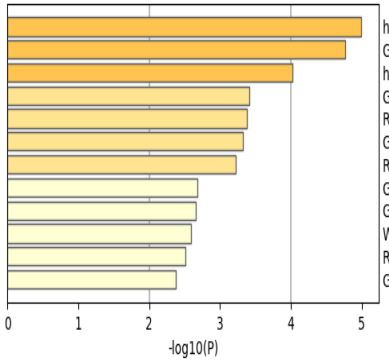
Proteomics in Korea

AE vs Stable (All) : 1577 proteins



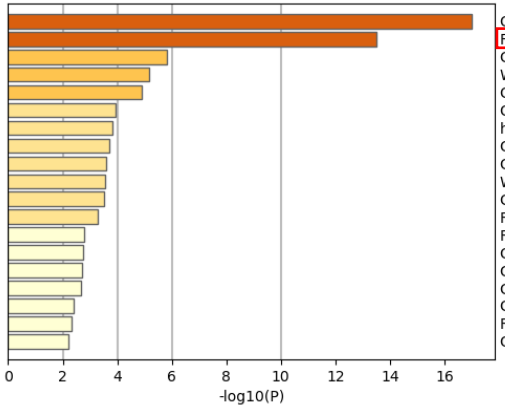
R-HSA-6798695: Neutrophil degranulation
R-HSA-114608: Platelet degranulation
GO:0043086: negative regulation of catalytic activity
ko04610: Complement and coagulation cascades
GO:0005975: carbohydrate metabolic process
GO:0009611: response to wounding
GO:0030155: regulation of cell adhesion
GO:0010035: response to inorganic substance
R-HSA-449147: Signaling by Interleukins
WP3888: VEGFA-VEGFR2 signaling pathway
ko04142: Lysosome
GO:0006457: protein folding
R-HSA-381426: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)
hsa01200: Carbon metabolism
R-HSA-5653656: Vesicle-mediated transport
GO:0006979: response to oxidative stress
GO:0097435: supramolecular fiber organization
GO:1903827: regulation of cellular protein localization
GO:1990748: cellular detoxification
GO:0044403: biological process involved in symbiotic interaction

AE vs Stable (Difference ≤ -0.5) : 41 proteins

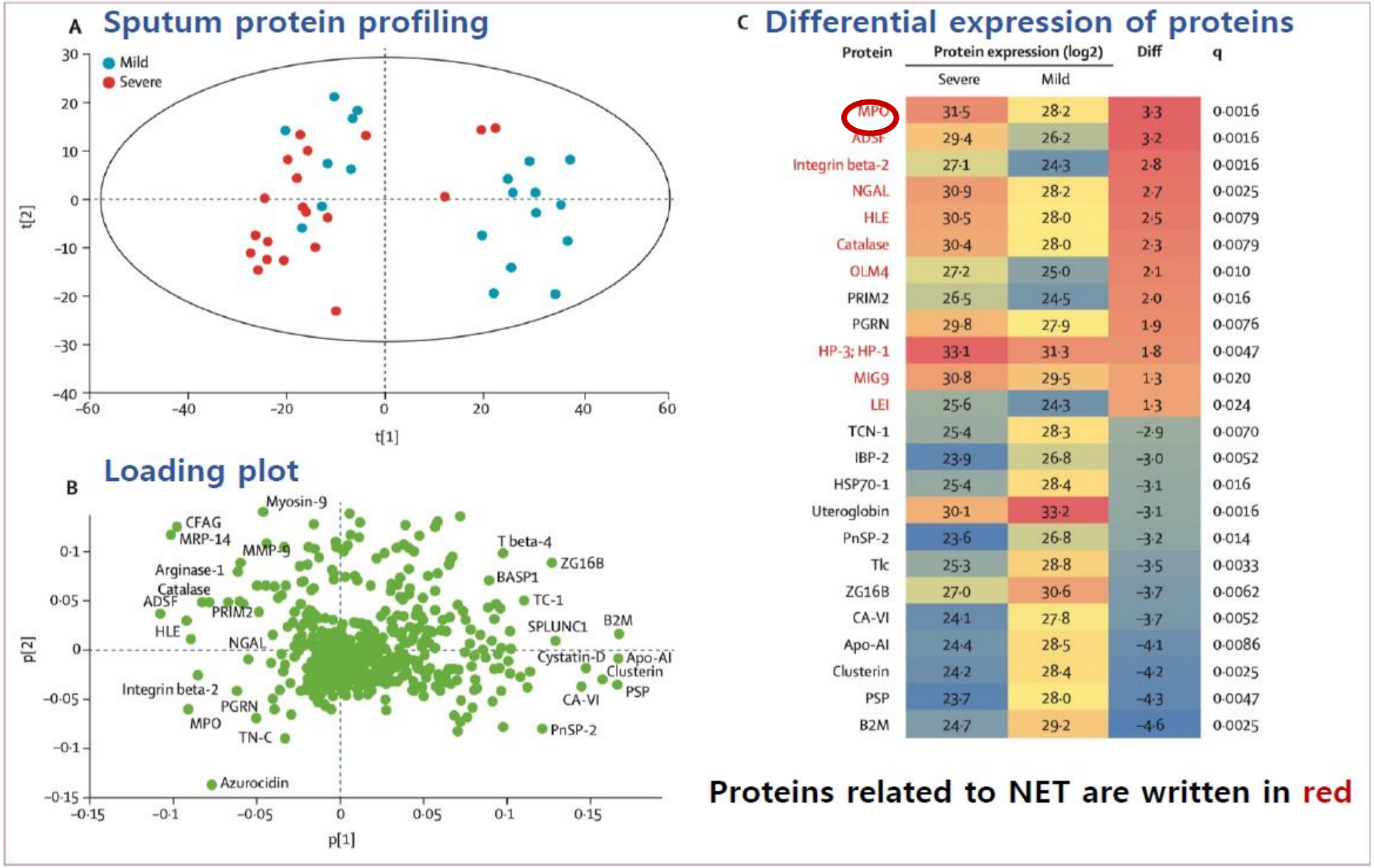


hsa00640: Propanoate metabolism
GO:0051402: neuron apoptotic process
hsa00010: Glycolysis / Gluconeogenesis
GO:0034446: substrate adhesion-dependent cell spreading
R-HSA-977225: Amyloid fiber formation
GO:1990748: cellular detoxification
R-HSA-381426: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)
GO:0072521: purine-containing compound metabolic process
GO:0031032: actomyosin structure organization
WP3888: VEGFA-VEGFR2 signaling pathway
R-HSA-211859: Biological oxidations
GO:0010817: regulation of hormone levels

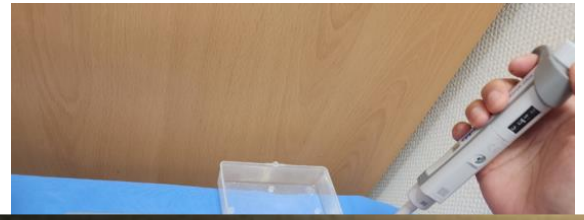
AE vs Stable (Difference ≥ 0.5) : 85 proteins

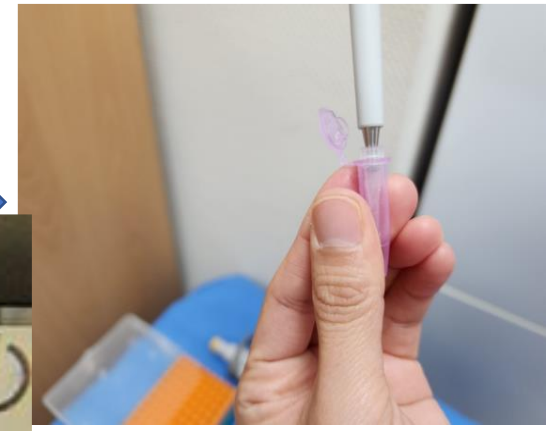


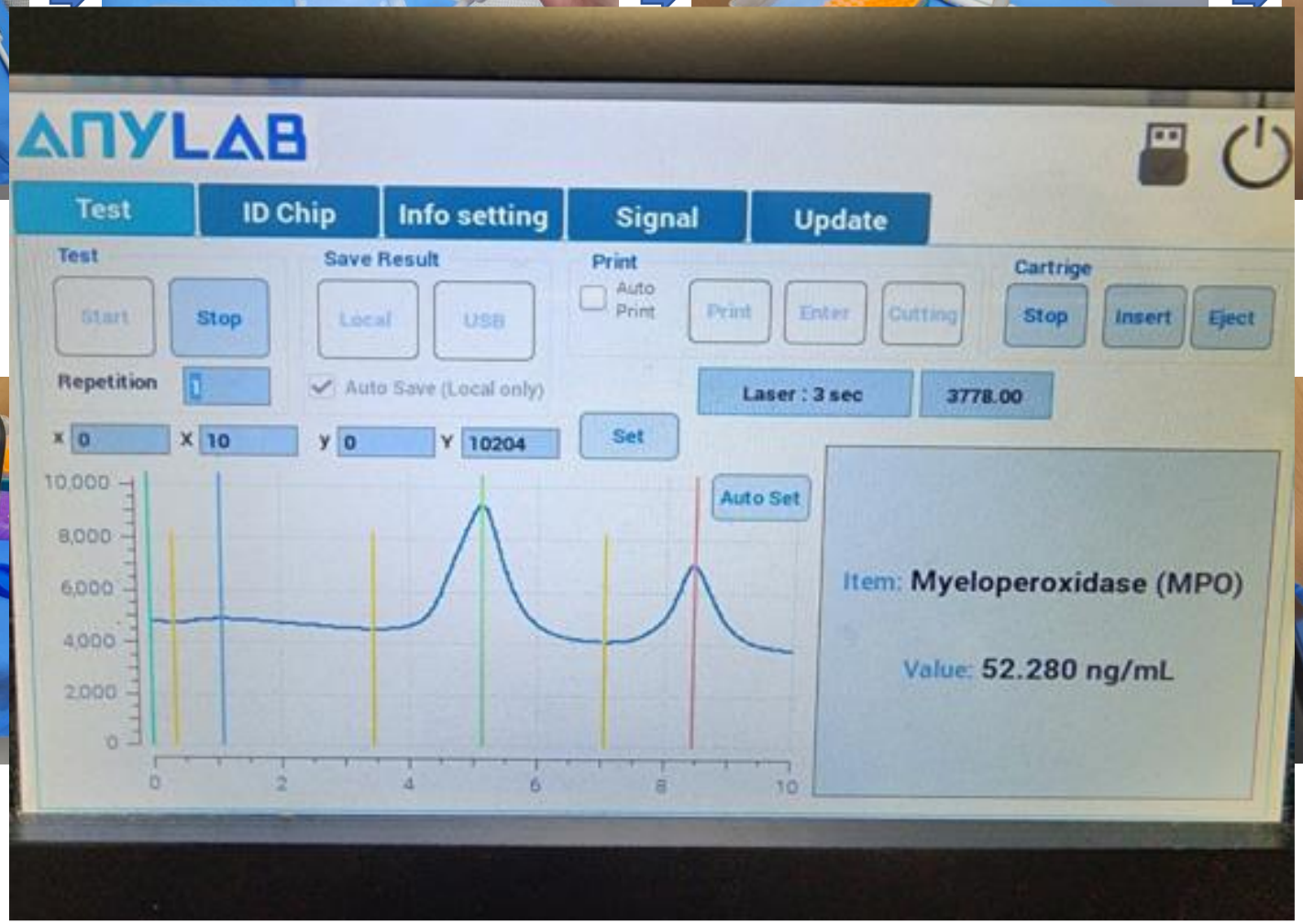
CORUM:191: 20S proteasome
R-HSA-6798695: Neutrophil degranulation
GO:0006091: generation of precursor metabolites and energy
WP15: Selenium micronutrient network
GO:0051238: sequestering of metal ion
GO:0032535: regulation of cellular component size
hsa00500: Starch and sucrose metabolism
GO:0044283: small molecule biosynthetic process
GO:0010035: response to inorganic substance
WP4290: Metabolic reprogramming in colon cancer
GO:0002526: acute inflammatory response
R-HSA-114608: Platelet degranulation
R-HSA-2559586: DNA Damage/Telomere Stress Induced Senescence
GO:0022411: cellular component disassembly
GO:0051047: positive regulation of secretion
GO:0007369: gastrulation
GO:0050769: positive regulation of neurogenesis
R-HSA-9610379: HCMV Late Events
GO:0034101: erythrocyte homeostasis



