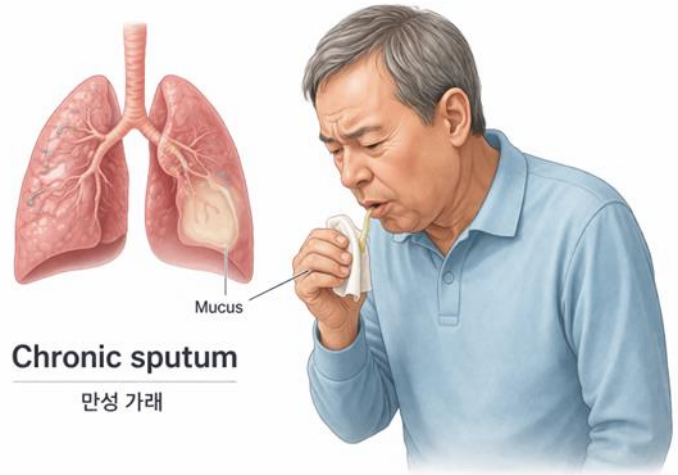
지속되는 가래 완치 가능한가?

경상국립의대
호흡기 알레르기내과
유정완



Content

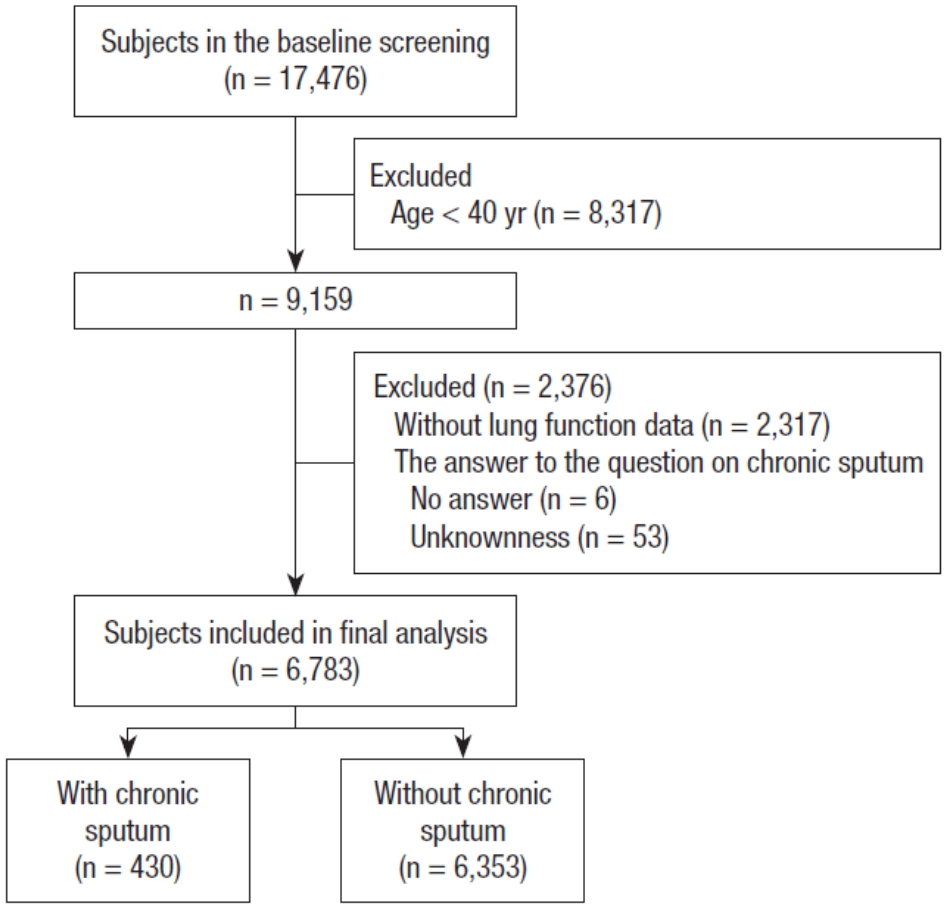
- **Epidemiology and clinical significance**
- **Pathogenesis and pathophysiology**
- **Clinical assessment**
- **Management**

Chronic sputum

- **Significant troublesome and symptom in practice**
- **Accelerated decline in lung function**
- **↑ Hospitalization and ↑ all-cause mortality**
- **Prevalence : 1.2% to 13%, globally**

Am J Respir Crit Care Med 1996; 153: 1530-5.
Chest 1994; 106: 827-34.
Eur Respir J 2003; 22: 413-7.
Am J Respir Crit Care Med 2007; 175: 32-9.

Prevalence of Chronic Sputum and Associated Factors in Korean Adults



(6.3%)

Variables	Classification	Sputum more than 3 months	
		Multivariate odds ratio (95% CI)	*P* value
Age	40-49	1	0.013
	50-59	1.315 (0.962-1.798)	0.086
	60-69	1.349 (0.944-1.928)	0.100
	≥ 70	1.954 (1.308-2.917)	0.001
Sex	Female	1	
	Male	1.198 (0.813-1.767)	0.361
Smoking	Never smoker	1	
	Past smoker	1.312 (0.834-2.064)	0.241
	Current smoker	4.496 (3.001-6.734)	< 0.001
COPD	No	1	
	Yes	1.483 (1.090-2.018)	0.012
Tuberculosis	No	1	
	Yes	1.959 (1.307-2.938)	0.001

Variables	Without chronic sputum, Mean ± SD	With chronic sputum, Mean ± SD	*P* value
FEV_1, liter	2.37 ± 1.07	2.28 ± 1.19	0.094
FEV_1, % predicted	81.73 ± 32.23	74.12 ± 35.48	< 0.001
FVC, liter	3.06 ± 1.36	3.07 ± 1.58	0.859
FVC, % predicted	82.07 ± 31.8	76.36 ± 35.63	< 0.001
FEV_1/FVC ratio	0.69 ± 0.26	0.62 ± 0.29	< 0.001

J Korean Med Sci 2014; 29: 825-830

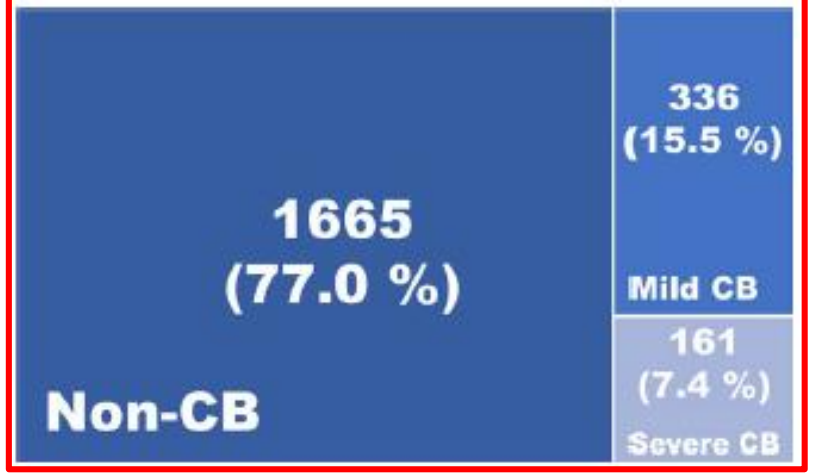
	EMBARC cohort (n=16 963)	UK (n=8163)	Southern Europe (n=4295)	Northern and western Europe (n=3444)	Central and eastern Europe (n=1061)
Age, years	67 (57–74)	69 (61–75)	66 (54–74)	65 (52–73)	62 (53–70)
Age >65 years	9943 (58·6%)	5465 (66·9%)	2174 (50·6%)	1841 (53·5%)	463 (43·6%)
Female	10 335 (60·9%)	4938 (60·5%)	2766 (64·4%)	2101 (61·0%)	530 (50·0%)
Male	6628 (39·1%)	3225 (39·5%)	1529 (35·6%)	1343 (39·0%)	531 (50·0%)
BMI, kg/m²*	24·9 (21·7–28·7)	25·7 (22·4–29·8)	24·3 (21·4–27·7)	23·8 (21·4–27·7)	24·8 (21·2–28·4)
Comorbidities					
Cardiovascular diseases	5509 (32·5%)	2413 (29·6%)	1397 (32·5%)	1135 (33·0%)	564 (53·2%)
Stroke	600 (3·5%)	388 (4·8%)	79 (1·8%)	101 (2·9%)	32 (3·0%)
Liver disease	103 (0·6%)	35 (0·4%)	15 (0·3%)	40 (1·2%)	13 (1·2%)
Osteoporosis	2228 (13·1%)	1255 (15·4%)	460 (10·7%)	398 (11·6%)	115 (10·8%)
Depression	2377 (14·0%)	1401 (17·2%)	493 (11·5%)	350 (10·2%)	133 (12·5%)
Anxiety	2428 (14·3%)	1290 (15·8%)	660 (15·4%)	339 (9·8%)	139 (13·1%)
Neoplastic disease	1863 (11·0%)	885 (10·8%)	435 (10·1%)	429 (12·5%)	114 (10·7%)
Chronic renal failure	667 (3·9%)	280 (3·4%)	173 (4·0%)	199 (5·8%)	15 (1·4%)
Diabetes	1724 (10·2%)	880 (10·8%)	403 (9·4%)	302 (8·8%)	139 (13·1%)
Asthma	5267 (31·0%)	3208 (39·3%)	811 (18·9%)	1046 (30·4%)	202 (19·0%)
COPD	4324 (25·5%)	2225 (27·3%)	828 (19·3%)	862 (25·0%)	409 (38·5%)
Smoking					
Never	9096 (53·6%)	4191 (51·3%)	2436 (56·7%)	1942 (56·4%)	527 (49·7%)
Ex-smoker	6785 (40·0%)	3591 (44·0%)	1501 (34·9%)	1328 (38·6%)	365 (34·4%)
Current	1082 (6·4%)	381 (4·7%)	358 (8·3%)	174 (5·1%)	169 (15·9%)
Severity of illness					
Modified MRC dyspnoea score	1 (0–2)	1 (1–2)	1 (0–2)	1 (0–2)	2 (1–3)
Does not produce daily sputum	4752 (28·0%)	2203 (27·0%)	1598 (37·2%)	947 (27·5%)	302 (28·5%)
Quality of life bronchiectasis respiratory symptom score†	63 (44–77·8)	59·3 (40·7–77·8)	70·4 (51·9–83·3)	62·9 (44·4–77·7)	59·3 (40·7–74·1)

Lancet Respir Med 2023; 11: 637–49

RESEARCH Open Access

Comparison of clinical characteristics between chronic bronchitis and non-chronic bronchitis in patients with chronic obstructive pulmonary disease

Joon Young Choi[1], Hyoung Kyu Yoon[2], Sang Yeub Lee[3], Jin Woo Kim[4], Hye Sook Choi[5], Yu-Il Kim[6], Ki-Suck Jung[7], Kwang Ha Yoo[8], Woo Jin Kim[9] and Chin Kook Rhee[10*]



	Moderate-to-severe exacerbation			Severe exacerbation		
	OR	95% CI	*p* value	OR	95% CI	*p* value
CB	1.46	1.20–1.79	< 0.01	1.40	0.96–2.03	0.08
Age	1.00	0.99–1.01	0.87	1.00	0.97–1.02	0.81
Sex (male)	0.76	0.53–1.09	0.13	0.40	0.19–0.81	0.01
Smoking Hx	1.06	0.89–1.26	0.52	0.96	0.68–1.36	0.81
FEV1	0.36	0.31–0.43	< 0.01	0.16	0.11–0.22	< 0.01

CB chronic bronchitis

	Moderate-to-severe exacerbation			Severe exacerbation		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Severe CB	1.29	0.92–1.82	0.14	2.52	1.23–5.32	0.01
Age	1.01	0.98–1.03	0.62	1.02	0.97–1.06	0.51
Sex (male)	0.70	0.34–1.45	0.33	0.19	0.03–1.11	0.08
Smoking Hx	1.13	0.83–1.55	0.42	0.91	0.44–1.92	0.80
FEV1	0.36	0.27–0.49	< 0.01	0.08	0.03–0.17	< 0.01

