Integrating Anti-Inflammatory Strategies in the Management of Bronchiectasis

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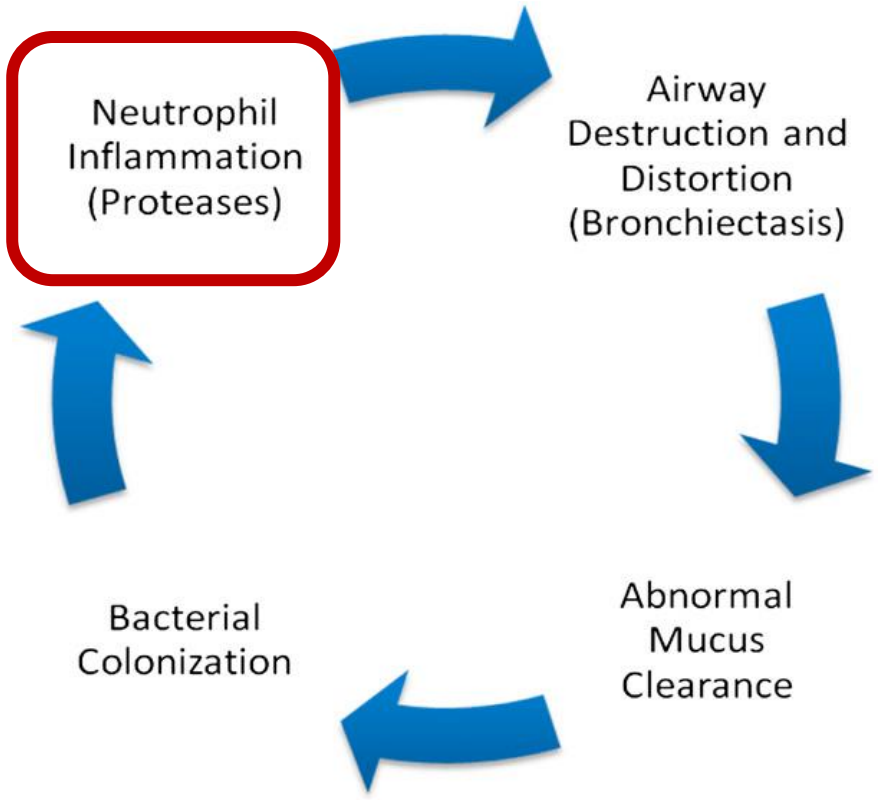
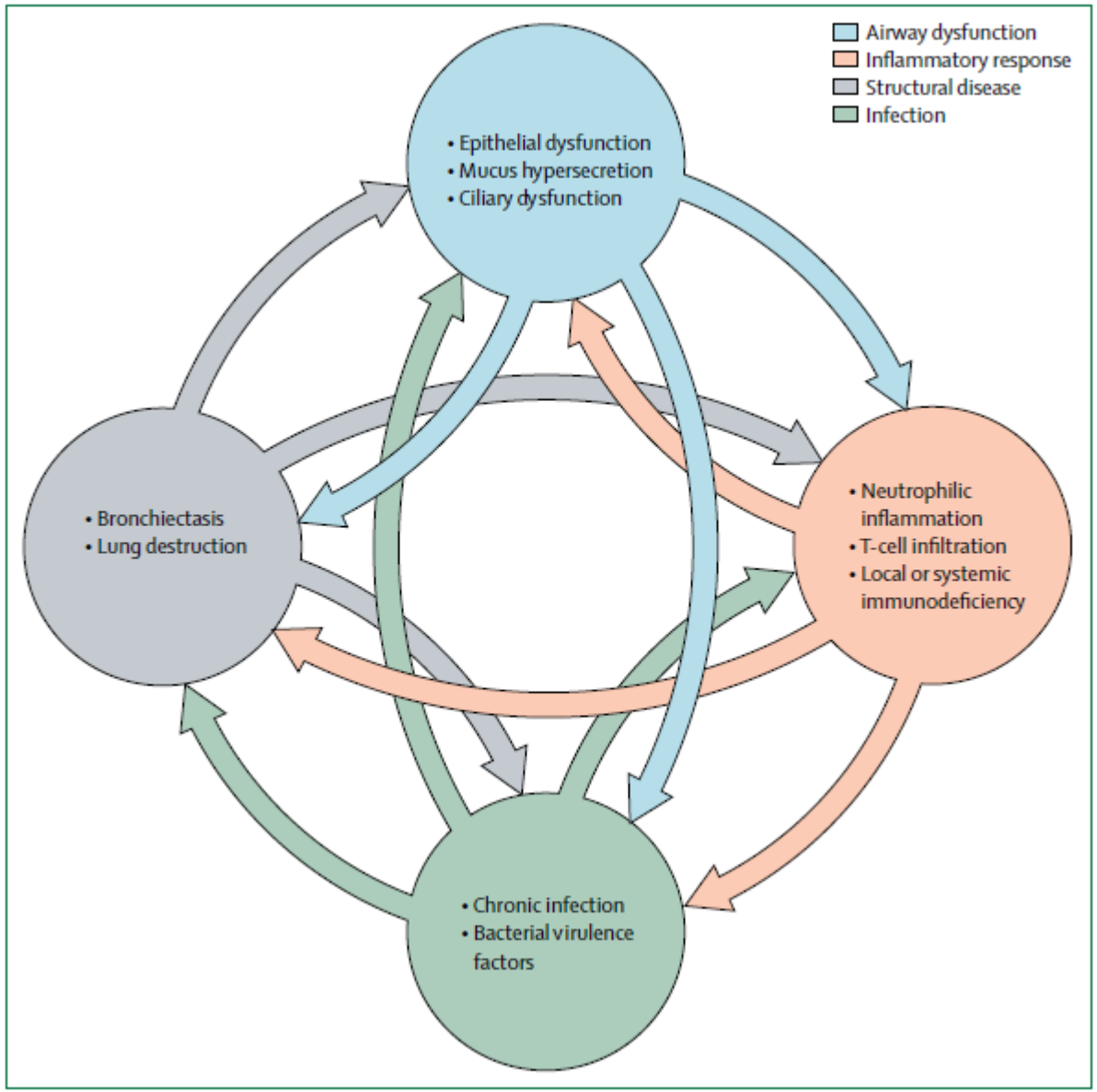
Pathophysiology of bronchiectasis