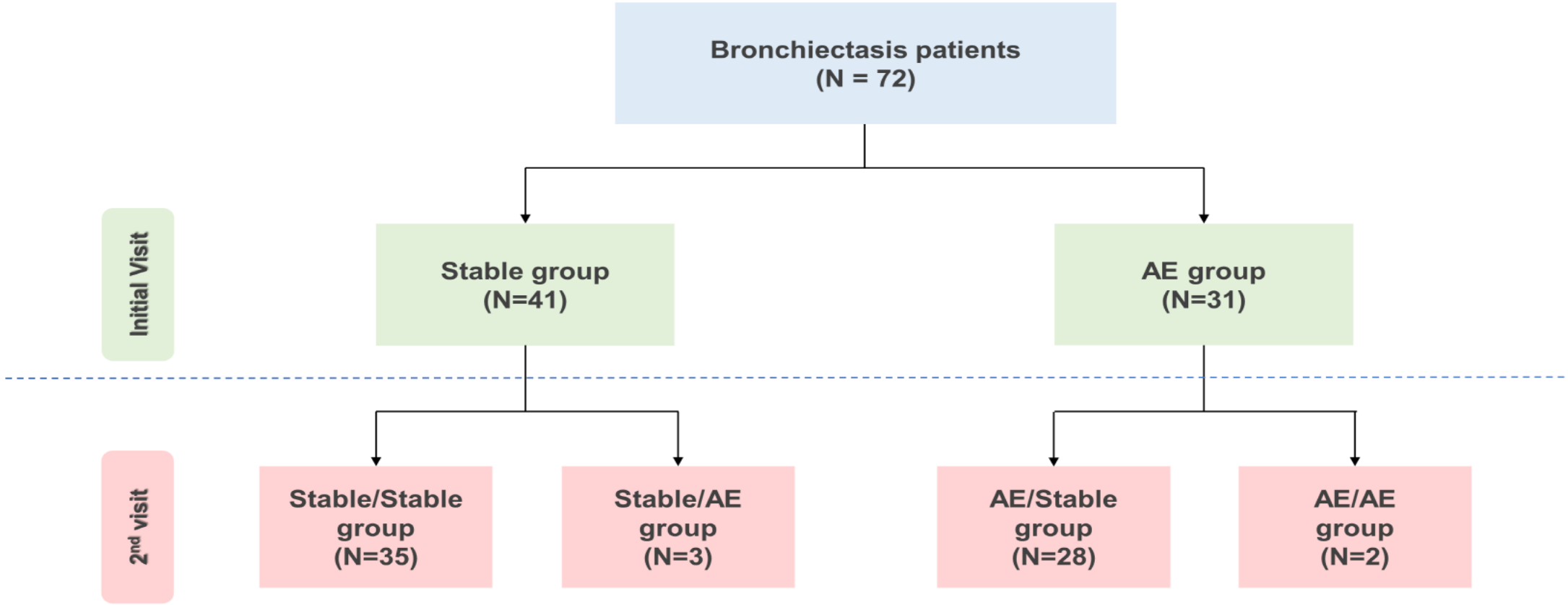
Lancet Respir Med. 2021 Aug;9(8):873-884.





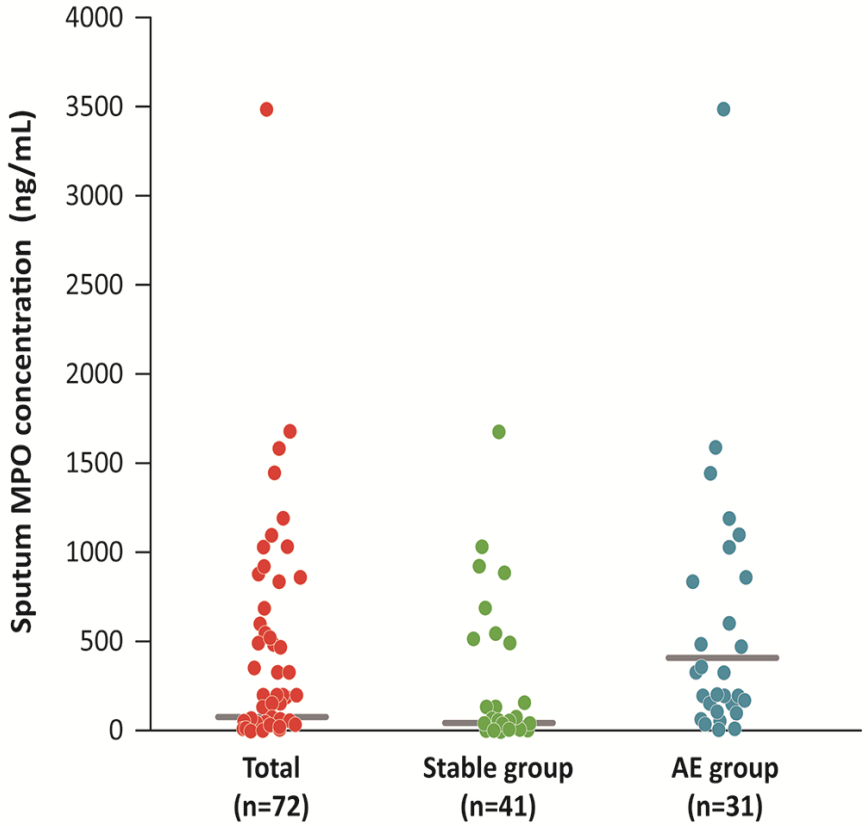

ANYLAB
Test
ID Chip
Info setting
Signal
Update
Test
Start
Stop
Save Result
Local
USB
Print
Auto Print
Print
Enter
Cutting
Cartrige
Stop
Insert
Eject
Repetition
1
Auto Save (Local only)
Laser : 3 sec
3778.00
x 0
X 10
y 0
Y 10204
Set
Auto Set
10,000
8,000
6,000
4,000
2,000
0
0
2
4
6
8
10
Item: Myeloperoxidase (MPO)
Value: 52.280 ng/mL

MPO and Bronchiectasis in Korea

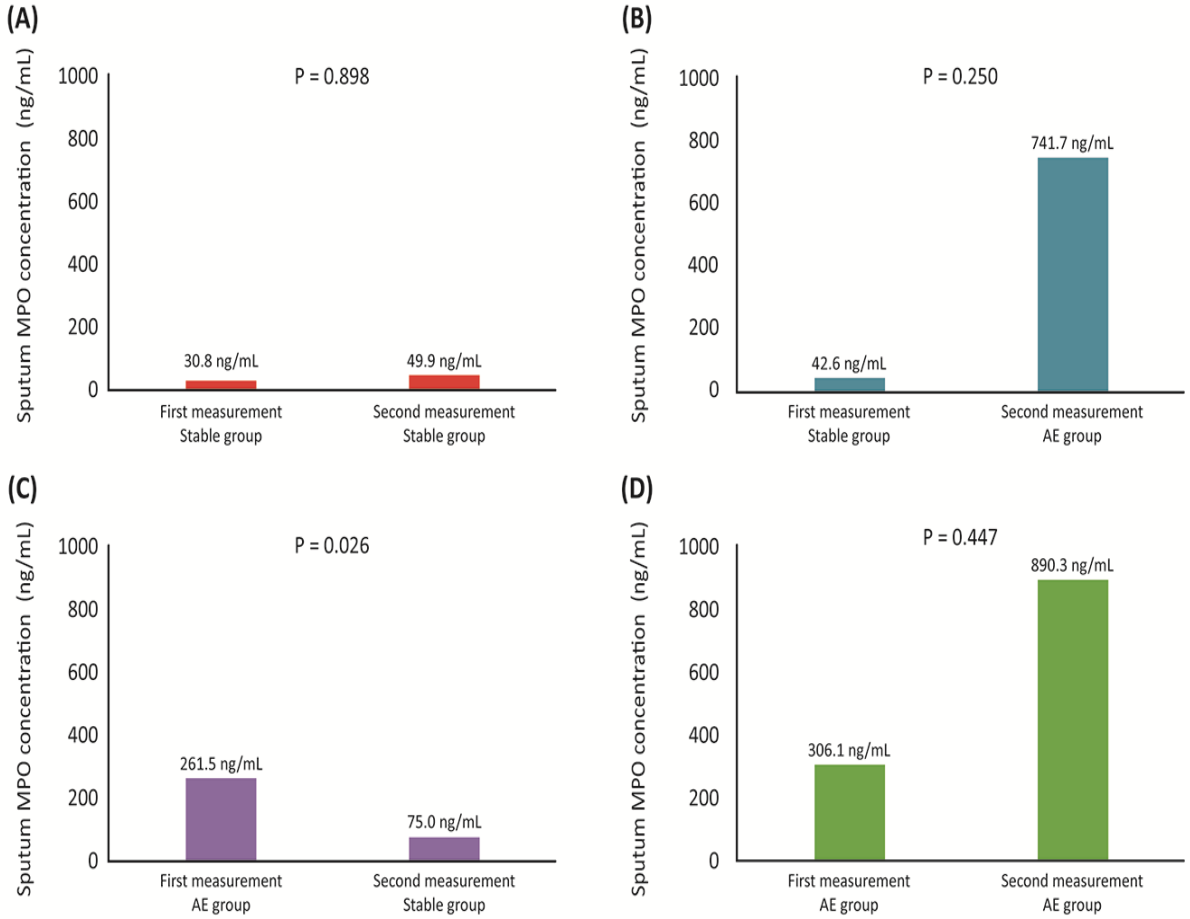


Unpublish data

MPO and Bronchiectasis in Korea



	Total (n=72)	Stable group (n=41)	AE group (n=31)	P-value
Sputum MPO concentration	77.0 (22.0-476.0)	33.0 (8.2-131.1)	195.8 (107.7-832.7)	< 0.001