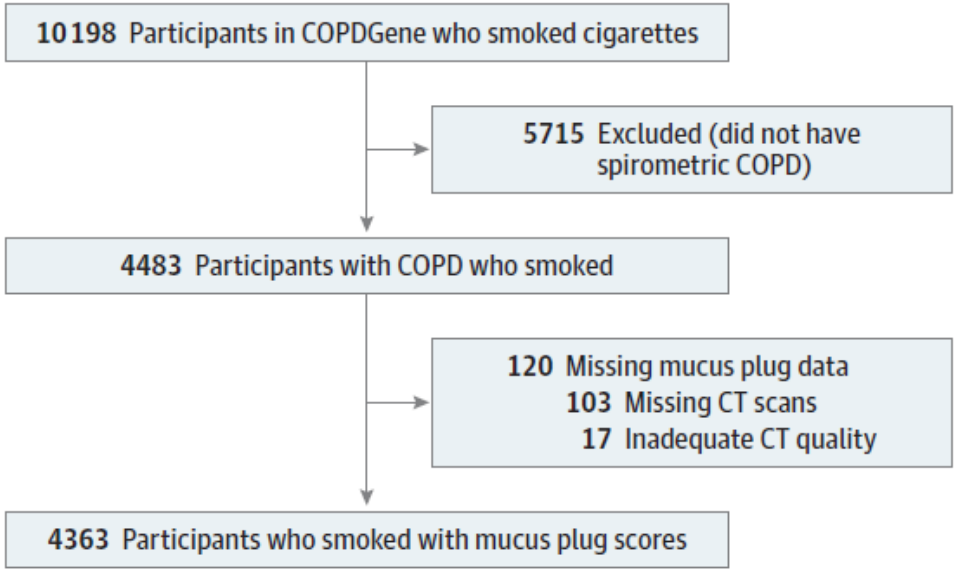
CB chronic bronchitis

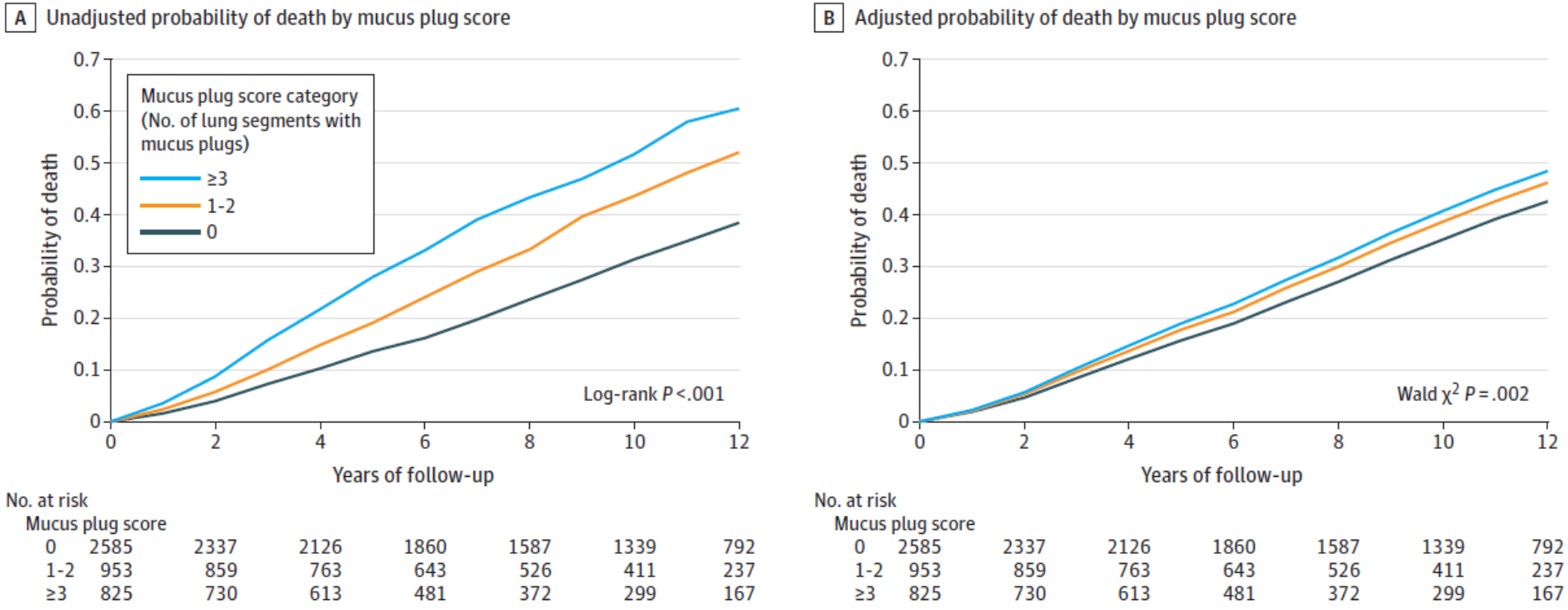
JAMA | Original Investigation

Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease

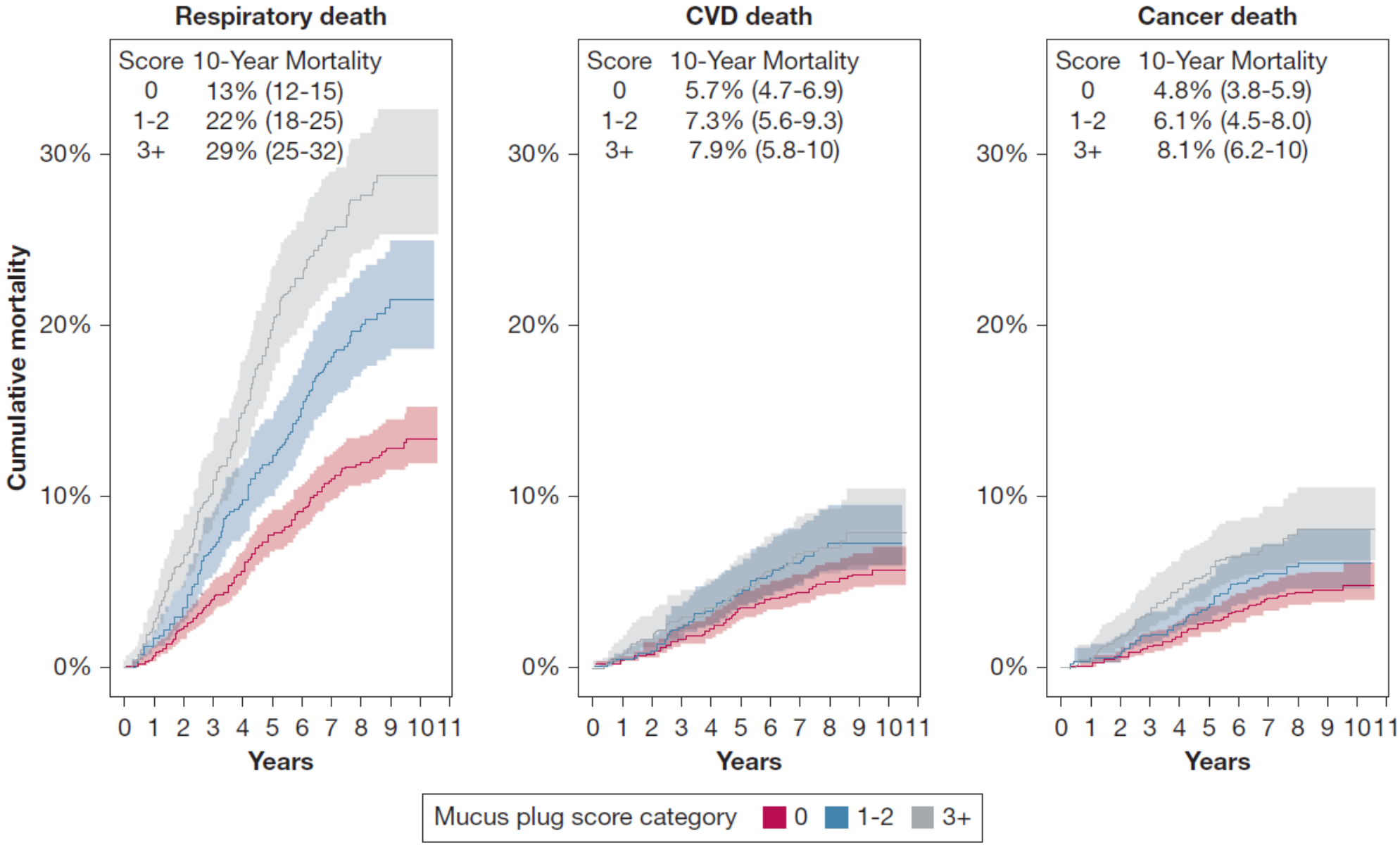
Alejandro A. Diaz, MD, MPH; José L. Orejas, MD; Scott Grumley, MD; Hrudaya P. Nath, MD; Wei Wang, PhD; Wojciech R. Dolliver, MD; Andrew Yen, MD; Seth J. Kligerman, MD; Kathleen Jacobs, MD; Padma P. Manapragada, MD; Mostafa Abozeed, MD, MSc, PhD; Muhammad Usman Aziz, MD; Mohd Zahid, MD; Asmaa N. Ahmed, MD, MBBCh, MSc; Nina L. Terry, MD; Ruben San José Estépar, MSc; Victor Kim, MD; Barry J. Make, MD; MeiLan K. Han, MD; Sushilkumar Sonavane, MD; George R. Washko, MD, MSc; Michael Cho, MD, MPH; Raúl San José Estépar, PhD

2585 (59.3%), 953 (21.8%), and 825 (18.9%) participants had mucus plugs in 0, 1 to 2, and 3 or more lung segments





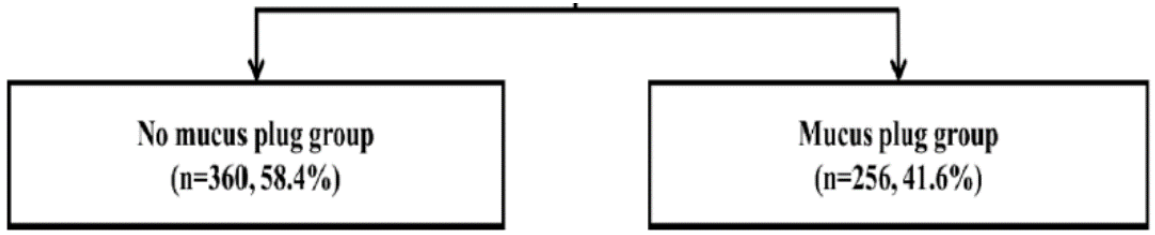
JAMA. 2023;329(21):1832-1839

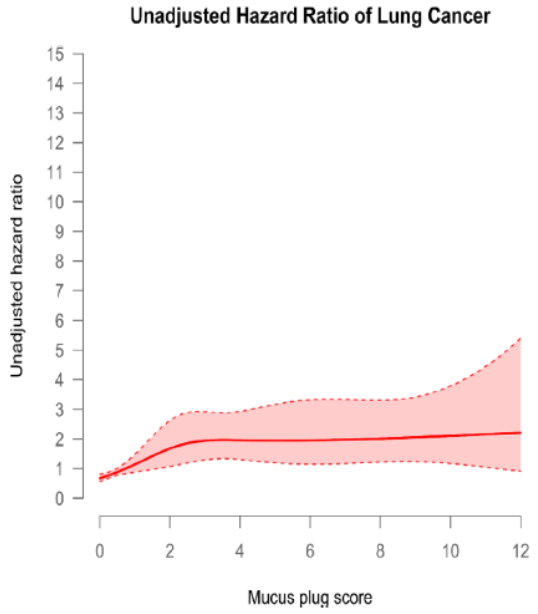


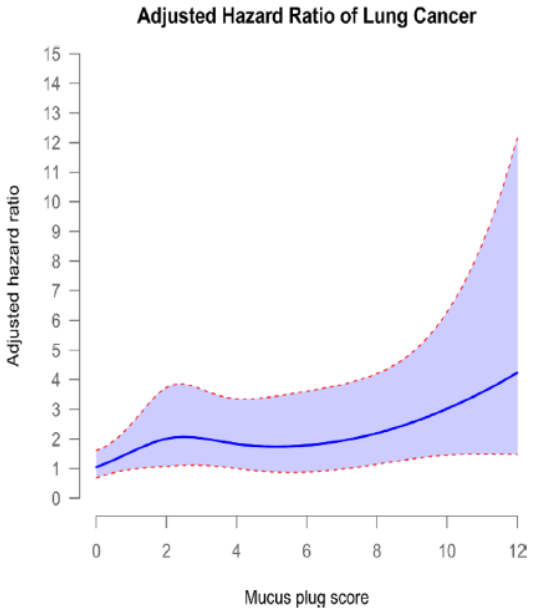
Am J Respir Crit Care Med. 2024;209(12):1508-1510

Mucus plug and lung cancer incidence in patients with COPD

So Jeong Kim[1], Heemoon Park[2], Hyo Jin Lee[2], Jung-Kyu Lee[2], Eun Young Heo[2], Kwang Nam Jin[3], Deog Kyeom Kim[2] & Hyun Woo Lee[2]✉



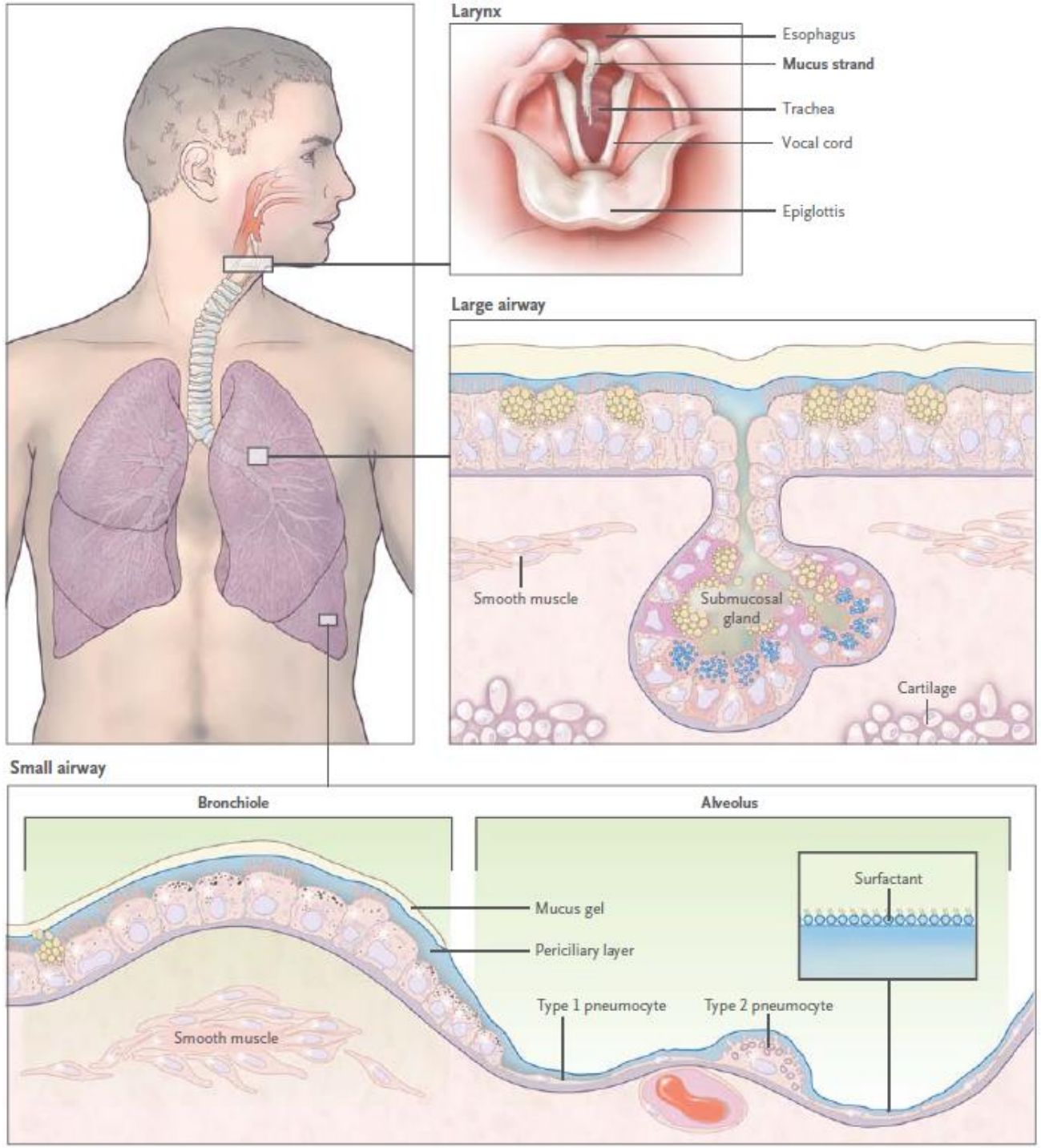




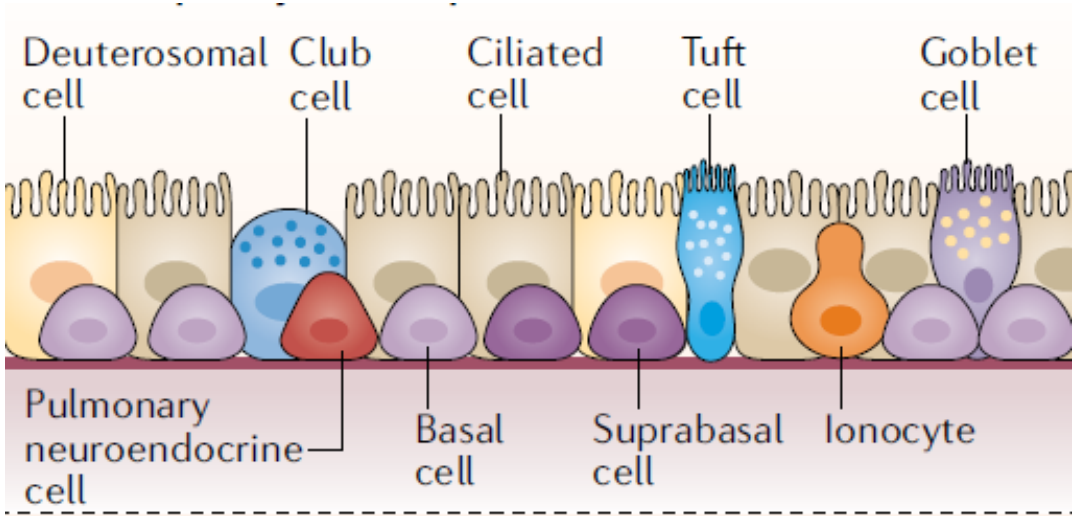
	Non-small cell lung cancer		Squamous cell carcinoma		Adenocarcinoma	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Unadjusted model	2.594 (1.370–4.911)	0.003	3.757 (1.596–8.841)	0.002	1.431 (0.519–3.948)	0.489
Adjusted model						
+ Age	2.373 (1.252–4.498)	0.008	3.391 (1.439–7.993)	0.005	1.340 (0.485–3.706)	0.573
+ Sex	2.150 (1.130–4.090)	0.020	3.104 (1.308–7.365)	0.010	1.202 (0.433–3.333)	0.724
+ Smoking history	2.008 (1.051–3.838)	0.035	2.935 (1.229–7.008)	0.015	1.204 (0.434–3.343)	0.722
+ Pack years	1.980 (1.036–3.784)	0.039	2.891 (1.211–6.904)	0.017	1.227 (0.439–3.425)	0.696
+ Blood neutrophil (%)	2.073 (1.081–3.976)	0.028	3.094 (1.293–7.402)	0.011	1.222 (0.437–3.421)	0.702
+ Post-bronchodilator FEV_1/FVC	2.098 (1.088–4.046)	0.027	3.076 (1.278–7.402)	0.012	1.256 (0.444–3.553)	0.668
+ History of asthma	2.011 (1.041–3.887)	0.038	2.899 (1.202–6.991)	0.018	1.197 (0.423–3.388)	0.734
+ History of pulmonary tuberculosis	2.078 (1.074–4.021)	0.030	3.057 (1.265–7.390)	0.013	1.193 (0.420–3.389)	0.741
+ Charlson comorbidity index	1.893 (0.967–3.706)	0.063	2.985 (1.207–7.383)	0.018	1.010 (0.350–2.914)	0.985

Scientific Reports | (2025) 15:30193

Pathogenesis and pathophysiology



Human Airway Epithelium



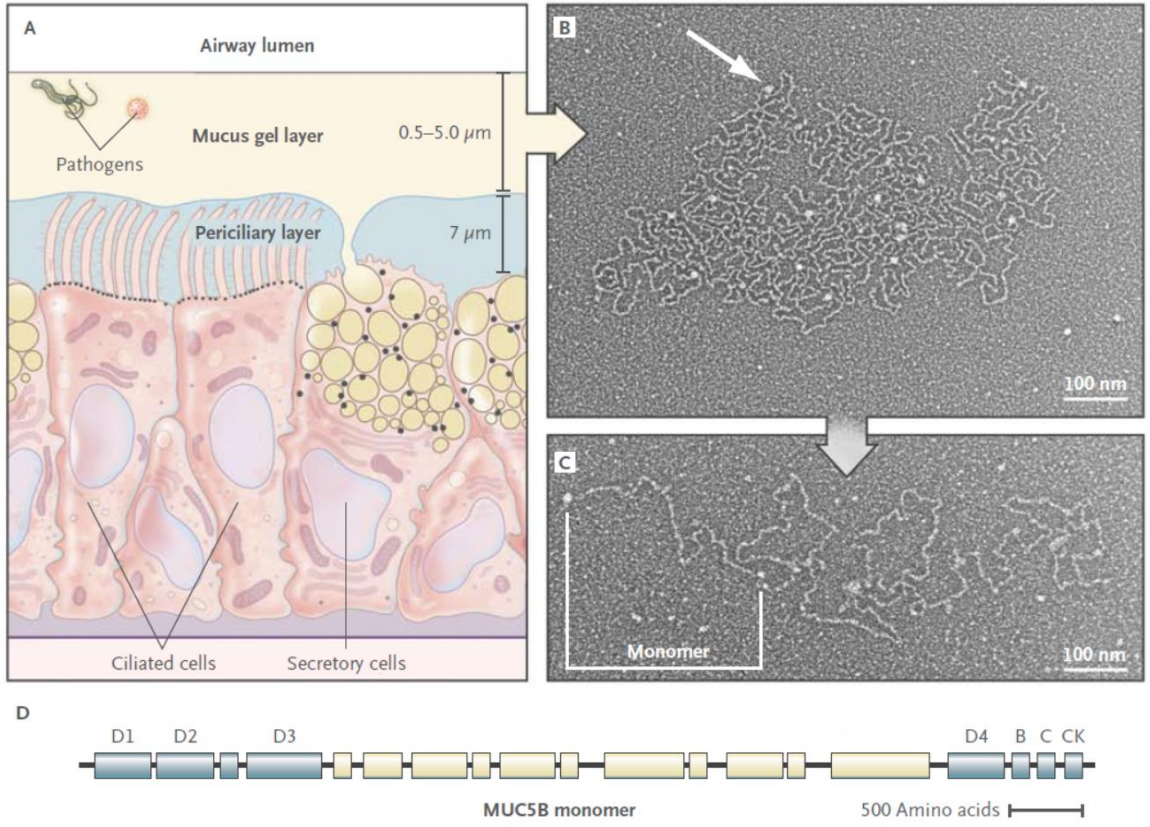
NEJM 2010; 363: 2233-47

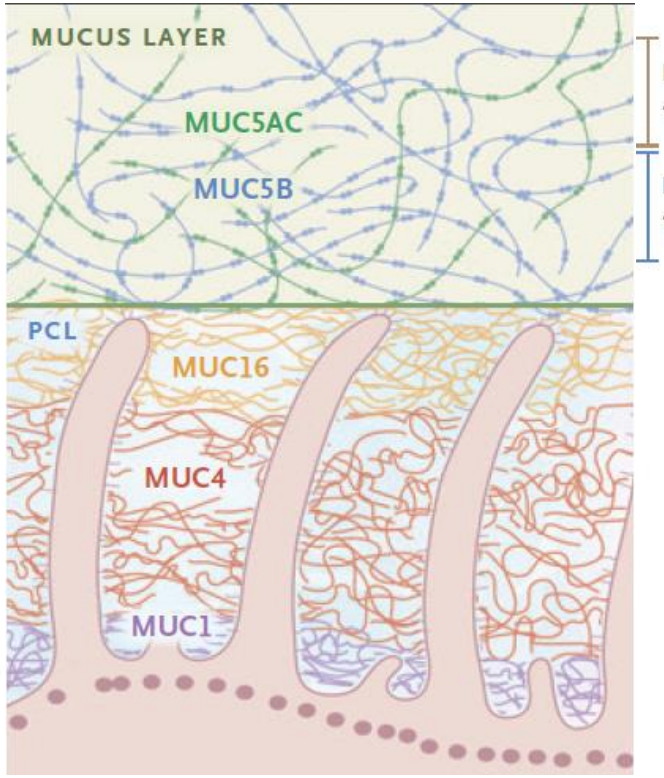
Nature Reviews Immunology **volume 21, pages347–362 (2021)**

