CLINICAL FORUM

QUELLING THE VICIOUS VORTEX:

Targeting Neutrophil Serine Proteases in Non-Cystic Fibrosis Bronchiectasis

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Taking Stock of the Burden of NCFBE

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Definition and Prevalence of NCFBE

- Chronic lung disease characterized by:[1]
  - Recurrent infection
  - Inflammation
  - Persistent cough and sputum production
- Bronchiectasis results from permanent dilation of the airways due to:[2]
  - Chronic infection
  - Exacerbations
  - Inflammation
- NCFBE is a **clinical diagnosis** supported by imaging[1]
- Prevalence estimated at 53 to 566 per 100,000 persons[3]
  - 1 patient with NCFBE for every 20 patients diagnosed with COPD[1]
  - Increase in prevalence and severe disease in the elderly[2]
  - Increased prevalence in female gender[3]

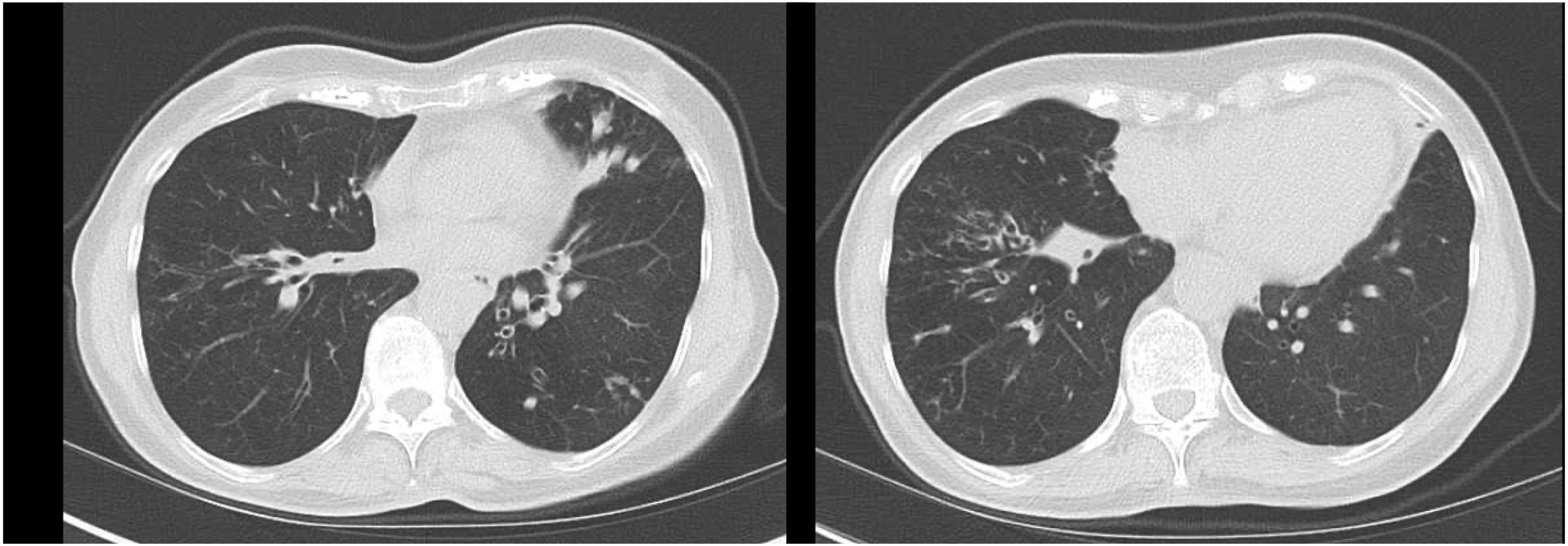
[1]Chalmers JD, Sethi S. *NPJ Primary Care Respir Med.* 2017;27(1):18.
[2]Chandrasekaran R, et al. *BMC Pulm Med.* 2018;18(1):83.
[3]Polverino E, et al. *Eur Resp J.* 2017;50:1700629.

Patient Case: Dana

- A 70-year-old female non-smoker, h/o GERD with intermittent productive cough while lying on her back over several months
- She went to see her internist who did a CXR which was abnormal, prompting a chest CT scan which revealed bronchiectasis
- She had multiple sputum cultures sent and had growth of *M. avium-intracellulare*, *staphylococcus aureus*, and *aspergillus fumigatus*
- She was started on guideline-based therapy for her NTM with azithromycin, ethambutol, and rifampin
  - Had multiple side effects from therapy, including tinnitus and GI upset

Patient Case: Dana

CT Images



Patient Case: Dana (cont'd)
Initial Management

- Her antibiotic therapy was stopped given the side effects and she was referred to an expert consultant for assistance with the management of her bronchiectasis and NTM
- She was started on airway clearance with PEP device (aerobika), hypertonic saline (7%) and high-frequency chest wall oscillation (vest)
- Eventually with several attempts, she ended up on daily clarithromycin and ethambutol
  - Converts sputum for MAI and completes therapy after several years
- Completed an extensive GI work-up with GI manometry to exclude persistent reflux, which was negative

Patient Case: Dana (cont'd)
Follow-up Presentation

- Increasing bronchiectasis exacerbations (increased cough; increased sputum and change in sputum color) occurring 2 to 3 times per year with cultures positive for *staphylococcus aureus*
- Repeated attempts with single, combination, and prophylactic antibiotics, all unsuccessful in preventing recurrent *staph* exacerbations from 2019 to 2021
- Chest CT scan that had been stable during MAI treatment revealed slow but progressive changes in the RUL, RLL, lingula, and LLL from 2019 to 2021
- In 2021, cultures continue to grow *staph* but in addition are growing *pseudomonas aeruginosa*
- She was enrolled in brensocatib trial and completed the study and is now on post-trial brensocatib 10 mg daily

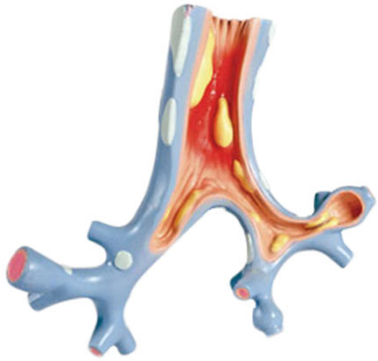
Challenges in Dana's Case

- NTM treatment related side effects
- Decision to treat versus not to treat
- No local NTM/bronchiectasis program for her care
- Frequent bronchiectasis exacerbations
- Progressive bronchiectasis with *staphylococcus aureus* and *pseudomonas aeruginosa*

Patient Perspectives on NCFBE

- How would you describe the feeling when you were diagnosed with bronchiectasis?
- Did you know what bronchiectasis was?
- How did bronchiectasis affect your quality of life?
- What challenges did you have with your bronchiectasis treatments, including airway clearance and antibiotics and how did you overcome them?
- Why did you decide to participate in the clinical trial for a new bronchiectasis treatment? How are you feeling now?
- What advice do you have for healthcare professionals who provide care for patients with frequent bronchiectasis exacerbations?

On the Path to Early NCFBE Diagnosis: Identifying Risk Factors and Employing Current Guidelines



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VITAZ hospitals
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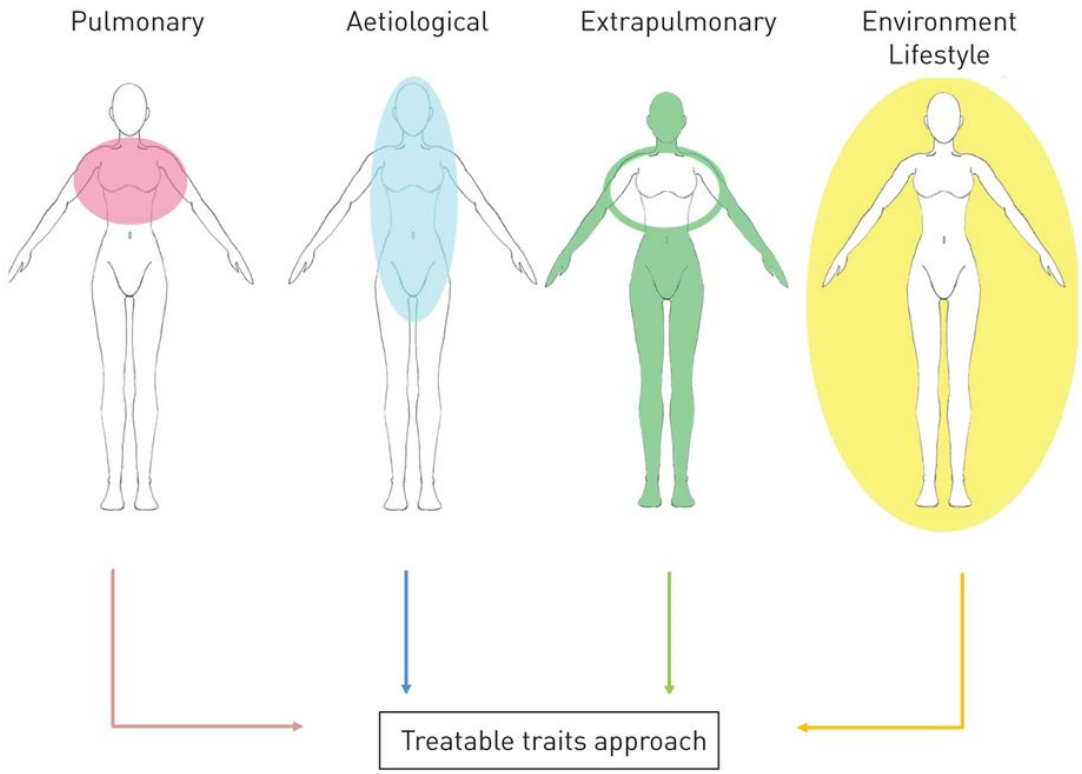
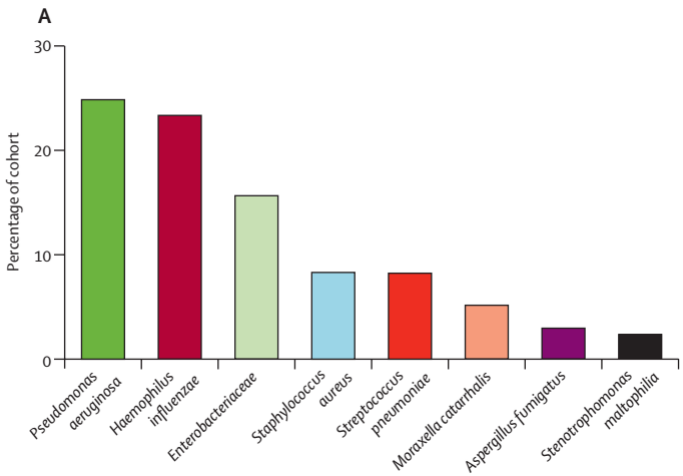
EMBARC
The European Bronchiectasis Registry

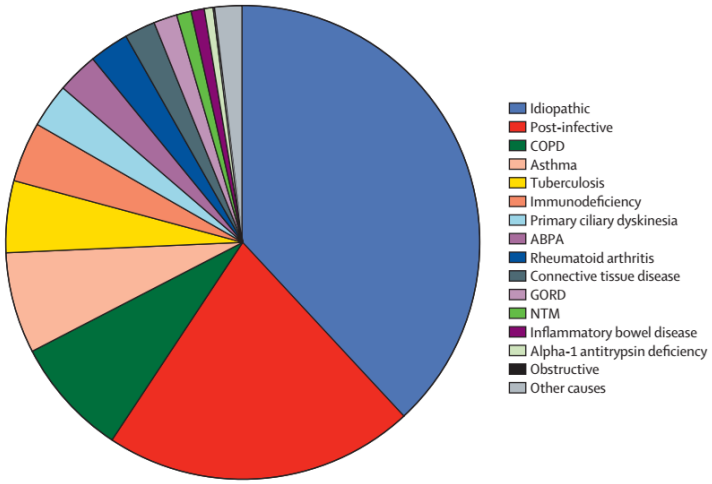
Risk Factors for Bronchiectasis



Boaventura R, et al. *Eur Respir J*. 2018;52(3):1801269.
Chalmers JD, et al. *Lancet Respir Med*. 2023:S2213-2600(23)00093-0.