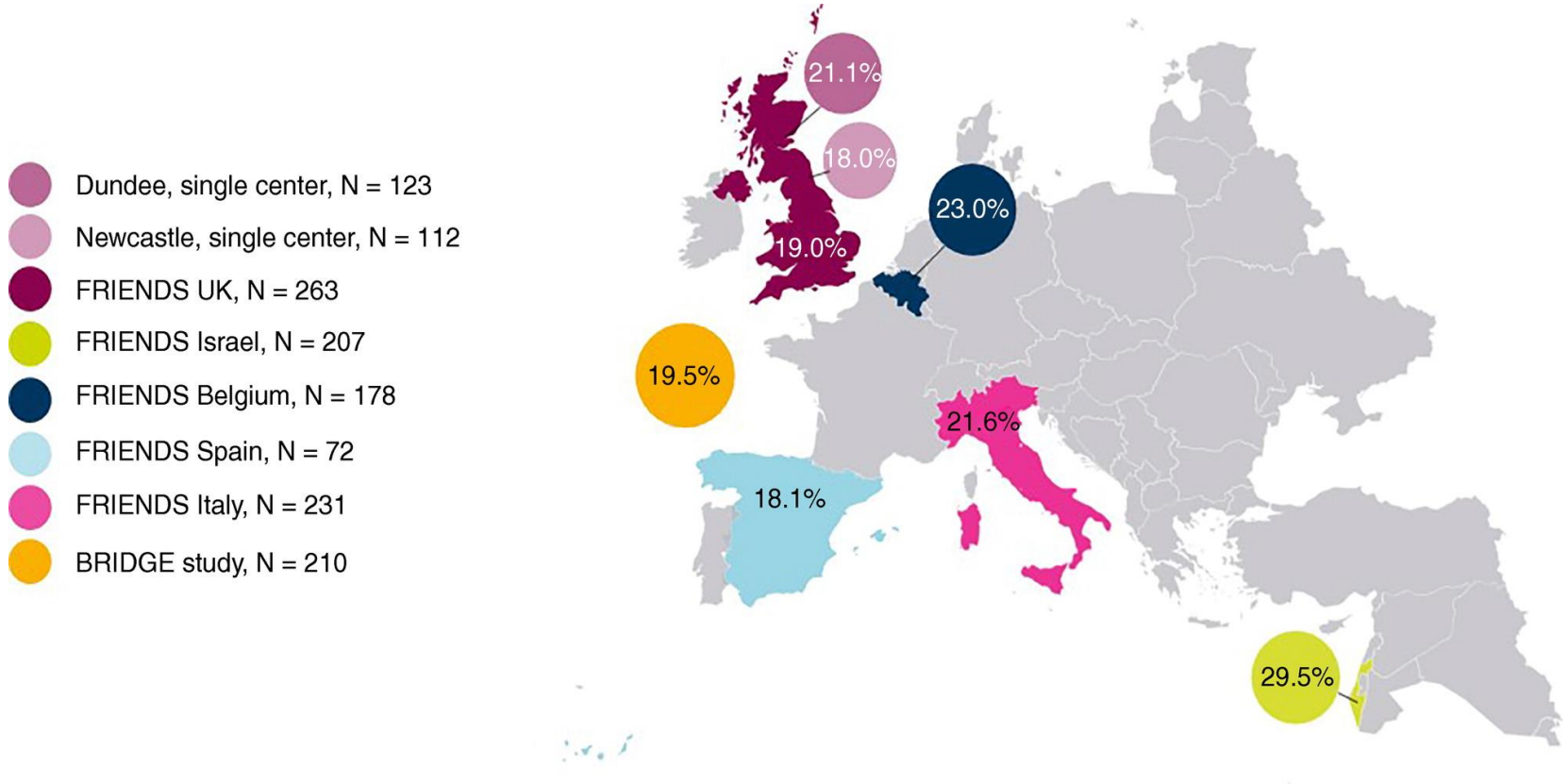


Unpublish data

Agenda

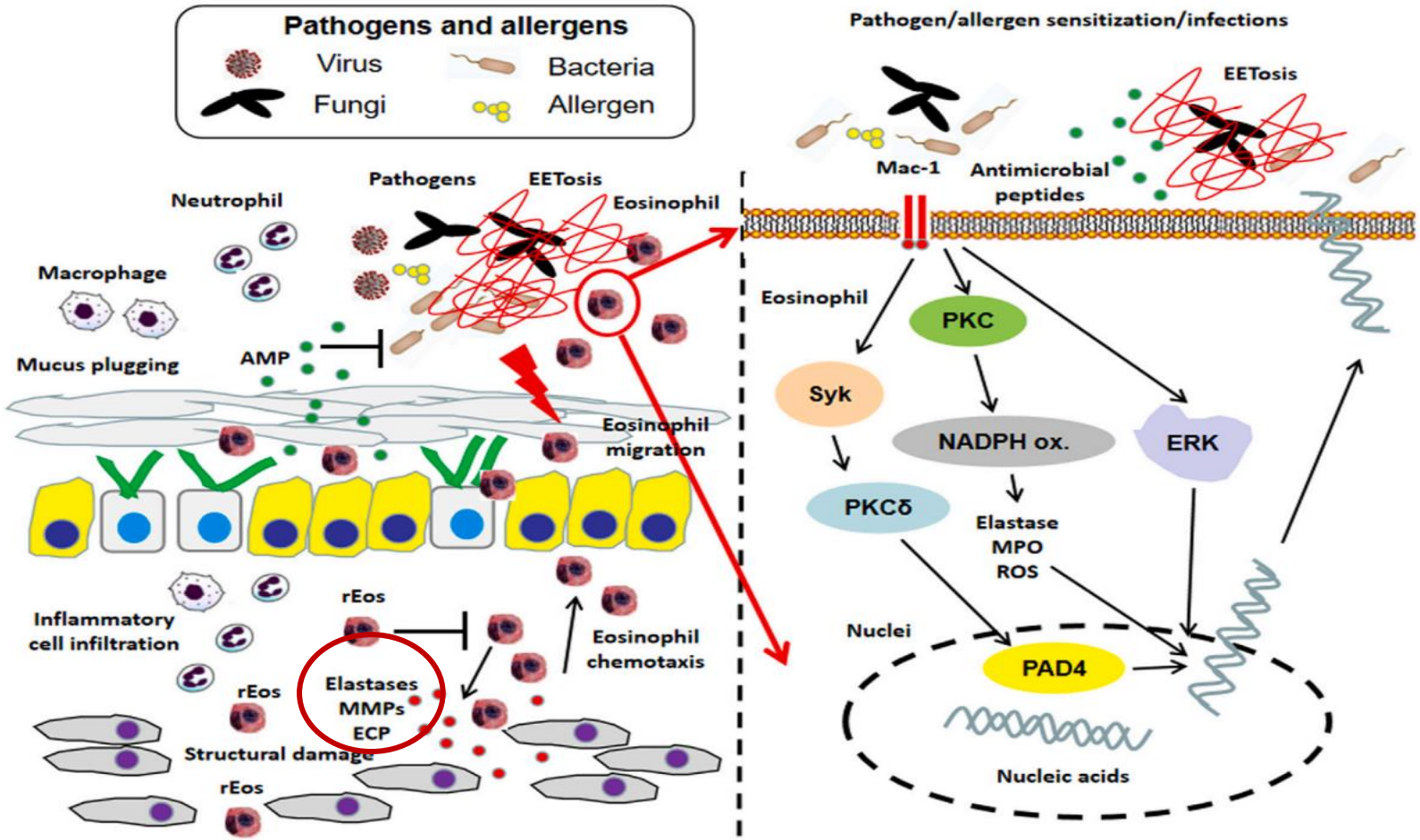
- Bronchiectasis heterogenicity
- **Personalized medicine and appropriately targeting treatment**
  - Targeting the neutrophil
  - **Targeting the eosinophil**
  - Immunomodulatory drugs
  - Targeting mucociliary clearance and cough
  - Multi-omics, and the microbiome
- Summary

The percentage of patients with eosinophil counts of ⩾300 cells/μl



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

The role of eosinophilic inflammation in the development of bronchiectasis



J Allergy Clin Immunol Pract. 2023 Apr;11(4):1089-1099.

Eosinophilic inflammation and bronchiectasis

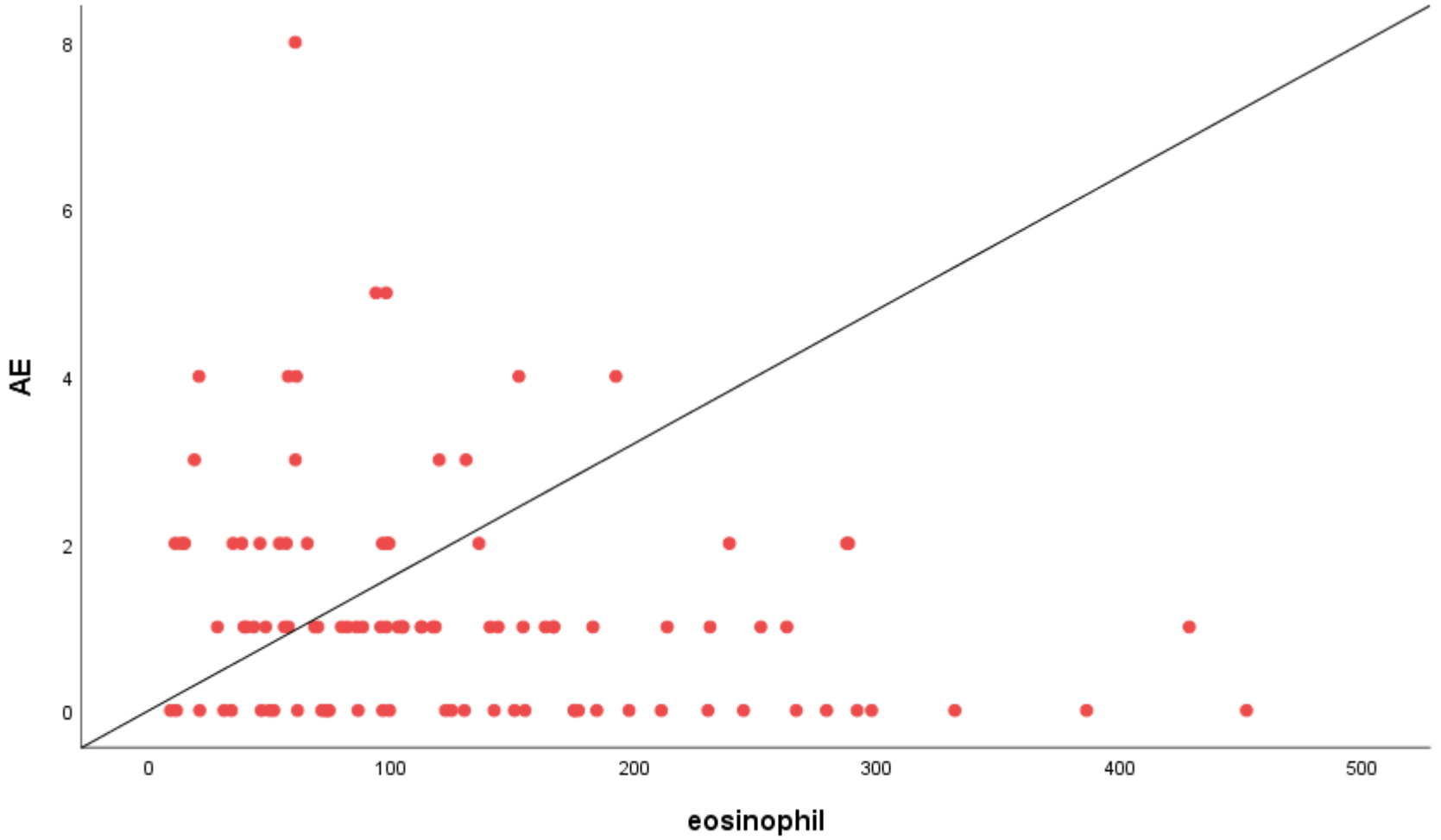
- BEC was **unrelated to a greater number or severity of exacerbations .**

- **Mortality was lower in patients with peripheral eosinophilia compared** with the reference group (hazard ratio [HR] = 0.47; 95% CI, 0.28-0.80; P = .005).

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

Bronchiectasis exacerbation and Blood eosinophil counts

- **Obs**
  - Blo



Risk of bronchiectasis exacerbation based on blood eosinophil counts

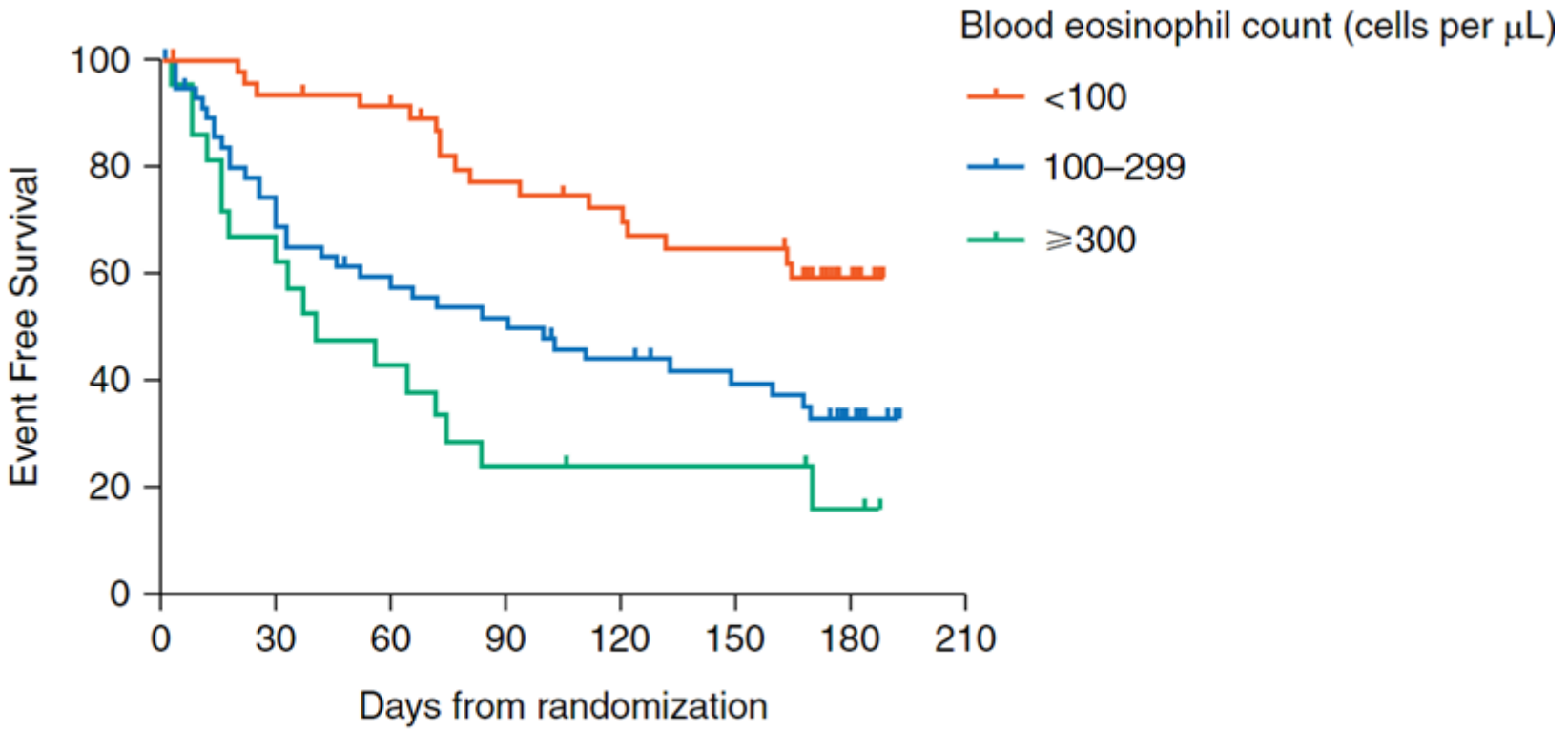


Figure 5. Kaplan-Meier survival curve showing the percentage of exacerbation event–free survival from randomization.