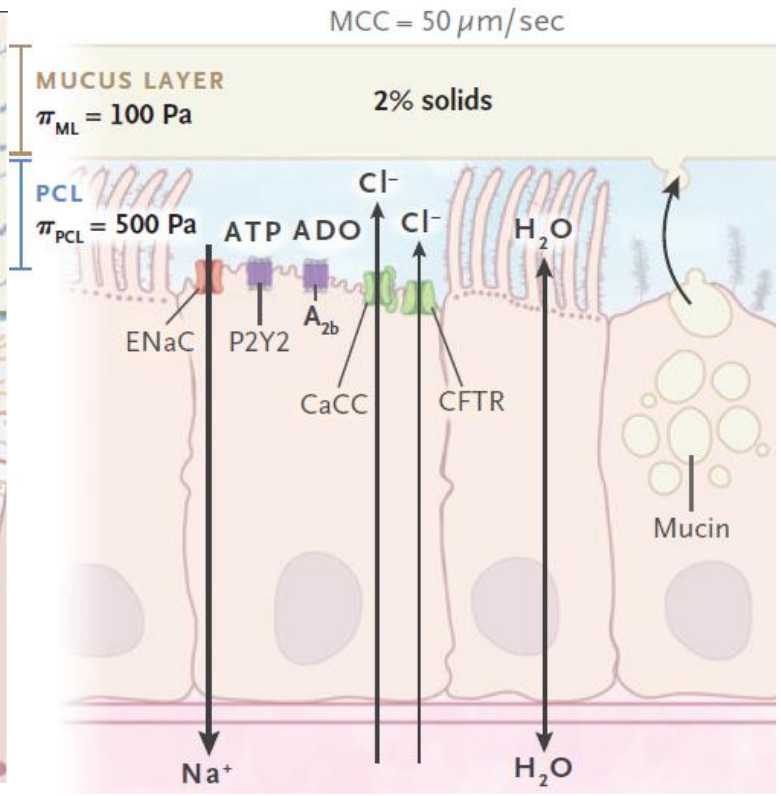
Mucus

- **97% water and 3% solids (mucins, non-mucin proteins, salts, lipids, and cellular debris)**
- **Maintaining hydration in the airway**
- **Trapping particulates, bacteria, and viruses**
- **Antioxidant, antiprotease, and antimicrobial activities**
- **The gel forming mucins: principal polymeric components of normal mucus**

Structure of Airway Mucus







NEJM 2010; 363: 2233-47

N Engl J Med 2019;380:1941-53

Mucin

- **Account for less than 30% of solids**
- **Large glycoproteins (up to 3×10^6 D per monomer)**
- **Tandemly repeating amino acids rich in serine and threonine residues linked by their hydroxyl side groups to sugar chains (O-glycosylation)**
- **50 to 90% carbohydrate, highly anionic**
- **17 genes encoding mucins (seven are secreted and the remainder is membrane-bound)**

Two subtypes of mucin

- **Secreted mucins**

  Forming mucus gel and not membraned-bound

  provide **physical barrier** **and enable** **mucocililary clearance**

  : MUC2, **MUC5AC, MUC5B**, MUC6, MUC7, MUC8, MUC9 and MUC 19

- **Transmembrane mucins**

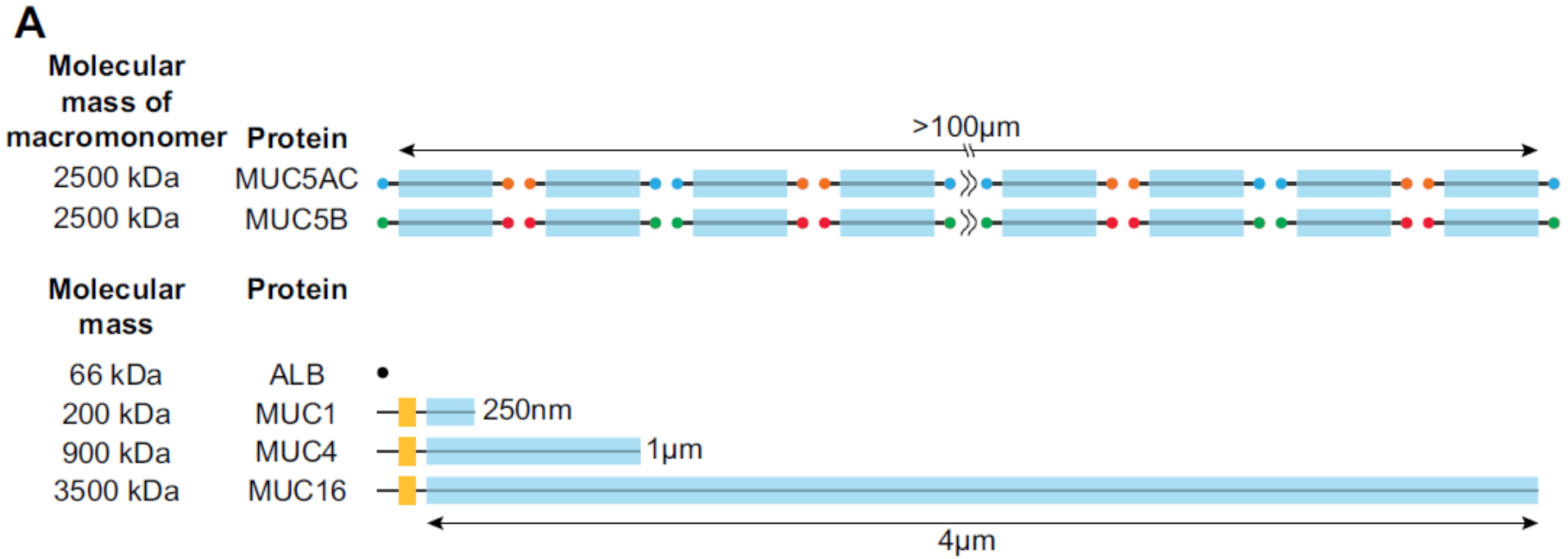
  Anchored to the cell membrane with extracellular, transmembrane and cytoplasmic domains

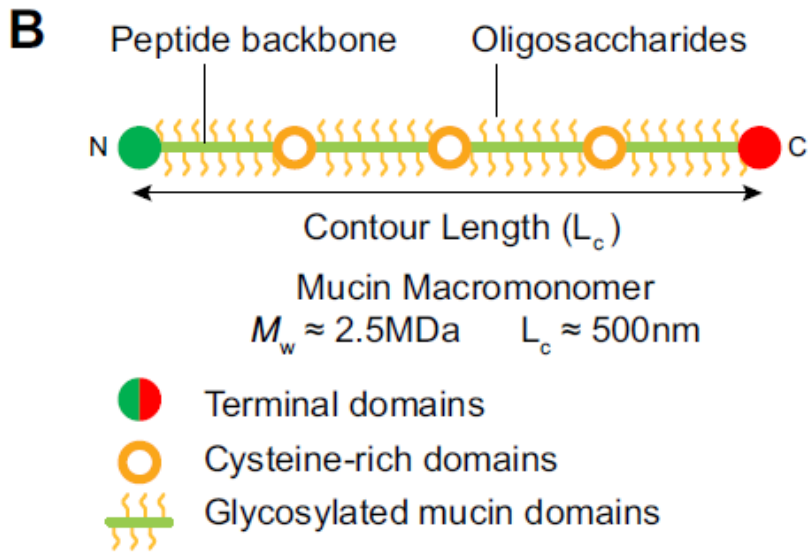
  Involved in **cell signaling, immune modulation and pathogen interference**

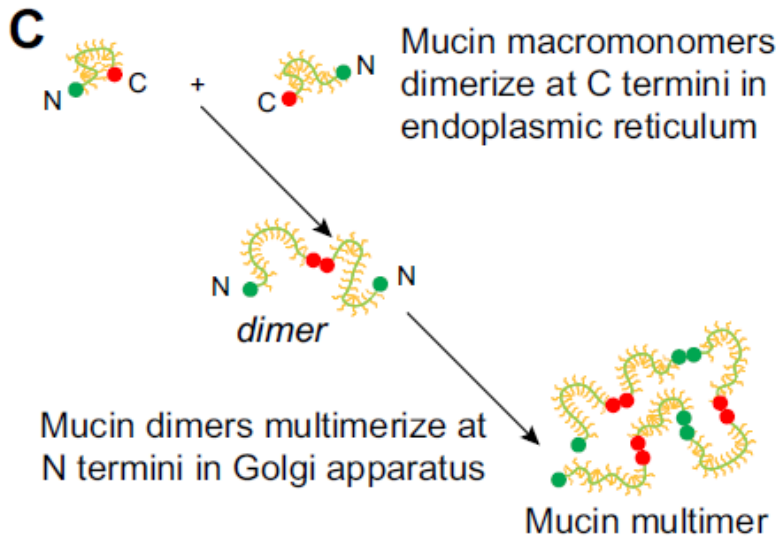
  MUC1, MUC3, MUC4, MUC11/12, MUC13, MUC14, MUC15, MUC16, MUC17, MUC20, MUC 21, and MUC 22

***Physiol Rev 2006;* 86: 245–278**

Characteristics of airway mucins







Physiol Rev 2022; 102: 1757–1836

MUC5B: protective mucin

- **Constantly expressed**
- **Produced in surface secretory cells throughout the airways and by submucosal glands**
- **Gel formation, maintaining structural stability and effective mucus clearance**
- **Mediates baseline barrier and clearance functions**
- **↓Proportion→ ↓airway protection and ↓mucus clearance**

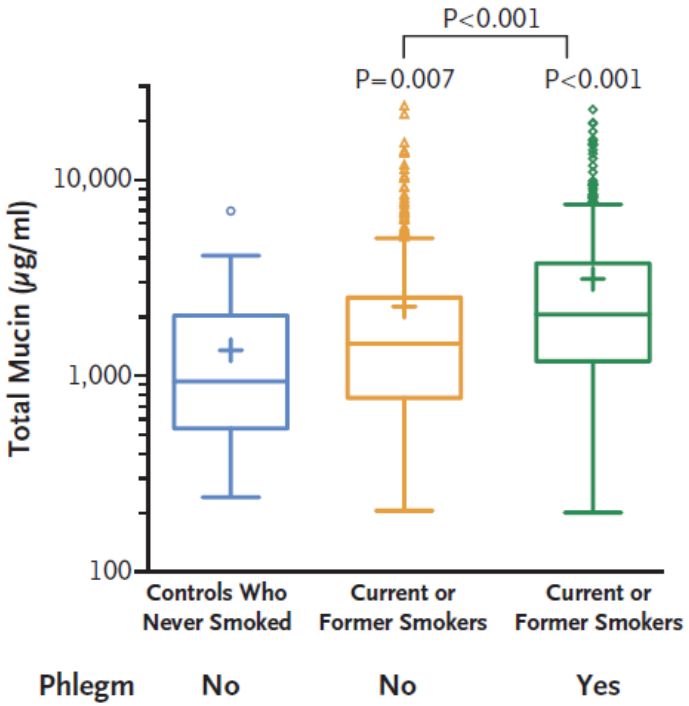
***Physiol Rev 2006;* 86: 245–278**

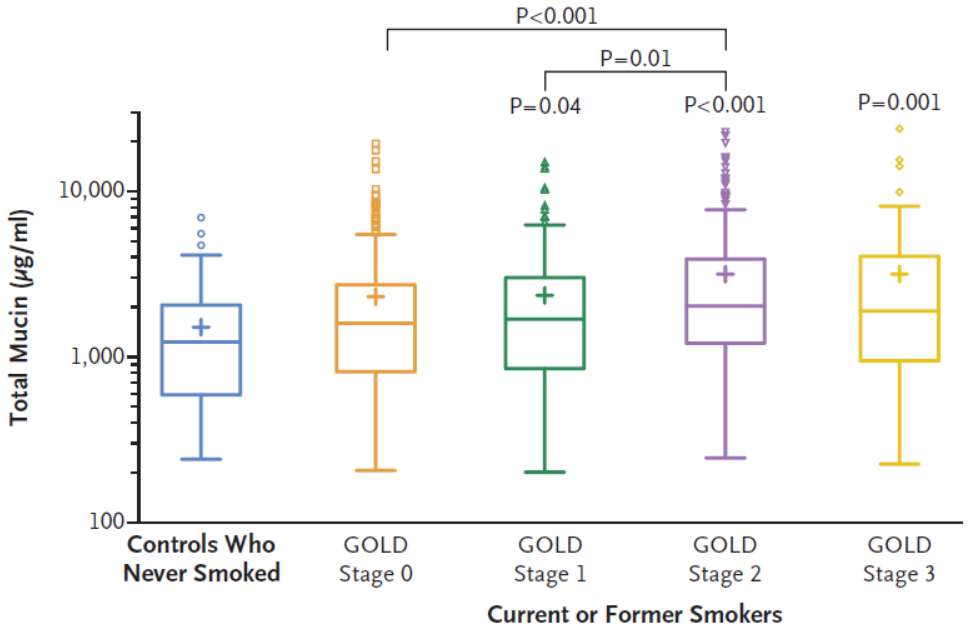
MUC5AC: Disease-related mucin

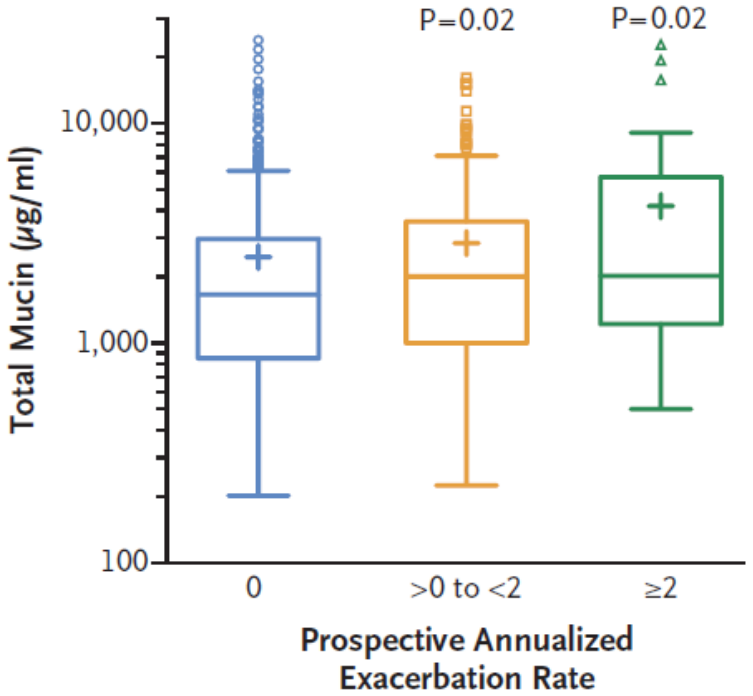
- **Induced by pathogens, gases, inflammatory mediators, adrenergic, cholinergic, and neurohumoral factors**
- **Predominantly produced in proximal airways by surface goblet cells**
- **Augmentation of proximal barrier and clearance function**
- **↑ Proportion→ ↑mucus production and viscosity**

***Physiol Rev 2006;* 86: 245–278**

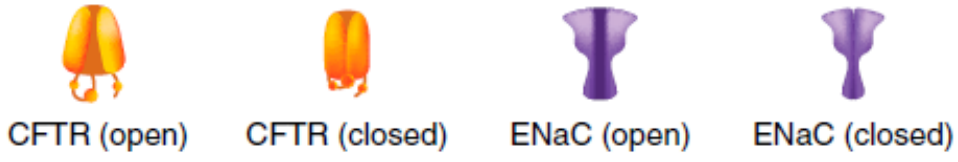
Associations between Total Mucin Concentrations and Phlegm Production and Disease Severity in COPD