Risk Factors for Bronchiectasis (cont'd)





	EMBARC cohort (n=16 963)
Age, years	67 (57–74)
Age >65 years	9943 (58·6%)
Female	10 335 (60·9%)
Male	6628 (39·1%)
BMI, kg/m²*	24·9 (21·7–28·7)
Comorbidities	
Cardiovascular diseases	5509 (32·5%)
Stroke	600 (3·5%)
Liver disease	103 (0·6%)
Osteoporosis	2228 (13·1%)
Depression	2377 (14·0%)
Anxiety	2428 (14·3%)
Neoplastic disease	1863 (11·0%)
Chronic renal failure	667 (3·9%)
Diabetes	1724 (10·2%)
Asthma	5267 (31·0%)
COPD	4324 (25·5%)

Boaventura R, et al. *Eur Respir J*. 2018;52(3):1801269.
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How to Make the Diagnosis

	Consensus statements	Level of consensus among experts
General statement		
Statement 1	Bronchiectasis is a chronic respiratory disease that has multiple causes and is associated with different conditions, although in some patients, a cause cannot be identified (idiopathic disease); the diagnosis of clinically significant bronchiectasis as a disease requires both clinical and radiological criteria	100%
Radiological statements		
Statement 1	Confirmation of the presence of bronchiectasis on chest CT scans on the basis of an a priori accepted definition (table 1) is recommended for all clinical trials in adults and this could be done either at a local level or through central reading	100%
Statement 2	Central reading to confirm the presence of bronchiectasis on chest CT scans on the basis of an a priori accepted definition (table 1) could improve accuracy and should be strongly considered in clinical trials, especially for regulatory phase 3 trials	100%
Clinical statements		
Statement 1	Although there is a wide spectrum of signs and symptoms of bronchiectasis, most patients who meet a definition of clinically significant bronchiectasis will have at least two of the following: (1) a cough most days of the week; (2) sputum production most days of the week; (3) a history of exacerbations	100%
Statement 2	Some patients with radiological bronchiectasis are asymptomatic; the long-term prognostic significance of asymptomatic radiological bronchiectasis is unknown and requires additional investigations with longitudinal studies	100%
Statement 3	Underlying causes or conditions associated with bronchiectasis should be investigated; we caution against use of the terms idiopathic or post-infectious bronchiectasis unless other potential causes or conditions have been excluded	100%
Statement 4	Bronchiectasis can coexist with other common chronic airway diseases including asthma and COPD; the identification of treatable traits in this complex group of patients is important for management, appropriate enrolment in clinical trials, and new drug registration purposes	100%
Statement 5	Chronic bacterial infection* can be clinically defined as evidence of positive respiratory tract cultures of the same microorganism, by standard microbiology, on two or more occasions at least 3 months apart over 1 year while in a stable state, in the context of clinically significant bronchiectasis; cultures should be tested in accredited laboratories dealing with high-quality samples	94%
Statement 6	Sustained culture conversion† can be pragmatically defined as evidence of negative respiratory tract cultures for the targeted microorganism, by standard microbiology, on two or more consecutive occasions at least 3 months apart over 1 year; cultures should be tested in accredited laboratories dealing with high-quality samples	94%

COPD=chronic obstructive pulmonary disease. *During discussions, the taskforce agreed that the term chronic bacterial infection is preferable to bacterial colonisation. †During discussions, the taskforce agreed that the term sustained culture conversion is preferable to eradication.

Table 2: **Consensus statements on radiological criteria and clinical definitions for the diagnosis of bronchiectasis in adults in clinical trials**

Aliberti S, et al. *Lancet Respir Med.* 2022;10(3):298-306.

How to Make the Diagnosis (cont'd)

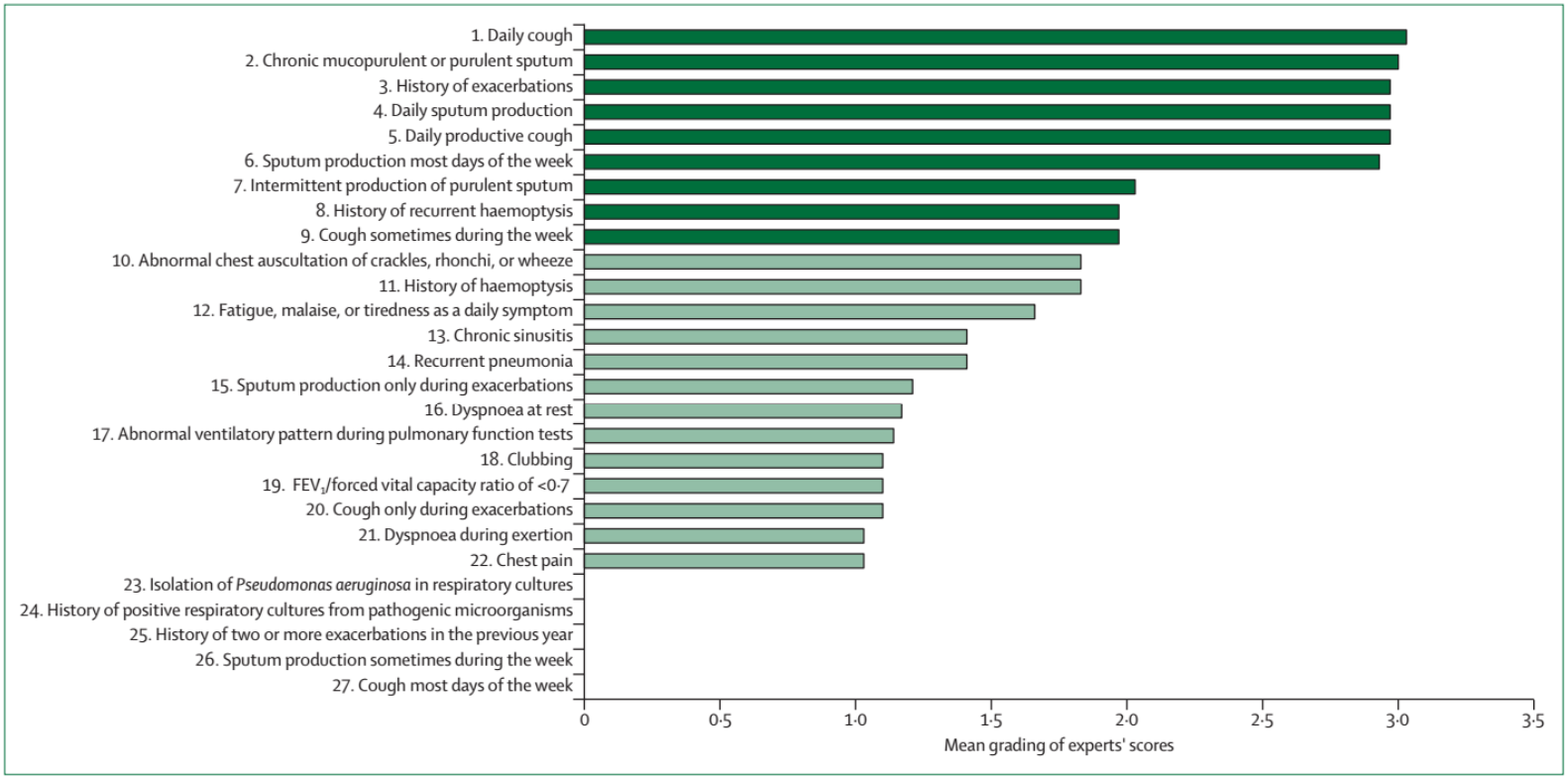

Figure 1: **Clinical signs and symptoms of bronchiectasis in adults graded by the taskforce**

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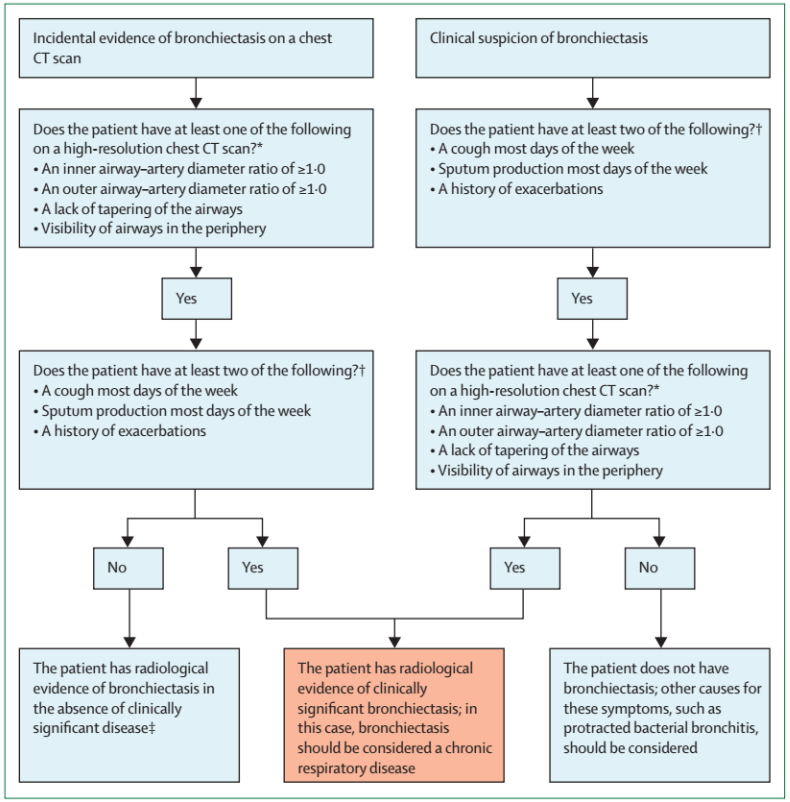

Figure 2: **Flow chart to define clinically significant bronchiectasis**

Aliberti S, et al. *Lancet Respir Med.* 2022;10(3):298-306.

Reasons for Diagnostic Delay

Is there delay?

- EMBARC/ELF survey shows that 26% had symptoms for 10 years or longer before diagnosis and 26% reported having been misdiagnosed

Spinou A, et al. *Eur Respir J*. 2021;58(Suppl 65):PA2005.

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3. Gender/age effect

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Diagnostic Delay by Gender and Age

Table 4.

Diagnostic delay, by gender and CF, according to age onset of symptoms.

Mean ± SD	Overall (*n* = 2099)	Men (*n* = 974)	Women (*n* = 1125)	*p* value (*t* test)
Age at diagnosis	45.7 ± 23.9	46.0 ± 25.1	45.5 ± 22.7	0.61
Age at symptoms onset	33.5 ± 25.1	34.9 ± 26.0	32.2 ± 24.3	0.01
Diagnostic delay	12.2 ± 15.5	11.1 ± 14.0	13.2 ± 16.6	0.001
All				
<20 years at onset (*n* = 825)	19 ± 19.19	16 ± 17.5	21 ± 20.13	<0.001
20–40 years (*n* = 411)	13.41 ± 14	13.9 ± 14.3	13.1 ± 13.8	0.51
>40 years (*n* = 863)	5.1 ± 6.5	5.7 ± 6.9	4.4 ± 6.1	0.003
Only individuals with CF	(*n* = 282)	(*n* = 154)	(*n* = 128)	
<20 years at onset (*n* = 251)	7.2 ± 12.4	6.23 ± 10.6	8.43 ± 14.5	0.18
20–40 years (*n* = 22)	5.32 ± 7.3	2.22 ± 2.9	7.5 ± 8.7	0.06
>40 years (*n* = 9)	7.7 ± 8.91	8 ± 7.1	7.57 ± 9.9	0.95
Only individuals without CF	(*n* = 1817)	(*n* = 820)	(*n* = 997)	
<20 years at onset (*n* = 574)	24.34 ± 19.3	22.2 ± 18.2	25.7 ± 19.9	0.03
20–40 years (*n* = 389)	13.9 ± 14.2	14.6 ± 14.4	13.4 ± 14	0.40
>40 years (*n* = 854)	5.04 ± 6.5	5.7 ± 6.9	4.4 ± 6	0.003

SD: standard deviation; CF: cystic fibrosis.

Giron RM, et al. *Chron Respir Dis*. 2017;14(4):360-369.

Reasons for Diagnostic Delay (cont'd)

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Reasons?

1. The former misconception that bronchiectasis is a rare/orphan disease
2. The rapid expansion of COPD and asthma programs, diverting attention
3. Gender/age effect
4. No difference between affluent and non-affluent countries, but different reasons
    - Affluent: CF screening; alternate diagnosis
    - Non-affluent: Lack of resources and access to medical care

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Brenner DJ, et al. *N Engl J Med.* 2007;357(22):2277-2284.

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5. CT scan was less widely used in the past
6. The broad scale of clinical signs and aetiologies

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Kapur N, et al. *Paediatric Resp Rev.* 2011;12(2):91-96.
Giron RM, et al. *Chron Respir Dis*. 2017;14(4):360-369.
Brenner DJ, et al. *N Engl J Med.* 2007;357(22): 2277-2284.