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

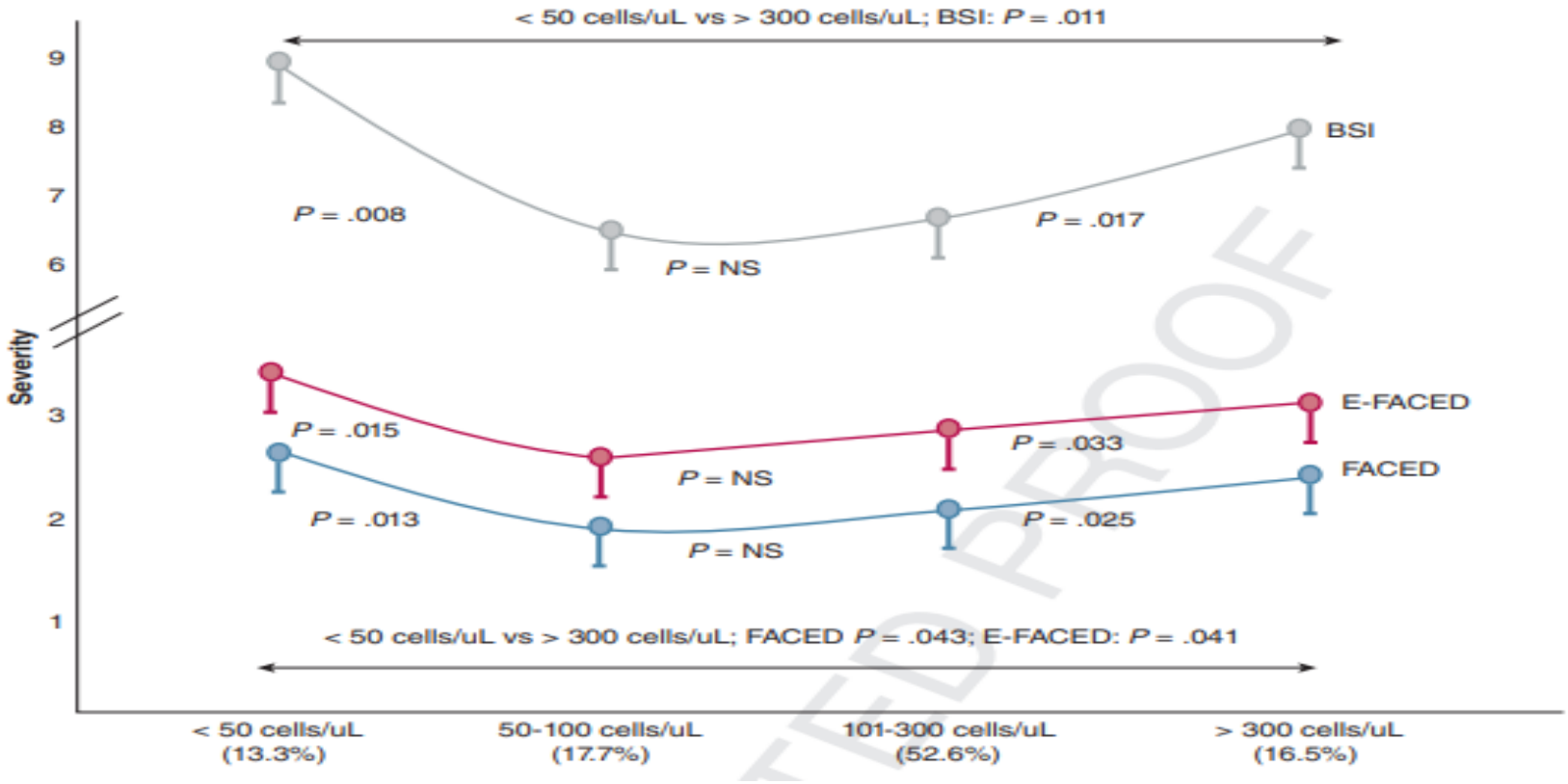
CHEST

The U-Shaped Relationship Between Eosinophil Count and Bronchiectasis Severity

The Effect of Inhaled Corticosteroids

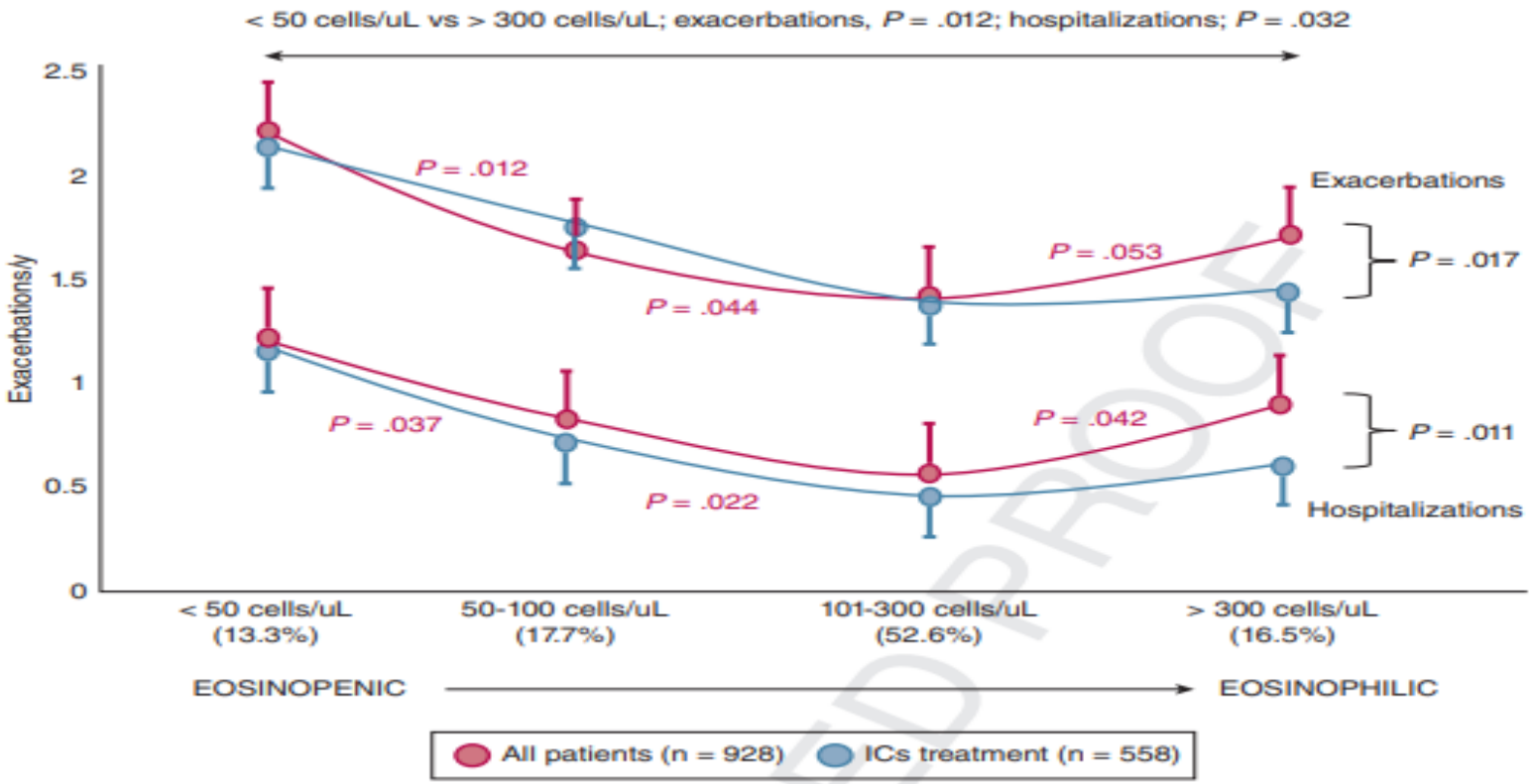
Miguel Ángel Martínez-García, MD; Raúl Méndez, MD; Casilda Olveira, MD; Rosa Girón, MD; Marta García-Clemente, MD; Luis Máiz, MD; Oriol Sibila, MD; Rafael Golpe, MD; Juan Luis Rodríguez-Hermosa, MD; Esther Barreiro, MD; Concepción Prados, MD; Juan Rodríguez-López, MD; Grace Oscullo, MD; Gonzalo Labarca,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

Figure 1. Graph showing the U-shaped relationship between exacerbations and hospitalizations and multidimensional severity indexes in bronchiectasis.



The relationship between the BEC and the severity of bronchiectasis presents a U-shaped relationship, whereas the group with < 50 eosinophils/mL showed the greatest severity.

Figure 2. Graph showing the U-shaped relationship between exacerbations and hospitalizations and number of peripheral eosinophils in the previous year.



e 2 – Graph showing the U-shaped relationship between exacerbations and hospitalizations and number of peripheral eosinophils in the previo

IC treatment significantly decreased the number and severity of exacerbations in those patients with bronchiectasis with > 300 eosinophils/mL.