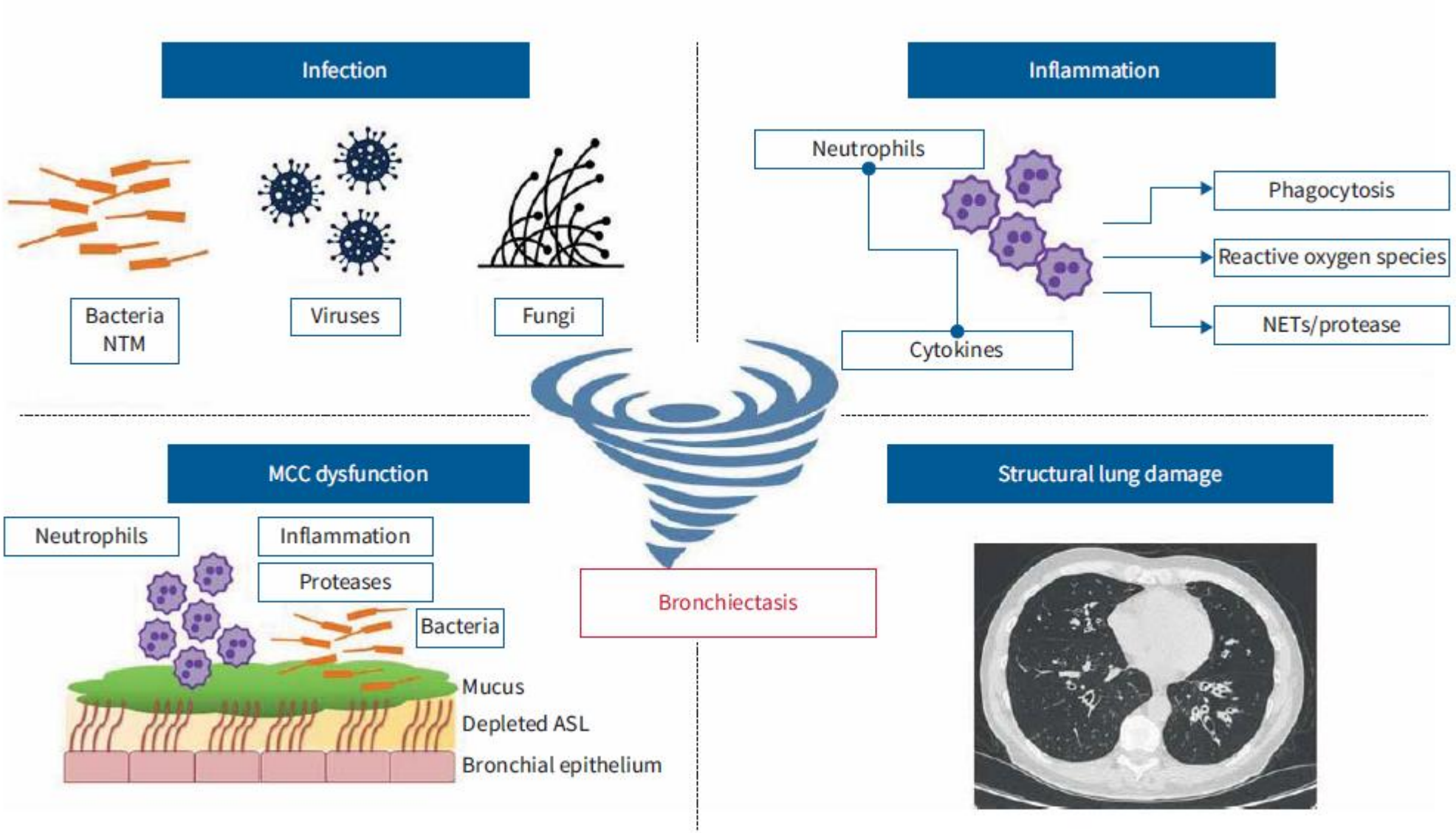
vicious cycle

Eur J Repir Dis Suppl. 1986:147:6-15



vicious vortex

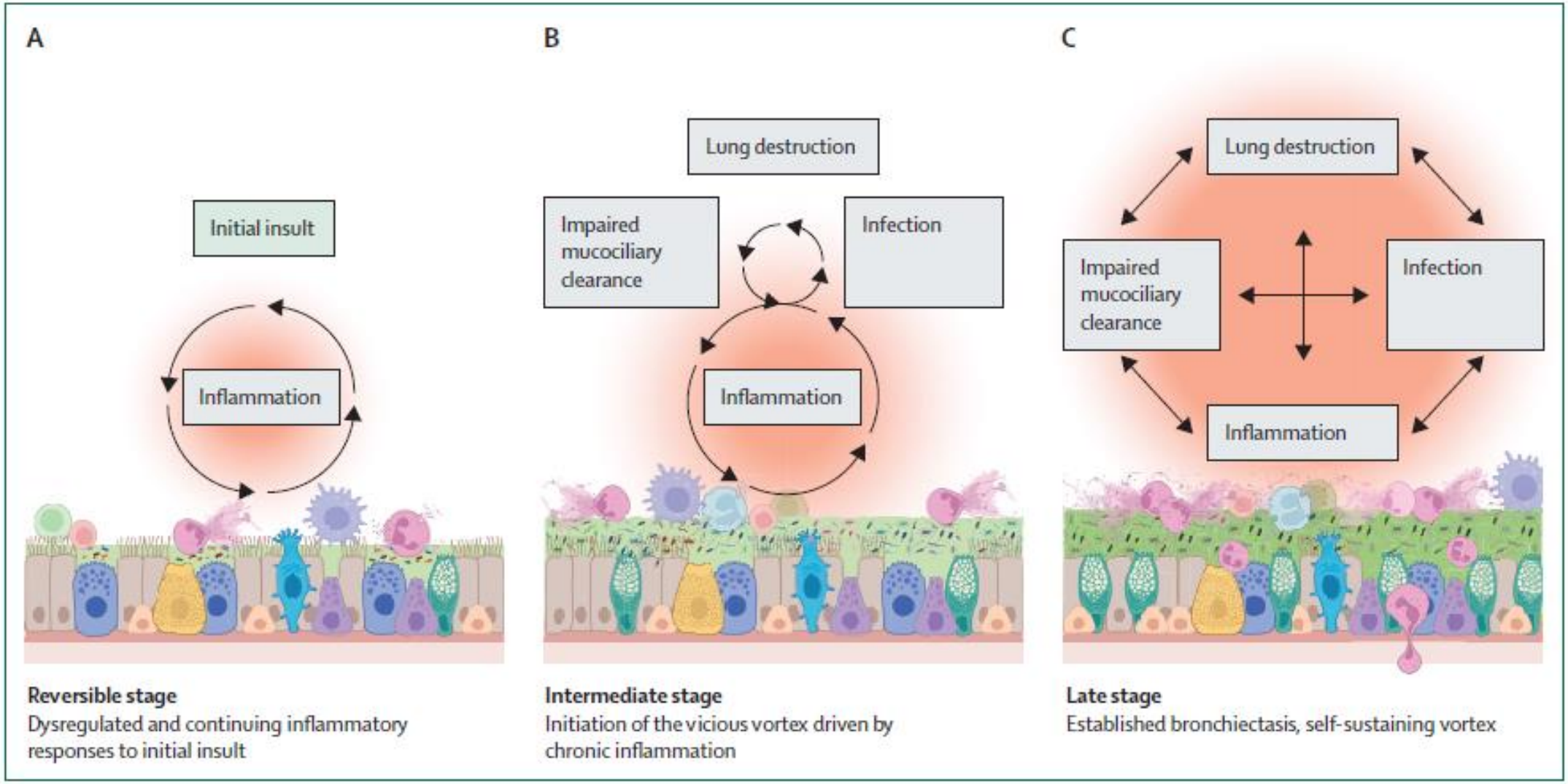
Lancet 2018; 392: 880–90



vicious vortex

Eur Respir Rev 2023; 32: 230015

The role of inflammation in the initiation and progression of bronchiectasis

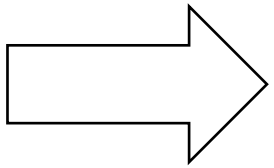


Lancet Respir Med 2024 Published online July 3, 2024

Bronchiectasis management

Treatment aims

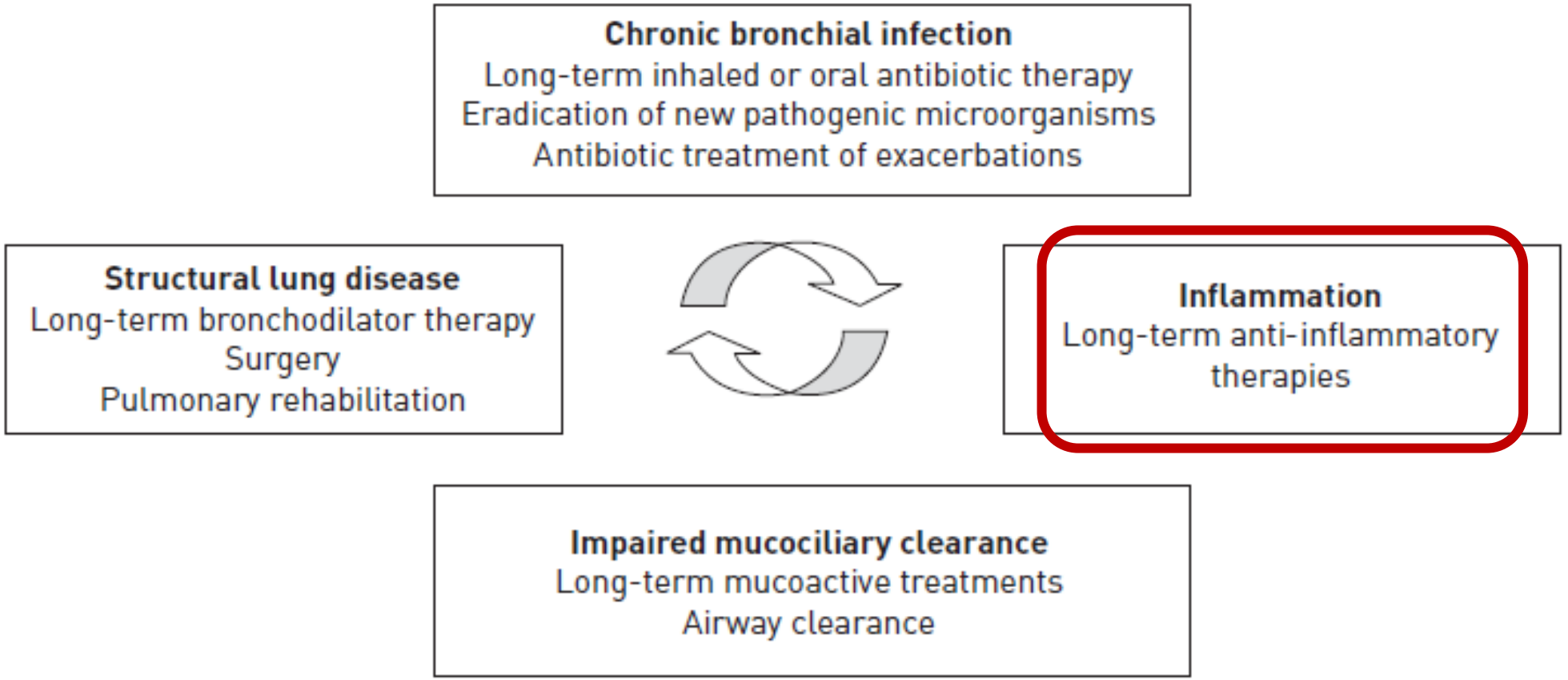
- ✓ **<u>Reduce inflammation</u>**
- ✓ To improve mucus clearance from the airways
- ✓ Prevent and reduce the impact of infection



Goal for therapy

- ✓ Reduce symptom burden
- ✓ Reduce exacerbations
- ✓ Prevent disease progression
- ✓ Improve quality of life

Guidelines for the management of bronchiectasis – ERS 2017



Eur Respir J 2017; 50: 1700629

Question: Should **long-term anti-inflammatory agents** be used in adult patients with bronchiectasis?

- Recommendation:
  - We suggest **not offering** treatment with **inhaled corticosteroids** to adults with bronchiectasis (conditional recommendation, low quality of evidence).
  - We recommend **not offering statins** for the treatment of bronchiectasis (strong recommendation, low quality of evidence).
  - We suggest that the diagnosis of bronchiectasis should not affect the use of inhaled corticosteroids in patients with comorbid asthma or COPD (best practice advice, indirect evidence).

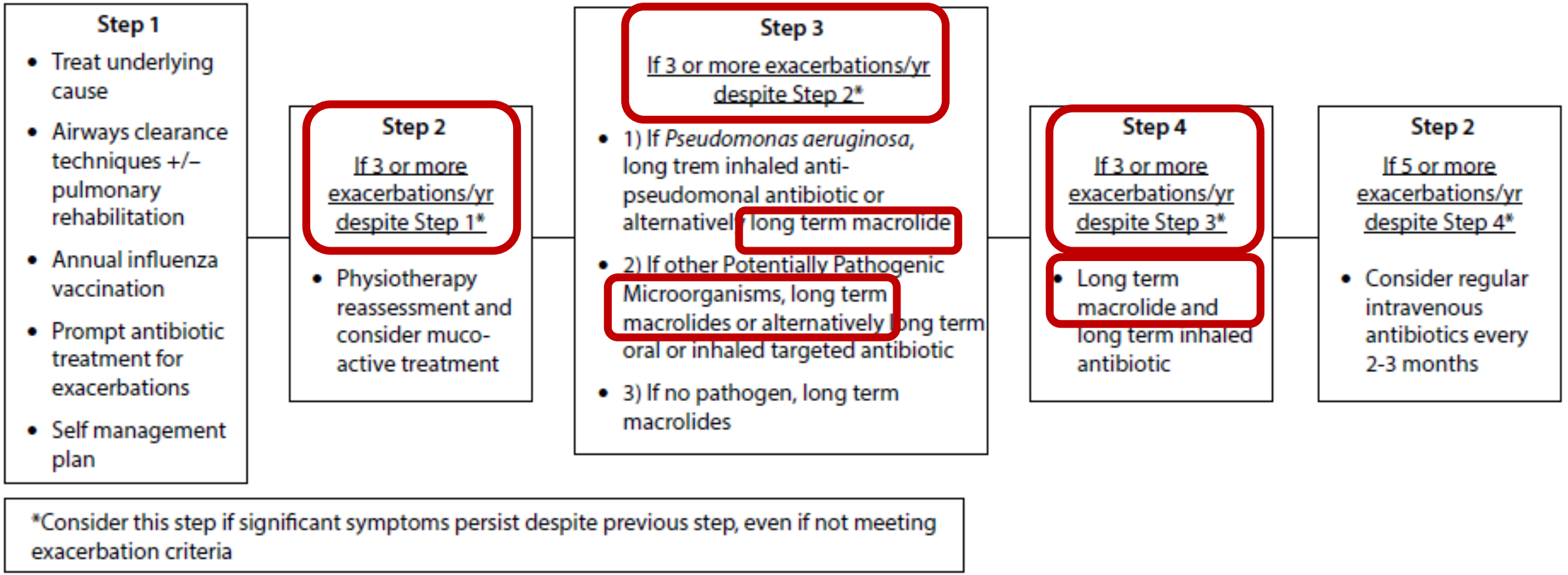
Eur Respir J 2017; 50: 1700629

Question: Is **long-term antibiotic treatment** (⩾3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?

- Recommendations
  - We suggest offering long-term antibiotic treatment for adults with bronchiectasis who have three or more exacerbations per year (conditional recommendation, moderate quality evidence).
  - All subsequent recommendations refer to patients with three or more exacerbations per year.
  - We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis and chronic *P. aeruginosa* infection (conditional recommendation, moderate quality evidence).
  - We suggest **long-term treatment with macrolides (azithromycin, erythromycin)** for adults with bronchiectasis and chronic *P. aeruginosa* infection in whom an inhaled antibiotic is contraindicated, not tolerated or not feasible (conditional recommendation, low quality evidence).
  - We suggest **long-term treatment with macrolides (azithromycin, erythromycin)** in addition to or in place of an inhaled antibiotic, for adults with bronchiectasis and chronic *P. aeruginosa* infection who have a high exacerbation frequency despite taking an inhaled antibiotic (conditional recommendation, low quality evidence).
  - We suggest **long-term treatment with macrolides (azithromycin, erythromycin)** for adults with bronchiectasis not infected with P. aeruginosa (conditional recommendation, moderate quality evidence).
  - We suggest long-term treatment with an oral antibiotic (choice based on antibiotic susceptibility and patient tolerance) for adults with bronchiectasis not infected with *P. aeruginosa* in whom macrolides are contraindicated, not tolerated or ineffective (conditional recommendation, low quality evidence).
  - We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis not infected with *P. aeruginosa* in whom oral antibiotic prophylaxis is contraindicated, not tolerated or ineffective (conditional recommendation, low quality of evidence).

Eur Respir J 2017; 50: 1700629

Guidelines for the management of bronchiectasis: stepwise management – 2019 BTS



Antibiotics are used to treat exacerbations that present with an acute deterioration (usually over several days) with worsening local symtoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset. The flow diagram refers to three or more annual exacerbations.

Thorax 2019;74 (Suppl 1):1–69.

What is the evidence for **long term anti-inflammatory therapies** in bronchiectasis?

- Recommendations
  - **Do not** routinely offer **inhaled corticosteroids** to patients with bronchiectasis without other indications (such as ABPA, chronic asthma, COPD and inflammatory bowel disease). (B)
  - **Do not** offer **long-term oral corticosteroids** for patients with bronchiectasis without other indications (such as ABPA, chronic asthma, COPD, inflammatory bowel disease). (D)
  - **Do not** routinely offer **phosphodiesterase type 4 (PDE4) inhibitors, methylxanthines or leukotriene receptor antagonists** for bronchiectasis treatment. (D)
  - **Do not** routinely offer **CXCR2 antagonists, neutrophil elastase inhibitors or statins** for bronchiectasis treatment. (B)
- Good practice point
  - Inhaled corticosteroids have an established role in the management of asthma and in a proportion of patients with COPD which are common co-morbid conditions in bronchiectasis.
- Research recommendation
  - Randomised controlled trials are needed to assess the long term impact of anti-inflammatory therapies.

Thorax 2019;74 (Suppl 1):1–69.

What treatments improve outcomes for patients with stable bronchiectasis?

Recommendations

- Consider long term antibiotics in patients with bronchiectasis who experience 3 or more exacerbations per year. (A)
- *In these patients, the following are recommended*

P. aeruginosa colonised patients

- a. Use inhaled colistin for patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. (B)
- b. Consider inhaled gentamicin as a second line alternative to colistin for patients with bronchiectasis and chronic *P. aeruginosa* infection. (B)
- c. Consider **azithromycin or erythromycin** as an alternative (eg, if a patient does not tolerate inhaled antibiotics) to an inhaled antibiotic for patients with bronchiectasis and chronic *P. aeruginosa* infection. (B)
- d. Consider **azithromycin or erythromycin** as an additive treatment to an inhaled antibiotic for patients with bronchiectasis and chronic *P. aeruginosa* infection who have a high exacerbation frequency. (D)

Non- P. aeruginosa colonised patients

- e. Use **azithromycin or erythromycin** for patient with bronchiectasis. (A)
- f. Consider inhaled gentamicin as a second line alternative to azithromycin or erythromycin. (B)
- g. Consider **doxycycline** as an alternative in patients intolerant of macrolides or in whom they are ineffective. (C)

Thorax 2019;74 (Suppl 1):1–69.