Guidelines for Diagnosis

Labs

- CBC with differential
- History directed lab work-up:
  - ✓ RF, anti-CCP, ANCA, A1AT, HIV-1 serology
- Respiratory Cultures
  - ✓ Bacteria; Fungus; AFB
- Antibody Testing
  - ✓ ABPA testing
  - ✓ Serum IgG and subclasses, IgA, IgM
  - ✓ Baseline antibodies against capsular polysaccharides of *S. pneumoniae*
  - ✓ Vaccinate if low and reassess titer at 4 to 8 weeks

Additional Testing (Selected)

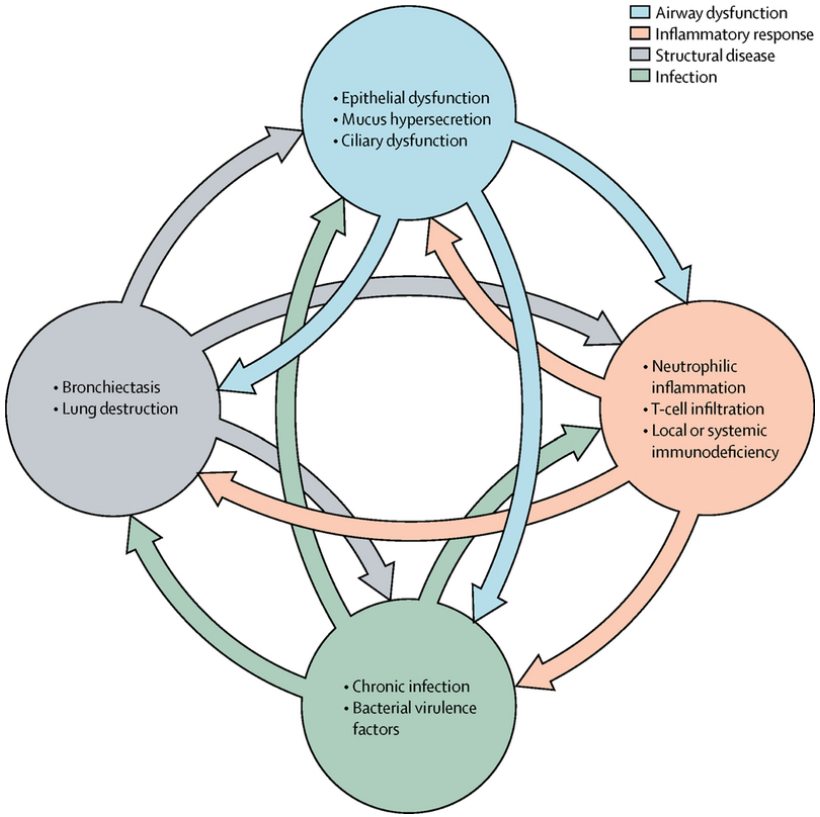
- Cystic fibrosis
- Primary ciliary dyskinesia
- Reflux and aspiration
- Bronchoscopy to rule out endobronchial lesion or foreign body

Idiopathic Cases

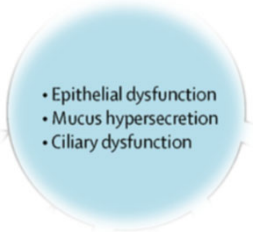
- About 40% of bronchiectasis cases are idiopathic

Hill AT, et al. *Thorax*. 2019;74(Suppl 1):1-69.

Guidelines for Treatment



Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

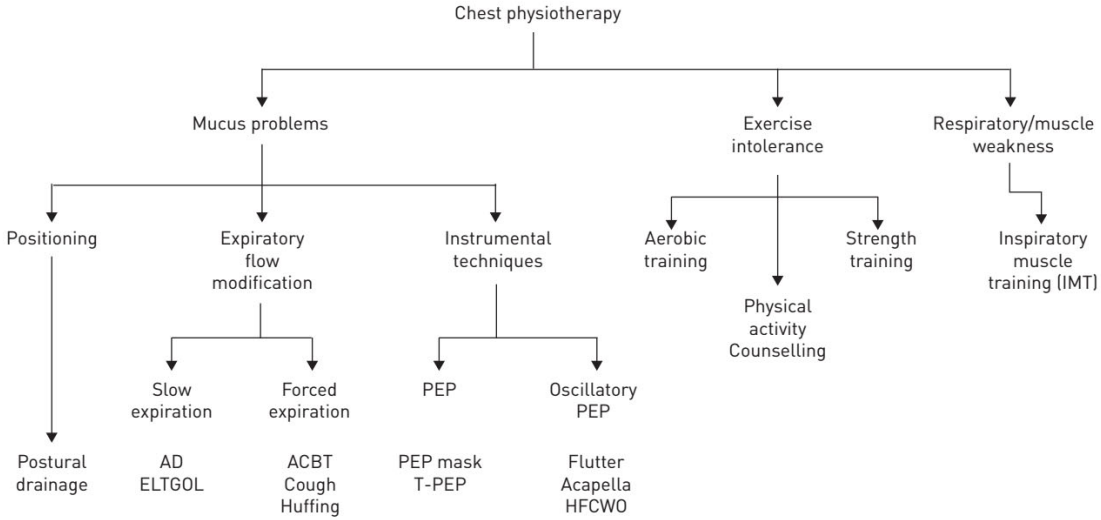


Guidelines for Treatment: Physiotherapy and Rehabilitation

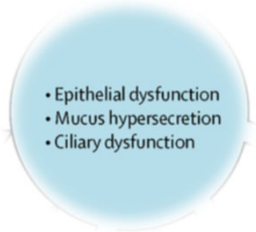
NEW ERS Guidelines

Question 4. What is the clinical evidence for the effectiveness of ACTs, in terms of function and disability (e.g., sputum expectoration), activity (e.g., physical activity) and participation (e.g., self-care), in adults with bronchiectasis?

- Although data on the effects of performing ACTs for periods over 6 or 12-months is limited, the findings demonstrate a reduction in the impact of cough, improvement in health-related quality of life and reduction in the risk of exacerbations. These findings support previously published clinical recommendations for the use of ACTs as part of bronchiectasis management in adults. However, no evidence is existing about the optimal frequency or the number of sessions.
- Randomised controlled trials have assessed a variety of ACTs, with oscillating positive expiratory pressure (mainly via Flutter and Acapella), gravity assisted drainage and active cycle of breathing being the most commonly studied techniques. The existing literature does not demonstrate superiority of one technique over another but supports the use of ACTs.



Herrero-Cortina B, et al. *Eur Resp J*. 2023;:2202053.
Polverino E, et al. *Eur Respir J*. 2017;50(3):1700629.



Guidelines for Treatment: Mucoactive Treatments

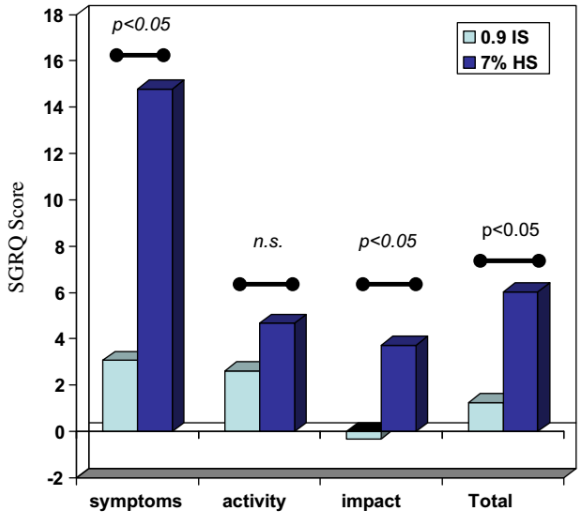
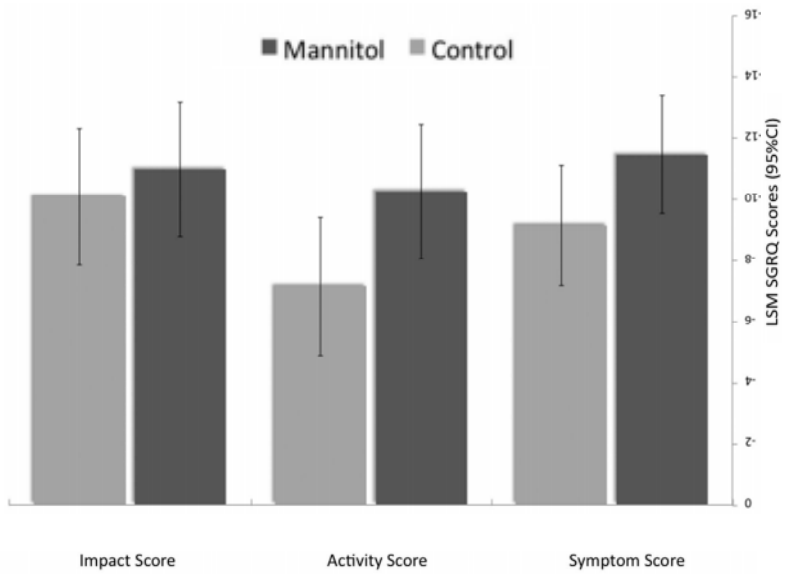


Figure 2 Changes in St Georges Respiratory Quality of Life Questionnaire for active and placebo phases.



	Baseline retrospective recall	Active prospective	Placebo prospective	*P* value active: placebo
Annualised antibiotic use *n*/year	2.11	2.43	5.43	<0.05
Annualised exacerbations *n*/year	2.60	2.14	4.85	<0.05

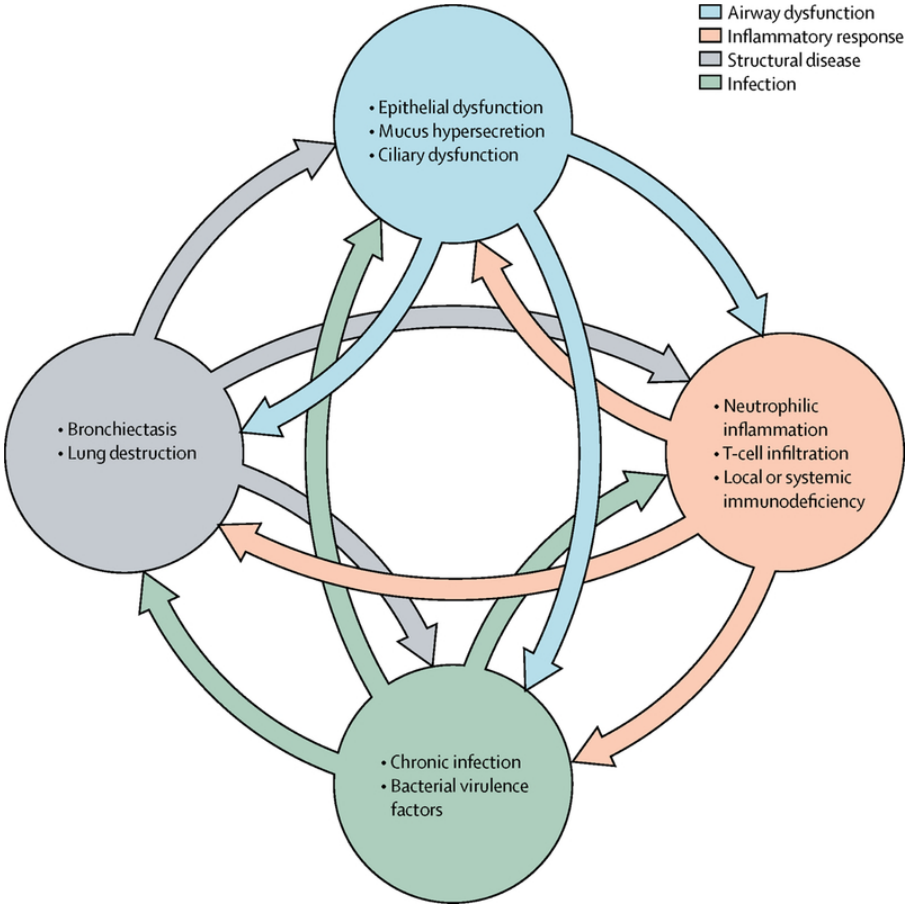
Table 3—*Pulmonary Exacerbations: Rates and Risk*

	Placebo Rate	rhDNase Rate	Relative Risk	95% CI
PDEs	0.56	0.66	1.17	0.85, 1.65
NPDEs	0.14	0.29	2.01	1.15, 3.50
PDEs and NPDEs	0.71	0.95	1.35	1.01, 1.79

rhDNase was not effective in the treatment of patients with stable idiopathic bronchiectasis. Overall pulmonary exacerbation rate (PDE and NPDE), one primary study end point, was higher in the rhDNase group than in the placebo group, although it did not achieve statistical significance. With regard to the second primary end point, mean percentage change in FEV_1, there was statistically significant deterioration in the patients who received rhDNase compared with placebo. Among secondary end points, increased hospitalization rates, increased use of antibiotics, and FVC decline were noted in patients who received rhDNase. Therefore, the long-term use of rhDNase in patients with idiopathic bronchiectasis cannot be recommended; in fact, it may be harmful in this population.