Eosinophilia and bronchiectasis in Korea

Variable	< 50 cells/μL (n=21 [8.9%])	50-100 cells/μL (n=56 [23.6%])	100-300 cells/μL (n=124 [52.3%])	> 300 cells/μL (n=36 [15.2%])	p-value
ICS 사용	3 (16.67%)	3 (7.5%)	16 (15.69%)	5 (15.62%)	0.5853
1년 간 추적관찰 후 총 악화 횟수	0.67 ± 0.99	0.41 ± 0.84	1.02 ± 2.09	0.39 ± 0.83	0.234
1년 간 추적관찰 후 심한악화 횟수	0.19 ± 0.5	0.04 ± 0.19	0.24 ± 0.87	0.03 ± 0.16	0.1062

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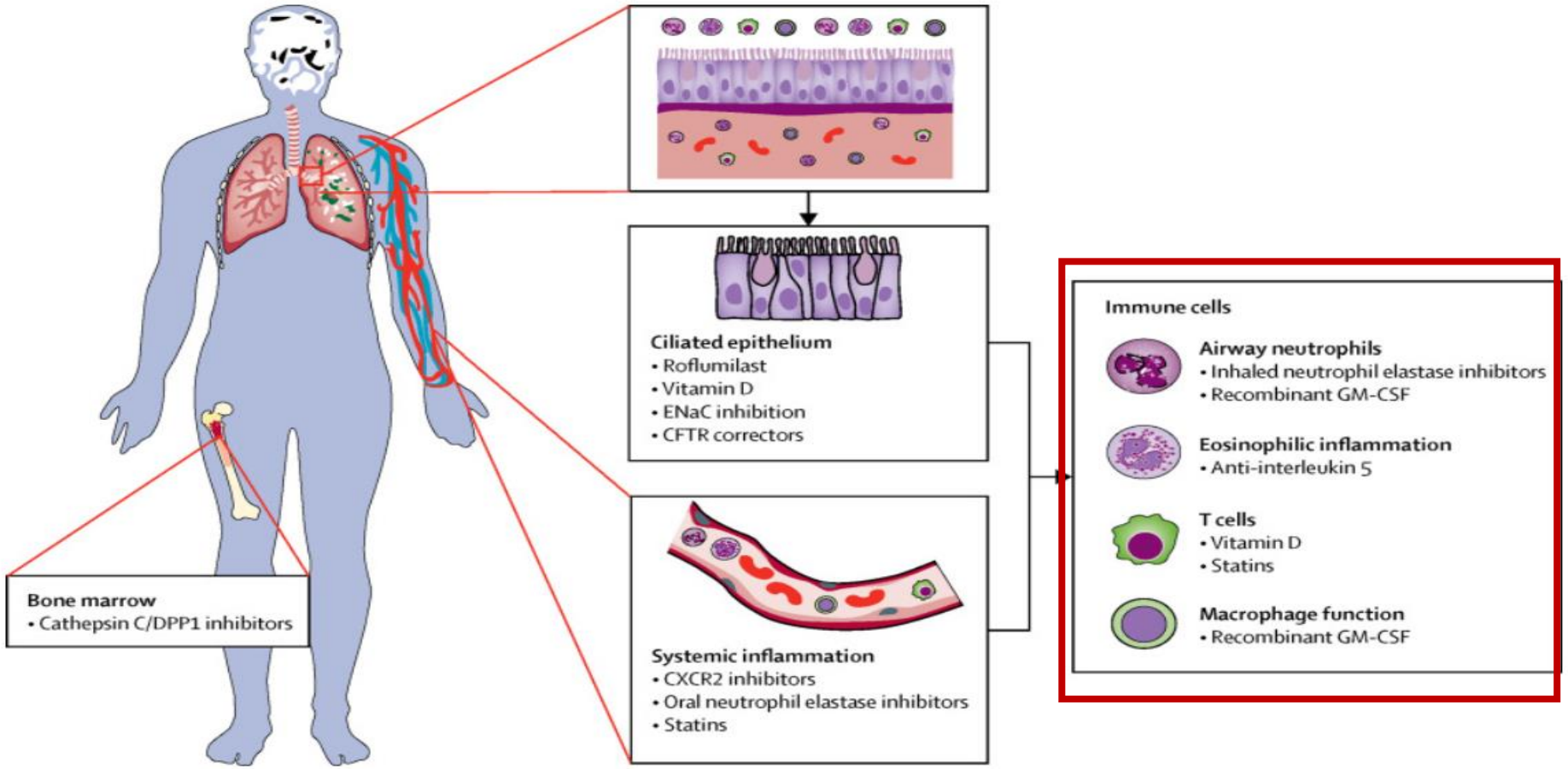
Treatments for bronchiectasis in active clinical development

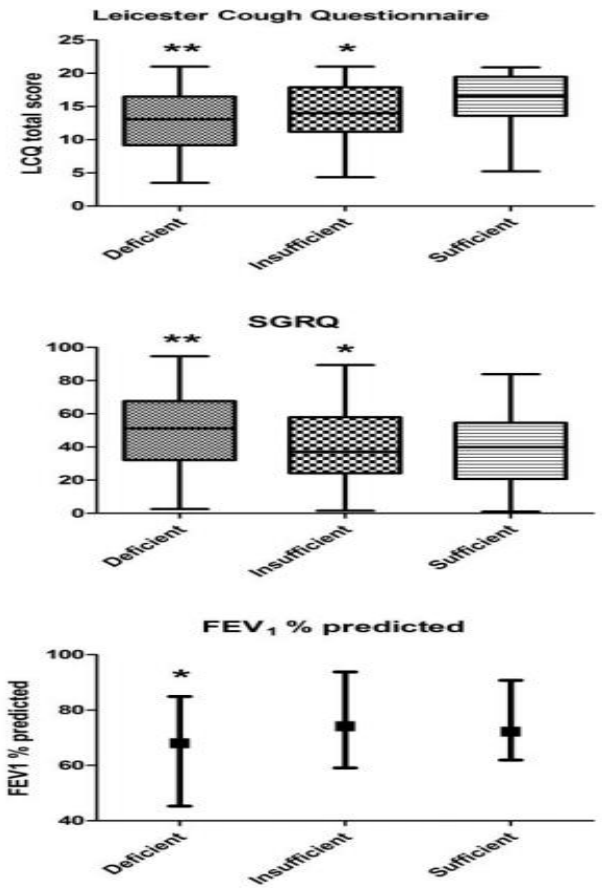


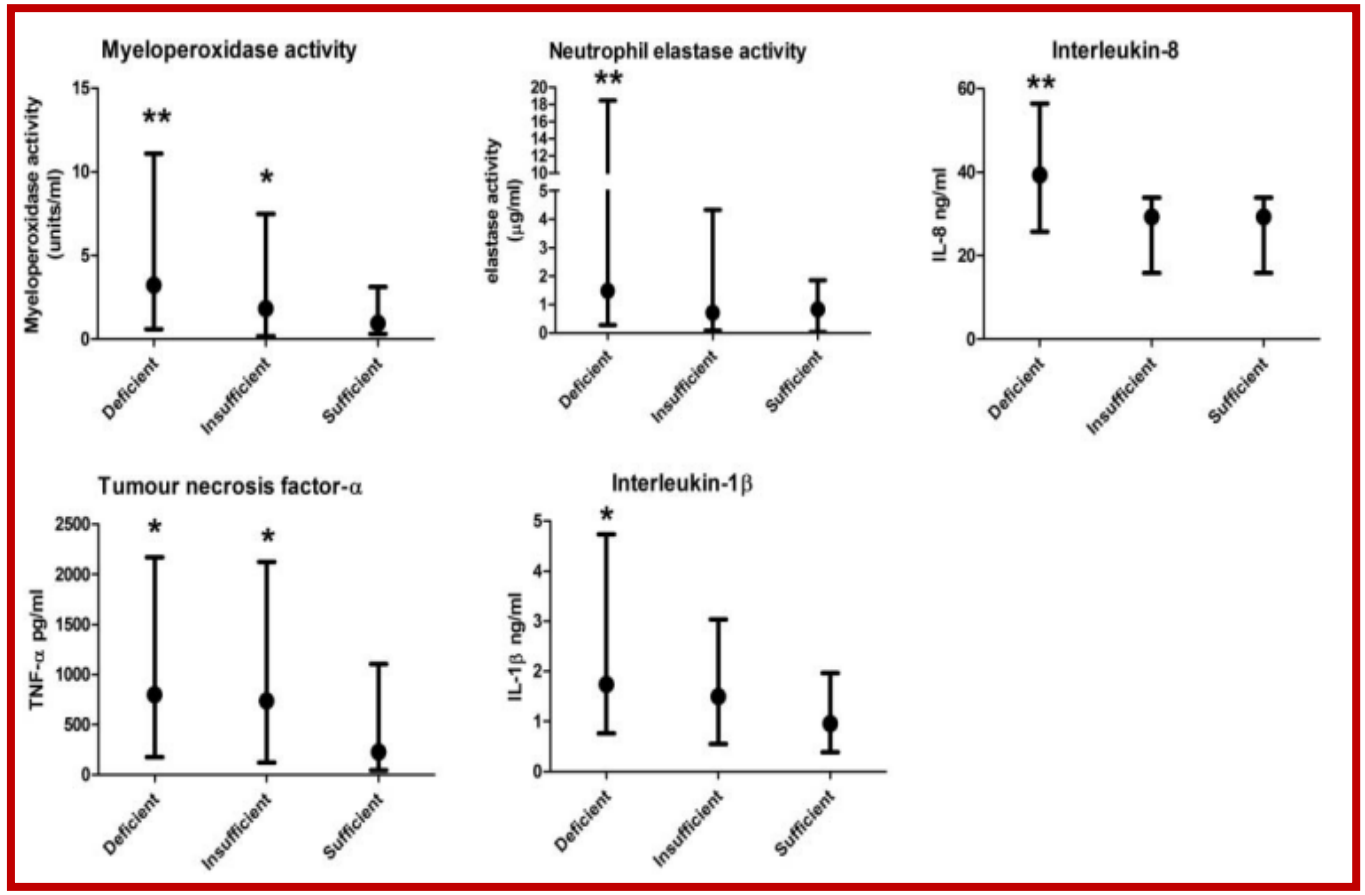
Lancet Respir Med. 2018 Sep;6(9):715-726.

Immunomodulatory drugs

- Inflammation in bronchiectasis is complex and it is uncertain that targeting neutrophils alone will be sufficient to improve clinical outcomes. **Several other anti-inflammatory treatments** with a wide range of clinical effects are in development or have been tested.
  - Vit. D
  - Granulocyte-macrophage colony-stimulating factor
  - Phosphodiesterase 4 inhibitors
  - Statins

Vitamin D and bronchiectasis





Vitamin-D deficiency is common in bronchiectasis and is associated with a higher frequency of bacterial colonization, more exacerbations and worse quality of life.

Thorax 2013; 68: pp. 39-47.

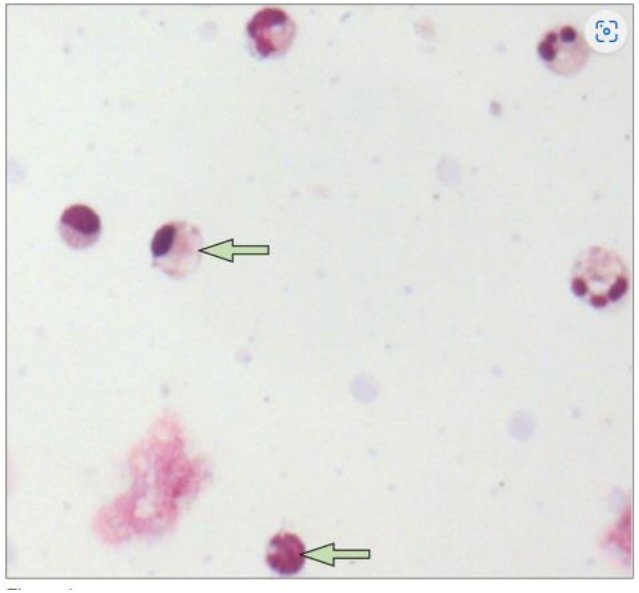
Granulocyte-macrophage colony-stimulating factor

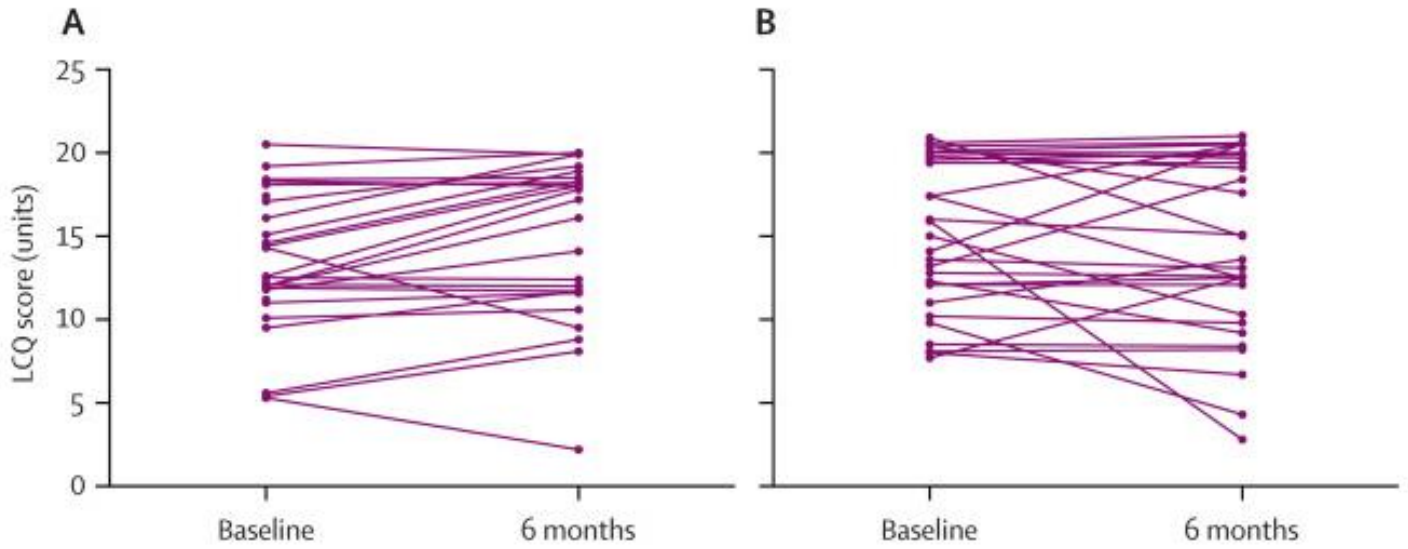
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
  - Glycoprotein secreted by macrophages, T cells, mast cells, natural killer cells, and epithelial cells
  - **Increased susceptibility to P aeruginosa infection** and defective alveolar macrophage phagocytosis, killing, and hydrogen peroxide generation

➡ GM-CSF could reverse abnormalities in diseased airway neutrophils is unknown and requires investigation.