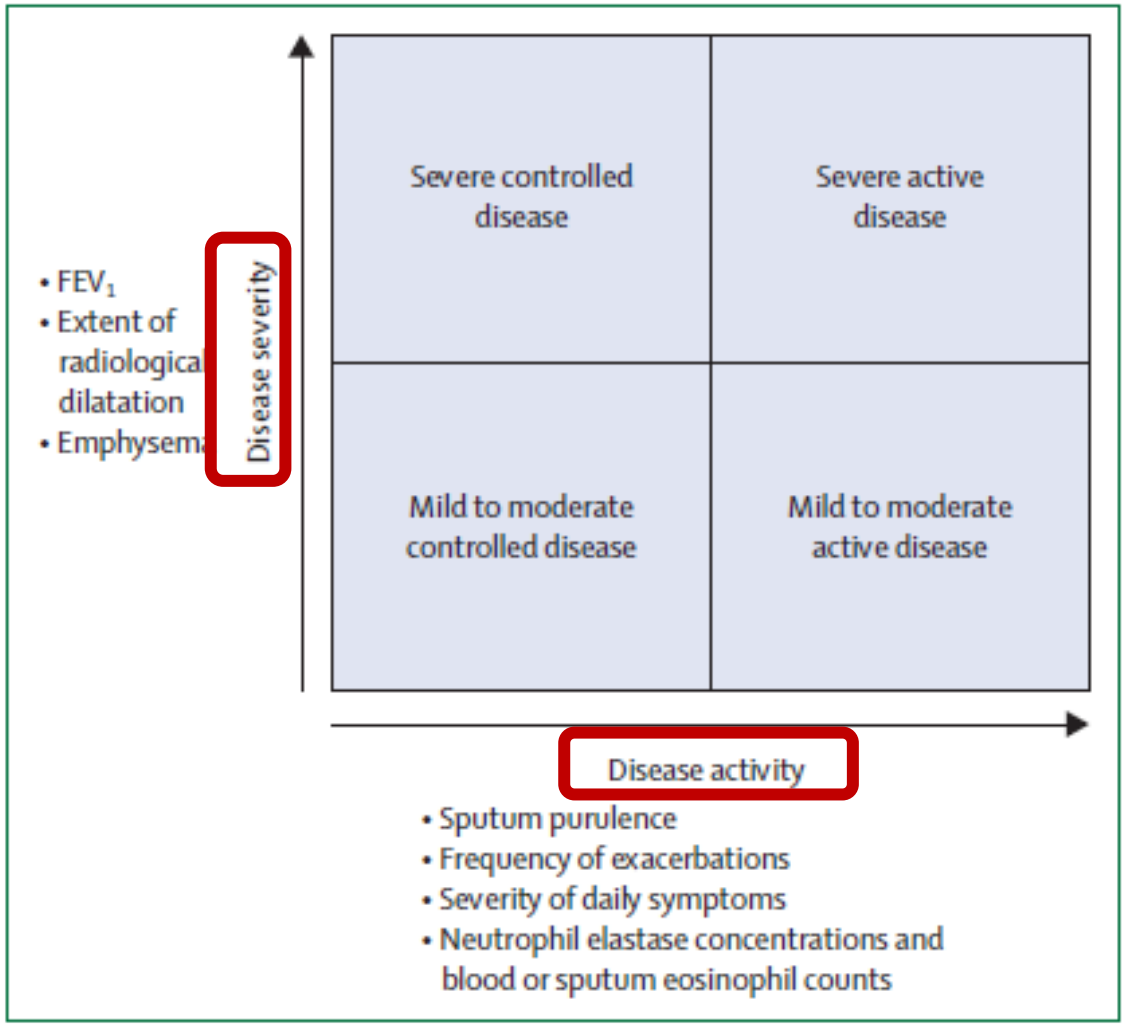
Rethinking bronchiectasis as an inflammatory disease

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

- Current therapeutic approaches to bronchiectasis are heavily focused on management of infection along with enhancing mucus clearance.
- In this Review, we argue that bronchiectasis is primarily a chronic inflammatory disease, requiring early identification of at-risk individuals, and we introduce a novel concept of disease activity with important implications for clinical practice and future research.
- "**Disease activity**": the degree to which the disease is progressing and affecting patients
  - **elevated clinical markers of inflammation** and/or **severe symptoms**
  - associated with an increased risk exacerbations.
- Thinking of bronchiectasis as an inflammatory disease suggests that rather than a stepwise approach in which treatments are escalated on the basis of worsening health status, patients at high risk are proactively identified and treated to prevent disease progression.

Lancet Respir Med 2024 Published online July 3, 2024

Disease activity & severity

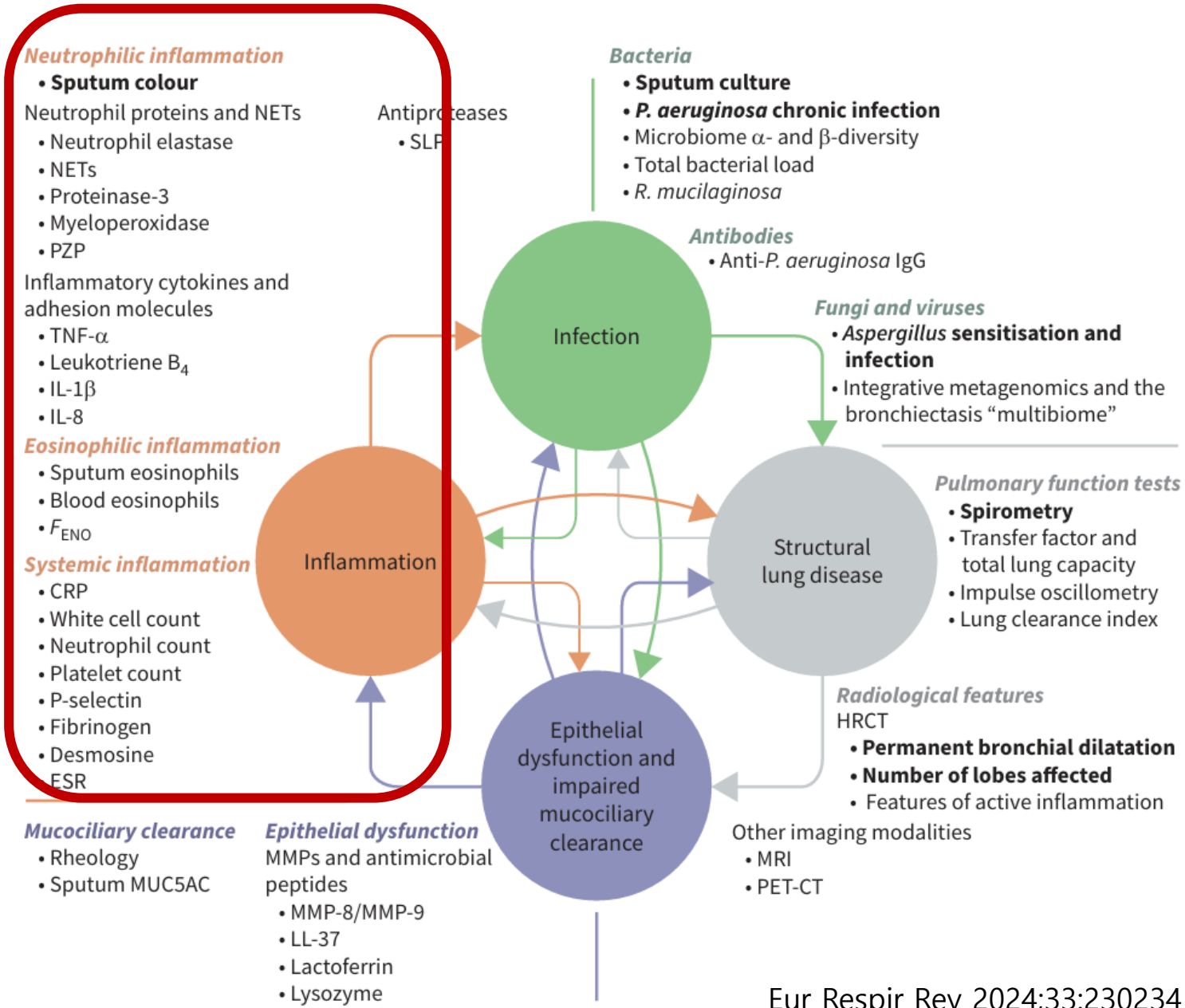


Lancet Respir Med 2024 Published online July 3, 2024

Heterogeneity of bronchiectasis

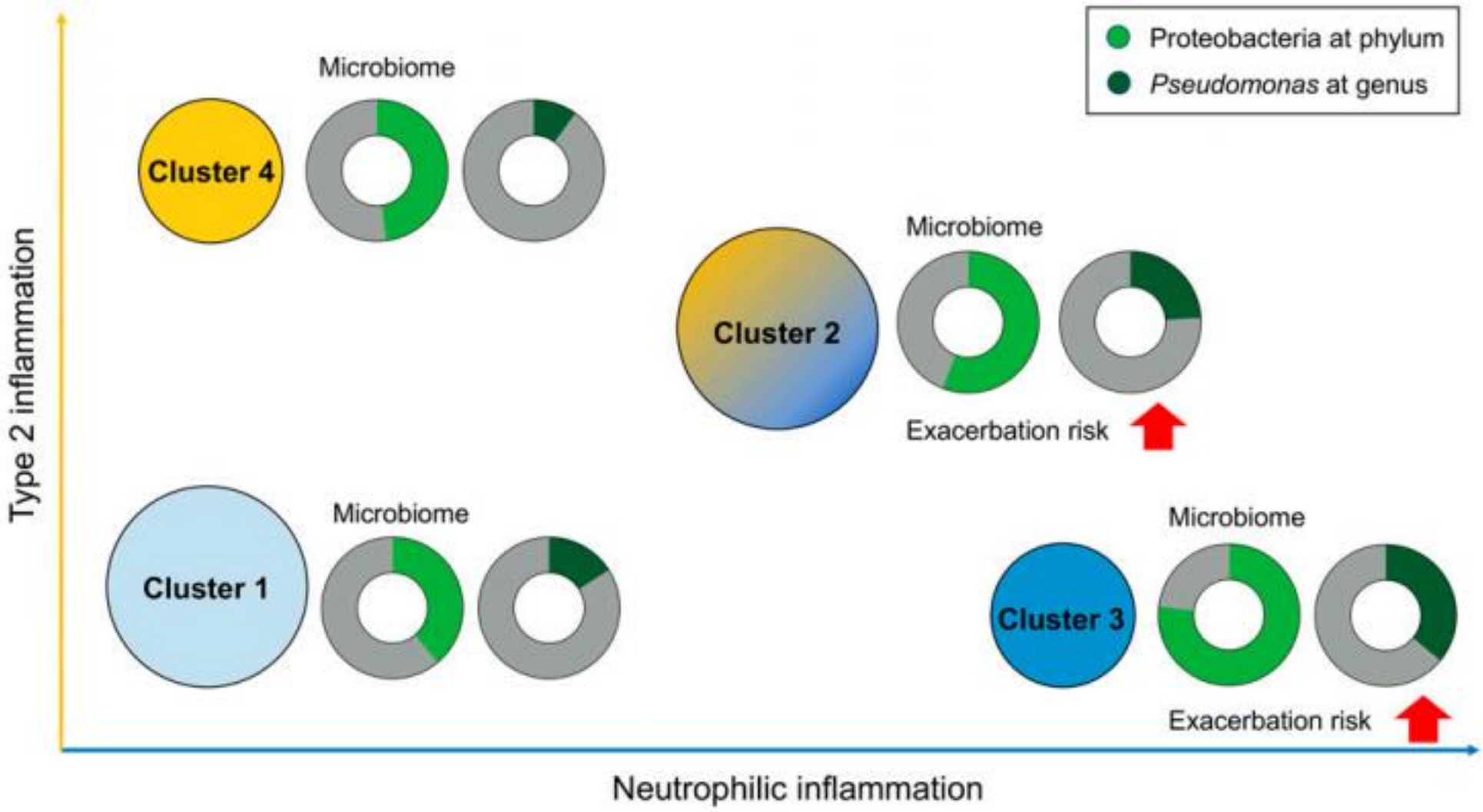
- "No typical bronchiectasis"

- **Treatable traits:** defined as therapeutic targets identified through either a phenotype or an endotype and using a validated biomarker
  - **Phenotypes**: defined as classifying disease through observable patient characteristics
  - **Endotypes**: defined as classifying disease through underlying biological mechanisms