Kellet F, Robert NM. *Respir Med.* 2011;105(12):1831-1835.
Bilton D, et al. *Thorax.* 2014;69(12):1073-1079.
O'Donnell AE, et al. *Chest.*1998;113(5):1329-1334.

Guidelines for Treatment



Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

- Chronic infection
- Bacterial virulence factors

Guidelines for Treatment: Inhaled Antibiotics

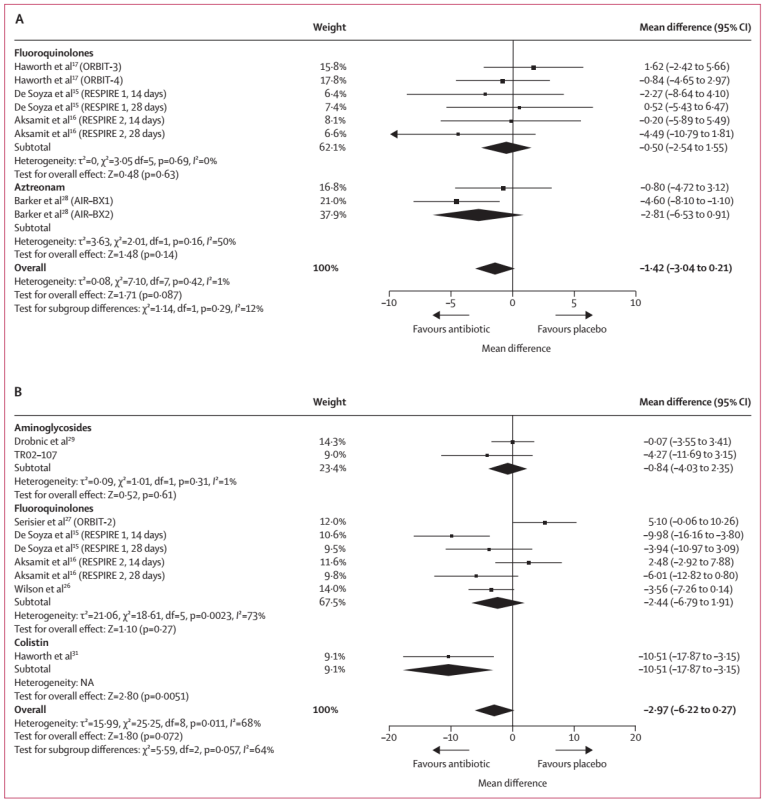


Figure 4: **Forest plot of quality of life and symptom scales according to the QOL-B questionnaire (A) and SGRQ (B)**
For both QOL-B and SGRQ, a negative score has been shown as a reduction in symptoms for ease of interpretation. In the scales themselves a reduction in the scale indicates an improvement in symptoms with SGRQ but a worsening with QOL-B. The weight represents the percentage contribution of each study to the summary effect estimate. Weights of individual studies might not add up to the subtotal or overall weights because of rounding. df=degrees of freedom. NA=not applicable. QOL-B=Quality of life—Bronchiectasis. SGRQ=St George's Respiratory Questionnaire.

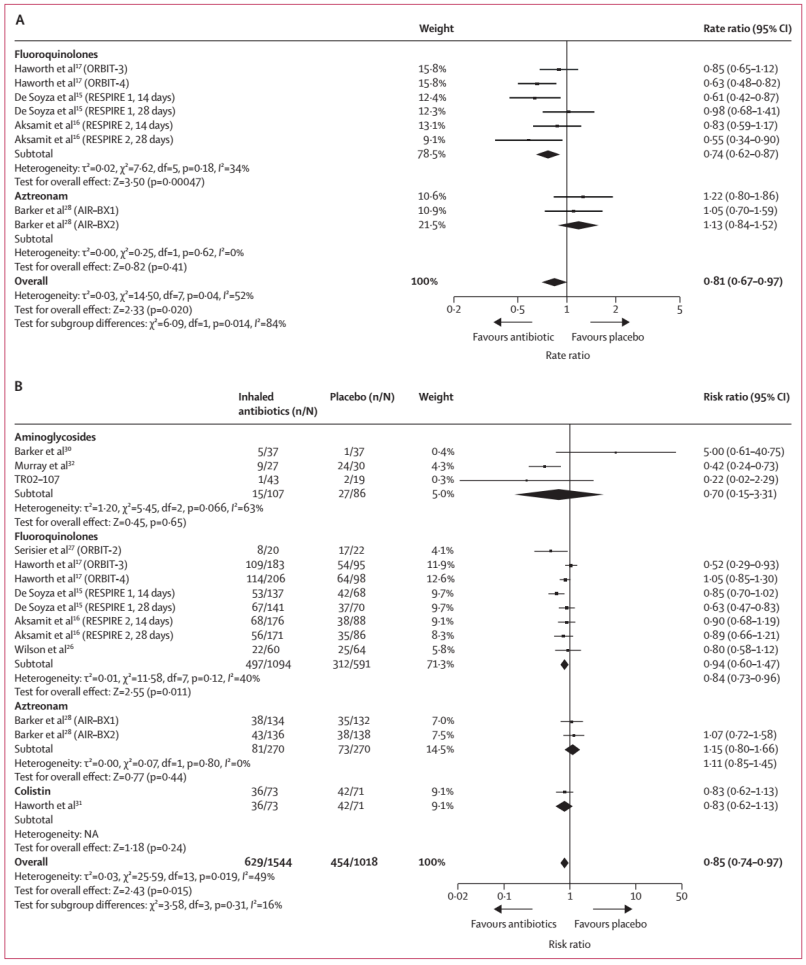
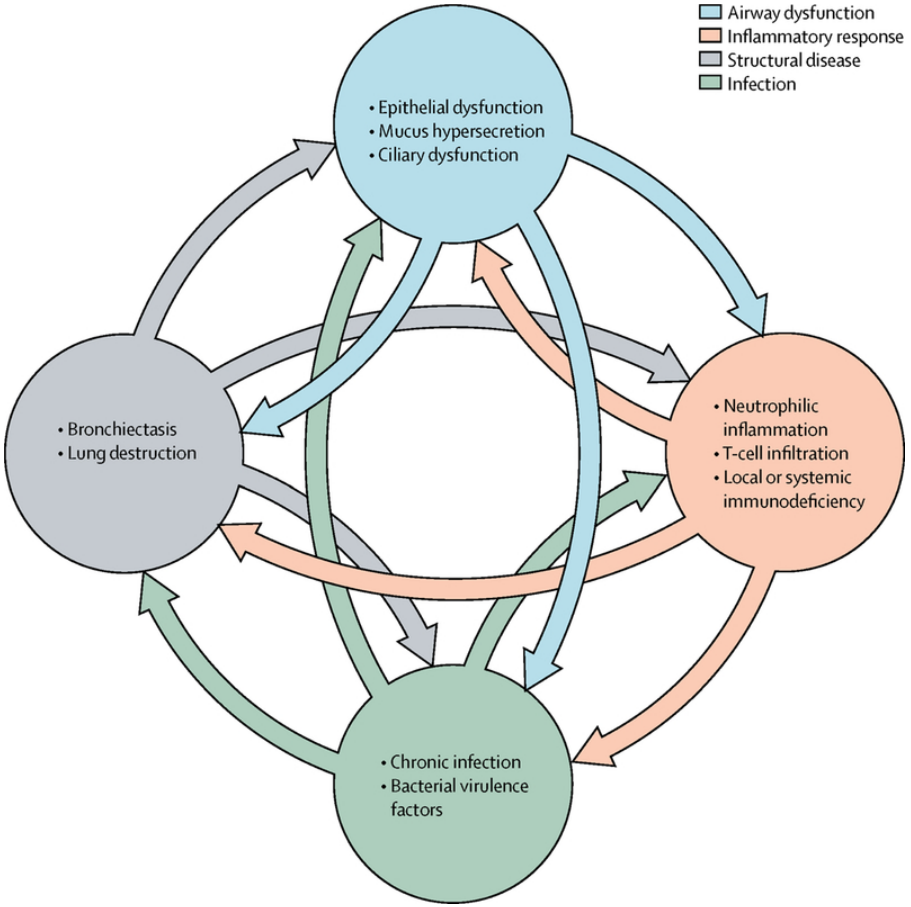


Figure 3: **Forest plot of frequency of exacerbations (A) and number of participants experiencing at least one exacerbation (B)**
The weight represents the percentage contribution of each study to the summary effect estimate. Weights of individual studies might not add up to the subtotal or overall weights because of rounding. df=degrees of freedom. NA=not applicable.

Laska IF, et al. *Lancet Respir Med*. 2019;7(10):855-869.

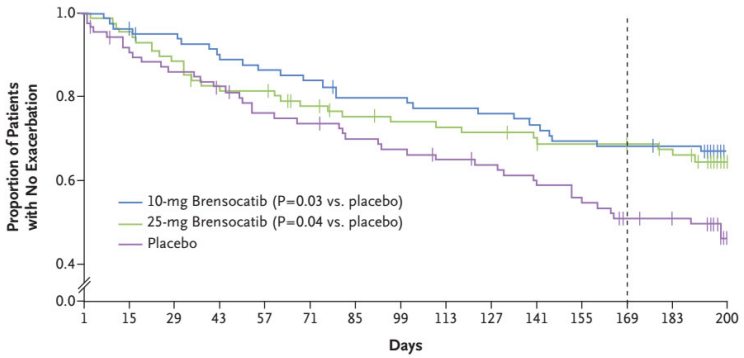
Guidelines for Treatment



Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

Guidelines for Treatment: Neutrophilic versus Eosinophilic

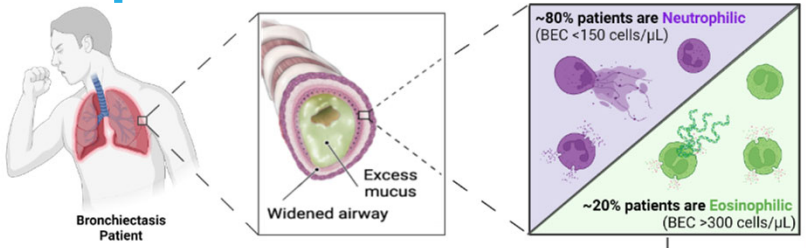
- Neutrophilic inflammation
- T-cell infiltration
- Local or systemic immunodeficiency



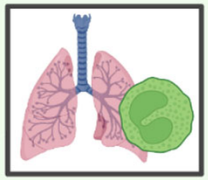
	HR (95% CI)	p value	$p_{interaction}$ value
Age group	..	..	0·15
<50 years	0·65 (0·29–1·44)	0·29	..
50–69 years	0·50 (0·35–0·72)	<0·0001	..
≥70 years or more	0·24 (0·11–0·54)	<0·0001	..
Sex	..	..	0·22
Male	0·57 (0·34–0·95)	0·030	..
Female	0·38 (0·27–0·55)	<0·0001	..
Previous exacerbations (per year)	..	..	0·45
1–2	0·40 (0·17–0·96)	0·040	..
3	0·47 (0·25–0·89)	0·020	..
≥4	0·48 (0·34–0·69)	<0·0001	..
Smoking status	..	..	0·34
Never	0·49 (0·34–0·72)	<0·0001	..
Former	0·37 (0·22–0·58)	<0·0001	..
Inhaled corticosteroid use	..	..	0·89
Yes	0·44 (0·31–0·63)	<0·0001	..
No	0·46 (0·27–0·76)	0·0039	..
BMI at baseline (kg/m²)	..	..	0·24
<21	0·22 (0·07–0·70)	0·010	..
21–24·9	0·56 (0·38–0·82)	0·0037	..
25–29·9	0·33 (0·17–0·67)	0·0020	..
≥30	0·26 (0·11–0·59)	0·0019	..
Cause	..	..	0·11
Idiopathic and post-infective	0·53 (0·38–0·75)	<0·0001	..
Other	0·29 (0·15–0·57)	<0·0001	..
Baseline concentration of C-reactive protein (mg/L)	..	..	0·20
<2	0·61 (0·35–1·05)	0·072	..
2–5	0·44 (0·26–0·76)	0·0031	..
5·1–10	0·27 (0·12–0·57)	0·0014	..
>10	0·39 (0·19–0·82)	0·013	..
Baseline FEV_1 (% predicted)	..	..	0·86
≥80	0·49 (0·31–0·77)	0·0023	..
50–79	0·37 (0·23–0·59)	<0·0001	..
<50	0·54 (0·27–1·09)	0·087	..
SGRQ total score	..	..	0·21
<30	0·60 (0·37–0·98)	0·039	..
30–49	0·37 (0·24–0·59)	<0·0001	..
≥50	0·42 (0·23–0·77)	0·0045	..
Pseudomonas aeruginosa infection	..	..	0·47
Yes	0·36 (0·19–0·69)	0·0017	..
No	0·47 (0·34–0·65)	<0·0001	..