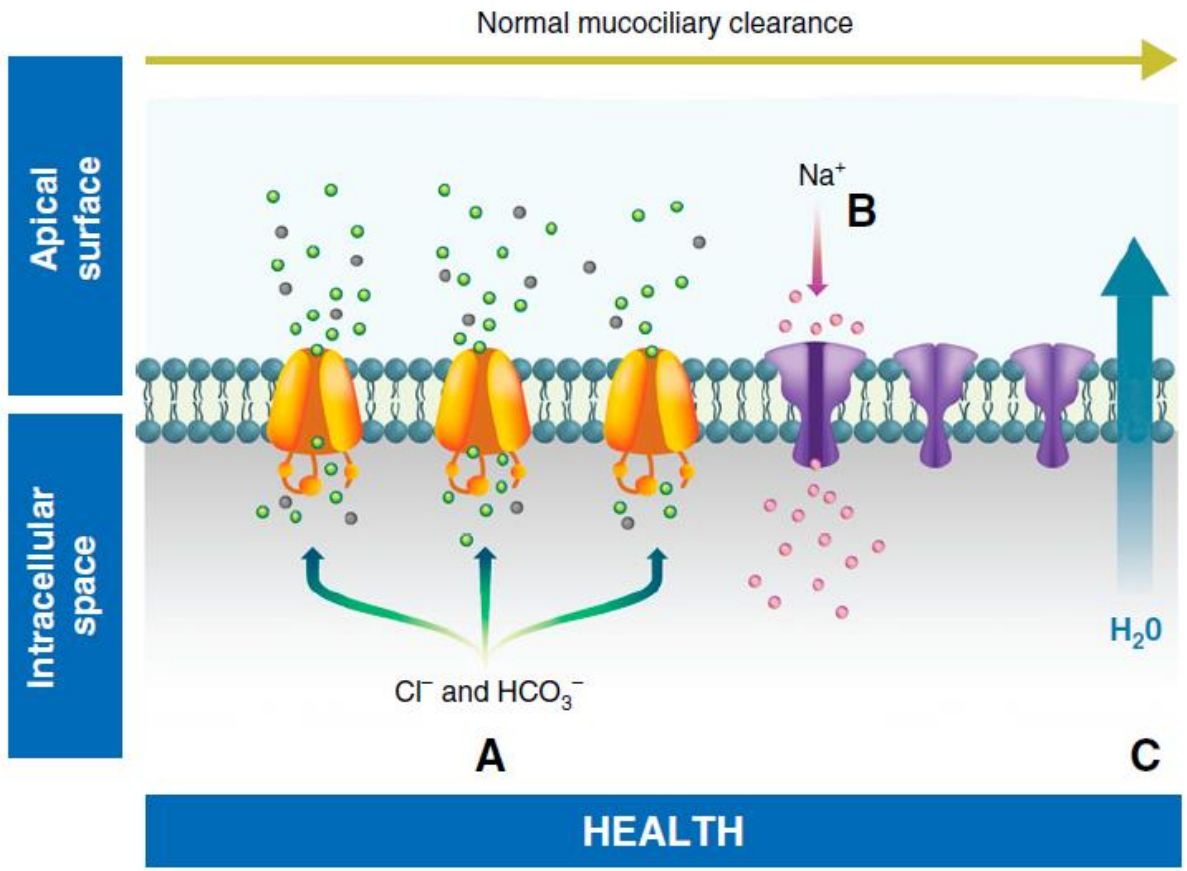


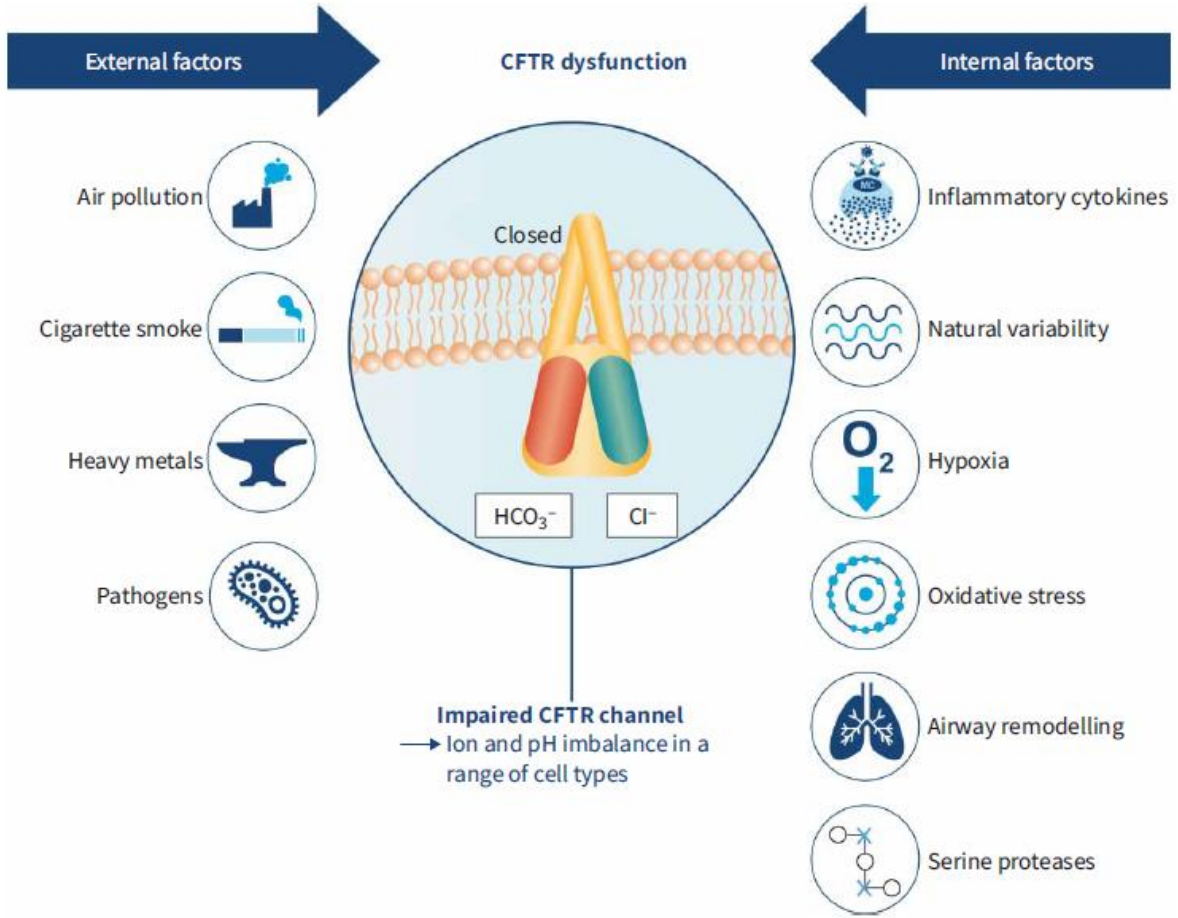




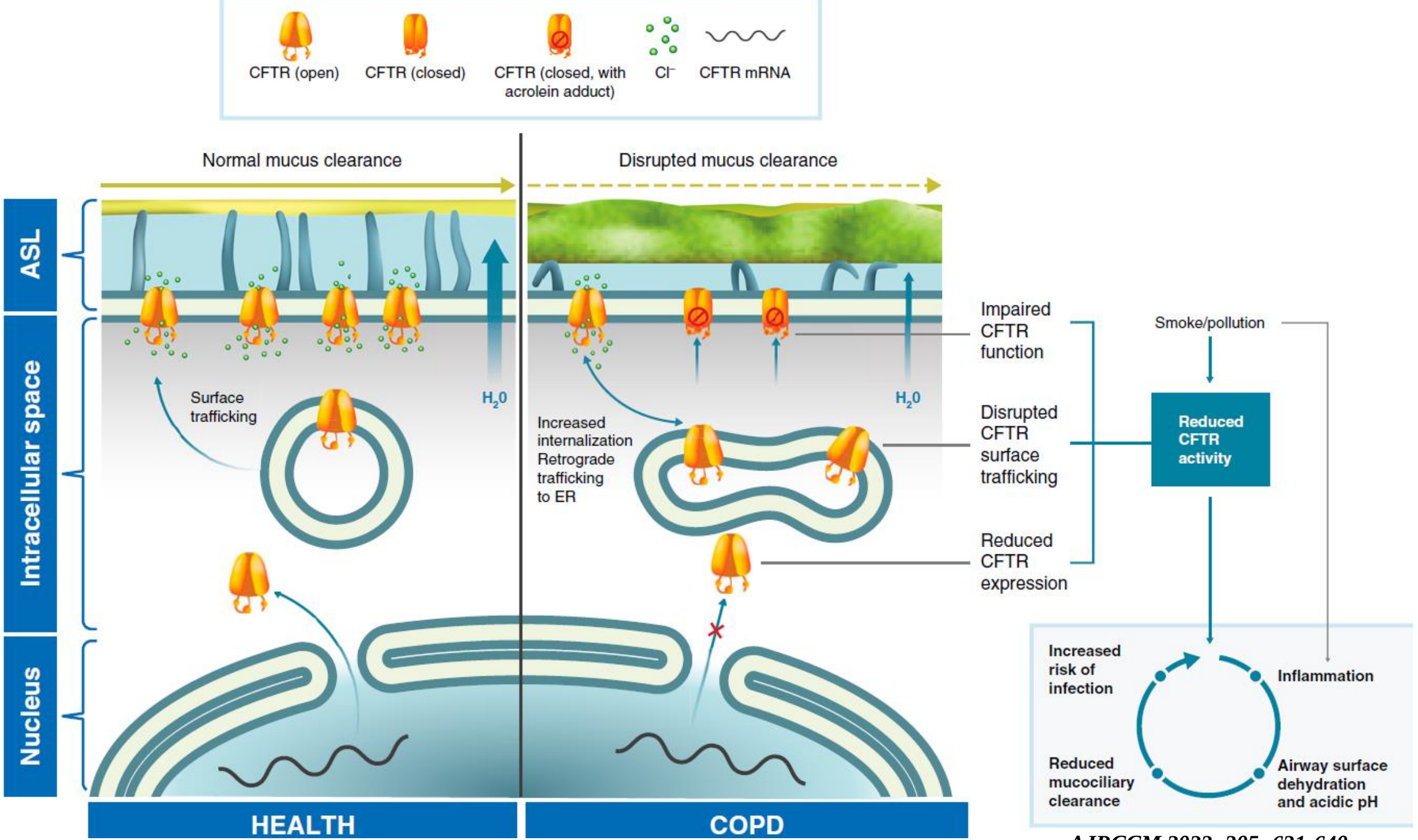
N Engl J Med 2017;377:911-22.



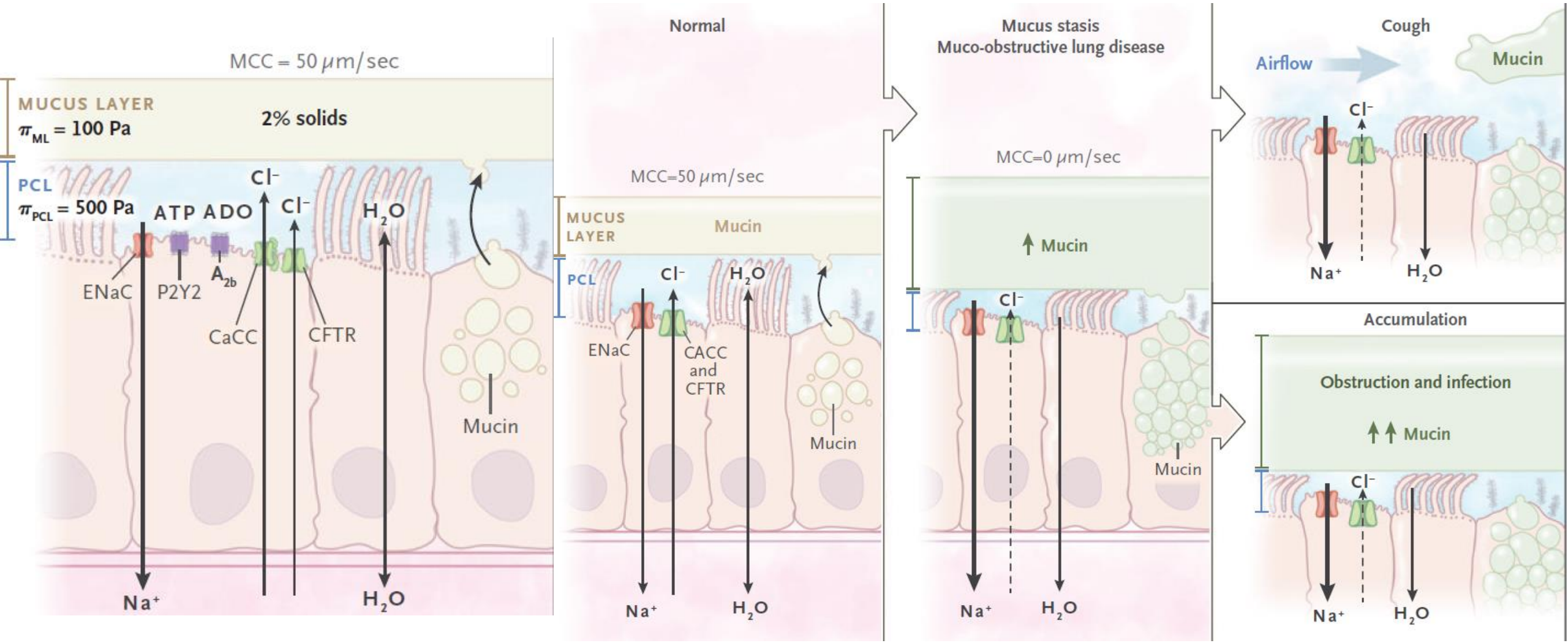




AJRCCM 2022; 205: 631-640



AJRCCM 2022; 205: 631-640



NEJM 2019;380:1941-53

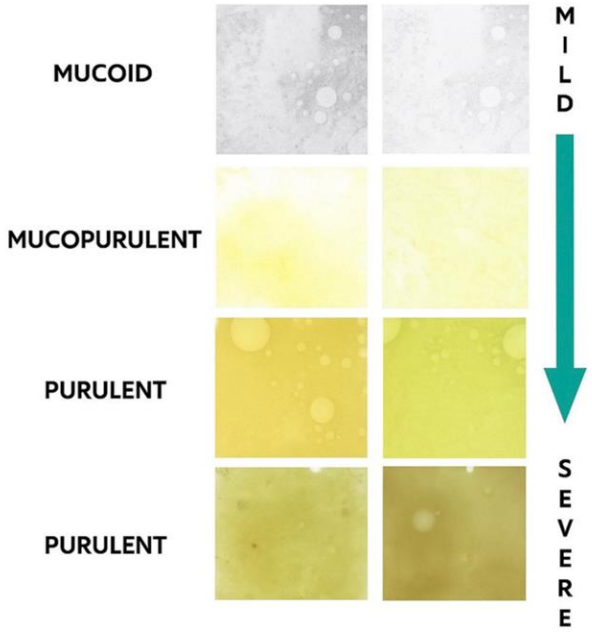
Clinical assessment

Causes of Sputum Production

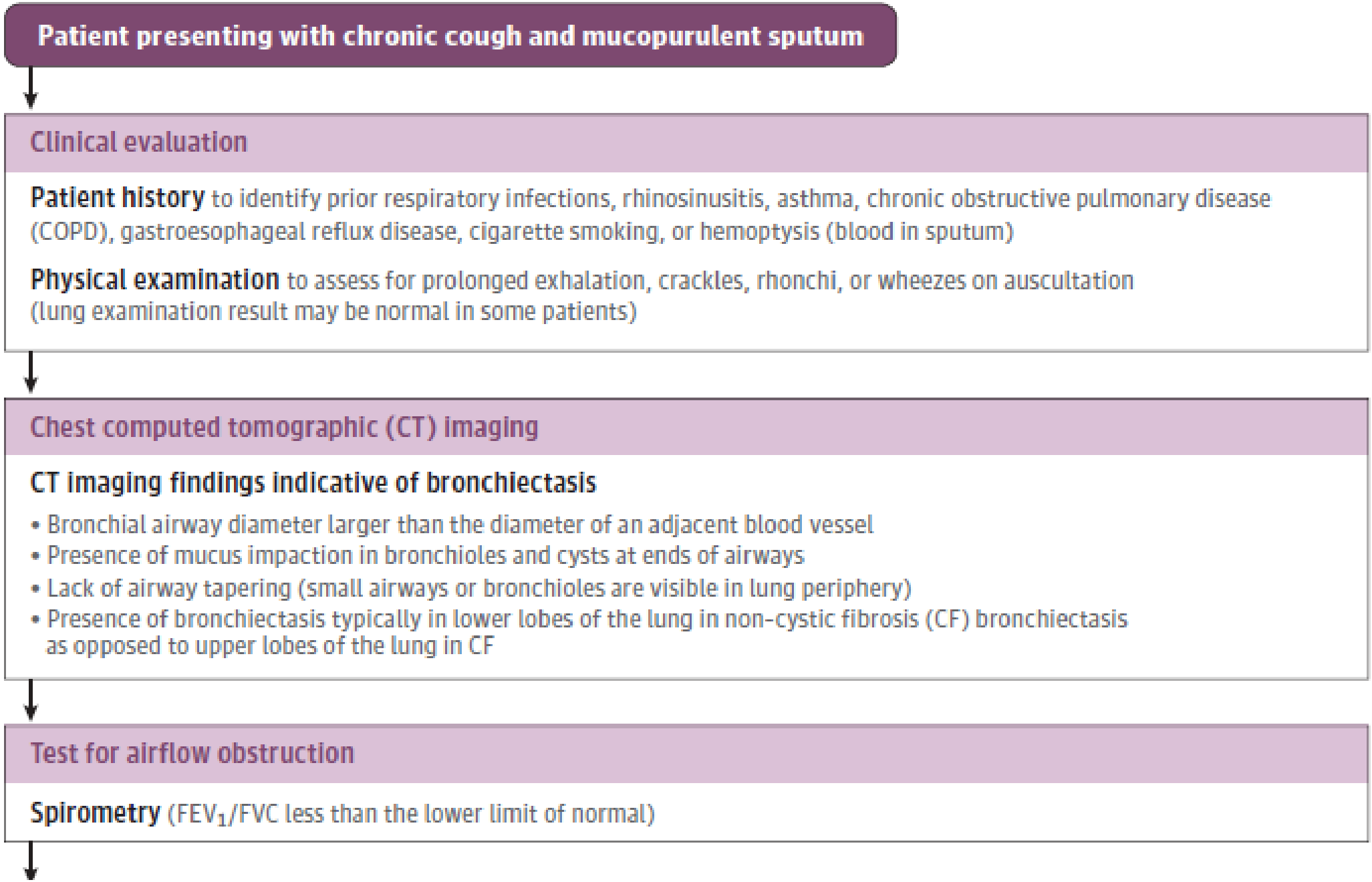
Category	Representative Causes
Upper airway	Postnasal drip (rhinitis, sinusitis)
Airway inflammation	Asthma
Chronic airway diseases	COPD, Bronchiectasis,
Infection	Bronchitis, pneumonia, TB, NTM
Reflux-related	GERD
Environmental	Smoking, pollution
Dehydration	Low fluid, dry air
Others	ACEi, aspiration

Clinical assessment

- ❖ Patients history
- ❖ Symptom Evaluation
- ❖ Imaging
- ❖ Pulmonary Function Tests
- ❖ Sputum evaluation