Cytokine 2014; 66: pp. 160-163.

Statin and bronchiectasis





6 months of atorvastatin improved cough on a quality-of-life scale in patients with bronchiectasis.

Lancet Respir Med 2014; 2: pp. 455-463.

Agenda

- Bronchiectasis heterogenicity
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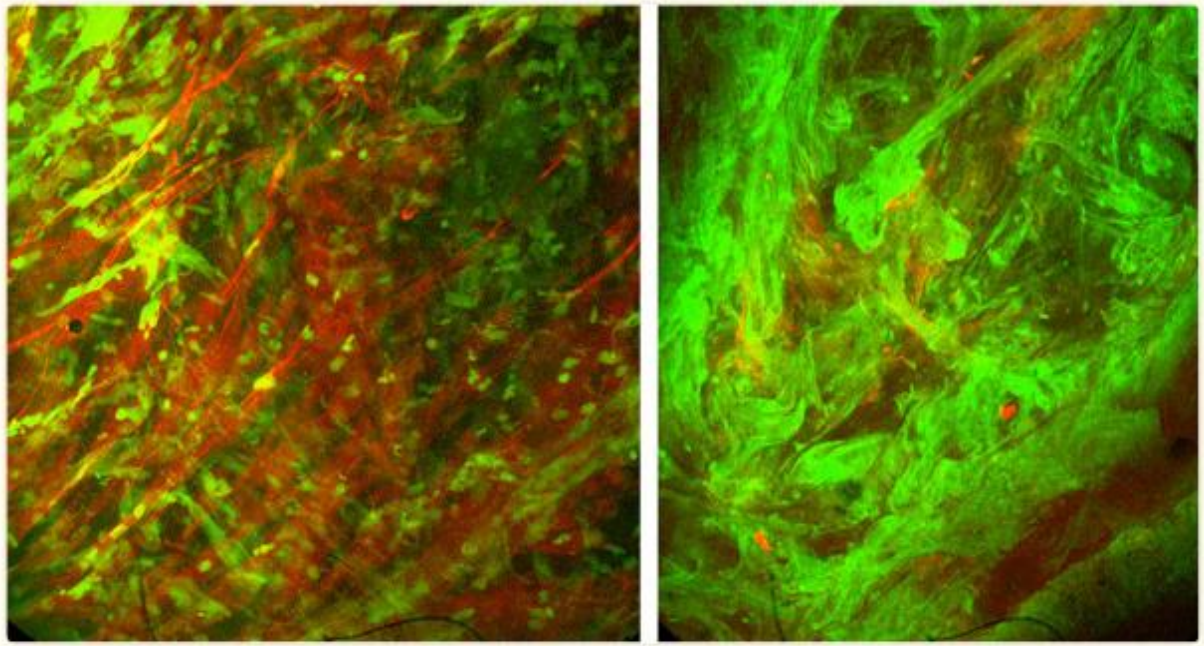
EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
B. HERRERO-CORTINA ET AL.

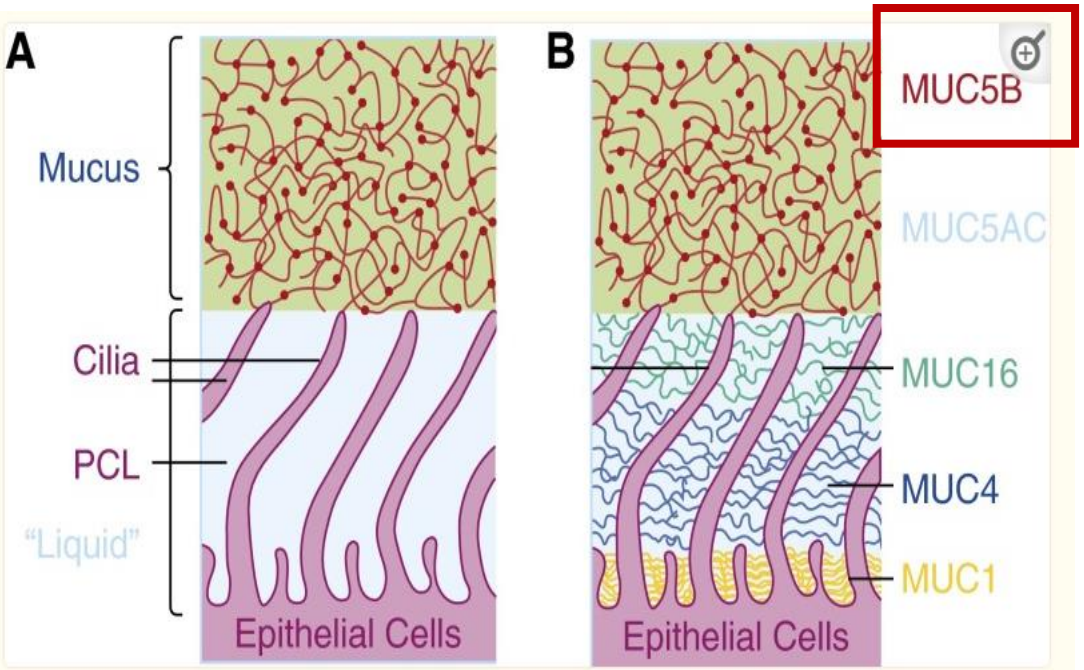
European Respiratory Society statement on airway clearance techniques in adults with bronchiectasis

Beatriz Herrero-Cortina[1,2,3], Annemarie L. Lee[4,5], Ana Oliveira[6,7,8,9], Brenda O'Neill[10], Cristina Jácome[11,12], Simone Dal Corso[13,14], William Poncin[15,16,17], Gerard Muñoz[18,19], Deniz Inal-Ince[20], Victoria Alcaraz-Serrano[21,22], Gregory Reychler[15,16,17], Angela Bellofiore[23,24], Annette Posthumus[25], Patient representative[26], Thomy Tonia[27], James D. Chalmers[28] and Arietta Spinou[29,30]

Eur Respir J. 2023 Jul 20;62(1):2202053

Q1. Physiological rationale for the use of ACTs in adults with bronchiectasis?





Ann Am Thorac Soc. 2016 Apr; 13(Suppl 2): S156–S162.
Transl Respir Med. 2014; 2: 6.

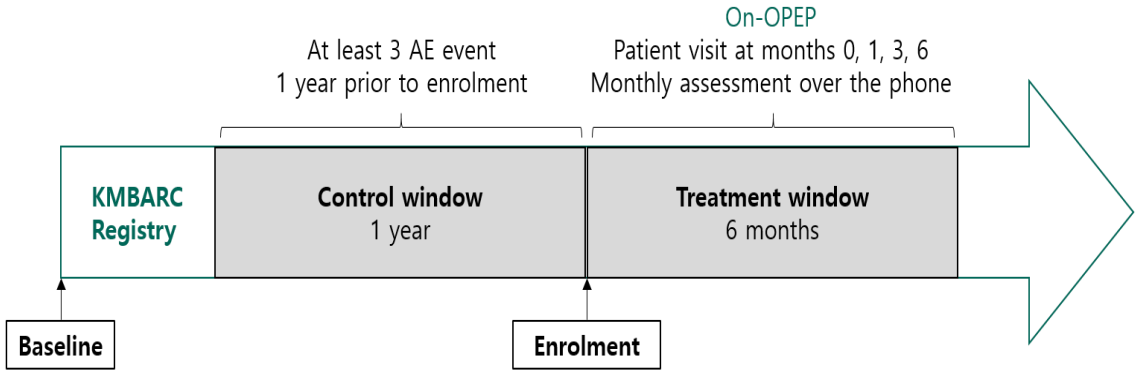
Q2. The effectiveness of ACTs,?

- **A reduction in the impact of cough, improvement in health-related quality of life and reduction in the risk of exacerbations**

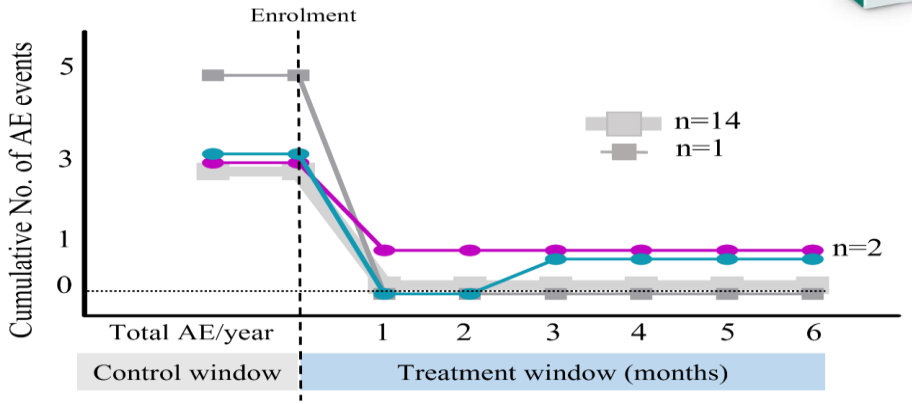
- ACTs **increase the expectorated sputum** during or following a single session of ACTs. Despite being frequently used in clinical practice, the interpretation of sputum changes is ambiguous.

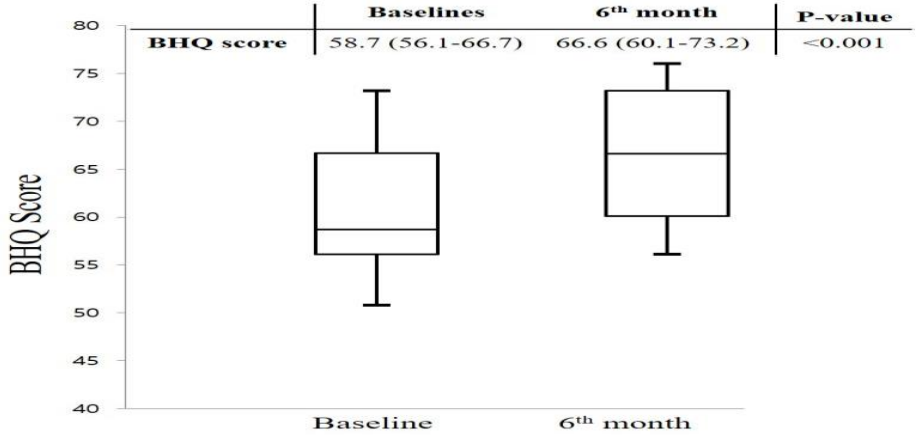
  - no evidence exists about the **optimal frequency or the number of sessions**
  - To date, no studies have investigated the effect of ACTs on **mortality or changes in disease severity using the bronchiectasis severity index or FACED.**