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

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



The "Eosinophilic Bronchiectasis" Patient



Patient Characteristics:

BEC >300 cells/μL
AND/OR
sputum eosinophils >3%

No history of asthma / ABPA

Severe disease

Frequent exacerbations

Possible *Pseudomonas* involvement

Possible Treatment Options

Inhaled corticosteroids (ICS)

Oral corticosteroids (OCS)

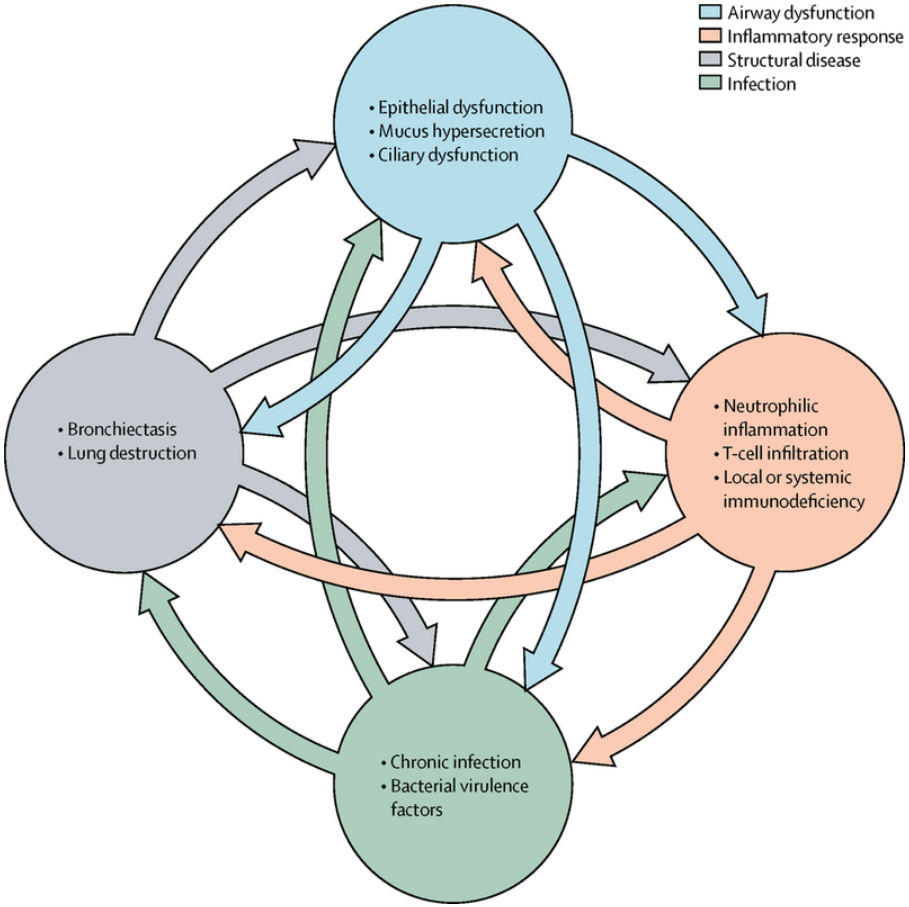
Anti-IL-5 receptor biologics
i.e. Benralizumab

Anti-IL-5 biologics
i.e. Mepolizumab, Reslizumab

Anti-IgE biologics
i.e. Omalizumab

Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137.
Chalmers JD, et al. *Lancet Respir Med.* 2019;7(10):845-854.
Pollock J, et al. *Chest.* 2023; In press.

Guidelines for Treatment



Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

Guidelines for Treatment: Surgery

Question 8: Are surgical interventions more beneficial compared to standard (non-surgical) treatment for adult bronchiectasis patients?

Recommendation

We suggest not offering surgical treatments for adult patients with bronchiectasis with the exception of patients with localised disease and a high exacerbation frequency despite optimisation of all other aspects of their bronchiectasis management (*weak recommendation, very low quality of evidence*).

The pooled mortality from 29 studies that focused on adult patients was 1.4% (95% CI 0.8%–2.5%) [98]. Post-operative pooled morbidity for adults was analysed in 26 observational studies and was 16.2% (95% CI,12.5%–19.8%) [98]. It needs to be emphasised that there are no data comparing morbidity to continued medical non-surgical management alone. Moreover, according to the aforementioned studies, some of the morbidity is considered relatively minor (air leak, atelectasis, wound infection). Symptomatic changes were analysed in 26 observational studies. In the pooled meta-analysis, complete alleviation of symptoms was seen in 71.5% (95% CI 68–74.9) and reduction of preoperative symptoms was seen in 20.2% of the adult population (95% CI 17.3–23.1) [98]. Other research has shown that extent of residual bronchiectasis and *P. aeruginosa* infection were reported as unfavourable prognostic factors [99].

Justification of the recommendations

Overall, surgical interventions seem to be beneficial only in very carefully selected patients requiring the best risk-benefit profile of improved symptoms against the morbidity associated with surgery. Feedback from the ELF/EMBARC patient advisory group suggests that patients would choose surgery only if there was no effective medical option for treatment and this feedback informs the recommendation.

Implementation considerations

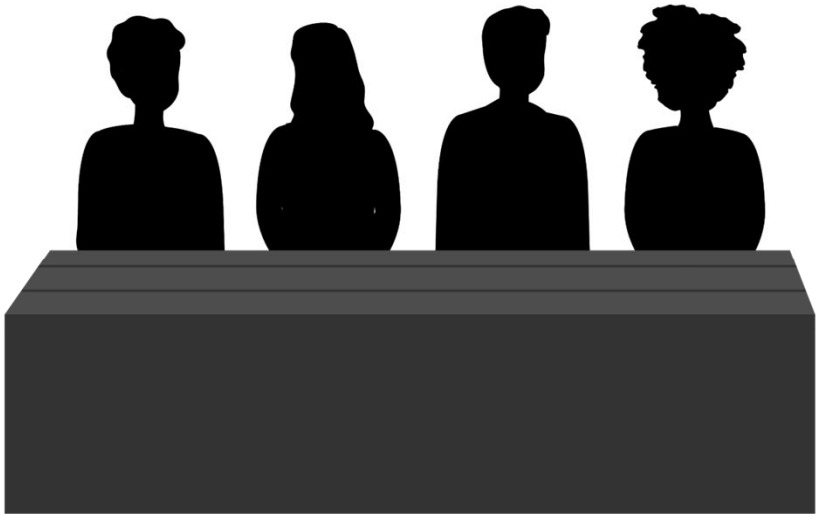
Involvement of an experienced surgeon in partnership with an expert respiratory physician is advisable if surgical treatment is being considered. Attention should be paid to pre-operative nutritional status and pulmonary rehabilitation. More research is needed on surgical interventions. Although a randomised trial would be very challenging future studies should include a matched control population with meticulous description of other treatments used in both populations.

Polverino, et al. *Eur Respir J*. 2017;50(3):1700629.

Acknowledgements

Panel Discussion

- Do you routinely check for sputum or blood eosinophilia in your bronchiectasis patients?
- Do you ever use corticosteroids (inhaled or oral) to treat your bronchiectasis patients?



Improving Upon the Current NCFBE Standard of Care: The Role of Emerging Therapies Aimed at Inhibiting NSP Activation

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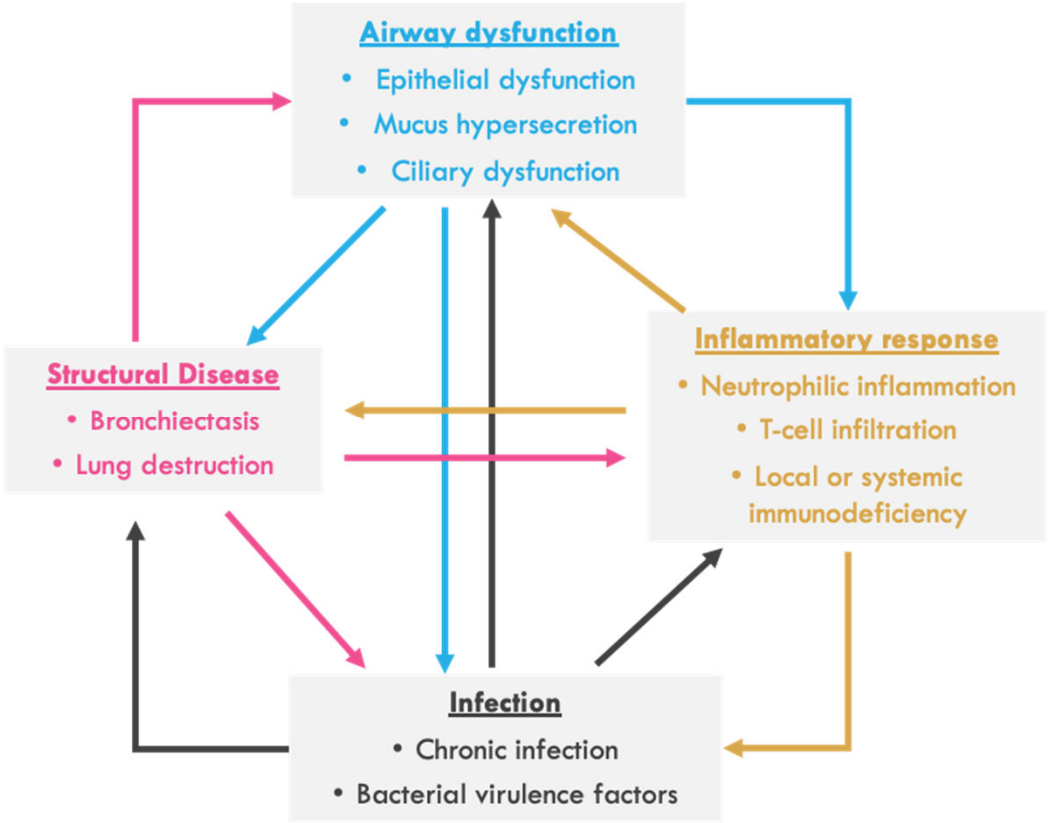
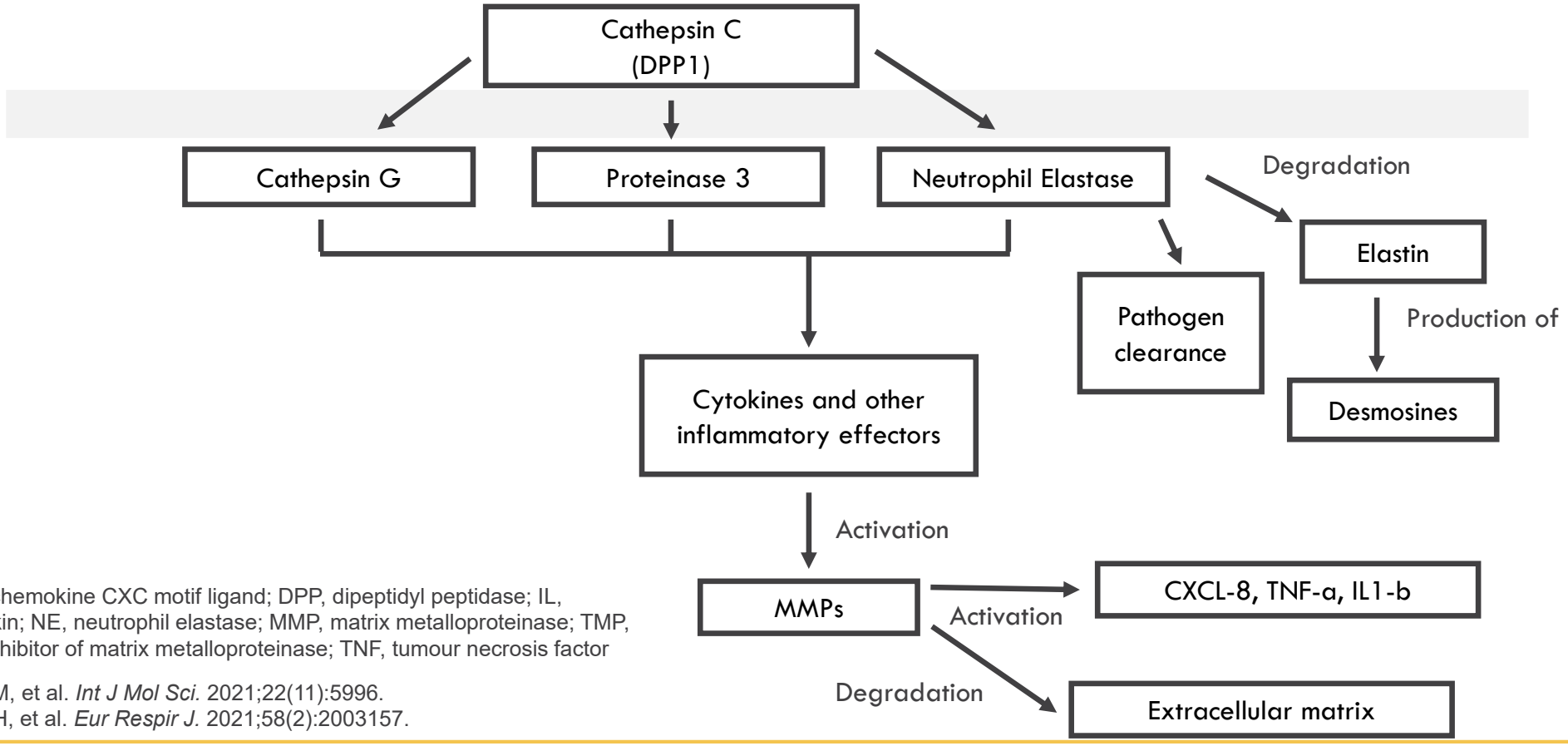
Humanitas University
Chief, Respiratory Unit
IRCCS Humanitas Research Hospital
Milan, Italy

Bronchiectasis Pathogenesis
The Vicious Vortex



Flume PA, et al. *Lancet.* 2018;392(10150):880-890.