Eur Respir Rev 2024;33:230234

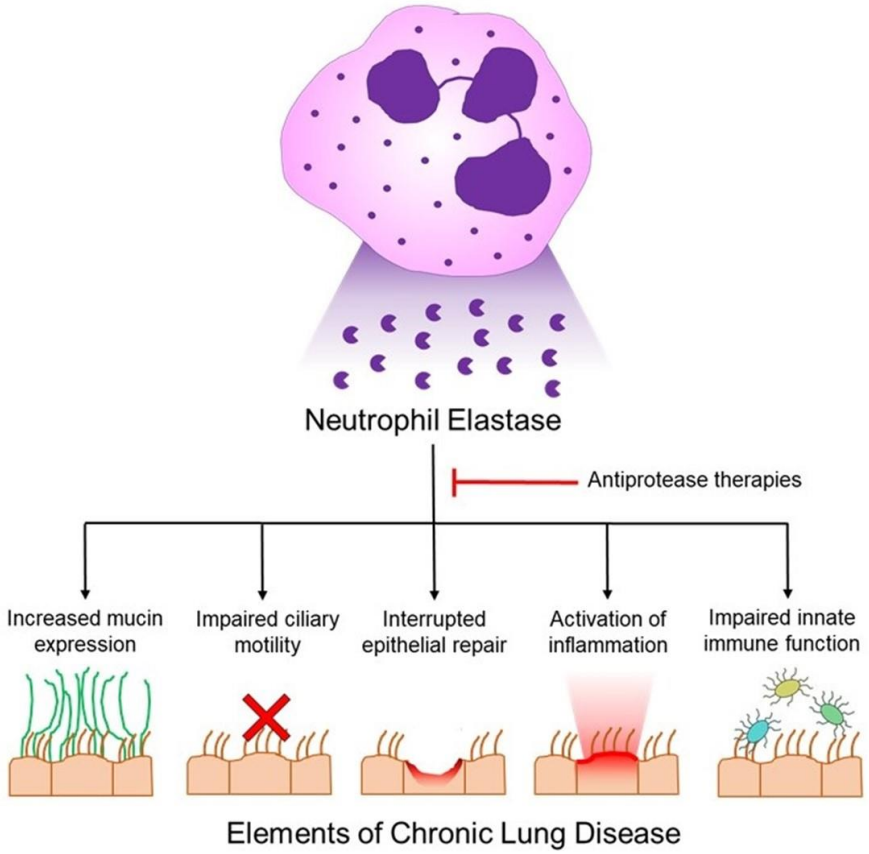
Type of inflammation

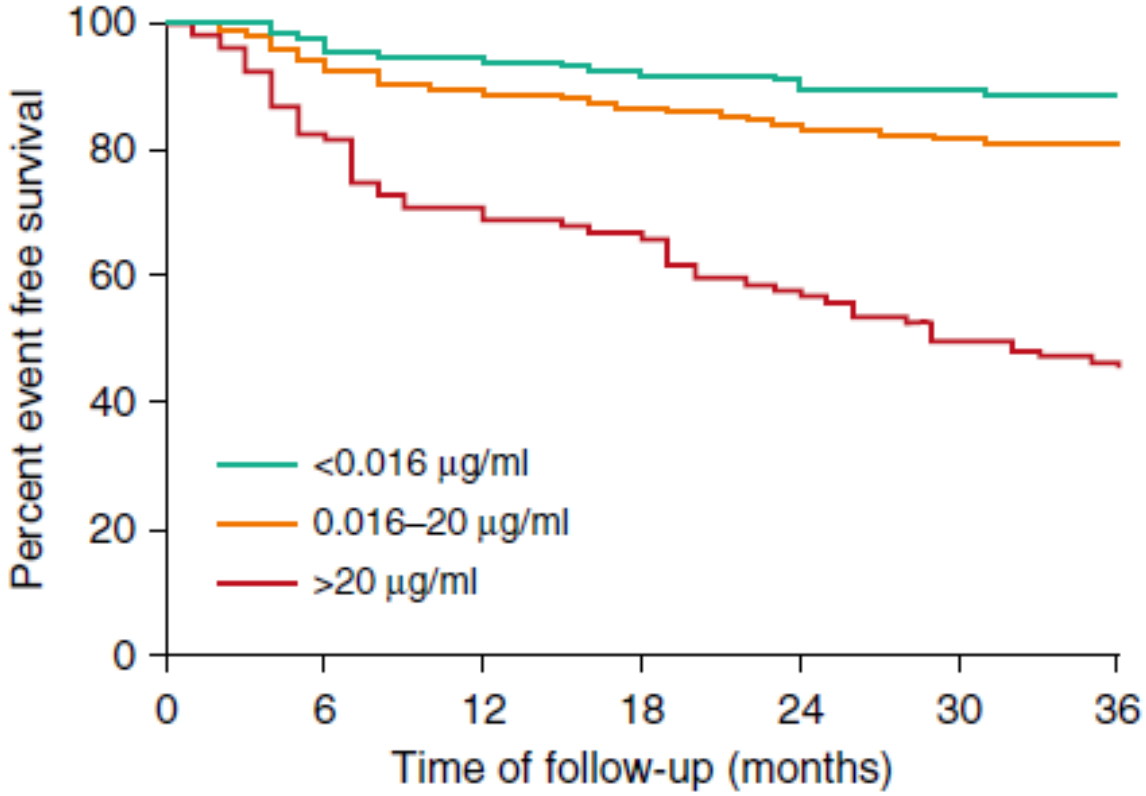


Am J Respir Crit Care Med 2023; 208(11): 1166–1176

Biomarkers of airway inflammation

- **Neutrophilic inflammation**
  - sputum neutrophil elastase activity

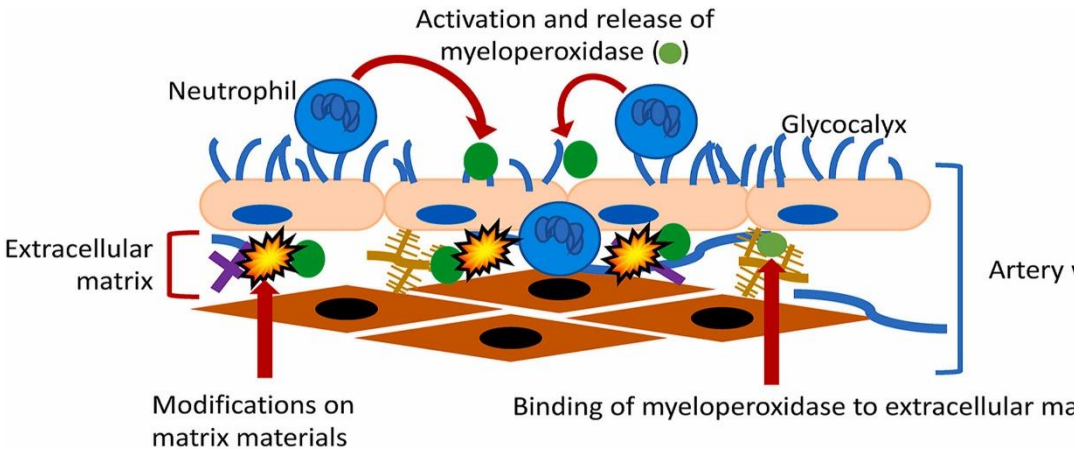


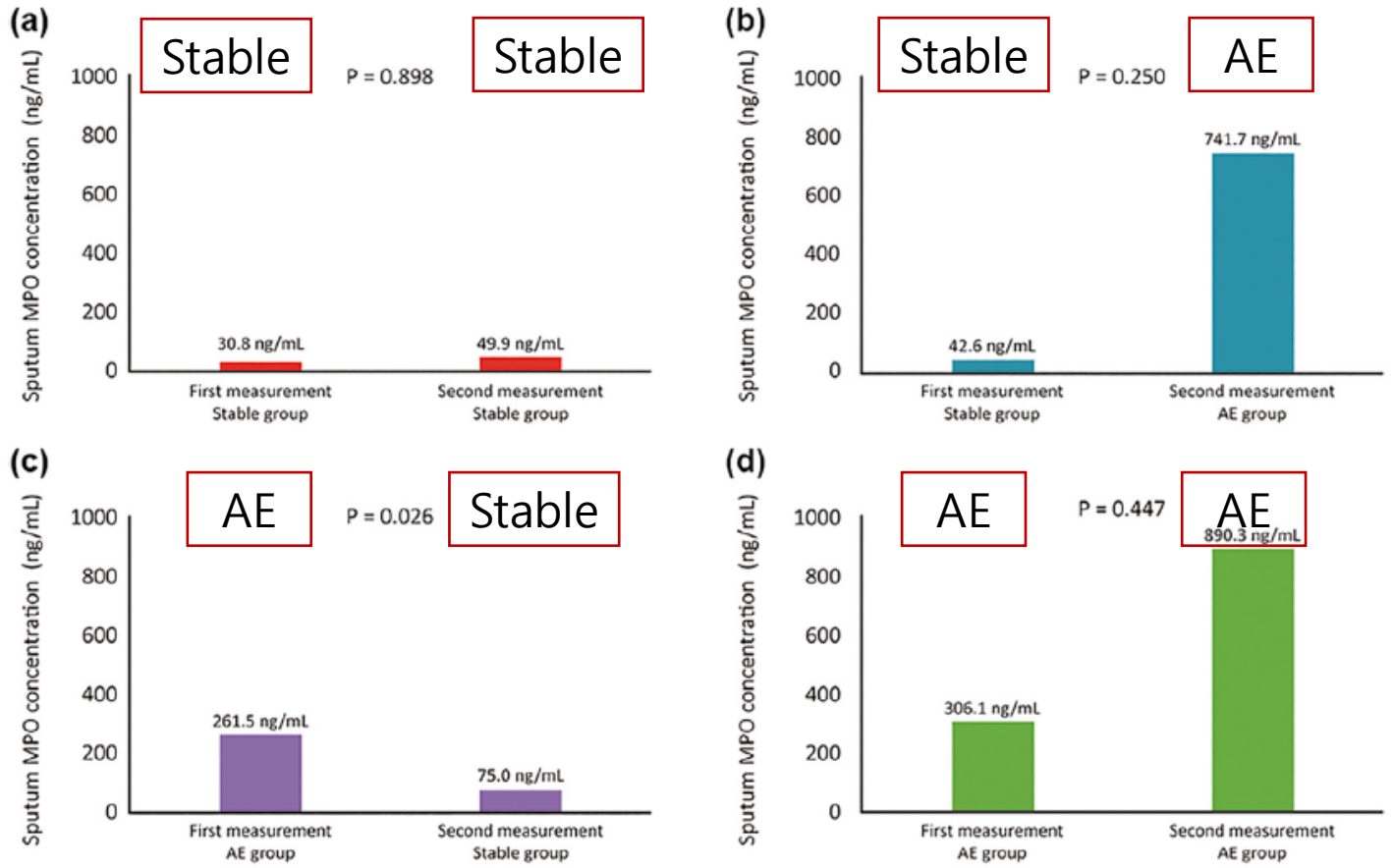


Biomolecules 2021;*11*(8):1065
Am J Respir Crit Care Med 2017; 195(10):1384–1393

Biomarkers of airway inflammation

- **Neutrophilic inflammation**
  - sputum myeloperoxidase

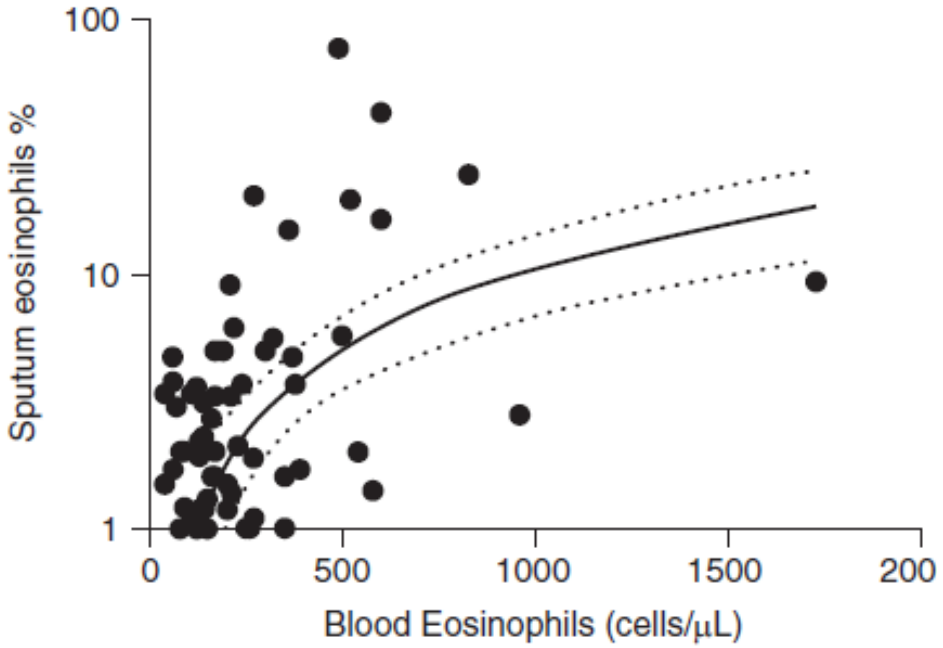


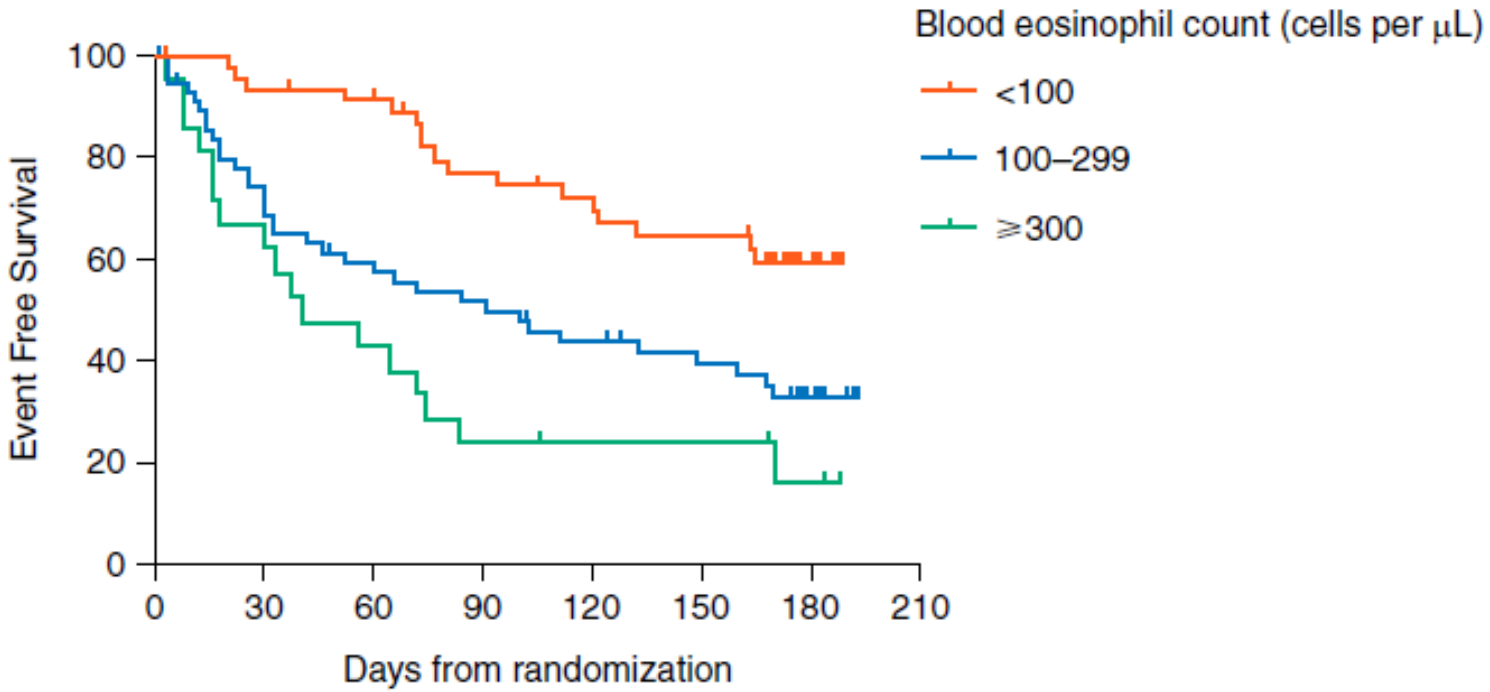


Free Radical Biology and Medicine 2021; 172: 633–651
Pulmonology 2024; 30:401-405

Biomarkers of airway inflammation

- **Eosinophilic inflammation**
  - blood eosinophil count
  - sputum eosinophil count