Thorax 2001;56:366-372



JAMA. 2025;334(3):253-264

Additional testing	Abnormal results may indicate
Complete blood cell count with differential	▶ **Asthma** Commonly, eosinophils >300 cells/μL ▶ **COPD** Occasionally, eosinophils >300 cells/μL
Aspergillus IgE and total IgE	▶ **Allergic bronchopulmonary aspergillosis** *Aspergillus* IgE >0.35 kU/L Total IgE >500 IU/mL
Immunoglobulin quantification	▶ **Common variable immunodeficiency** IgG <700 mg/dL, IgA <60 mg/dL, and IgM <35 mg/dL
Sputum culture Bacterial, mycobacterial (nontuberculous mycobacteria [NTM]), and fungal culture	▶ **NTM** Growth of NTM in at least 2 sputum cultures collected on different days establishes NTM diagnosis

Additional evaluation and testing that may be considered

Genetic conditions	Autoimmune diseases	Other conditions
• CF	• Inflammatory bowel disease	• Aspiration
• α_1-Antitrypsin deficiency	• Rheumatoid arthritis	
• Primary ciliary dyskinesia	• Sjogren syndrome	

Management

❖Primary goal

Reduction of mucus viscosity

Enhancement of airway hydration

Improvement of mucociliary clearance

❖Multimodal approach

Lifestyle modification

Airway clearance technique

Pharmacological therapies

Non-pharmacological interventions

Life style modification

- **Hydration**
- **Smoking cessation**

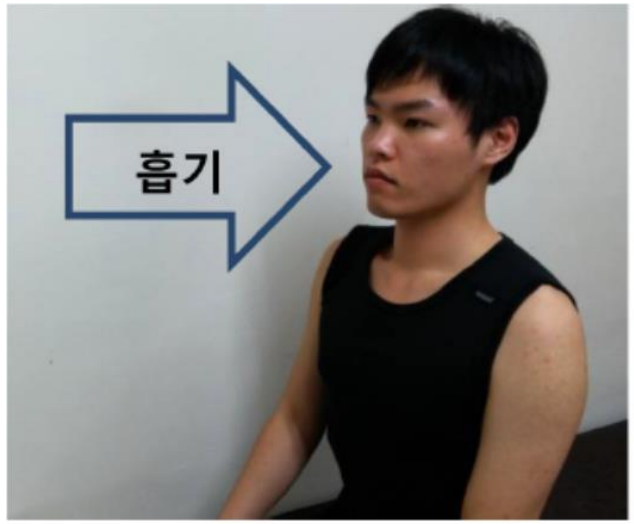
  reverses goblet cell hyperplasia, improves mucociliary function, and decreases mucus viscosity.

  smoking induces airway dehydration, increases mucus viscosity, and impairs MCC
- **Regular physical activity and pulmonary rehabilitation**

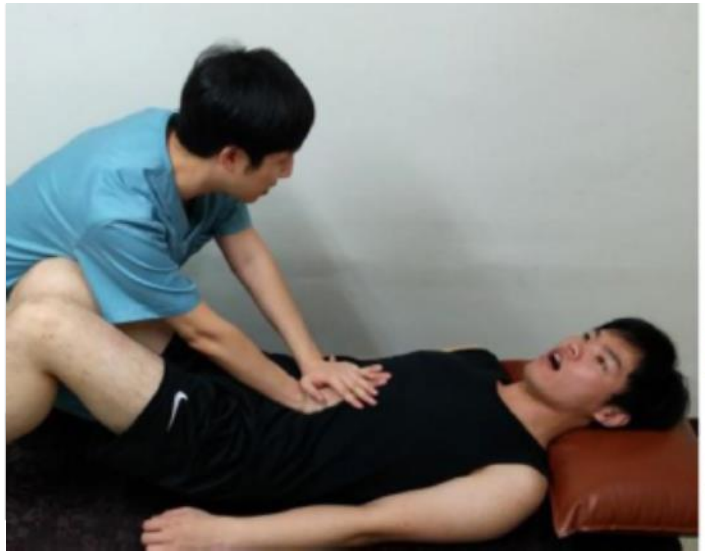
  : indirectly enhance airway clearance by improving ventilatory mechanics and cough efficacy

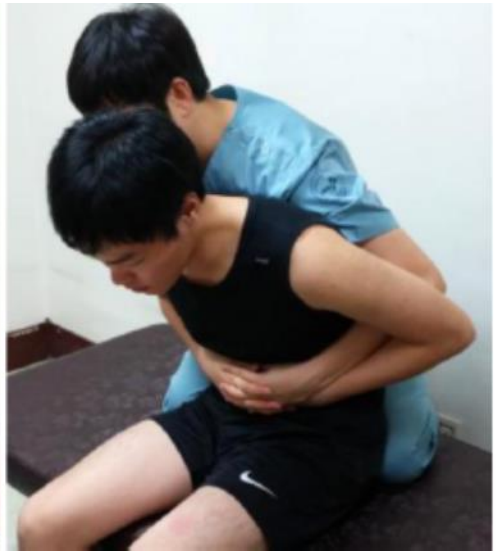
분류 (Category)	기술명 (Technique)
능동적 기술 (Active)	기침법 (Coughing)
	허핑 (Huffing)
	가슴팽창운동 (Chest Expansion Exercise)
	능동주기 호흡법 (Active Cycle of Breathing, ACBT)
	자가배출법 (Autogenic Drainage)
	보조기침법 (Assisted Coughing)
	덧대기 기침법 (Splinted Coughing)
수동적 기술 (Passive)	자세변경 배출법 (Postural Drainage)
	두드리기 (Percussion)
	진동법 및 흔들기 (Vibration & Shaking)
	가슴팽창운동과 자세변경 배출법
도구 활용 (Devices)	에어로비카, 플루터, 아카펠라
	BPET (Positive Expiratory Pressure Device)
	High-frequency chest wall oscillation (고주파 가슴벽 진동)
	IPPB (Intermittent Positive Pressure Breathing, 간헐적 양압 호흡)

기침법



허핑 기침(Huffing cough)

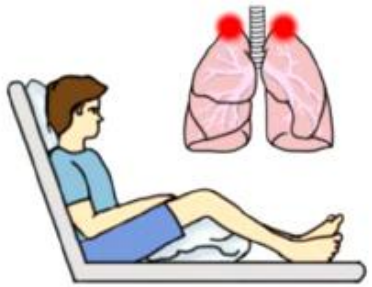




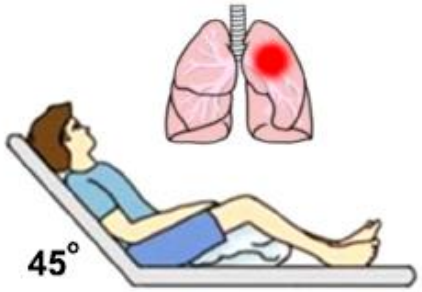
보조 기침(Assist cough)

호흡재활 지침서 2015
대한결핵및호흡기학회 외

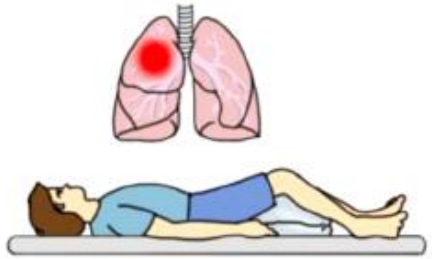
체위배담법(Postural drainage)



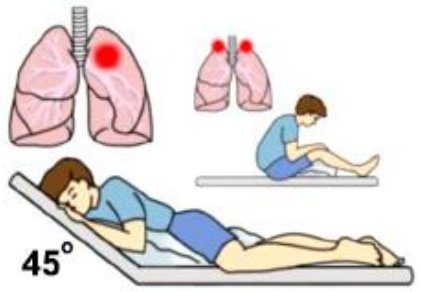
BUL anterior segments



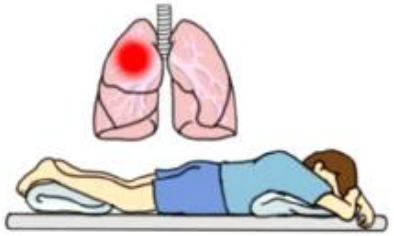
LUL anterior segments



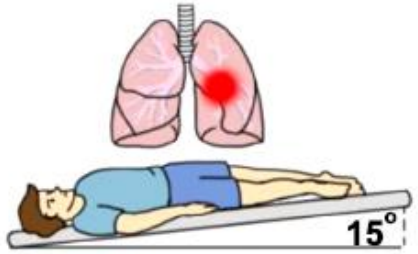
RUL anterior segments



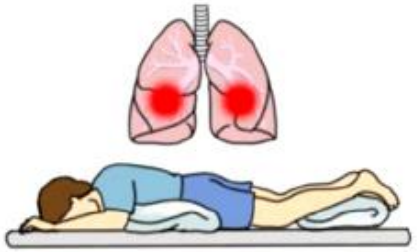
LUL posterior segments



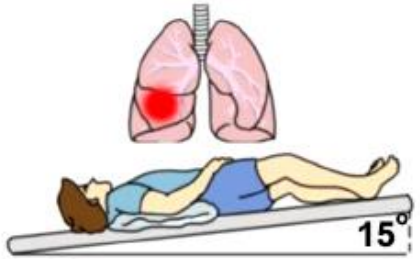
RUL posterior segments



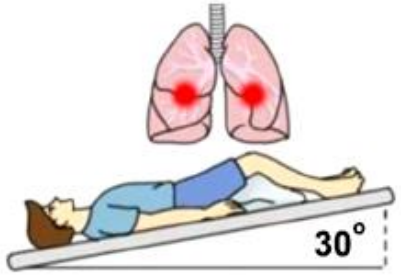
LUL Lingula



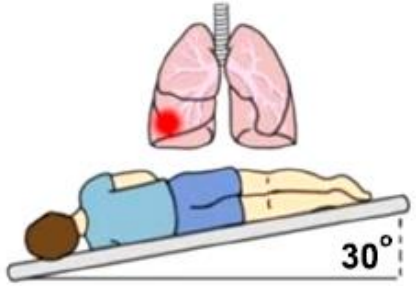
BLL superior segments



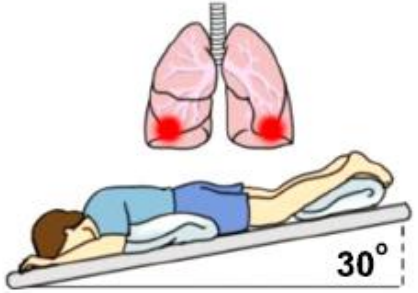
RML



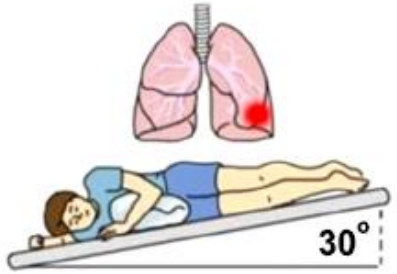
BLL anterior segments



RLL lateral segments



BLL posterior segments



LLL lateral segments

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호기양압치료(Positive expiratory pressure; PEP therapy)

① TheraPEP

② 플루터(Flutter)

③ 아카펠라(Acapella)

1) **목적:** 환자가 숨을 내쉴 때 10～20 cmH2O 정도의 압력을 받게하여 호기 기간동안 기도를 개방하게 하는 도구이다. 말초 분비물이 큰 기도로 이동하도록 도와준다. 플루터와 아카펠라는 진동법이 동시에 적용되는 도구이다.
2) **방법:**
기구를 통해 흡기 시간보다 2～3배 길게 숨을 내쉬고 약 10～20회 반복하고 기침을 시행한다

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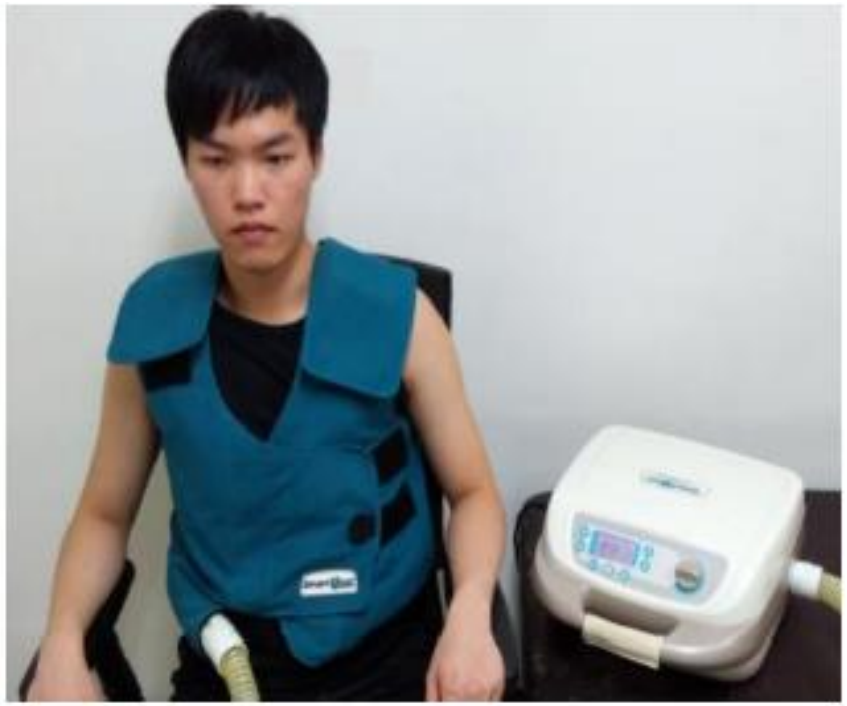
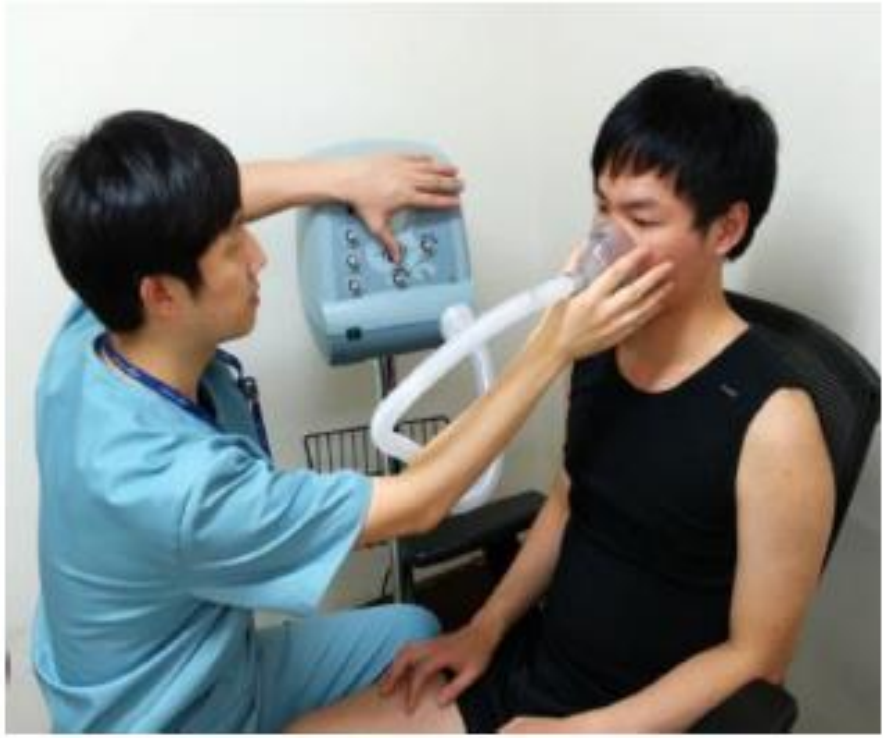
대한결핵및호흡기학회 외

고빈도흉벽진동기(High frequency chest wall oscilation)



기침보조기(Mechanical insufflations-exsufflator(MIE)/Cough assist machine)



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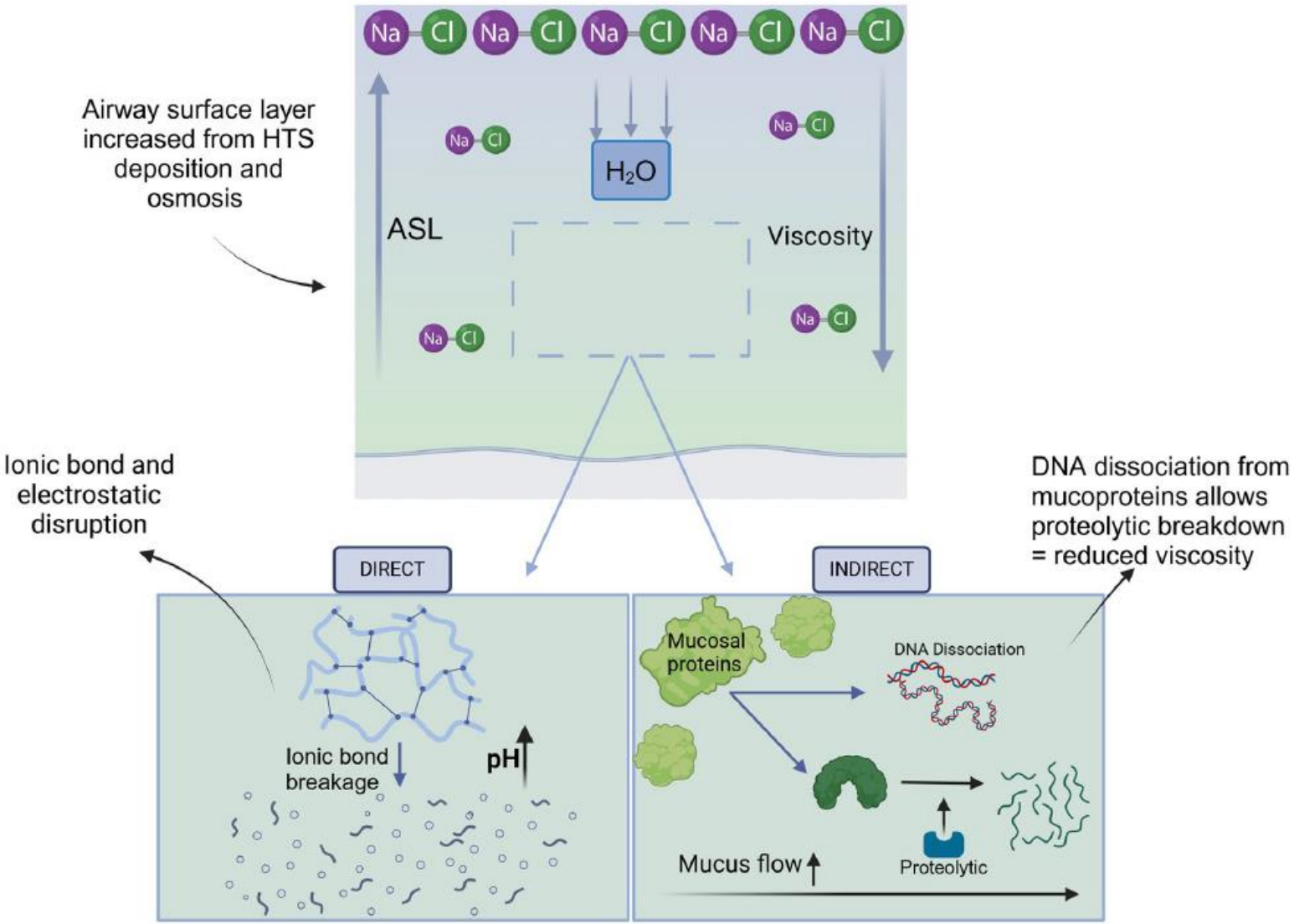
Mucoactive drugs