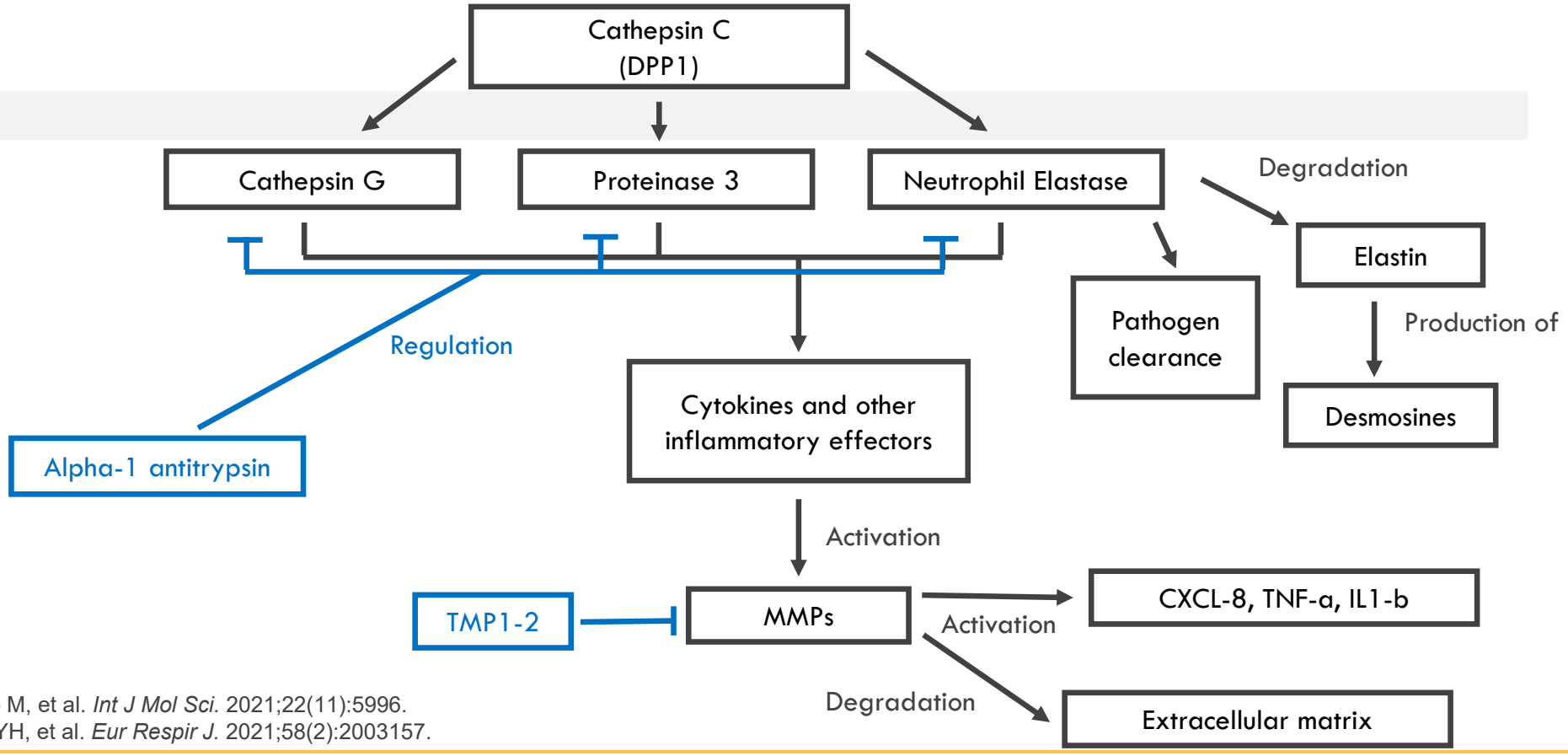
Neutrophil Serine Proteases in Bronchiectasis



CXCL, chemokine CXC motif ligand; DPP, dipeptidyl peptidase; IL, interleukin; NE, neutrophil elastase; MMP, matrix metalloproteinase; TMP, tissue inhibitor of matrix metalloproteinase; TNF, tumour necrosis factor

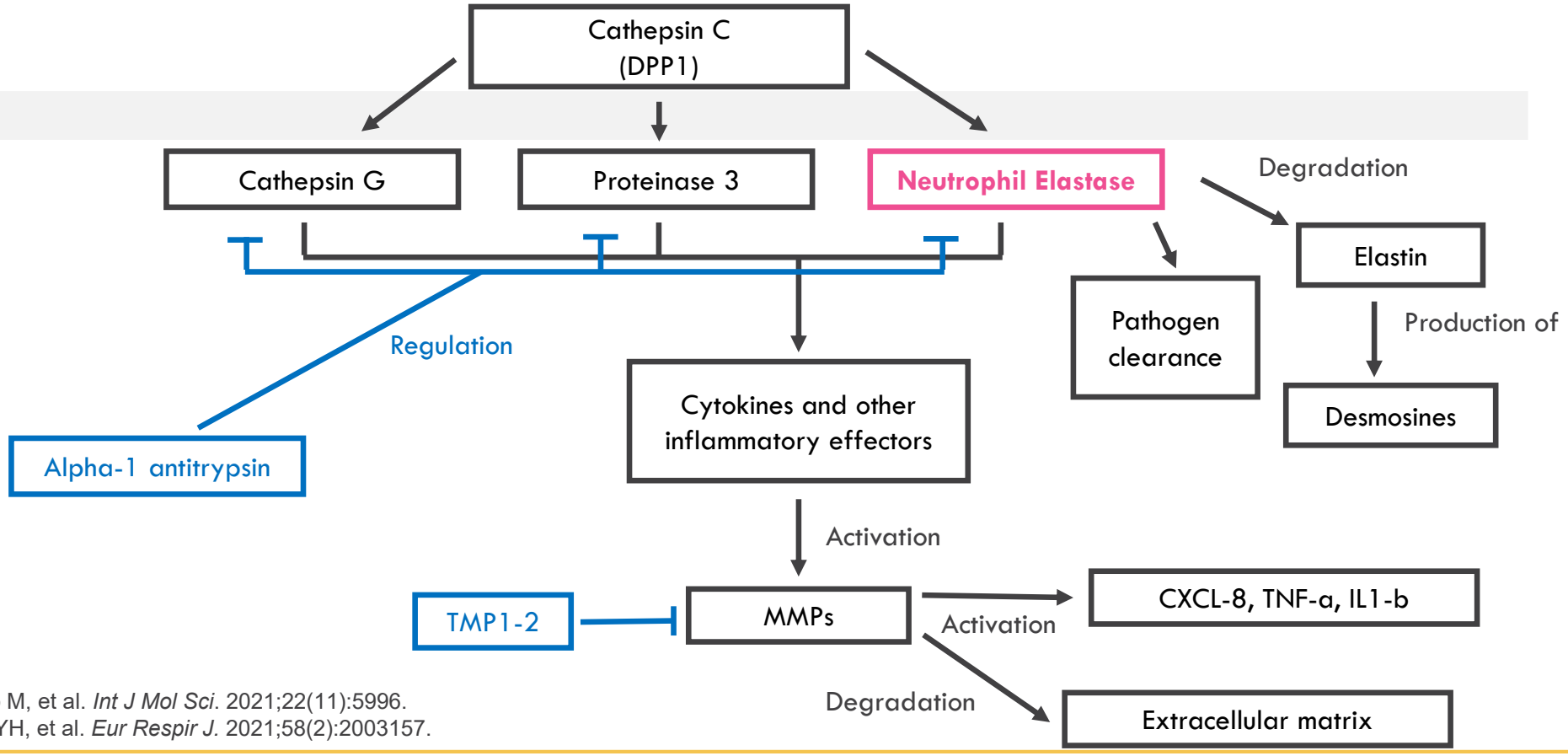
Oriano M, et al. *Int J Mol Sci.* 2021;22(11):5996.
Giam YH, et al. *Eur Respir J.* 2021;58(2):2003157.

Neutrophil Serine Proteases in Bronchiectasis



Oriano M, et al. *Int J Mol Sci.* 2021;22(11):5996.
Giam YH, et al. *Eur Respir J.* 2021;58(2):2003157.

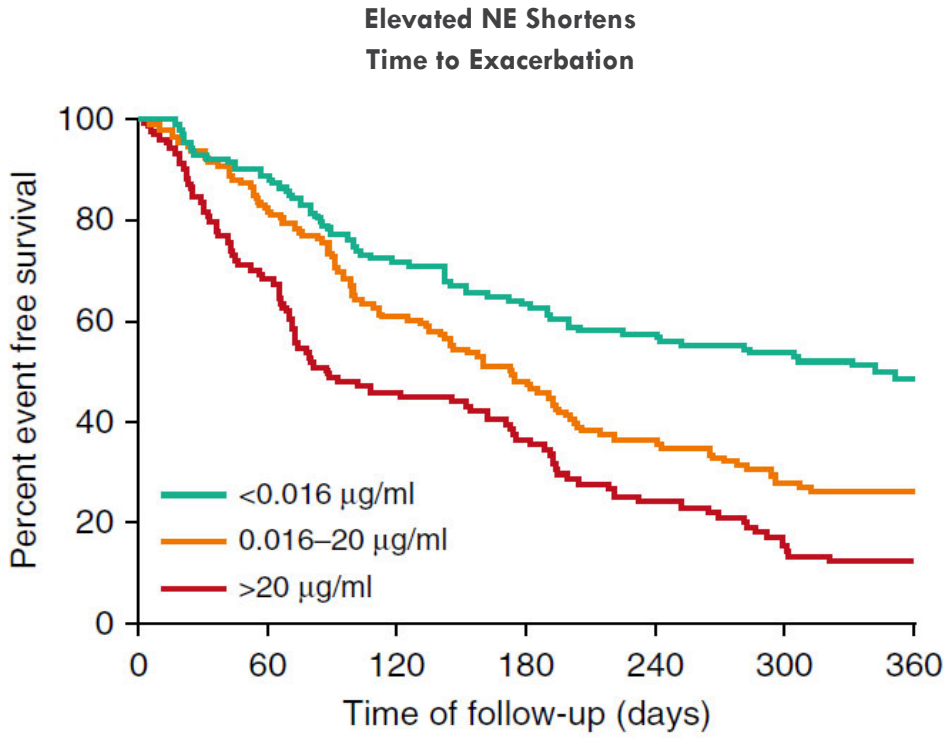
Neutrophil Serine Proteases in Bronchiectasis



Oriano M, et al. *Int J Mol Sci*. 2021;22(11):5996.
Giam YH, et al. *Eur Respir J*. 2021;58(2):2003157.

Neutrophil Elastase in Bronchiectasis

- Elevated neutrophil elastase (NE) is associated with exacerbations and poor quality of life



Chalmers JD, et al. *Am J Respir Crit Care Med.* 2017;195(10):1384.