Am J Respir Crit Care Med 2022 ; 205 (8): 894–902

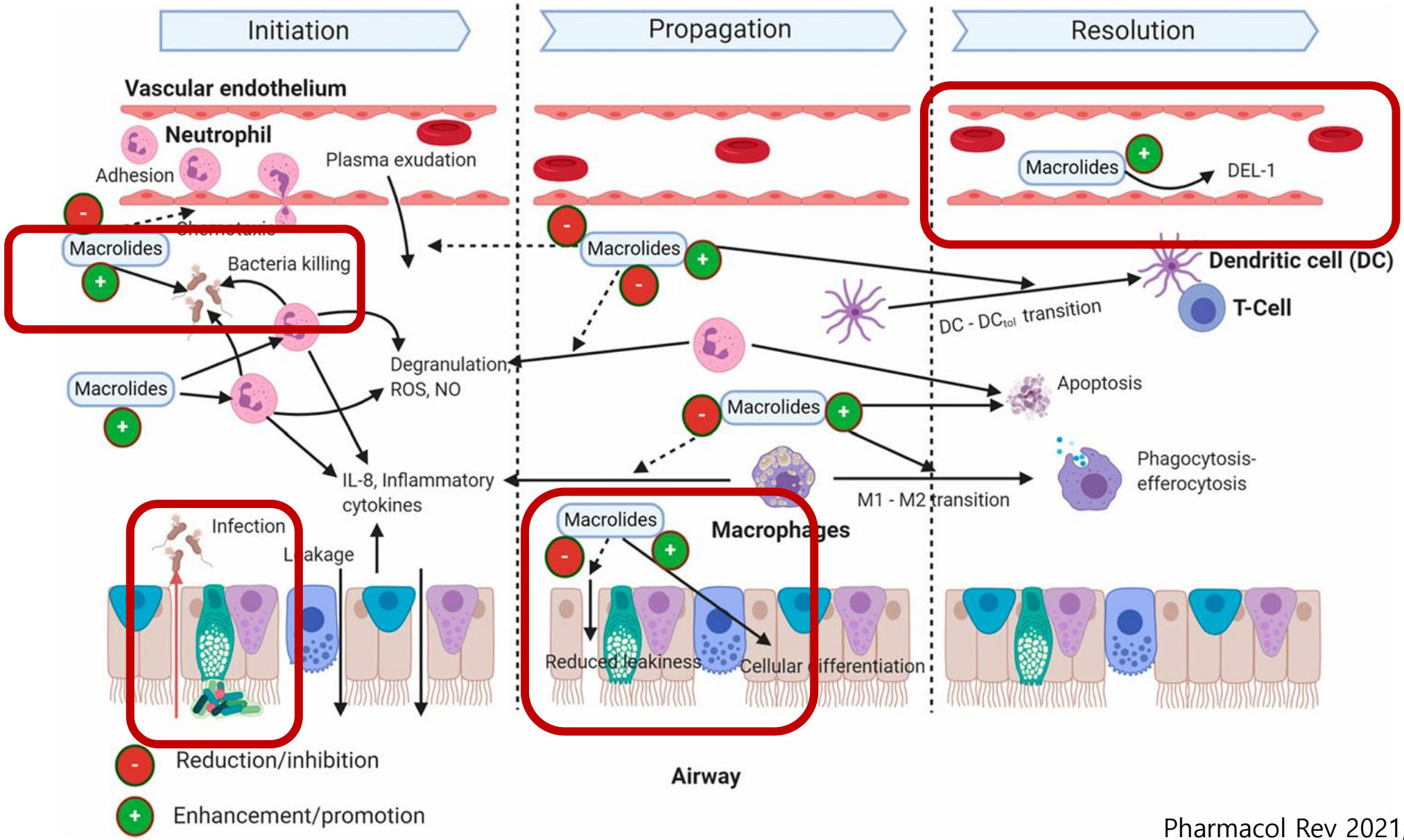
Anti-inflammatory therapies

1) Present treatment options
2) New anti-inflammatory and immunomodulatory therapies
3) The repurposing of anti-inflammatory and immunomodulatory treatments

1) Present treatment options

- **Neutrophilic inflammation**
  - long-term macrolide
- **Eosinophilic inflammation**
  - Inhaled corticosteroids
  - biologics targeting type 2 inflammation

Neutrophilic inflammation – long-term macrolide

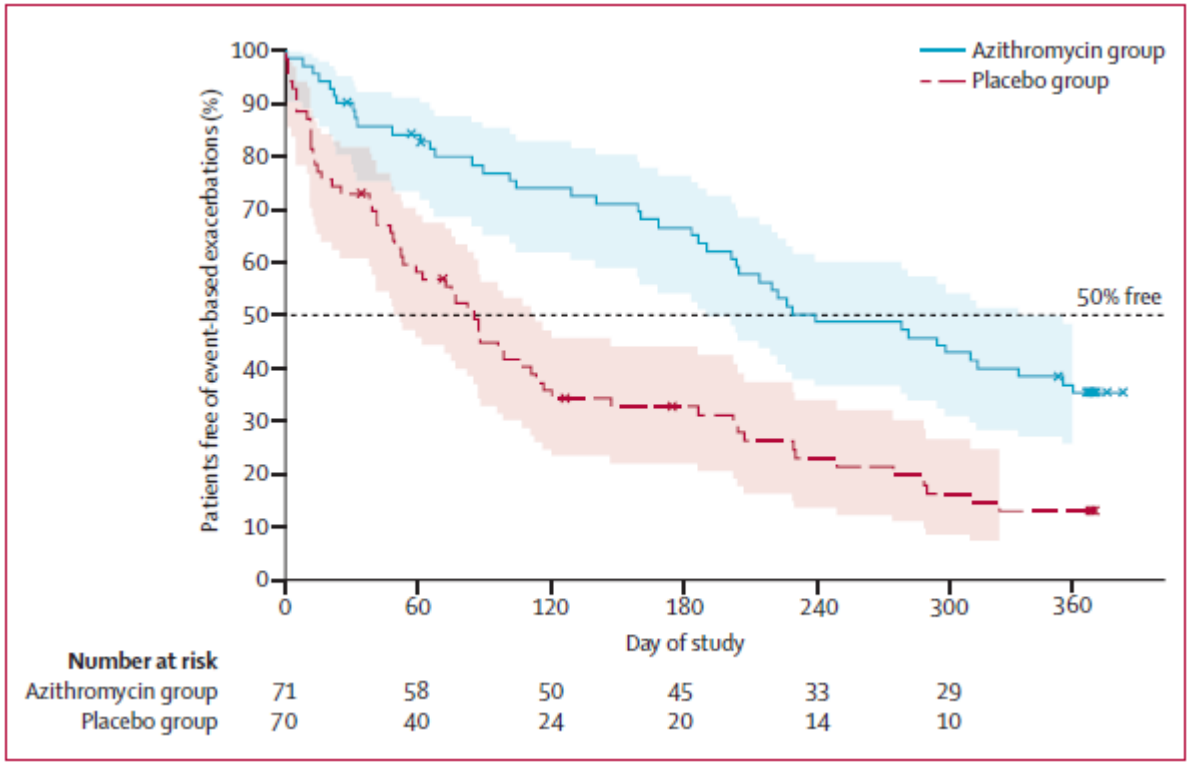


Pharmacol Rev 2021;73:1404–1433

Neutrophilic inflammation – long-term macrolide

Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial

Conroy Wong, Lata Jayaram, Noel Karalus, Tam Eaton, Cecilia Tong, Hans Hockey, David Milne, Wendy Fergusson, Christine Tuffery, Paul Sexton, Louanne Storey, Toni Ashton



- 2008.02.-2009.10. New Zealand
- at least **one AE** requiring antibiotic treatment in the past year
- **500 mg** azithromycin (or placebo) **TIW**
- treatment duration: **6** months
- azithromycin (n=71) vs. placebo (n=70)
- the rate of event-based exacerbations RR 0.38 (95% CI, 0.26-0.54)

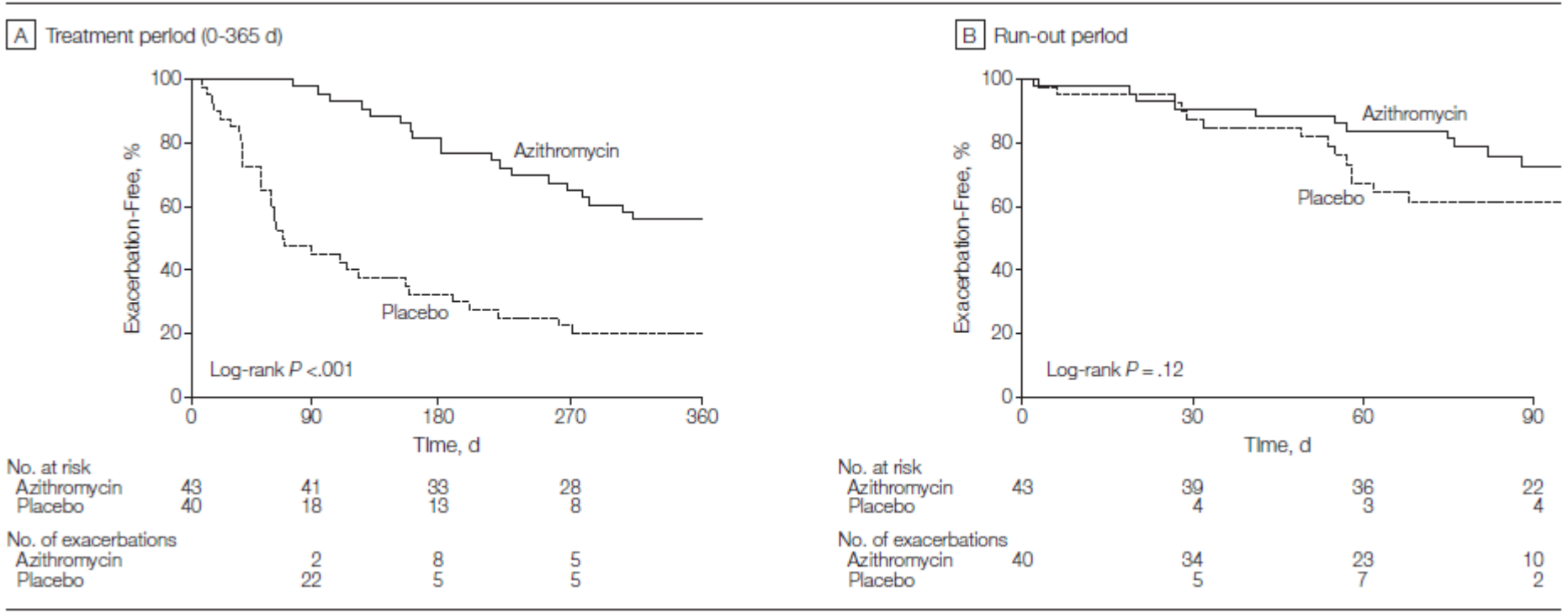
Lancet, 2012; 380: 660–67

Neutrophilic inflammation – long-term macrolide

- 2008.04.-2010.09. Netherlands
- at least **3 AEs** requiring antibiotic treatment in the past year
- **250 mg** azithromycin (or placebo) **daily**
- treatment duration: **12** months
- azithromycin (n=43) vs. placebo (n=40)
- time to a first exacerbation
  HR 0.29 (95% CI, 0.16-0.51)

Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis

The BAT Randomized Controlled Trial



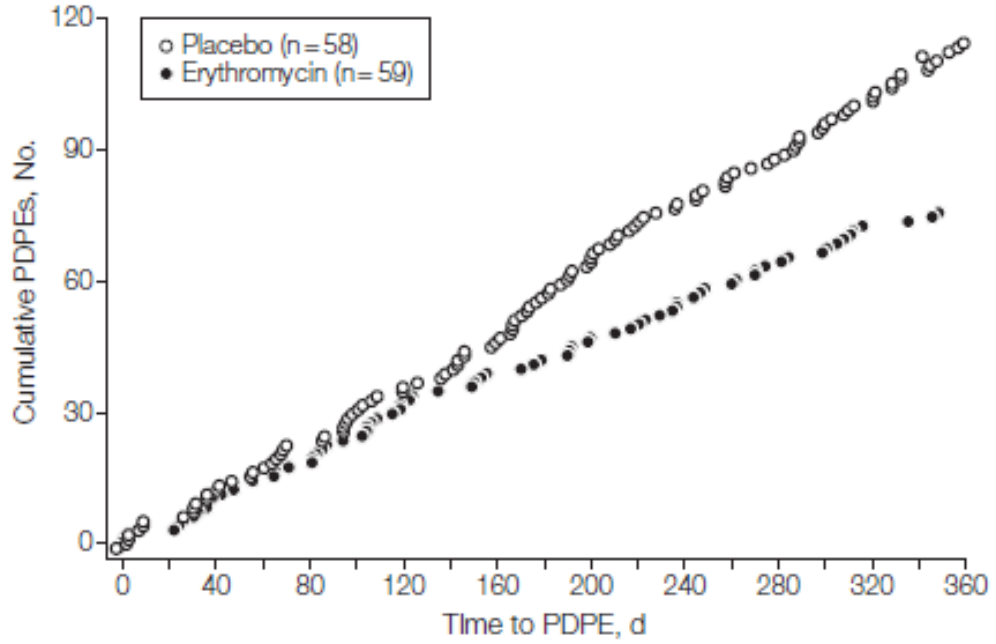
JAMA, 2013; 309(12):1251-1259

Neutrophilic inflammation – long-term macrolide

Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis

The BLESS Randomized Controlled Trial

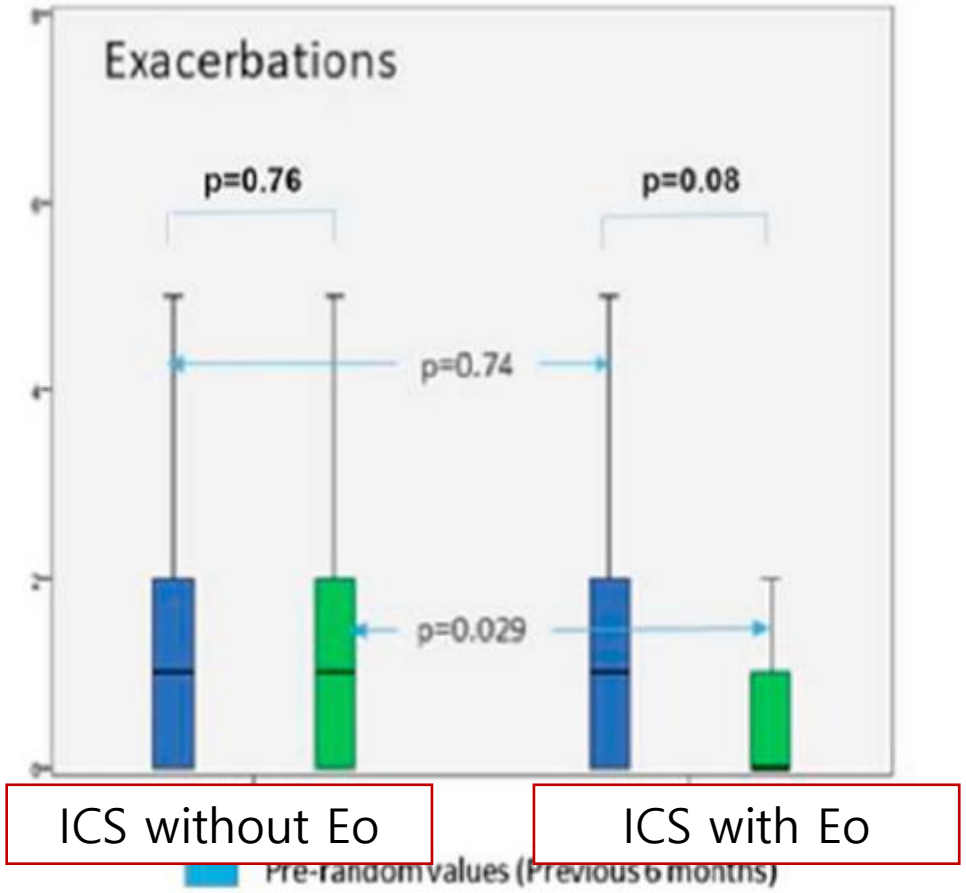
Figure 2. Cumulative Occurrence of Protocol-Defined Pulmonary Exacerbations

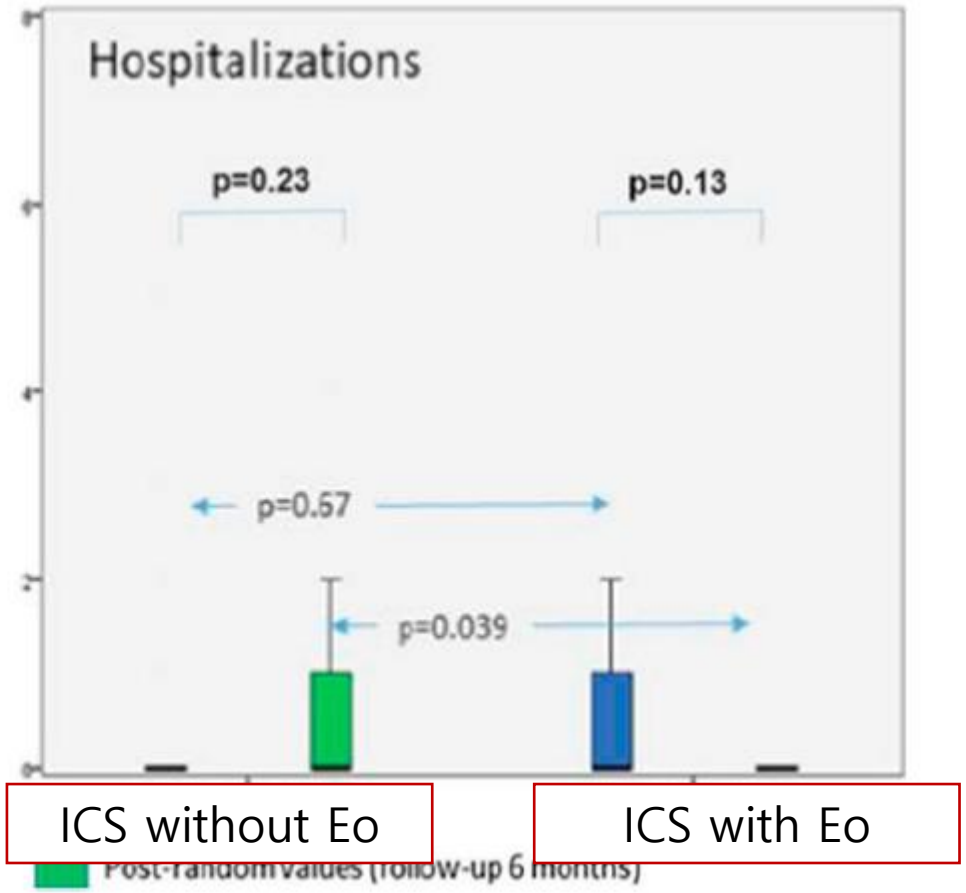


- 2008.10.-2011.12. Australia
- at least **2 AEs** requiring antibiotic treatment in the past year
- **400 mg** erythromycin (or placebo) **twice daily**
- treatment duration: **12** months
- erythromycin (n=59) vs. placebo (n=58)
- time to a first exacerbation
  IRR 0.57 (95% CI, 0.42-0.77)

JAMA. 2013;309(12):1260-1267

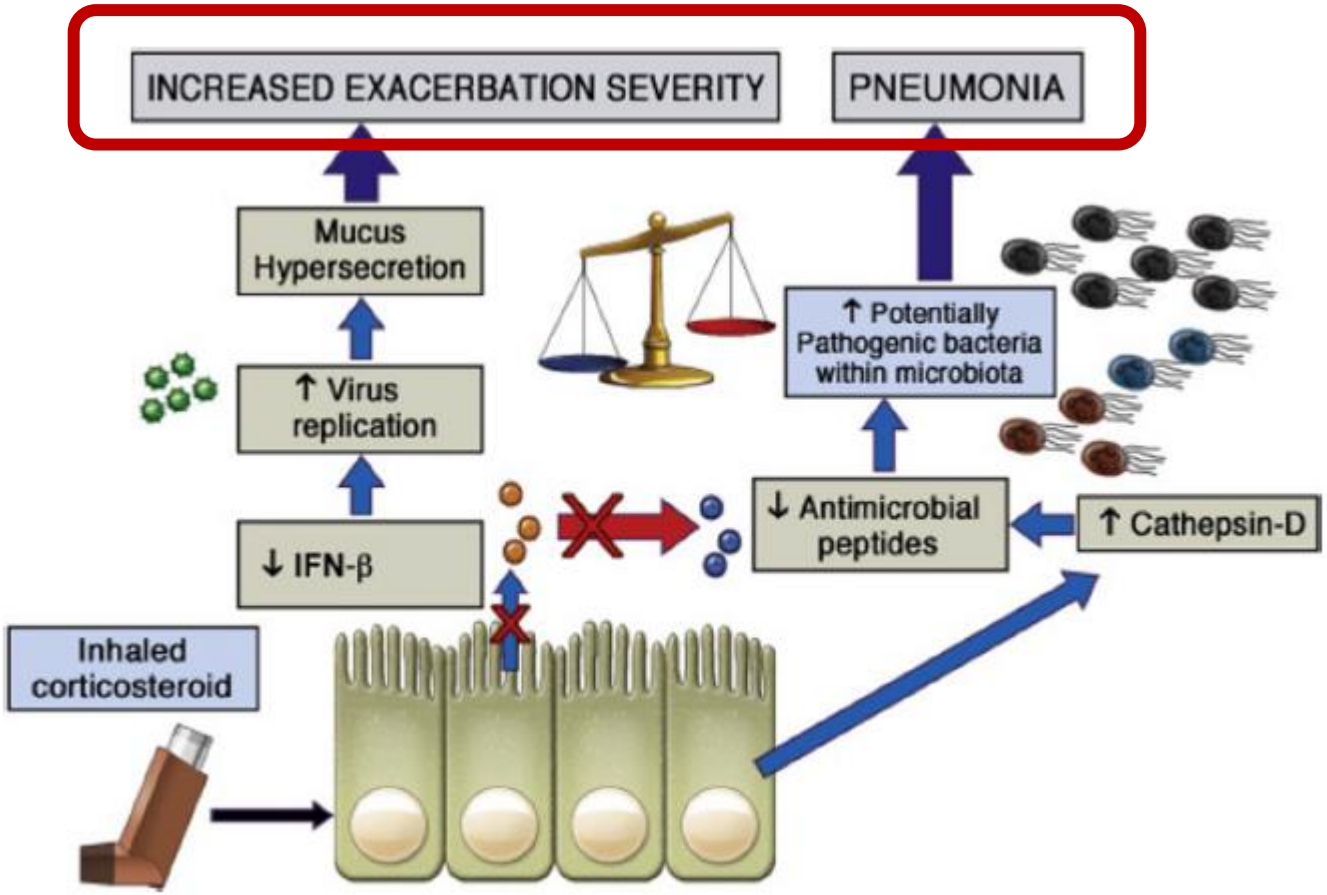
Eosinophilic inflammation - inhaled corticosteroids





Arch Bronconeumol (Engl Ed). 2020;56(10):681–3

Eosinophilic inflammation - inhaled corticosteroids

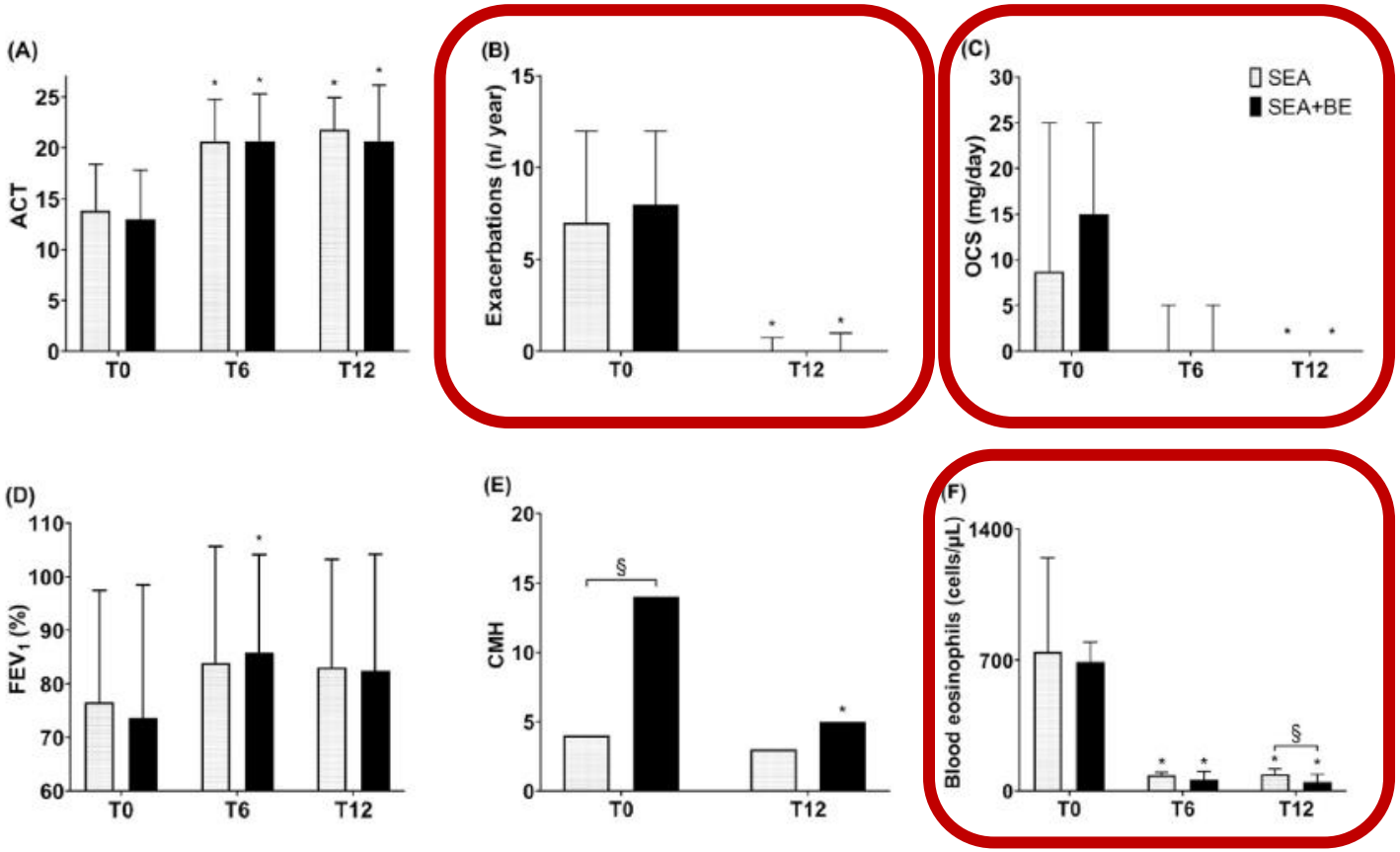


Drugs (2022) 82:1453–1468

Eosinophilic inflammation – biologics targeting type 2 inflammation

Mepolizumab effectiveness in patients with severe eosinophilic asthma and co-presence of bronchiectasis: A real-world retrospective pilot study

Claudia Crimi [a,*], Raffaele Campisi [a], Santi Nolasco [b], Giulia Cacopardo [b], Rossella Intravaia [b], Morena Porto [b], Pietro Impellizzeri [b], Corrado Pelaia [c], Nunzio Crimi [a,b]



- 2018.12.-2020.01. Italy
- severe eosinophilic asthma(SEA) c BE
- **100 mg** mepolizumab SC every 4 wks
- treatment duration: **12** months
- SEA (n=16), SEA + BE (n=16)
- AE rate 8 (4-12) to 0 (0-1)