Mucoactive drugs	Potential mechanism of action
Expectorants	
Hypertonic saline	Increases secretion volume and/or hydration
Guaifenesin	Stimulates secretion and reduces mucus viscosity
Mucoregulators	
Carbocysteine	Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production
Anticholinergic agents	Decreases secretion volume
Glucocorticoids	Reduces airway inflammation and mucin secretion
Macrolide antibiotics	Reduces airway inflammation and mucin secretion
Mucolytics	
N-Acetylcysteine	Breaks disulphide bonds linking mucin polymers Antioxidant and anti-inflammatory effects
N-Acystelyn	Increases chloride secretion and breaks disulphide bonds
Erdosteine	Modulates mucus production and increases mucociliary transport
Dornase alfa	Hydrolyses the DNA in mucus and reduces viscosity in the lungs
Gelsolin	Severs actin filament cross-links
Thymosin β_4	Severs actin filament cross-links
Dextran	Breaks hydrogen bonds and increases secretion hydration
Heparin	Breaks both hydrogen and ionic bonds
Mucokinetics[#]	
Bronchodilators	Improves cough clearance by increasing expiratory flow
Surfactants	Decreases sputum/mucus adhesiveness
Ambroxol	Stimulates surfactant production and inhibits neuronal sodium channels

Hypertonic saline



Critical Care (2025) 29:68

ORIGINAL ARTICLE

Mucus Clearance and Lung Function in Cystic Fibrosis with Hypertonic Saline

Scott H. Donaldson, M.D., William D. Bennett, Ph.D., Kirby L. Zeman, Ph.D., Michael R. Knowles, M.D., Robert Tarran, Ph.D., and Richard C. Boucher, M.D.

N Engl J Med 2006;354:241-50

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2006 VOL. 354 NO. 3

A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis

Mark R. Elkins, M.H.Sc., Michael Robinson, Ph.D., Barbara R. Rose, Ph.D., Colin Harbour, Ph.D., Carmel P. Moriarty, R.N., Guy B. Marks, Ph.D., Elena G. Belousova, M.Appl.Sc., Wei Xuan, Ph.D., and Peter T.P. Bye, Ph.D., for the National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group*

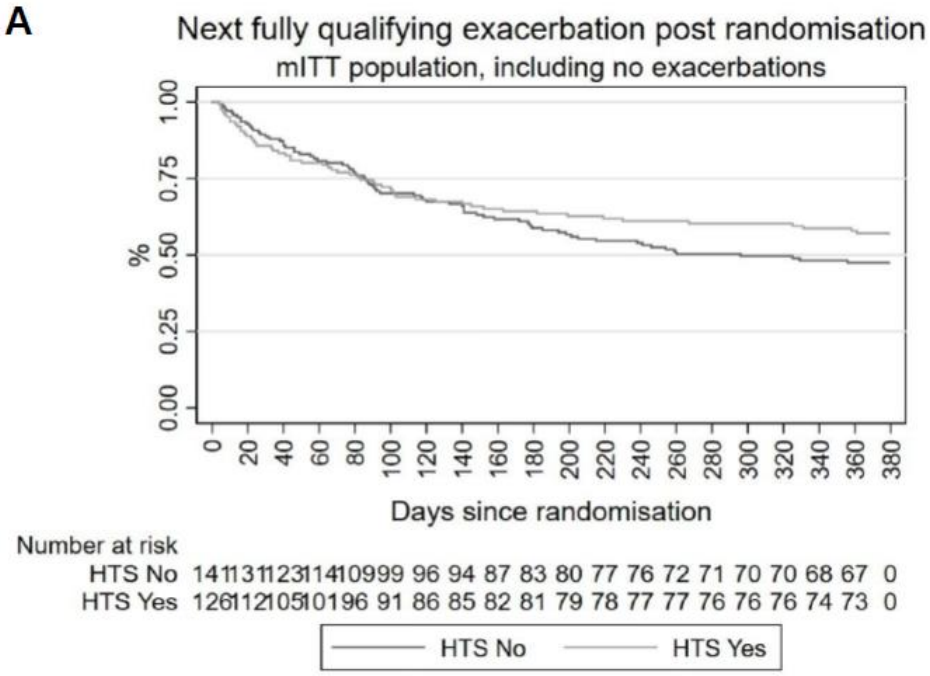
N Engl J Med 2006;354:229-40

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2025 VOL. 393 NO. 16

Hypertonic Saline or Carbocisteine in Bronchiectasis

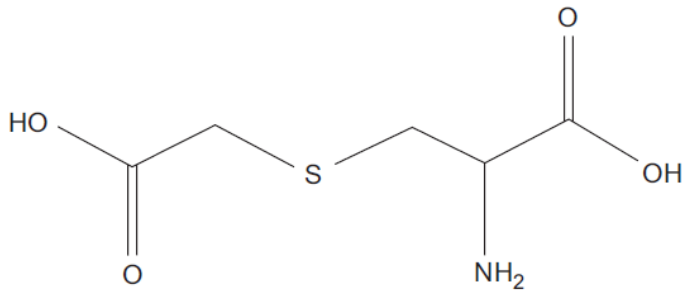
J.M. Bradley,[1] B. O'Neill,[2] D.F. McAuley,[1] J.D. Chalmers,[3] A. De Soyza,[4] A.T. Hill,[5,6] M. Carroll,[7] M.R. Loebinger,[8,9] J. Duckers,[10] M. Clarke,[11,12] R.H. McLeese,[13] K. Ferguson,[14,15] A. Jackson,[12] C. Campbell,[12] C. McDowell,[12] A. Agus,[12] J. Norrie,[11] F. Copeland,[16] D.G. Downey,[1,15] R. Convery,[17] M. Kelly,[14] W. Flight,[18] N.P. Talbot,[18] J.R. Hurst,[19] J. Steer,[20] M. Anwar,[21] M. Shahidi,[22] T. Gatheral,[23] M. Etumi,[24] A.L. Sullivan,[25] A.A. Ionescu,[26] V. Patil,[27] M. Bhattacharya,[28] S. Caskey,[15] D. Cosgrove,[17] C. Hagan,[17] A. Shoemark,[3] T. McManus,[13] G. Davies,[4] and J.S. Elborn,[1] for the CLEAR Investigator Team*



Outcome	HTS (N=126)	No HTS (N=141)	Mean Difference or Hazard Ratio, HTS vs. No HTS (95% CI)
	mean (95% CI)		
Primary outcome: no. of pulmonary exacerbations over 52 wk†	0.76 (0.58 to 0.95)	0.98 (0.78 to 1.19)	–0.25 (–0.57 to 0.07)
Secondary outcomes			
Health-related quality-of-life measures‡			
QoL-B respiratory symptoms	59.8 (57.0 to 62.6)	60.5 (57.9 to 63.1)	–0.7 (–4.6 to 3.1)
SGRQ total score	42.5 (39.9 to 45.0)	42.7 (40.4 to 45.1)	–0.3 (–3.8 to 3.2)
EQ-5D-5L utility index	0.73 (0.68 to 0.78)	0.72 (0.67 to 0.77)	0.01 (–0.06 to 0.08)
EQ-VAS score	70.9 (68.0 to 73.8)	68.4 (65.6 to 71.1)	2.6 (–1.5 to 6.7)
No. of days from randomization to next pulmonary exacerbation§	256.5 (229.4 to 283.6)	239.2 (214.7 to 263.7)	0.80 (0.56 to 1.14)
No. of days of antibiotic treatment for exacerbations over 52 wk¶	18.9 (13.3 to 24.6)	21.7 (15.5 to 27.8)	–0.14 (–0.5 to 0.3)
Change in lung function from baseline‖			
FEV_1 — liters	–0.01 (–0.10 to 0.08)	–0.02 (–0.10 to 0.06)	0.01 (–0.1 to 0.1)
FEV_1 — % of predicted	1.6 (–1.9 to 5.2)	–0.0 (–3.1 to 3.1)	1.6 (–3.1 to 6.4)
FVC — liters	–0.0 (–0.11 to 0.11)	–0.06 (–0.16 to 0.03)	0.06 (–0.08 to 0.2)
$FEF_{25–75}$ z score	–1.3 (–3.0 to 0.3)	–0.4 (–1.9 to 1.0)	–0.9 (–3.2 to 1.4)

N Engl J Med 2025;393:1565-1577

Carbocisteine



Carbocysteine (mucoregulator)

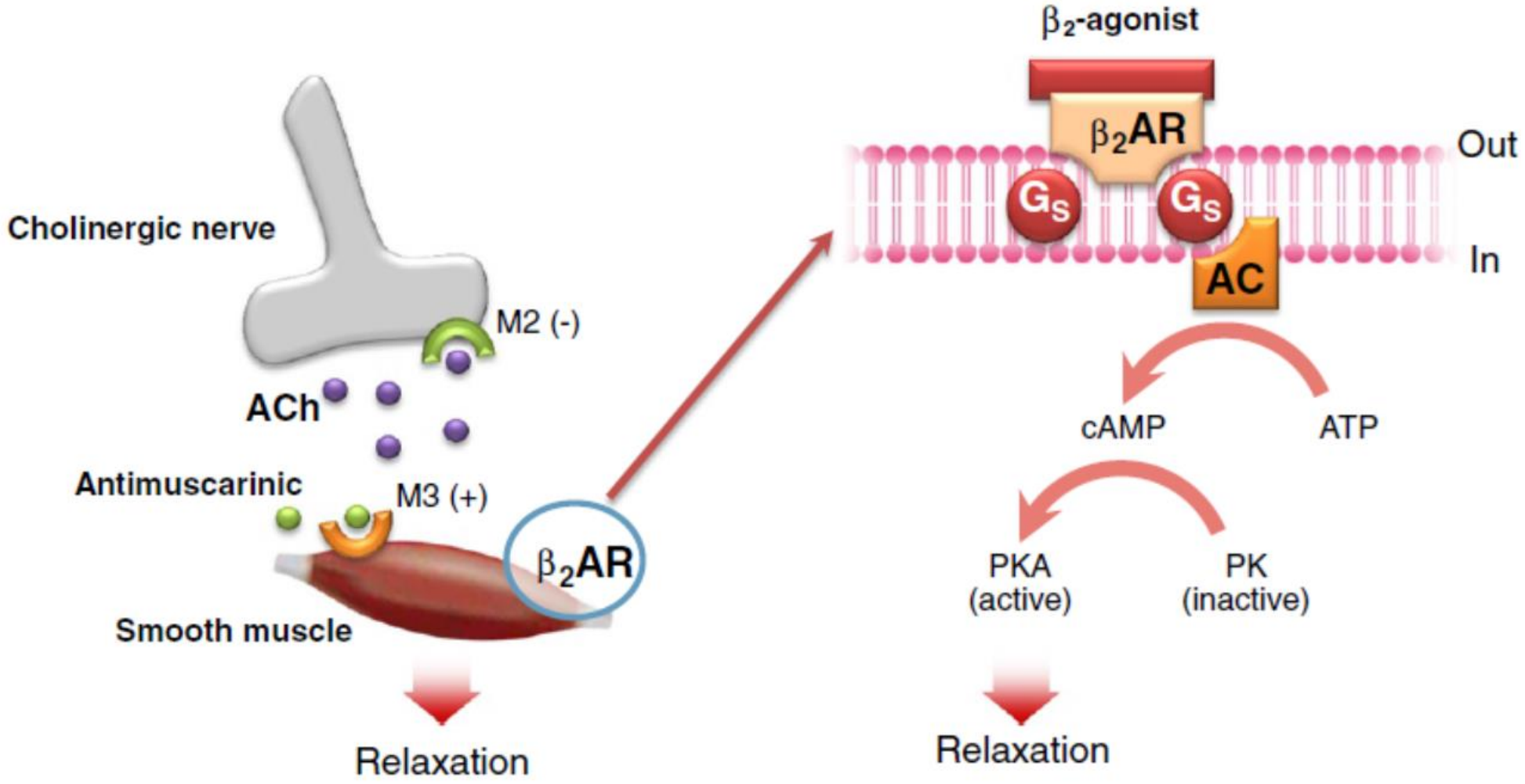
- **Restoring equilibrium between sialomucins and focomucins (glycoproteins that regulate viscoelastic properties of bronchial mucus) via the intracellular stimulation of sialyl transferase enzyme**
- **Reducing cellular damage by activating protein kinase B phosphorylation**
- **Antioxidant and anti-inflammatory effects by Suppression of NF-KB and ERK1/2 MAPK signaling pathways**
- **Potential benefits through the inhibition of bacterial adherence to ciliated epithelial cells, reducing levels of IL-6/8 and scavenging reactive oxygen species (ROS)**

Critical Care (2025) 29:68

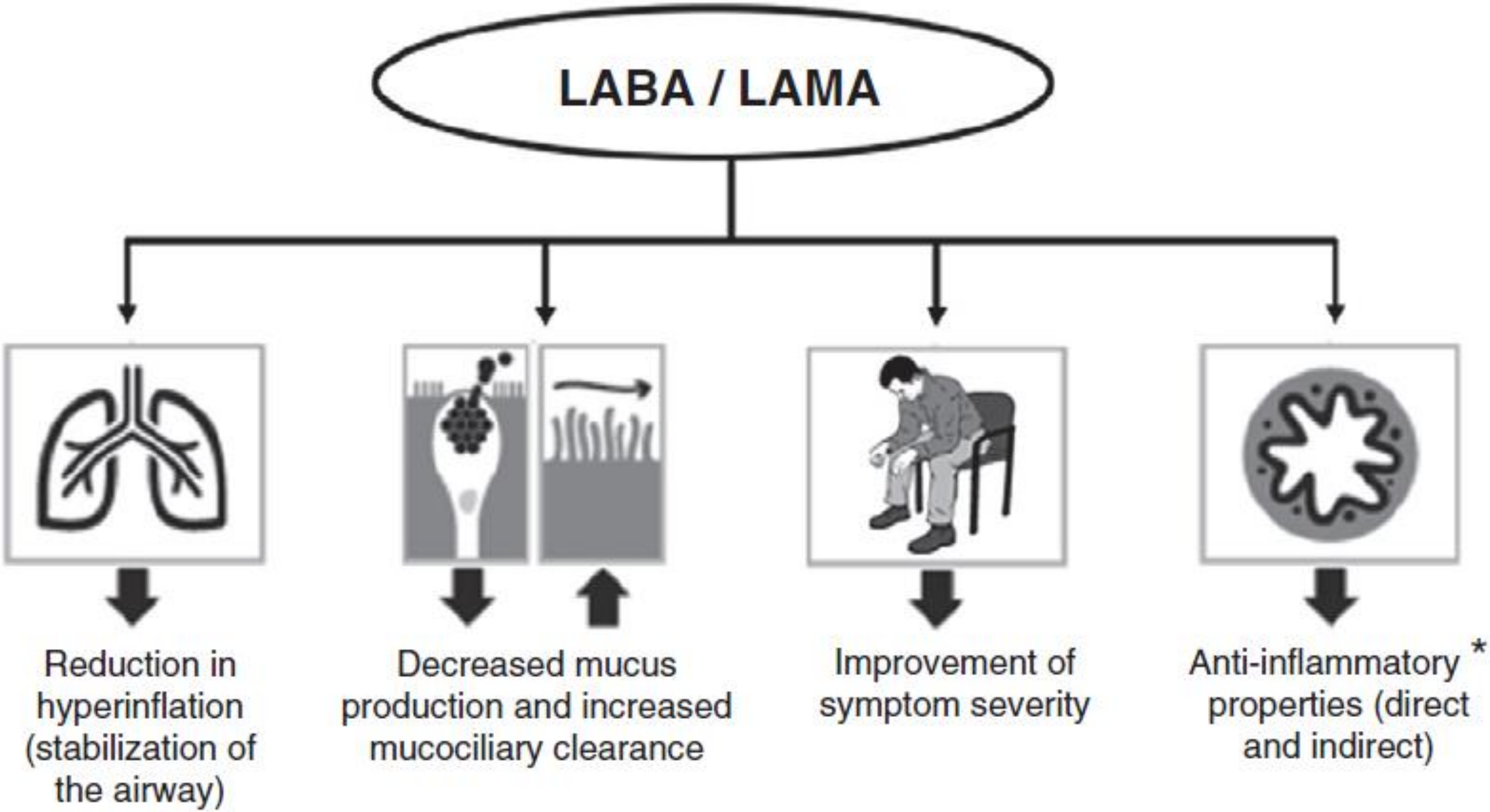
Outcome	HTS (N=126)	No HTS (N=141)	Mean Difference or Hazard Ratio, HTS vs. No HTS (95% CI)	Carbocisteine (N=129)	No Carbocisteine (N=138)	Mean Difference or Hazard Ratio, Carbocisteine vs. No Carbocisteine (95% CI)
	mean (95% CI)			*mean (95% CI)*		
Primary outcome: no. of pulmonary exacerbations over 52 wk†	0.76 (0.58 to 0.95)	0.98 (0.78 to 1.19)	−0.25 (−0.57 to 0.07)	0.86 (0.66 to 1.06)	0.90 (0.70 to 1.09)	−0.04 (−0.36 to 0.28)
Secondary outcomes						
Health-related quality-of-life measures‡						
QoL-B respiratory symptoms	59.8 (57.0 to 62.6)	60.5 (57.9 to 63.1)	−0.7 (−4.6 to 3.1)	60.0 (57.2 to 62.8)	60.3 (57.7 to 62.9)	−0.3 (−4.2 to 3.5)
SGRQ total score	42.5 (39.9 to 45.0)	42.7 (40.4 to 45.1)	−0.3 (−3.8 to 3.2)	42.8 (40.2 to 45.3)	42.5 (40.1 to 44.9)	0.3 (−3.2 to 3.8)
EQ-5D-5L utility index	0.73 (0.68 to 0.78)	0.72 (0.67 to 0.77)	0.01 (−0.06 to 0.08)	0.75 (0.70 to 0.80)	0.70 (0.65 to 0.75)	0.05 (−0.02 to 0.13)
EQ-VAS score	70.9 (68.0 to 73.8)	68.4 (65.6 to 71.1)	2.6 (−1.5 to 6.7)	71.2 (68.3 to 74.1)	68.1 (65.4 to 70.9)	3.1 (−1.1 to 7.2)
No. of days from randomization to next pulmonary exacerbation§	256.5 (229.4 to 283.6)	239.2 (214.7 to 263.7)	0.80 (0.56 to 1.14)	244.8 (219.2 to 270.4)	249.8 (224.0 to 275.6)	1.17 (0.83 to 1.67)
No. of days of antibiotic treatment for exacerbations over 52 wk¶	18.9 (13.3 to 24.6)	21.7 (15.5 to 27.8)	−0.14 (−0.5 to 0.3)	19.6 (13.8 to 25.3)	21.2 (15.1 to 27.2)	−0.08 (−0.5 to 0.3)
Change in lung function from baseline‖						
FEV_1 — liters	−0.01 (−0.10 to 0.08)	−0.02 (−0.10 to 0.06)	0.01 (−0.1 to 0.1)	−0.003 (−0.09 to 0.09)	−0.03 (−0.12 to 0.05)	0.03 (−0.09 to 0.2)
FEV_1 — % of predicted	1.6 (−1.9 to 5.2)	−0.0 (−3.1 to 3.1)	1.6 (−3.1 to 6.4)	1.6 (−1.9 to 5.1)	−0.05 (−3.2 to 3.1)	1.7 (−3.2 to 6.5)
FVC — liters	−0.0 (−0.11 to 0.11)	−0.06 (−0.16 to 0.03)	0.06 (−0.08 to 0.2)	−0.02 (−0.13 to 0.08)	−0.05 (−0.15 to 0.05)	0.02 (−0.1 to 0.2)
$FEF_{25–75}$ z score	−1.3 (−3.0 to 0.3)	−0.4 (−1.9 to 1.0)	−0.9 (−3.2 to 1.4)	−0.6 (−2.3 to 1.0)	−1.0 (−2.5 to 0.5)	0.4 (−1.9 to 2.7)