OPEP and bronchiectasis in Korea



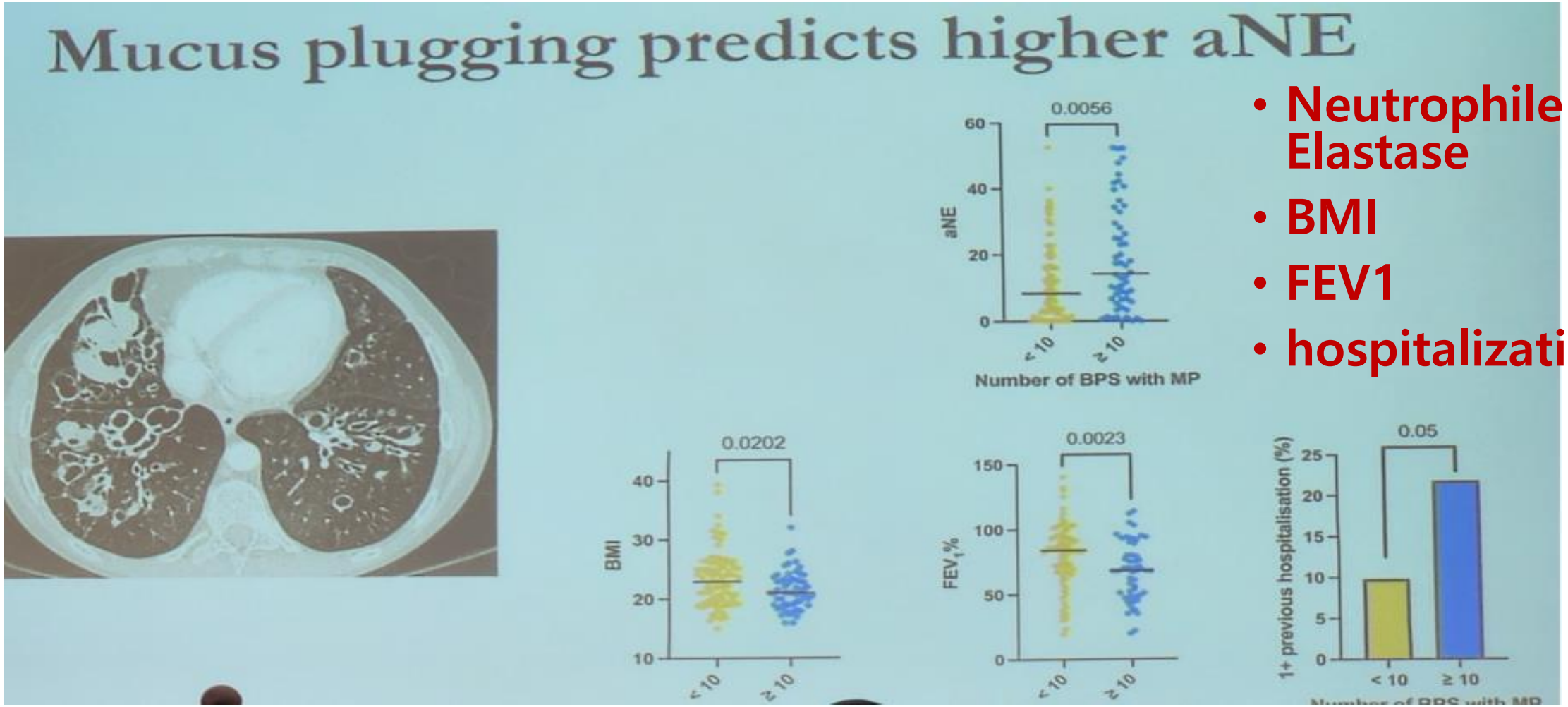
Patient visit Months 0, 1, 3, 6	Monthly assessment Over the phone
• Sputum volume • Patient questionnaire : mMRC score • Patient questionnaire : BHQ score (Baseline, 6 months) • Spirometry, laboratory test (Baseline, 6 months)	• Acute exacerbation : incidence of AE • Adverse events : pneumothorax, haemoptysis, bronchospasm





Physiotherapy with an OPEP device in patients with bronchiectasis who have frequent exacerbations may facilitate subjective symptom improvement and AE prevention without severe adverse events.

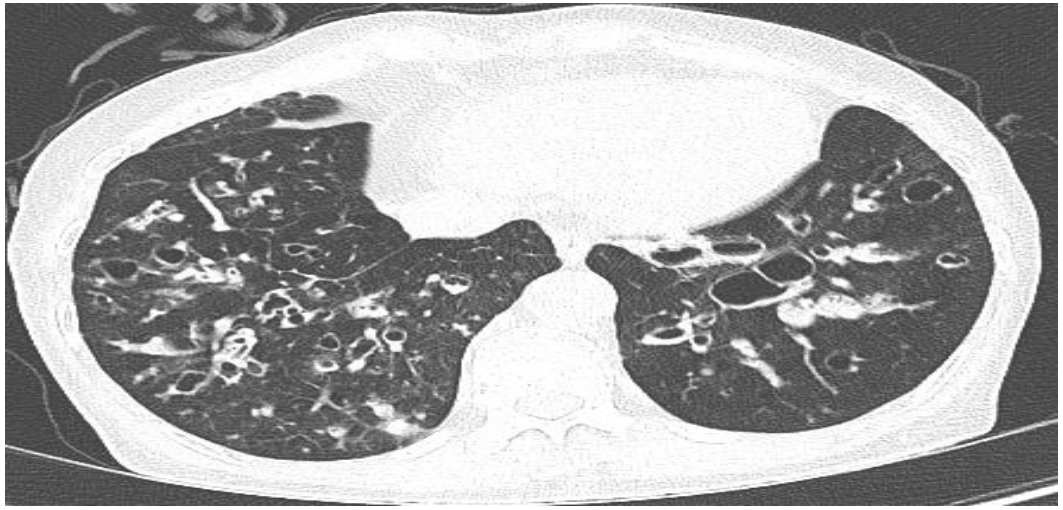
Mucus plugging predicts higher NE?

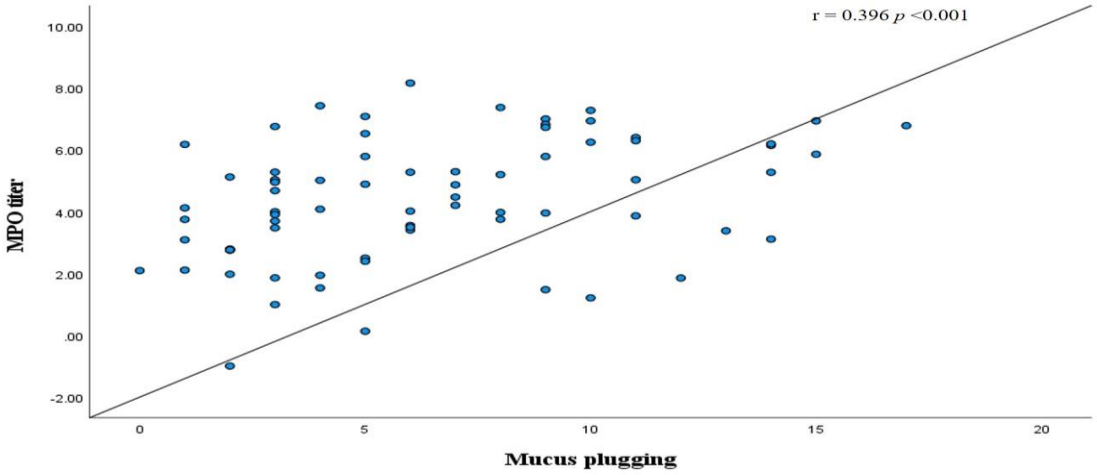


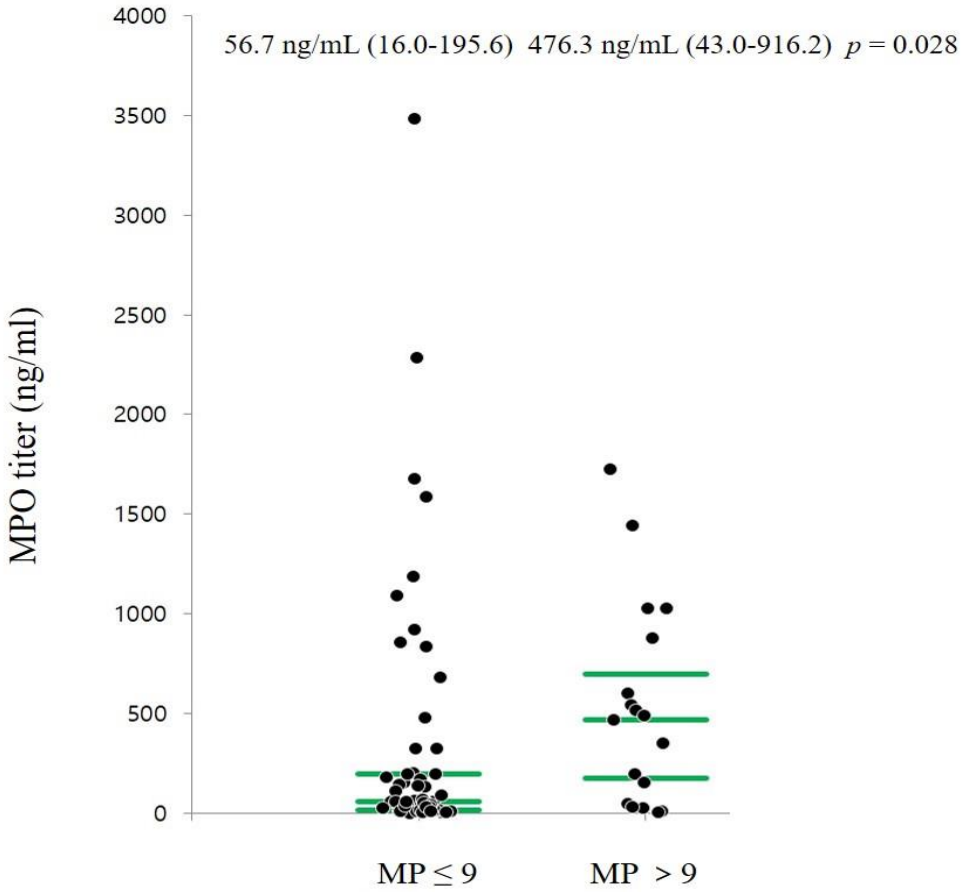
- Neutrophile Elastase
- BMI
- FEV1
- hospitalization

Unpublished data

Mucus plugging predicts higher MPO?







Unpublished data

- 증상/삶의 질 : (-)
- 악화 (분석중)
- **폐기능 (+)**
- **BMI**
- **MPO**

Table 2. Comparison of baseline characteristic according to the extent of mucus plugging

	Extent of mucus plugging ≤ 9 N=60	Extent of mucus plugging > 9 N=18	P-value
Age, years	65 (59-71)	70 (65-75)	0.061
Sex, male	35 (58.3)	7 (38.9)	0.182
BMI, kg/m^2	22.1 (19.5-23.7)	20.6 (18.3-21.2)	0.024
Smoking history			0.243
Never-smoker	40 (66.7)	15 (83.3)	
Current- or ex-smoker	20 (33.3)	3 (16.7)	
Comorbidities			
Hypertension	11 (18.3)	0	0.059
COPD	21 (35.0)	6 (33.3)	1.000
Asthma	5 (8.3)	4 (22.2)	0.199
Diabetes Mellitus	10 (16.7)	2 (11.1)	0.722
Cardiovascular disease	13 (21.7)	3 (16.7)	0.751
Neurologic disease	5 (8.3)	0	0.336
Malignancy	3 (5.0)	2 (6.4)	0.584
Connective tissue disease	6 (10.0)	1 (5.6)	0.684
History of tuberculosis	20 (33.3)	6 (33.3)	1.000
History of Pertussis	6 (10.0)	0	0.327
NTM	16 (26.7)	5 (27.8)	1.000
Microbiology			
P. aeruginosa	14 (3.3)	3 (16.7)	0.748
Others	26 (43.3)	11 (61.1)	0.282
Spirometry			
FVC, L	2.6 (2.3-3.1)	2.0 (1.8-2.6)	0.011
FVC, % predicted	77 (70-87)	65 (62-73)	0.004
FEV1, L	1.9 (1.4-2.2)	1.3 (0.9-1.6)	0.005
FEV1, % predicted	73 (58-85)	54 (47-66)	0.004
FEV1/FVC ratio	72 (63-76)	62 (52-69)	0.012
mMRC	1 (0-2)	1 (1-2)	0.143
BSI score	8 (5-9)	8 (6-12)	0.192
Previous history of AE	1 (0-1)	0 (0-1)	0.596
WBC count, /μL	6535 (5615-7910)	9690 (7705-11875)	<0.001
Neutrophil count, /μL	4050 (3079-4804)	6311 (4556-9657)	<0.001
Albumin, g/dL	4.2 (4.0-4.4)	4.3 (3.4-4.5)	0.506
hs-CRP, mg/dL	0.3 (0.1-1.4)	1.1 (0.4-4.0)	0.023