Respiratory Medicine 2021;185:106491

2) New anti-inflammatory and immunomodulatory therapies

- Novel class of drugs that directly target neutrophilic inflammation in bronchiectasis
  - **Brensocatib** (an oral reversible DPP1 inhibitor): WILLOW phase 2 RCT
  - BI 1291583
- Biologic treatments in eosinophilic (NCT05006573) and non-eosinophilic (NCT06280391) bronchiectasis

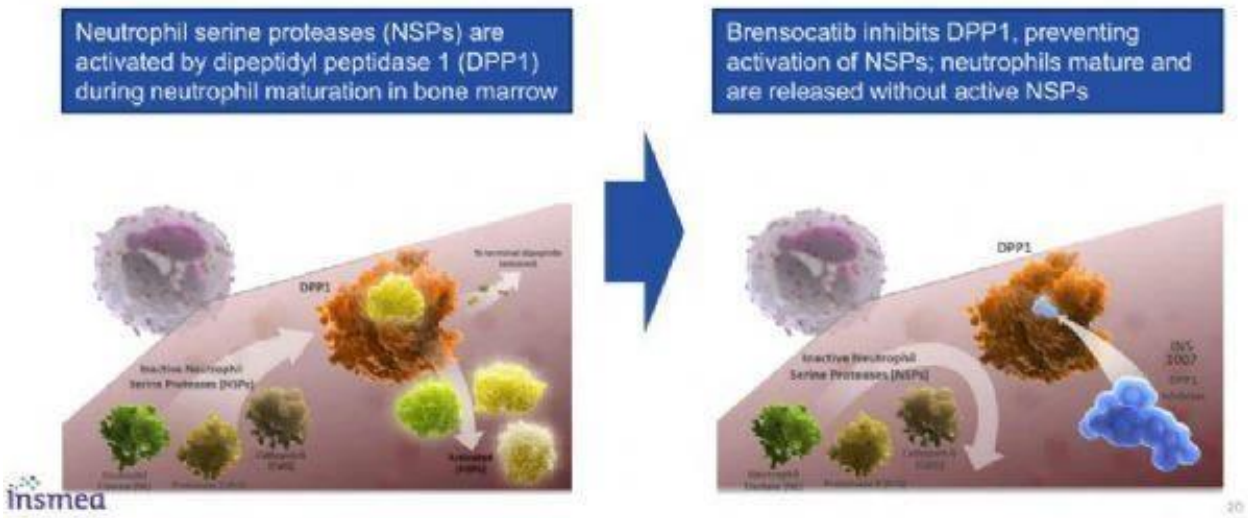
The NEW ENGLAND JOURNAL of MEDICINE

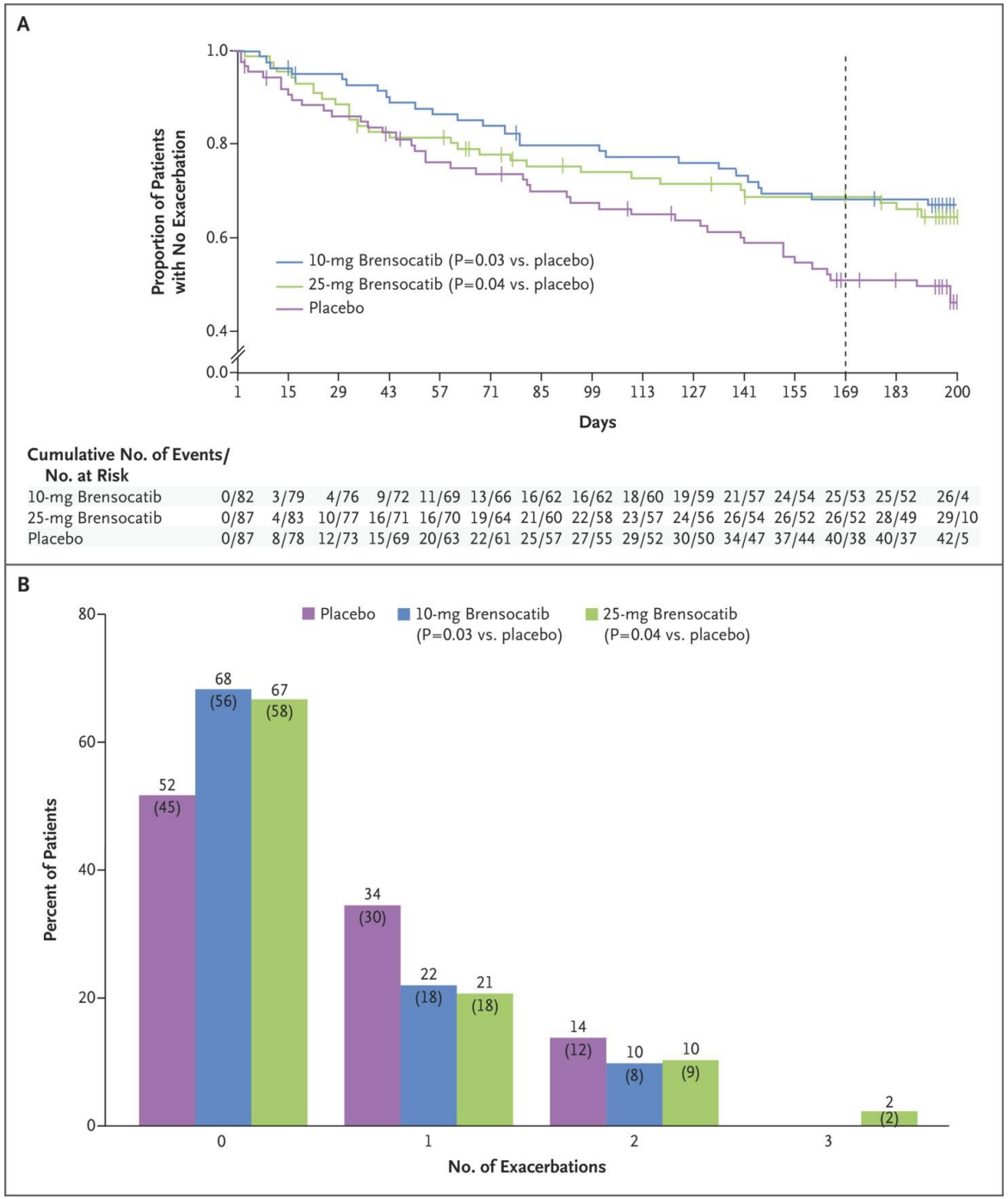
ORIGINAL ARTICLE

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

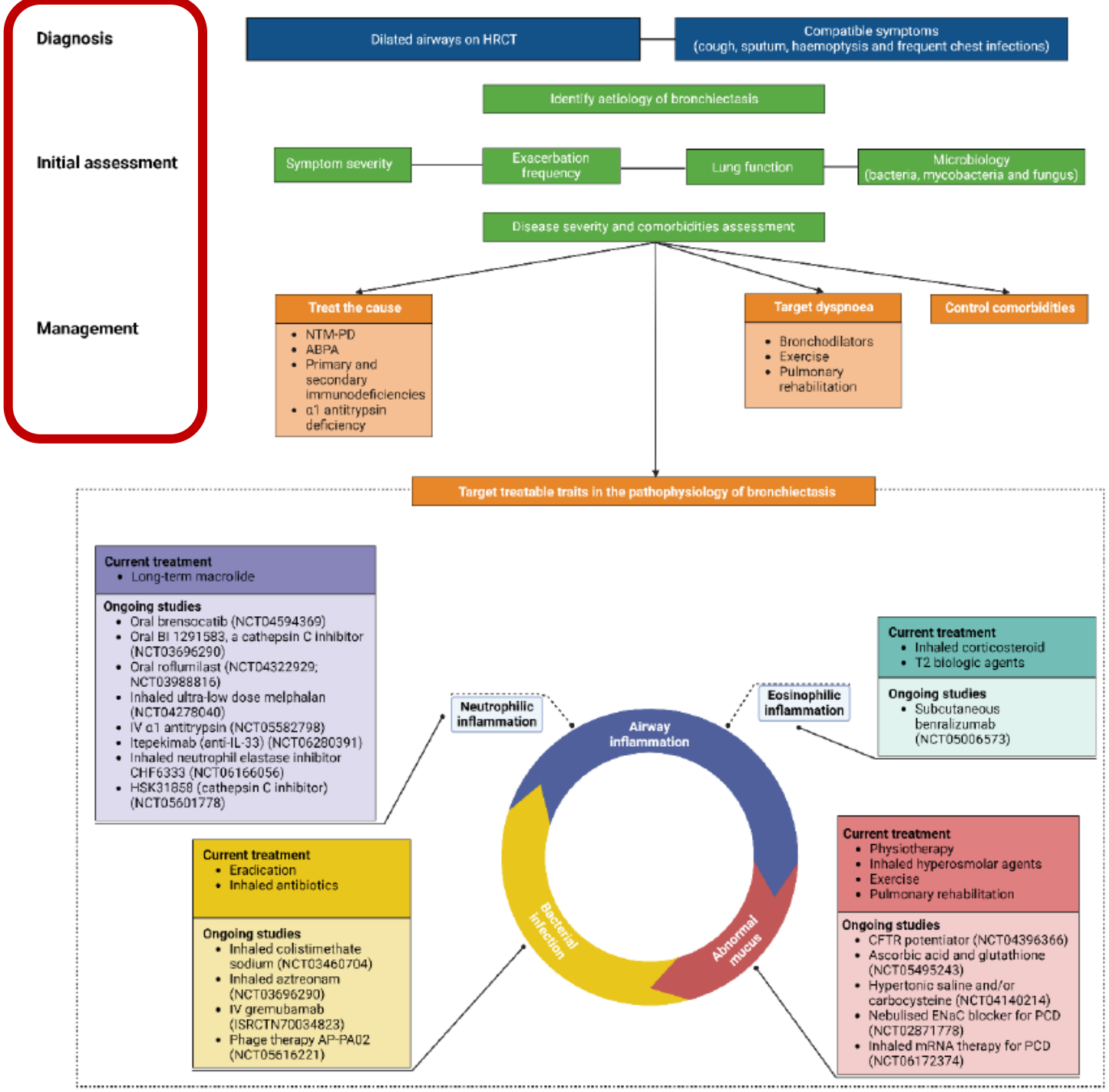
James D. Chalmers, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., Mark L. Metersky, M.D., Michael R. Loebinger, B.M., B.Ch., Ph.D., Francesco Blasi, M.D., Ph.D., Oriol Sibila, M.D., Ph.D., Anne E. O'Donnell, M.D., Eugene J. Sullivan, M.D., Kevin C. Mange, M.D., M.S.C.E., Carlos Fernandez,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

Brensocatib (INS1007) is a Potent DPP1 Inhibitor that Prevents NSP Activation During Neutrophil Maturation