NEJM 2025; 393: 1565-1577

Mechanisms of bronchodilatory action of antimuscarinic agents and beta2-adrenergic receptor agonists



Multidisciplinary Respiratory Medicine 2014, 9:50

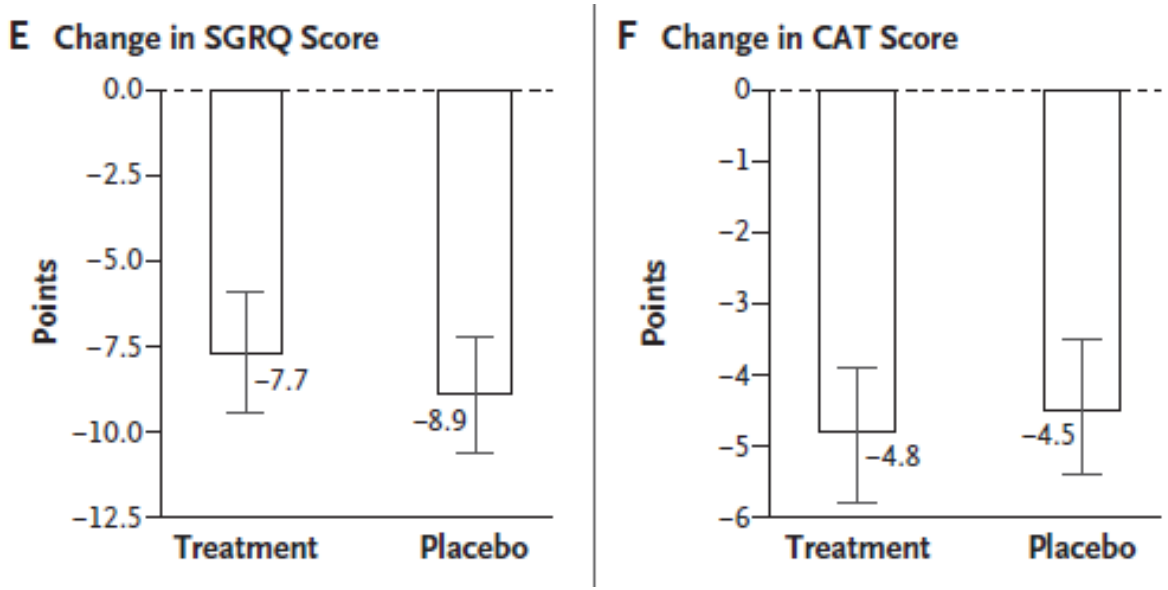


AJRCCM 2017; 196: 139-149

ORIGINAL ARTICLE

Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function

M.K. Han, W. Ye, D. Wang, E. White, M. Arjomandi, I.Z. Barjaktarevic, S.-A. Brown, R.G. Buhr, A.P. Comellas, C.B. Cooper, G.J. Criner, M.T. Dransfield, F. Drescher, R.J. Folz, N.N. Hansel, R. Kalhan, R.J. Kaner, R.E. Kanner, J.A. Krishnan, S.C. Lazarus, V. Maddipati, F.J. Martinez, A. Mathews, C. Meldrum, C. McEvoy, T. Nyunoya, L. Rogers, W.W. Stringer, C.H. Wendt, R.A. Wise, S.R. Wisniewski, F.C. Sciurba, and P.G. Woodruff, for the RETHINC Study Group*

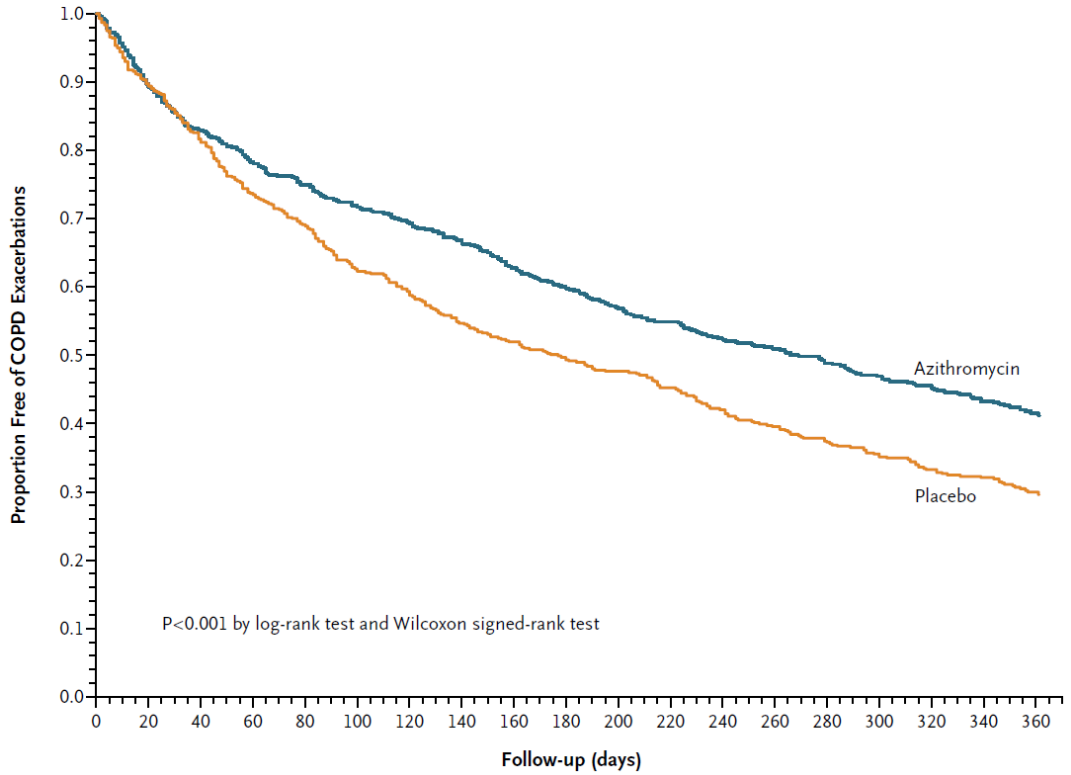


Outcome	Treatment (N=227)	Placebo (N=244)
	Mean (95% CI)	
Change in questionnaire results from baseline to week 12		
SGRQ score	−7.7 (−9.4 to −5.9)	−8.9 (−10.6 to −7.2)
CAT score	−4.8 (−5.8 to −3.9)	−4.5 (−5.4 to −3.5)
TDI score†	0.93 (0.59 to 1.27)	0.92 (0.59 to 1.26)
Change in pulmonary function from baseline to week 12		
Inspiratory capacity — liters	0.12 (0.07 to 0.18)	0.02 (−0.03 to 0.08)
FEV_1 — liters	0.04 (0.01 to 0.08)	−0.01 (−0.04 to 0.02)
Percent of predicted FEV_1 — percentage points	2.48 (1.49 to 3.47)	−0.09 (−1.06 to 0.89)
FEF_{25-75} — liters/sec	0.07 (0.00 to 0.15)	−0.08 (−0.15 to 0.00)
AUC_{0-3hr} for FEV_1 at week 12 — liters	8.09 (7.99 to 8.20)	7.82 (7.72 to 7.92)
Outcomes from daily diary — % of days		
Any symptoms or use of albuterol	67.0 (59.0 to 75.0)	63.6 (55.7 to 71.5)
Shortness of breath	30.7 (23.6 to 37.7)	32.5 (25.6 to 39.4)
Chest tightness	21.2 (15.0 to 27.4)	23.5 (17.4 to 29.6)
Wheezing	23.5 (17.8 to 29.2)	24.3 (18.7 to 29.8)
Cough	53.1 (45.9 to 60.2)	48.0 (41.1 to 54.9)
Sputum	45.1 (37.7 to 52.5)	43.4 (36.1 to 50.6)
Use of albuterol	9.3 (5.0 to 13.6)	9.7 (5.5 to 14.0)

N Engl J Med 2022;387:1173-84

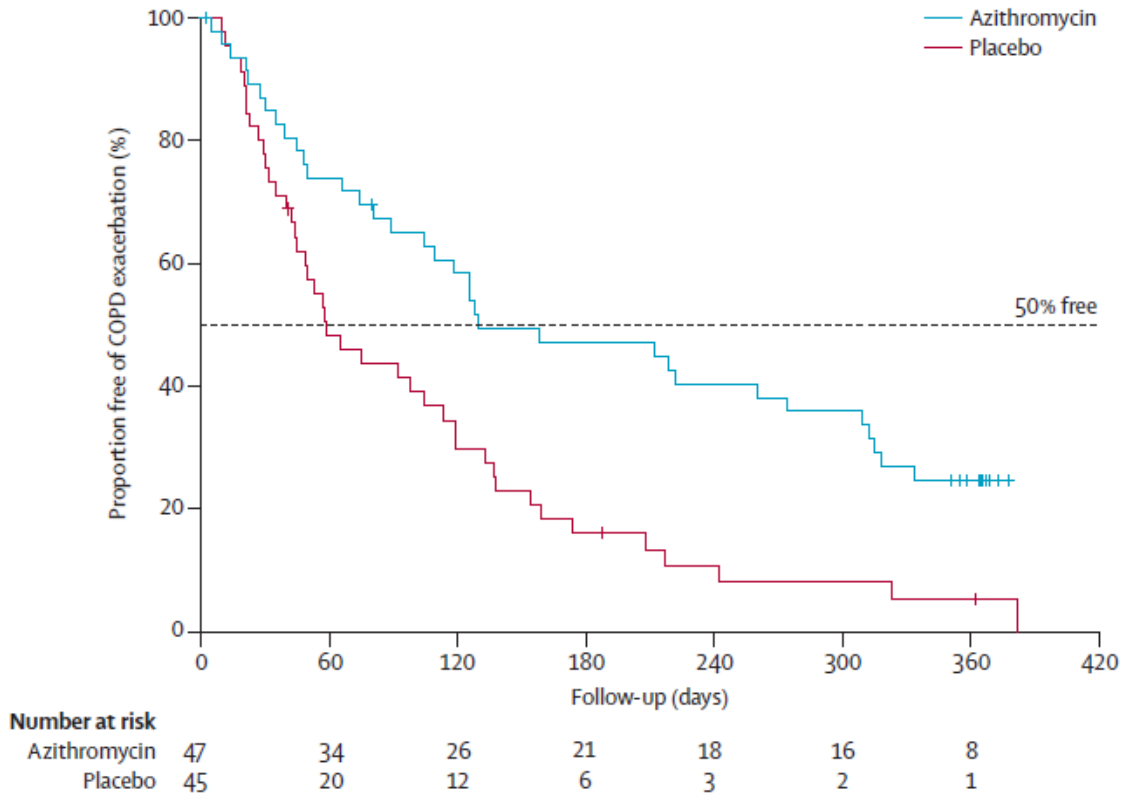
Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network



N Engl J Med 2011;365:689-698

Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial

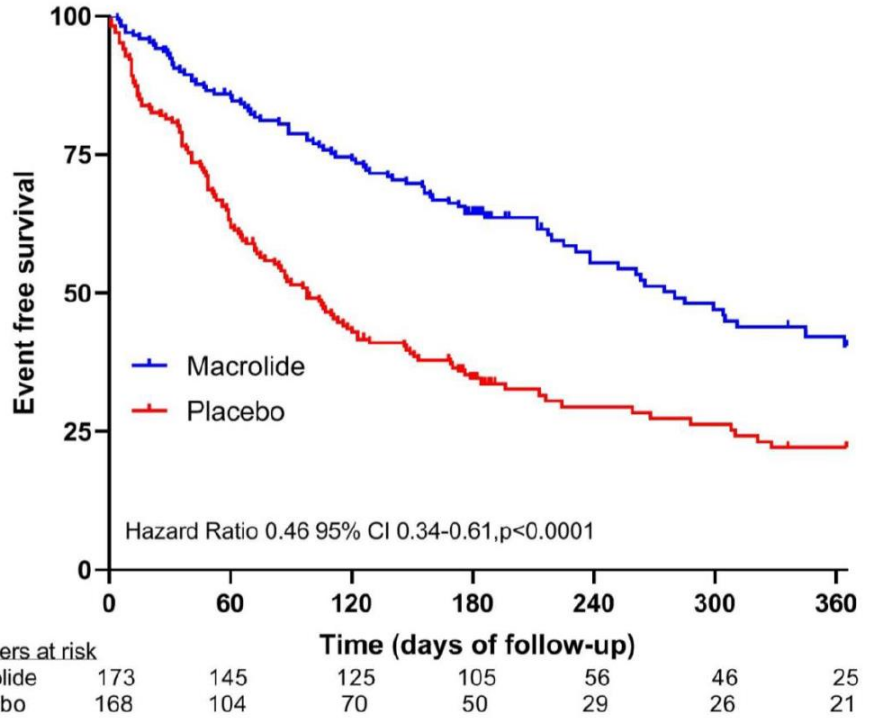


Lancet Respir Med 2014;2: 361–68

Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

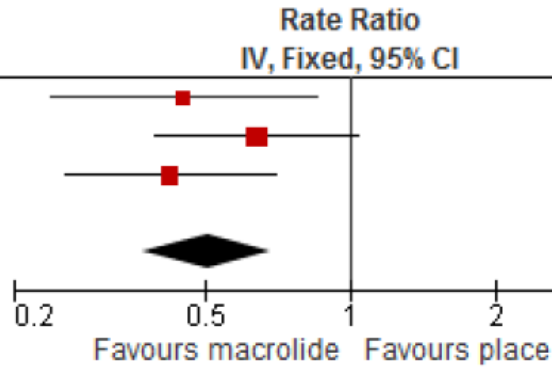
James D Chalmers, Wim Boersma*, Mike Lonergan, Lata Jayaram, Megan L Crichton, Noel Karalus, Steven L Taylor, Megan L Martin, Lucy D Burr, Conroy Wong, Josje Altenburg*

Time to first exacerbation survival curves



Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
BAT	-0.796	0.3225	23.4%	0.45 [0.24, 0.85]
BLESS	-0.449	0.2473	39.8%	0.64 [0.39, 1.04]
EMBRACE	-0.862	0.2576	36.7%	0.42 [0.25, 0.70]
Total (95% CI)			**100.0%**	**0.51 [0.37, 0.69]**