Data are presented as the median (interquartile range) or numbers (%)

Unpublished data

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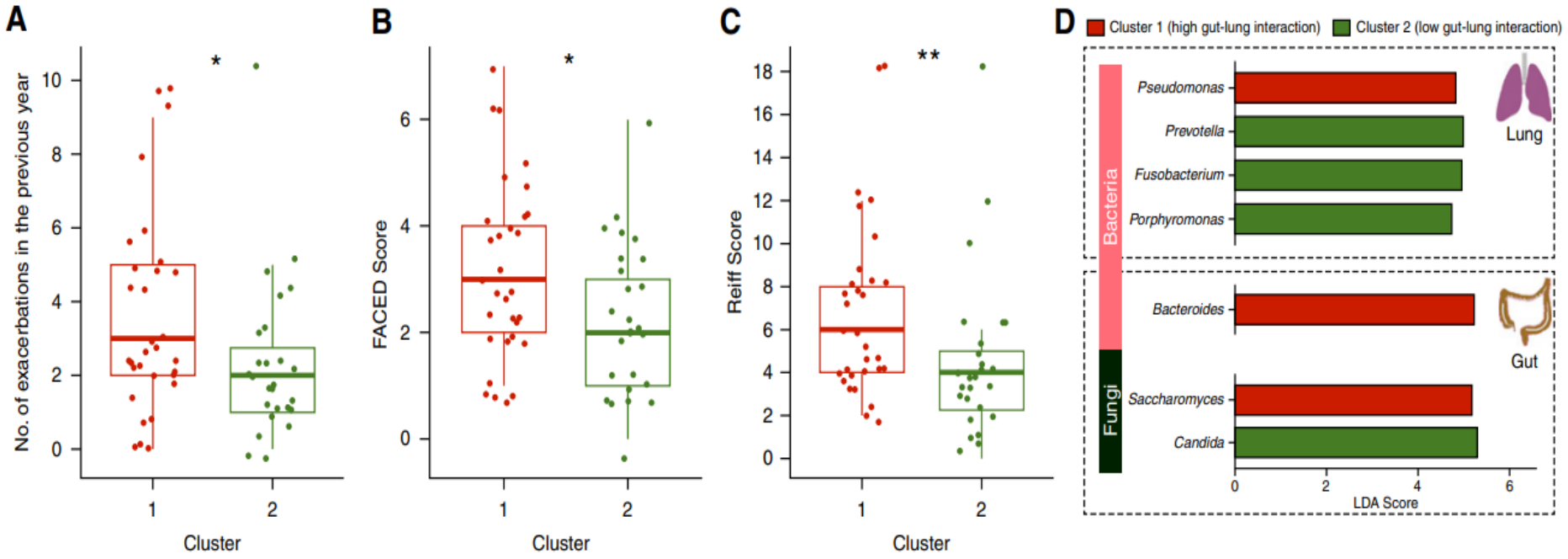
Microbiome and broncbiectasis

- **Patients with *Veillonella spp.*** predominance had frequent exacerbations despite lower levels of neutrophilic inflammation than in patients with other bacterial taxa.

Frequent exacerbations not caused by an underlying infection, who are unlikely to respond to antibiotic therapy, but who might respond to another type of immunomodulatory or mucoactive approach.

Ann Am Thorac Soc. 2014 May;11(4):496-503.

Microbial Dysregulation of the Gut-Lung Axis in Bronchiectasis



A dysregulated gut-lung axis, driven by lung Pseudomonas, associates with poorer clinical outcomes in bronchiectasis.

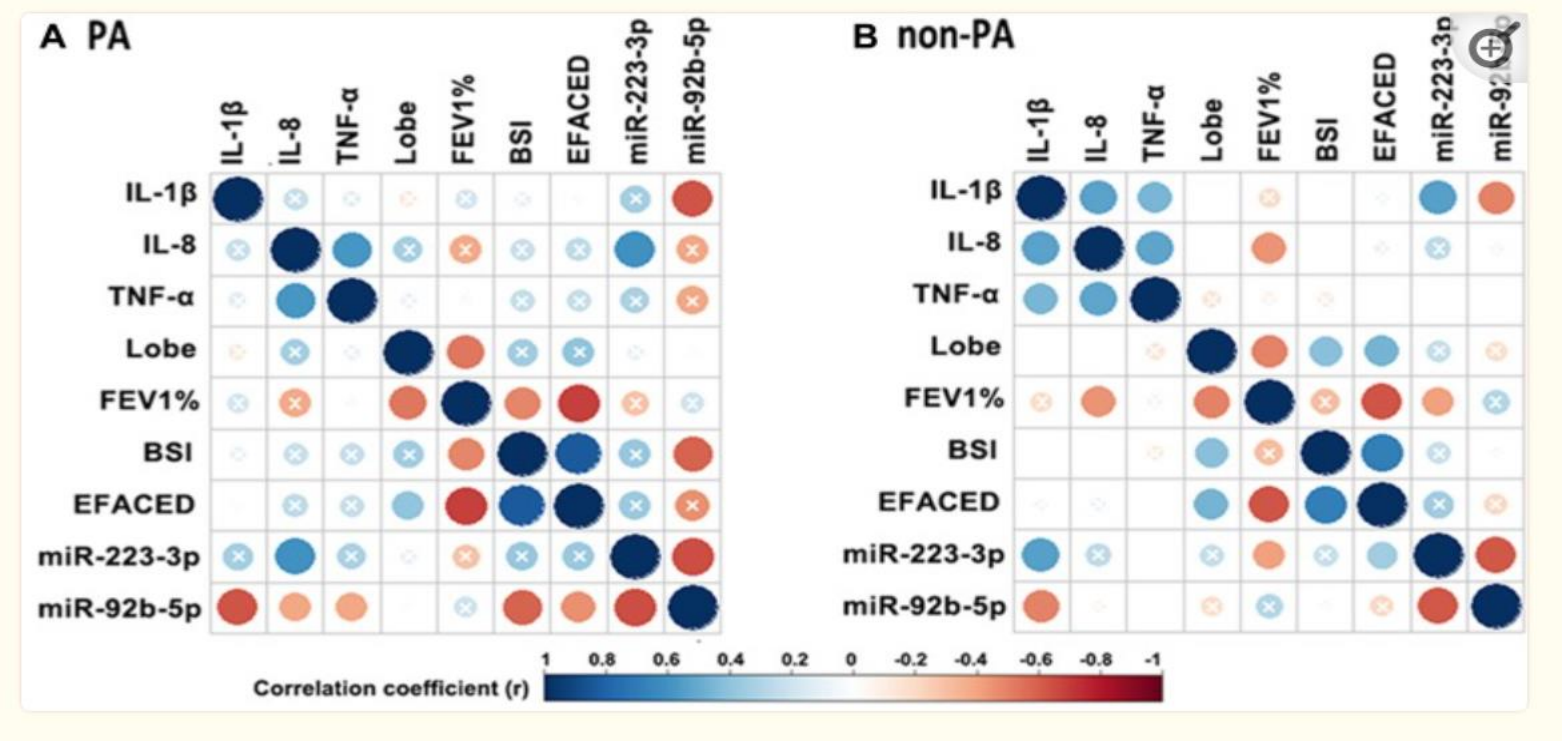
Ann Am Thorac Soc. 2015 Nov;12(11):1602-11.

Multi-omics

- Aiming to **individualize therapeutic interventions** based on multi-omic datasets and integrate this information with the type and severity of disease and the individual's potential response to a particular treatment regimen.

Considering bronchiectasis heterogeneity, understanding of patients' subtypes with translational research should now be a priority.

Sputum Exosomal microRNAs Profiling



Pseudomonas colonization
->sputum inflammation biomarker (IL-1β & IL-8)
miR-92b-5p, miR-223-3p

Int J Chron Obstruct Pulmon Dis. 2019; 14: 2563–2573.

Agenda

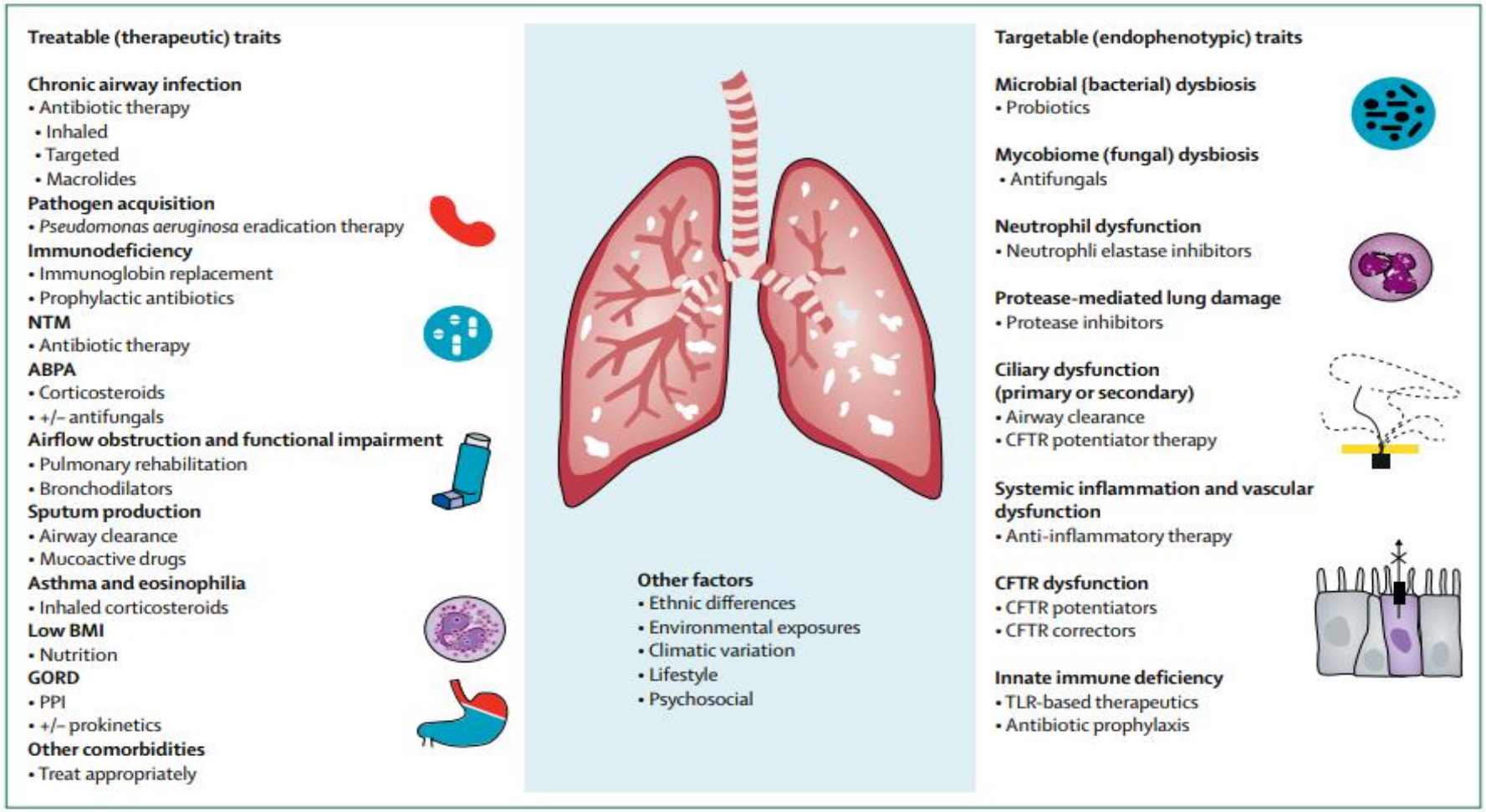
- Bronchiectasis heterogenicity
- Personalized medicine and appropriately targeting treatment
  - Targeting the neutrophil
  - Targeting the eosinophil
  - Immunomodulatory drugs
  - Targeting mucociliary clearance and cough
  - Multi-omics, and the microbiome
- **Summary**

Summary

- **One therapeutic approach will be not effective** in all groups of patients with bronchiectasis?

- **The clinical and molecular heterogeneity of bronchiectasis must be addressed through detailed endo-phenotyping studies**, which might then permit enhanced patients' stratification leading to better treatment and translate to improved clinical trial designs and outcomes.

Personalized medicine and appropriately targeting treatment



감사합니다