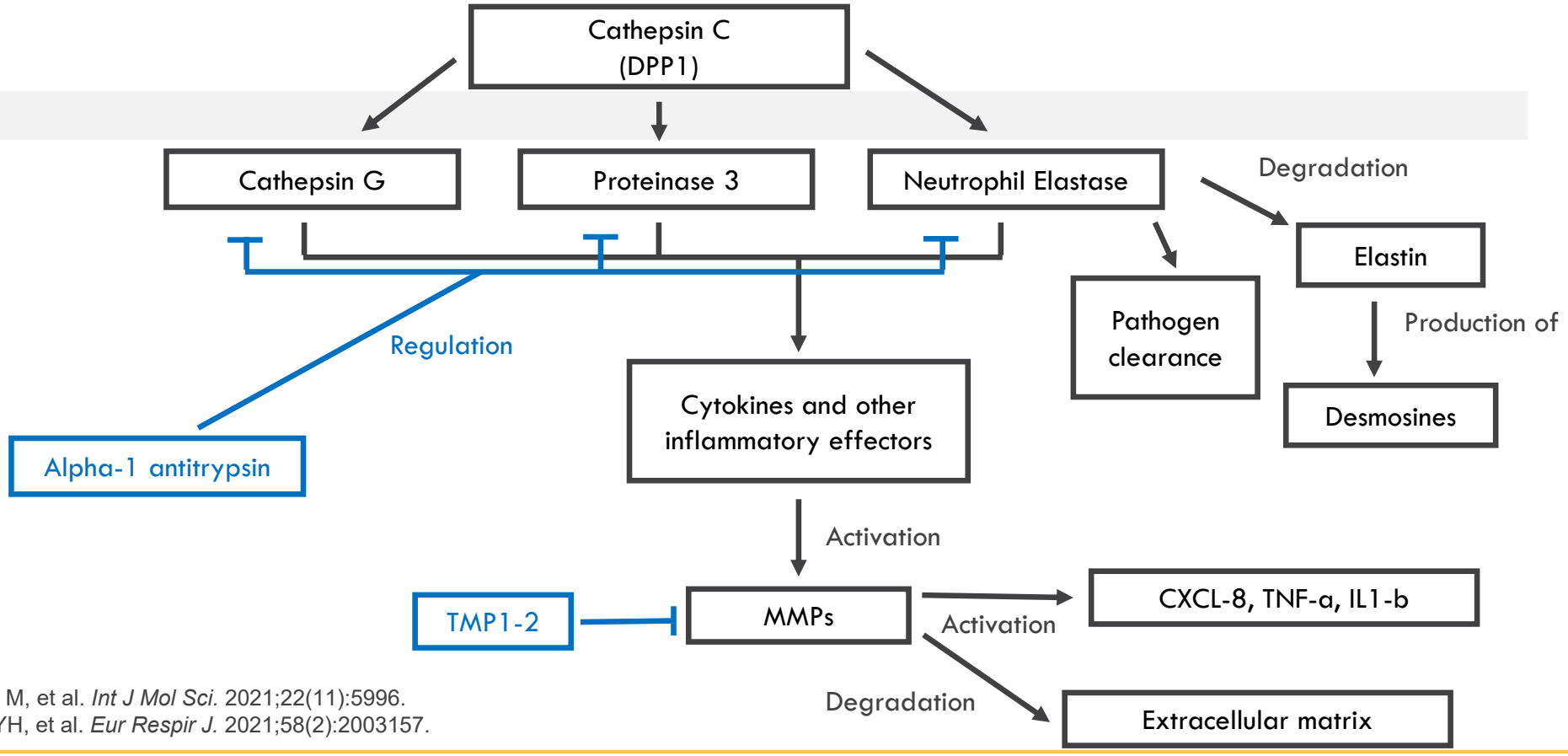
Inhibition of Neutrophil Elastase

- AZD9668 (selective inhibitor of NE)[1]
  - Phase 2a, randomized, placebo-controlled, parallel-group trial
  - 38 people treated for 28 days
  - Primary outcome: Reduced sputum neutrophil count was not achieved
  - Secondary outcomes: Significant 100 mL increase in FEV_1 occurred and positive trend in St. George's Respiratory Questionnaire
- BAY85-8501 (selective and reversible inhibitor of NE)[2]
  - Phase 2a, randomized, placebo-controlled, double-blind trial
  - 94 people treated for 28 days
  - No changes in pulmonary function or QoL in any group

Small studies, short duration, low doses, and some without neutrophilic inflammation

[1]Stockley R, et al. *Respir Med*. 2013;107(4):524-533.
[2]Watz H, et al. *Pulm Pharmacol Ther.* 2019;56:86-93.

Neutrophil Serine Proteases in Bronchiectasis



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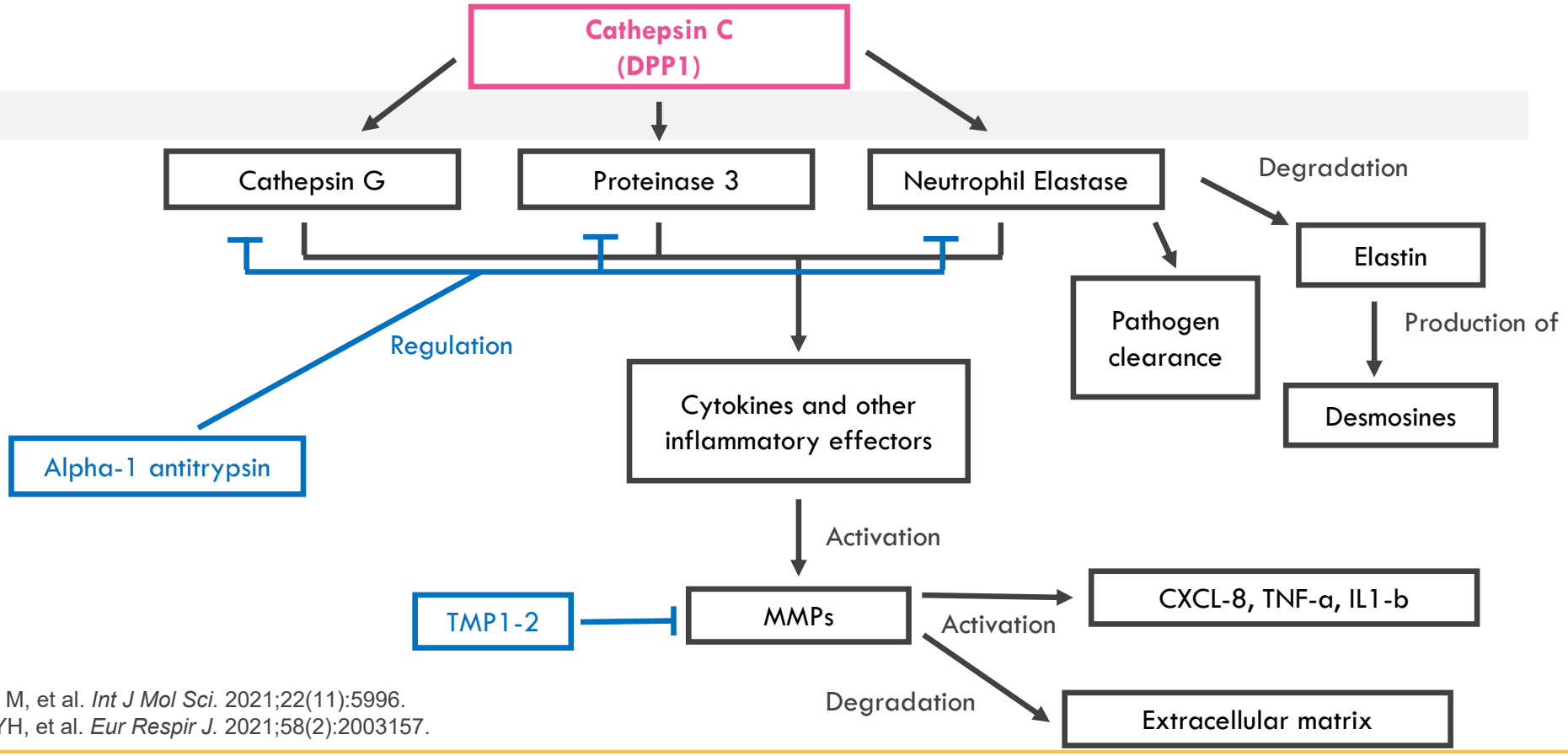
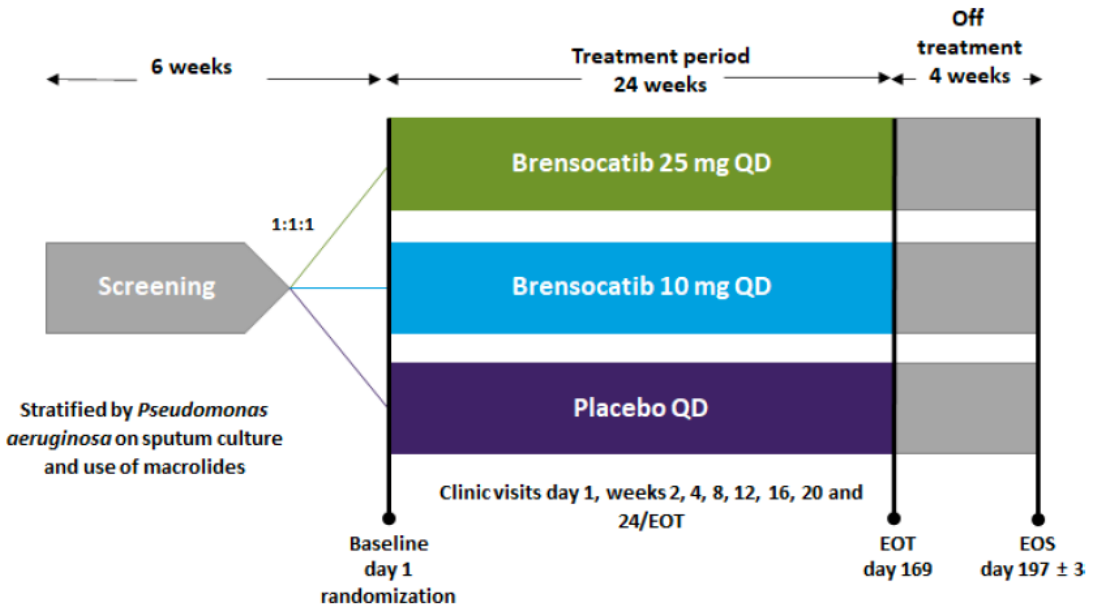
Neutrophil Serine Proteases in Bronchiectasis



Oriano M, et al. *Int J Mol Sci.* 2021;22(11):5996.
Giam YH, et al. *Eur Respir J.* 2021;58(2):2003157.

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



Primary Endpoint:

- Time to first bronchiectasis exacerbation

Secondary Endpoints:

- Rate of exacerbations
- Change in QOL-B Respiratory Symptoms domain
- Change in post-bronchodilator ppFEV$_1$
- Change in sputum neutrophil elastase activity

Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137.

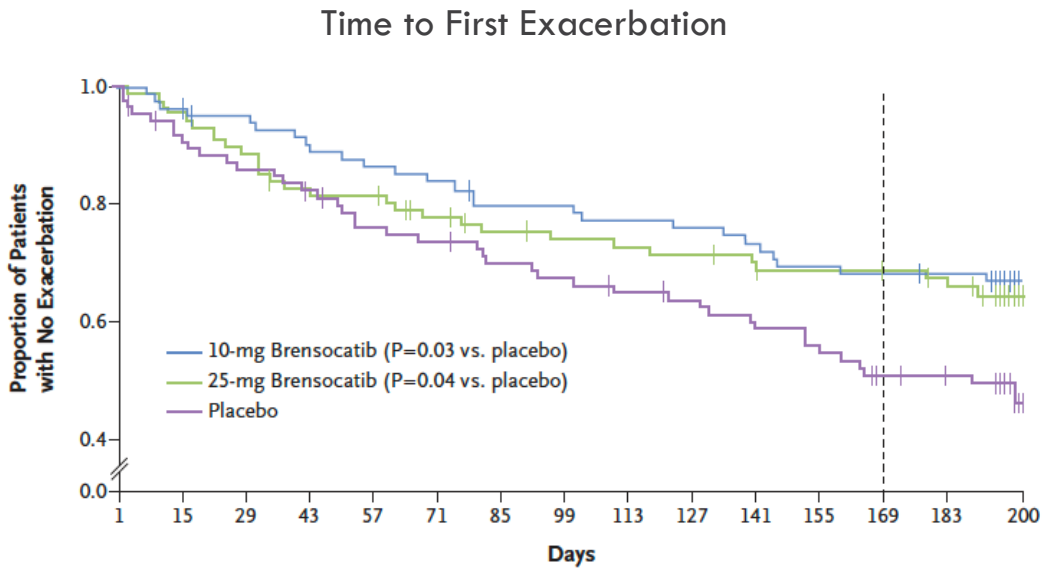
Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis: Study Populations

Characteristic	Placebo (n=87)	10 mg Brensocatib (n=82)	25 mg Brensocatib (n=87)
Age			
Mean (SD) — yr	64.0 (11.86)	64.6 (12.42)	63.7 (12.67)
≥ 65 years — no. (%)	54 (62.1)	48 (58.5)	48 (55.2)
≥ 75 years — no. (%)	14 (16.1)	20 (24.4)	14 (16.1)
Female sex — no. (%)	55 (63.2)	57 (69.5)	62 (71.3)
Race White — no. (%)	71 (81.6)	76 (92.7)	78 (89.7)
History of COPD — no. (%)	17 (19.5)	12 (14.6)	13 (14.9)
History of asthma — no. (%)	25 (28.7)	18 (22.0)	21 (24.1)
Pseudomonas aeruginosa positive — no. (%)*†	29 (33.3)	27 (32.9)	33 (37.9)
Chronic macrolide use — no. (%)*	14 (16.1)	10 (12.2)	16 (18.4)
Median Bronchiectasis Severity Index (range) ‡	7.0 (0–19)	8.0 (1–21)	8.0 (0–19)
≥3 exacerbations in prior 12 months — no. (%)	25 (28.7)	23 (28.0)	36 (41.4)
Hospitalized for exacerbation in prior 24 months — no. (%)	30 (34.5)	31 (37.8)	31 (35.6)
Mean FEV_1 % predicted (SD)	67.3 (23.93)	65.9 (23.91)	70.0 (23.24)
Neutrophil elastase in sputum — no. (%)			
BLQ	18 (20.7)	23 (28.0)	21 (24.1)
LLQ to < 20 mg/mL	42 (48.3)	28 (34.1)	36 (41.4)
≥ 20 mg/mL	24 (27.6)	31 (37.8)	29 (33.3)

* Stratification criterion. † Positive culture at the time of randomization. ‡ Disease severity classified by validated Bronchiectasis Severity Index. BLQ, below the limit of quantification; COPD, chronic obstructive pulmonary disease; LLQ, lower limit of quantification.

Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.

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



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

Brensocatib prolonged time to first exacerbation c/w placebo:

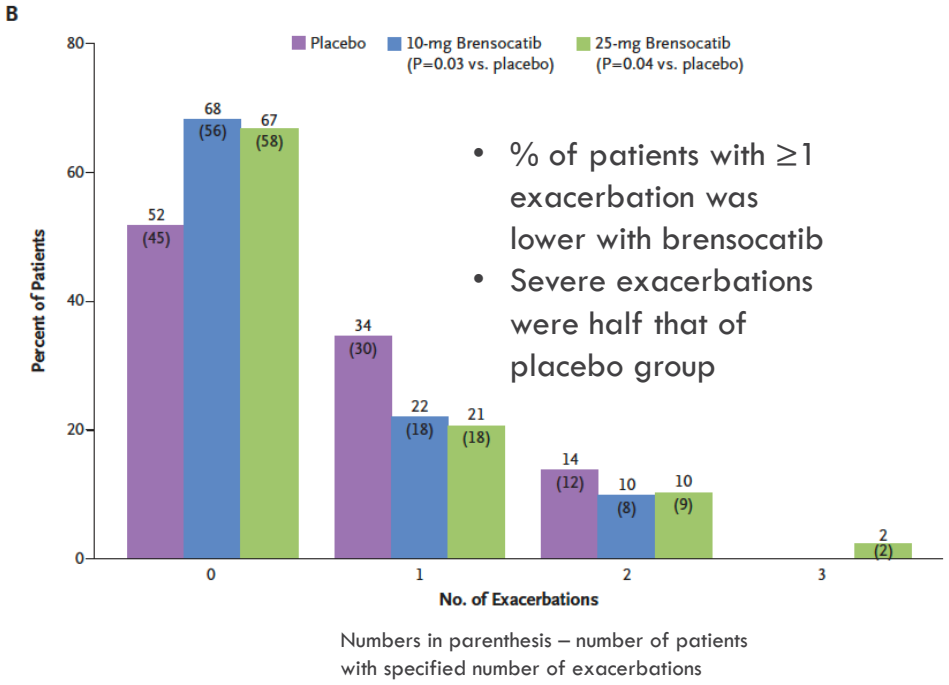
10 mg (*P*=.03)

25 mg (*P*=.04)

Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.

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

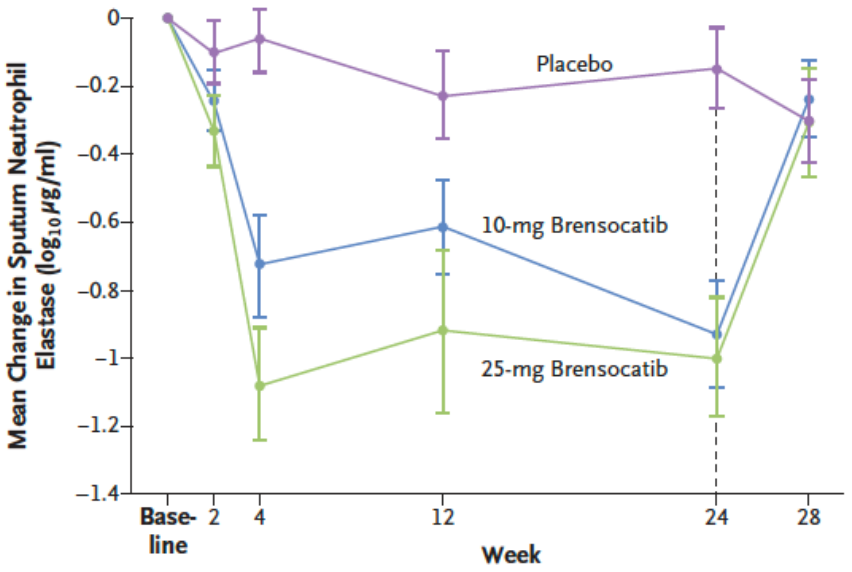
Number of Exacerbations



- % of patients with ≥1 exacerbation was lower with brensocatib
- Severe exacerbations were half that of placebo group

Numbers in parenthesis – number of patients with specified number of exacerbations

Mean Change in Sputum Neutrophil Elastase Concentration



Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.

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

n (%)	Placebo (N=85)	10 mg Brensocatib (N=81)	15 mg Brensocatib (N=89)
Adverse events of special interest	23 (27.1)	27 (33.3)	35 (39.3)
Skin	10 (11.8)	12 (14.8)	21 (23.6)
Dental	3 (3.5)	13 (16.0)	9 (10.1)
Infection	15 (17.6)	11 (13.6)	15 (16.9)
Change in periodontal pocket depth ≥ 2 mm and ≥ 5 mm absolute depth[a]	8 (11.6)	8 (11.3)	9 (12.3)

Safety analyses were based on the safety population, which included all patients who received at least one dose of brensocatib or placebo.
[a] Pocket depth was evaluated at three dental visits (baseline, week 8, week 24). Data shown include patients with both a baseline and week-24 dental evaluation (placebo, n=69; brensocatib 10 mg, n=71; brensocatib 25 mg, n=73).

Chalmers JD, et al. *N Engl J Med*. 2020;383(22):2127-2137.

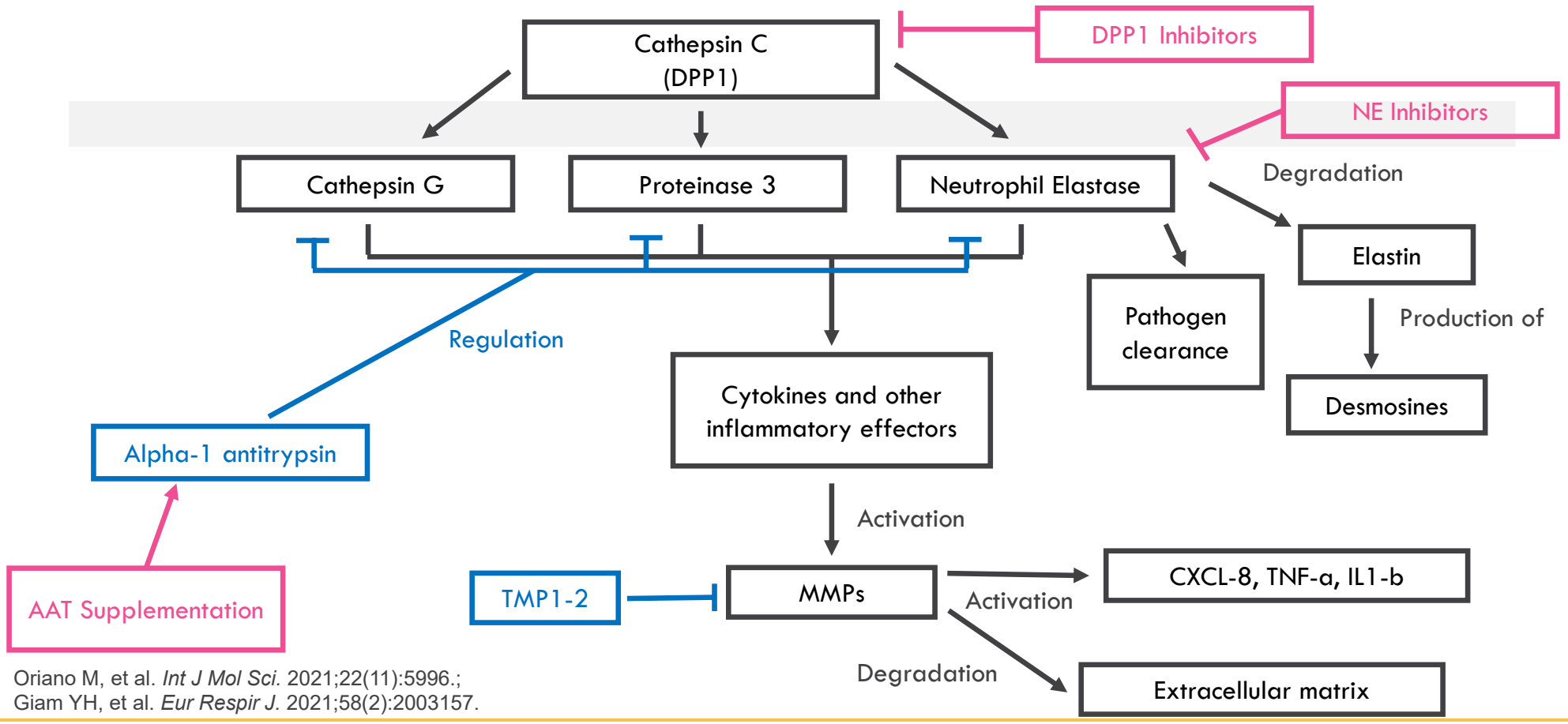
Brensocatib: Phase 3 Trial

ASPEN – Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis

- More than 1,700 adult patients with NCFBE enrolled; adolescent enrollment ongoing
- Primary outcome
  - Rate of adjudicated pulmonary exacerbations
- Select secondary outcomes
  - Time to first adjudicated exacerbation
  - Percentage free from exacerbation
  - Postbronchodilator FEV_1
  - Rate of severe adjudicated pulmonary exacerbations
  - QoL
- Results expected Q2 2024

ClinicalTrials.gov NCT04594369

Neutrophil Serine Proteases in Bronchiectasis



Oriano M, et al. *Int J Mol Sci.* 2021;22(11):5996.;
Giam YH, et al. *Eur Respir J.* 2021;58(2):2003157.

Other Therapies Under Investigation for NCFBE

- Human derived immunoglobulin
- Monoclonal antibody (mepolizumab)
- Oral DPP-1 inhibitor (BI1291583)
- Nebulized NE inhibitor (CHF 6333)
- Phosphodiesterase inhibitor (roflumilast)
- Nebulized ascorbic acid and reduced glutathione
- CFTR potentiator (QBW 251)
- Transplantation of autologous bronchial basal cells
- Mesenchymal stem cells

DPP-1, dipeptidyl peptidase-1; NE, neutrophil elastase; CFTR, cystic fibrosis transmembrane conductance regulator

www.clinicaltrials.gov

Summary

Sputum Neutrophils are Associated with:

- Decline in pulmonary function
- Bacterial colonization
- Severe disease
- Inflammatory morbidity

Neutrophil Elastase is an NSP Associated with:

- Extracellular matrix degradation
- Mucus gland hyperplasia
- Increased mucus production
- Reduced ciliary beating rate
- Direct epithelial damage

Inhibiting DPP-1

- DPP-1 activates neutrophil elastase in the bone marrow during neutrophil maturation
- Direct neutrophil elastase inhibition failed to improve NCFBE in Phase 2 studies
- DPP-1 is currently an investigational target

NSP, neutrophil serine protease; DPP-1, dipeptidyl peptidase 1

Usansky H, et al. *Clin Pharmacol Drug Dev.* 2022;11(7):832-842.

Panel Discussion

- What are the potential benefits of preventing the activation of neutrophil elastase in NCFBE?