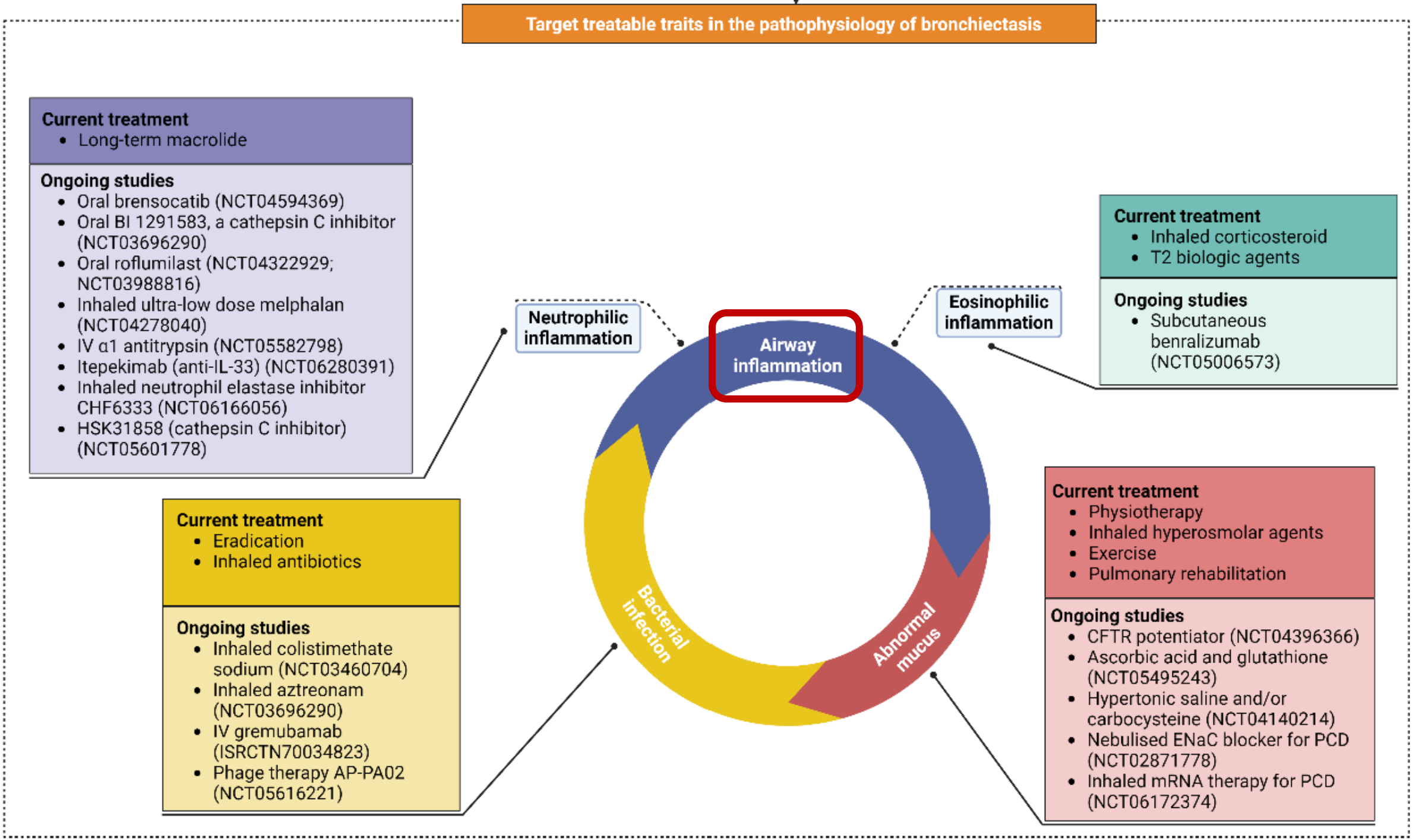




N Engl J Med 2020;383(22):2127-2137



Eur Respir J 2024; 63: 2400518


Target treatable traits in the pathophysiology of bronchiectasis
Current treatment
Long-term macrolide
Ongoing studies
Oral brensocatib (NCT04594369)
Oral BI 1291583, a cathepsin C inhibitor (NCT03696290)
Oral roflumilast (NCT04322929; NCT03988816)
Inhaled ultra-low dose melphalan (NCT04278040)
IV α1 antitrypsin (NCT05582798)
Itepekimab (anti-IL-33) (NCT06280391)
Inhaled neutrophil elastase inhibitor CHF6333 (NCT06166056)
HSK31858 (cathepsin C inhibitor) (NCT05601778)
Neutrophilic inflammation
Airway inflammation
Eosinophilic inflammation
Current treatment
Inhaled corticosteroid
T2 biologic agents
Ongoing studies
Subcutaneous benralizumab (NCT05006573)
Current treatment
Eradication
Inhaled antibiotics
Ongoing studies
Inhaled colistimethate sodium (NCT03460704)
Inhaled aztreonam (NCT03696290)
IV gremubamab (ISRCTN70034823)
Phage therapy AP-PA02 (NCT05616221)
Bacterial infection
Abnormal mucus
Current treatment
Physiotherapy
Inhaled hyperosmolar agents
Exercise
Pulmonary rehabilitation
Ongoing studies
CFTR potentiator (NCT04396366)
Ascorbic acid and glutathione (NCT05495243)
Hypertonic saline and/or carbocysteine (NCT04140214)
Nebulised ENaC blocker for PCD (NCT02871778)
Inhaled mRNA therapy for PCD (NCT06172374)

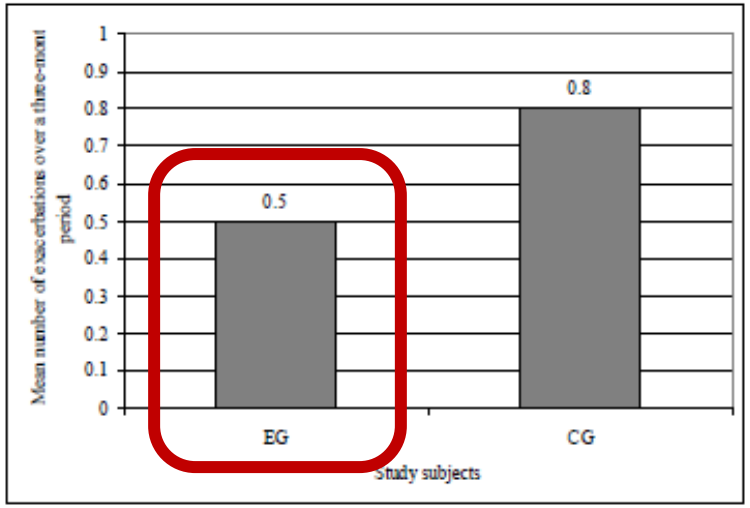
3) The repurposing of anti-inflammatory and immunomodulatory treatments : carbocysteine

Effects of a Long-Term Use of Carbocysteine on Frequency and Duration of Exacerbations in Patients with Bronchiectasis

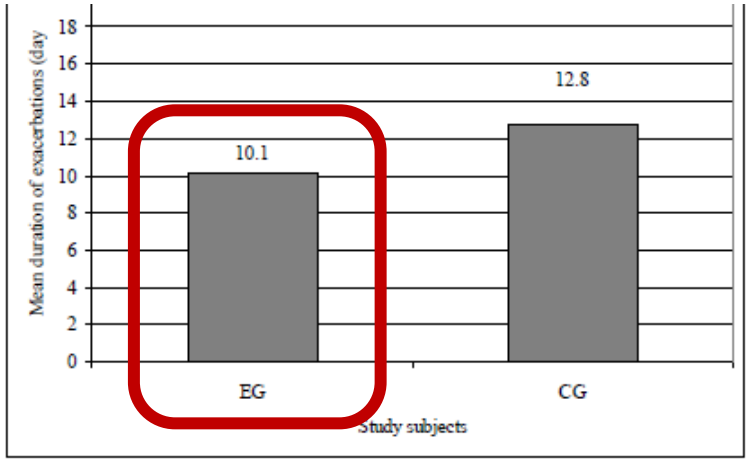
Jordan Minov[1*], Sasho Stoleski[1], Tatjana Petrova[2], Kristin Vasilevska[3], Dragan Mijakoski[1], J Bislimovska[1]

- 2019.02.-2019.12. Macedonia
- Patients with BE who had to have difficulties in expectorating sputum and poor quality of life
- **375*2 mg** carbocysteine three times **daily**
- treatment duration: 3 months
- examined group (n=32) vs. control group (n=32)
- mean number of exacerbations
  EG 0.5+-1 vs. CG 0.8 +-0.2

No. of AEs



AE duration



Maced J Med Sci. 2019 ; 7(23):4030-4035

3) The repurposing of anti-inflammatory and immunomodulatory treatments : N-acetylcysteine

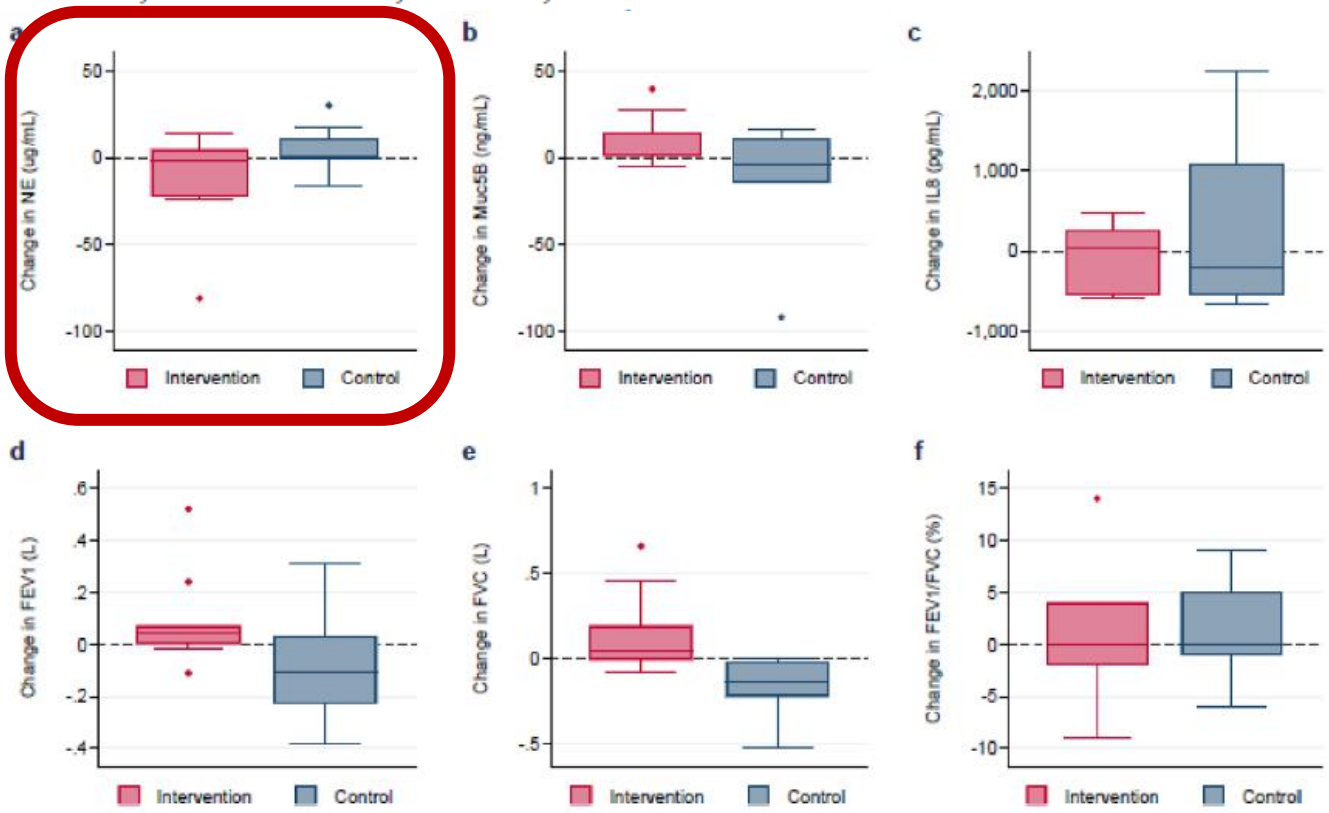
Evaluation of high dose N- Acetylcysteine on airway inflammation and quality of life outcomes in adults with bronchiectasis: A randomised placebo-controlled pilot study

L. Jayaram [a,b,*], P.T. King [c,d], J. Hunt [a], M. Lim [a], C. Park [a], E. Hu [a], L. Dousha [c,d], P. Ha [a], J.B. Bartlett [a,b], A.M. Southcott [a,b], S. Muruganandan [b,e], S. V[illegible] C.A. Wong [i,j]

- 2018.-2022. Australia
- clinically stable BE, history of chronic sputum expectoration
- **2400 mg** NAC (or placebo) **daily**
- treatment duration: **6 weeks**
- NAC (n=9) vs. placebo (n=8)

- sputum NE

	NAC	placebo
Baseline	16.0 (2.2-26.5)	2.0 (1.0-28.8)
At week 6	2.5 (1.3-15.4)	3.9 (1.1-37.3)



Pulmonary Pharmacology & Therapeutics 2024;84:102283

3) The repurposing of anti-inflammatory and immunomodulatory treatments : PDE3 and PDE4 inhibitor

Efficacy of Roflumilast in Bronchiectasis Patients with Frequent Exacerbations: A Double-Blinded, Randomized, Placebo-Controlled Pilot Clinical Trial

Siwasak Juthong, M.D., Pattaraporn Panyarath, M.D.

- 2015.01.-2015.11. Thailand
- at least **2 AEs** requiring antibiotic treatment in the past year
- **500 mcg** roflumilast **daily**
- treatment duration: 24 weeks
- roflumilast (n=15) vs. placebo (n=15)
- No difference of rate of AEs (0.57 vs. 0.59), FEV1, SGRQ scores
- Side effects : loss of appetite, headache

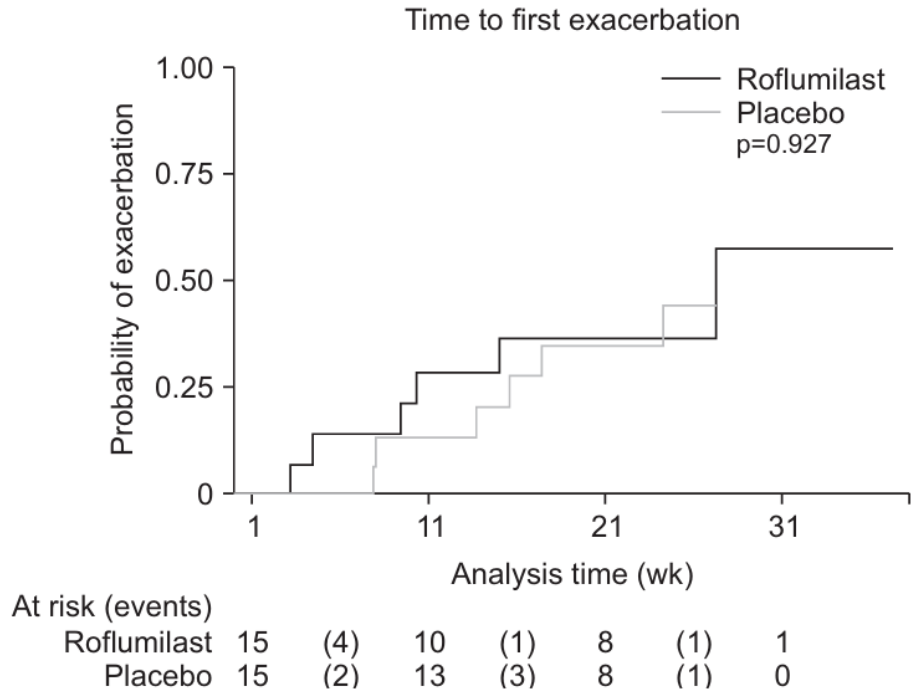


Figure 2. Kaplan-Meier curve for the time of first exacerbation in bronchiectasis patients who received roflumilast or placebo.

Tuberc Respir Dis 2022;85:67-73

Summary

- Bronchiectasis: an inflammatory disease

Assessment of
Disease Activity and Severity

<Severity>
- FEV1, mMRC
- radiological extent
- Age, BMI
- Previous exacerbation history
- Pseudomonas colonization

<Activity>
- respiratory symptoms including sputum purulence
- inflammatory markers

<Types – phenotype, endotype>
- sputum neutrophil elastase activity
- sputum myeloperoxidase
- blood eosinophil count
- sputum eosinophil count

Tailored
treatments

Therapeutic options

<Present treatment options>
- Neutrophilic inflammation
  - long-term macrolide
- Eosinophilic inflammation
  - Inhaled corticosteroids
  - biologics targeting type 2 inflammation

<New drugs>
- Oral brensocatib
- Oral cathepsin C inhibitor
- …

<The repurposing treatments>
- ….