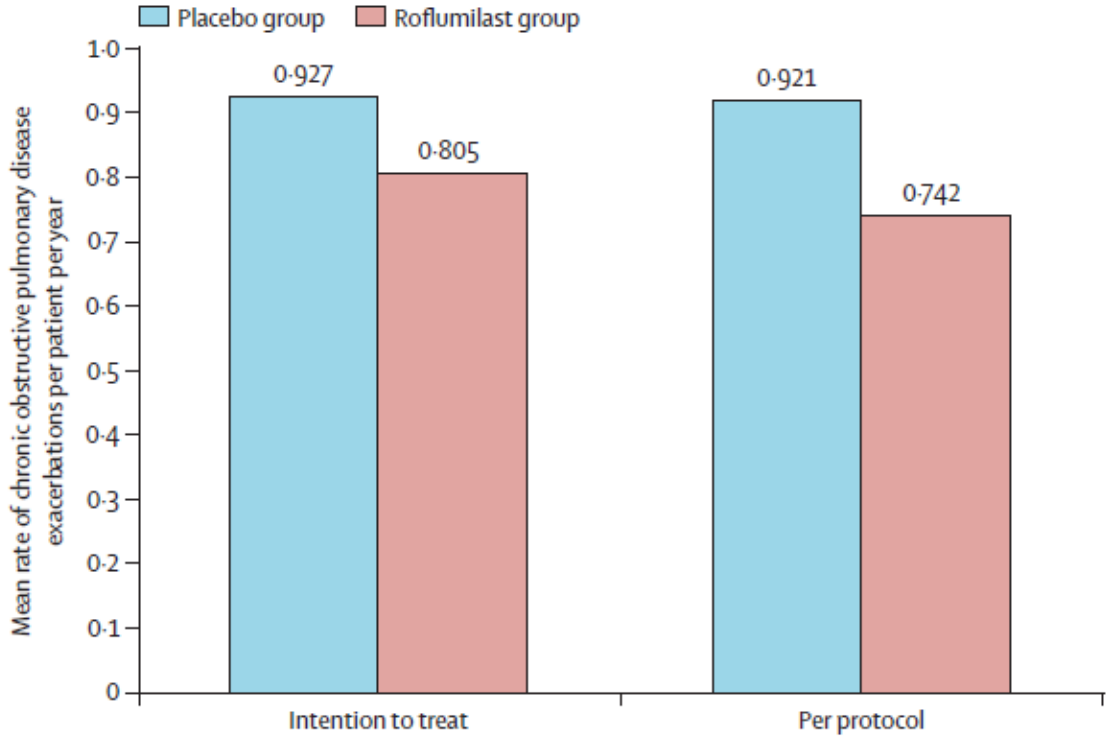
Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.37 (P < 0.0001)



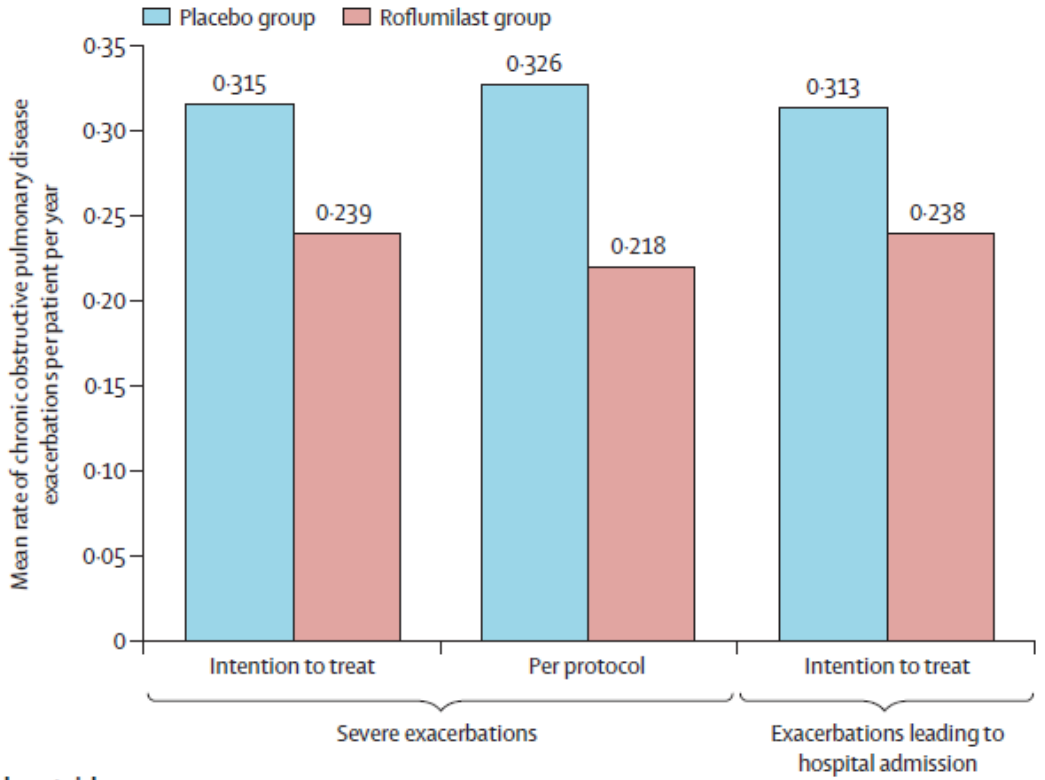
Primary outcome of frequency of exacerbations

***Lancet Respir Med* 2019; 7: 845–54**

Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial



Number at risk	Intention to treat	Per protocol
Patients with at least one exacerbation (n)	Placebo 432; roflumilast 380	Placebo 369; roflumilast 310
Rate ratio (95% CI)	0·868 (0·753–1·002)	0·806 (0·688–0·943)
Two-sided p value	0·0529	0·0070

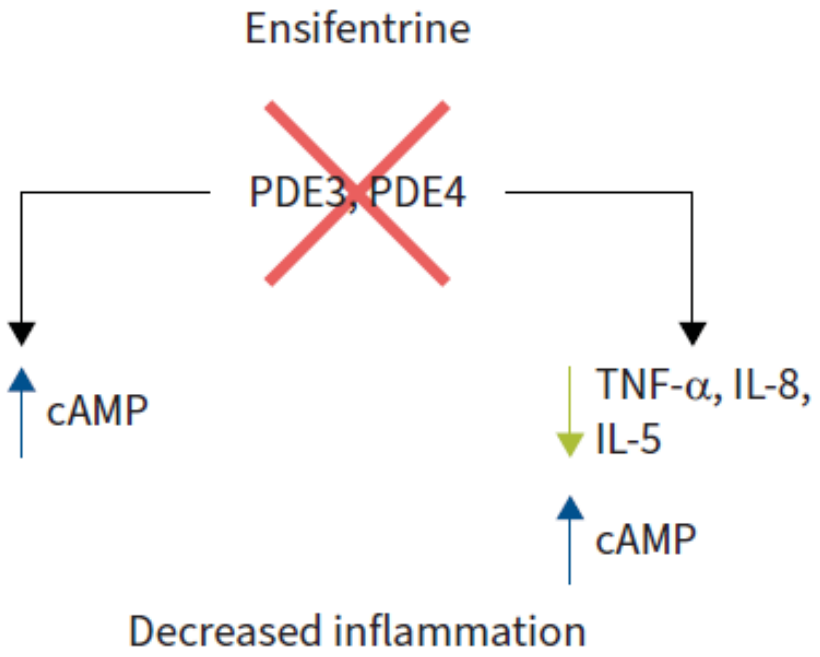


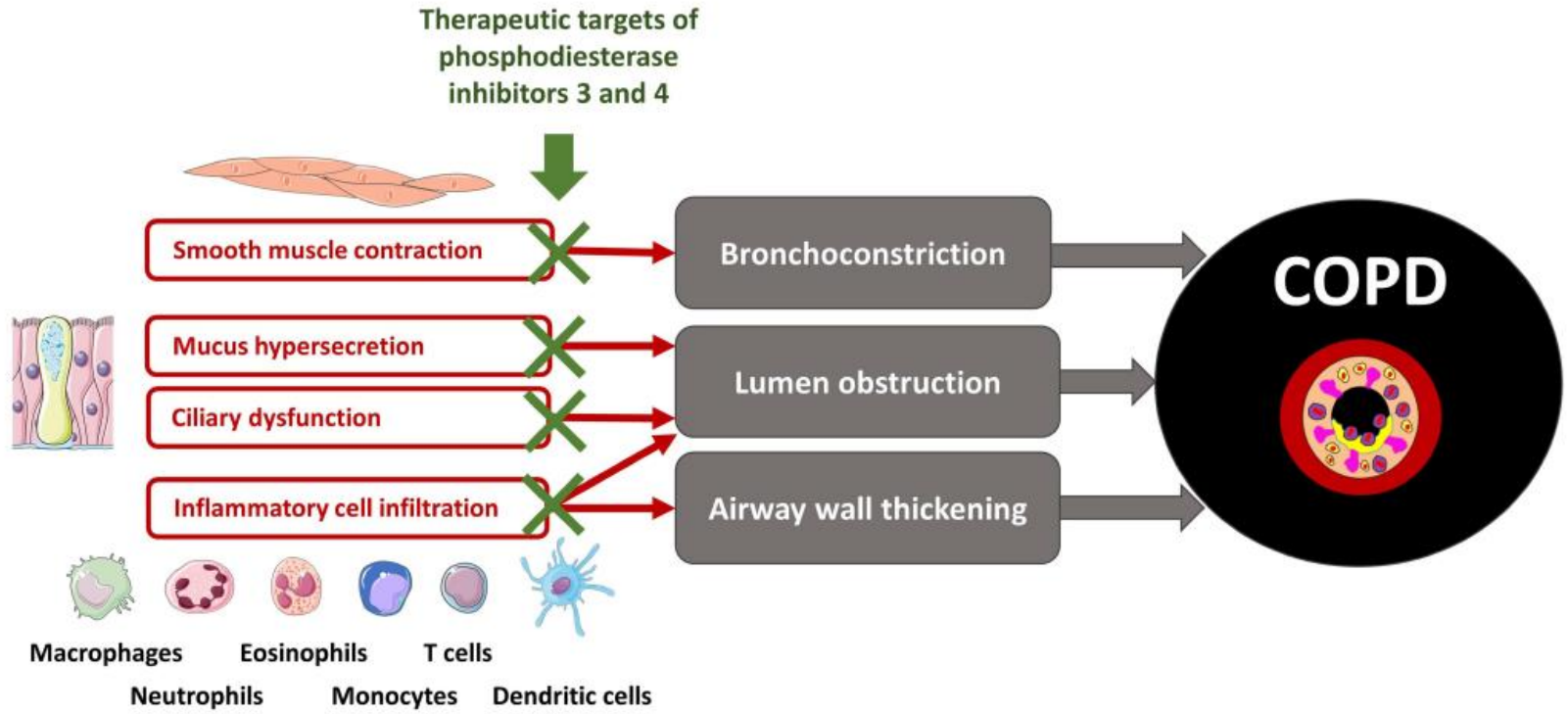
Number at risk	Intention to treat	Per protocol	Intention to treat
Patients with at least one exacerbation (n)	Placebo 192; roflumilast 151	Placebo 167; roflumilast 120	Placebo 190; roflumilast 150
Rate ratio (95% CI)	0·757 (0·601–0·952)	0·668 (0·518–0·861)	0·761 (0·604–0·960)
Two-sided p value	0·0175	0·0018	0·0209

Lancet 2015; 385: 857–66

Ensifentrine

activates cystic fibrosis transmembrane conductance regulator (CFTR), enhancing chloride ion secretion and mucociliary clearance



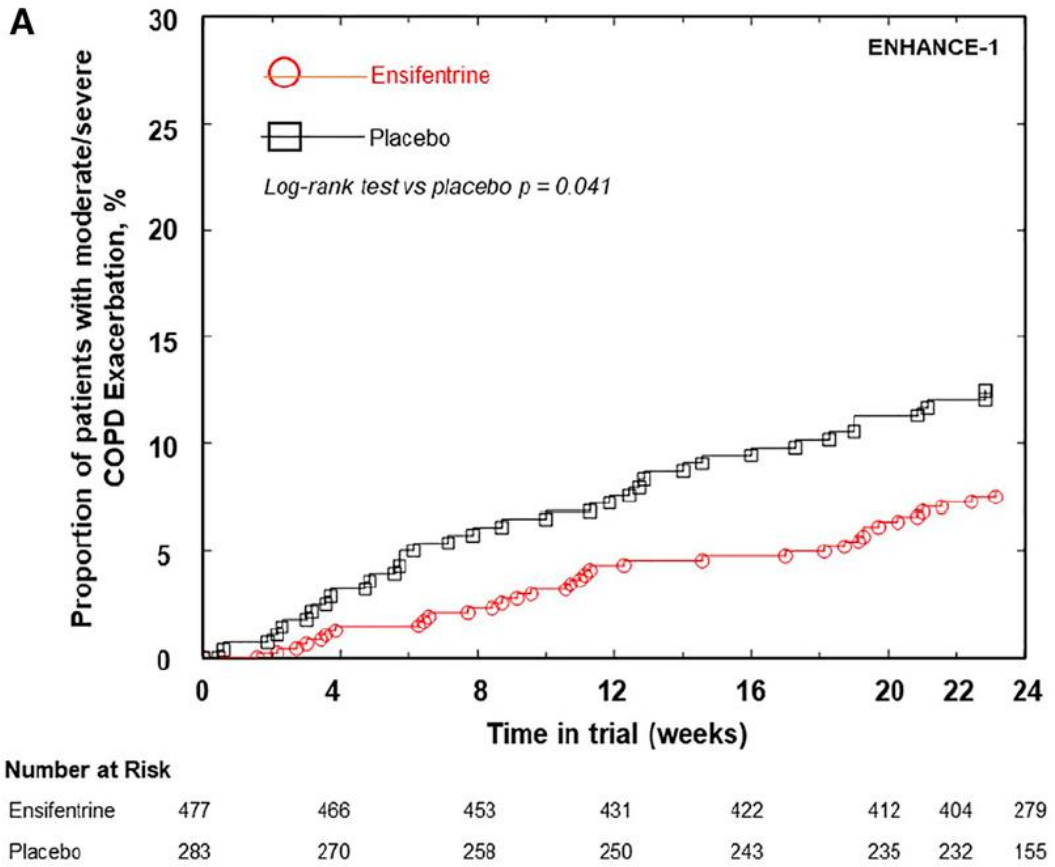


Breathe 2025; 21: 250206
International Journal of Chronic Obstructive Pulmonary Disease 2021:16 2363–2373

Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease

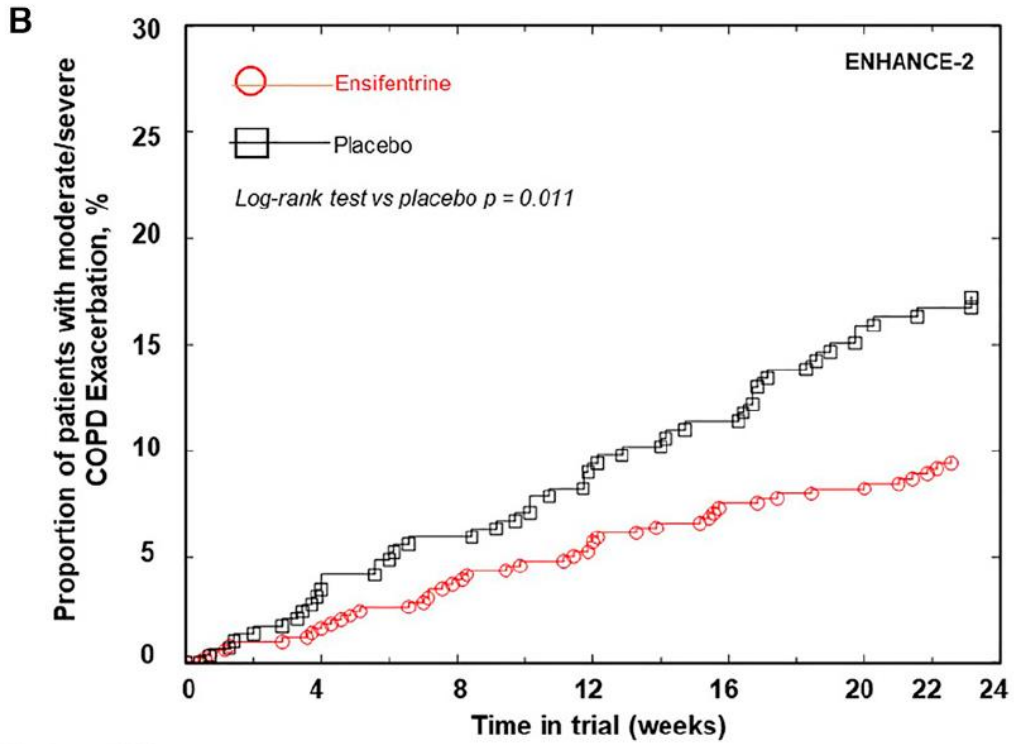
Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials)

Antonio Anzueto[1,2], Igor Z. Barjaktarevic[3], Thomas M. Siler[4], Tara Rheault[5], Thomas Bengtsson[6], Kathleen Rickard[5], and Frank Sciurba[7]; for the ENHANCE investigators



Number at Risk

Ensifentrine	477	466	453	431	422	412	404	279
Placebo	283	270	258	250	243	235	232	155



Number at Risk

Ensifentrine	498	481	443	422	399	390	380	278
Placebo	291	275	257	232	218	201	196	151

Am J Respir Crit Care Med 2023; 208: 406–416

Follow-up Pharmacological Treatment

Figure 3.9

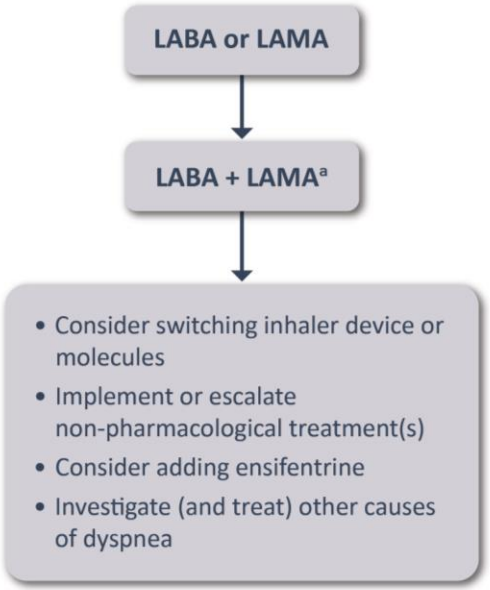
2026

2 Adjust Treatment

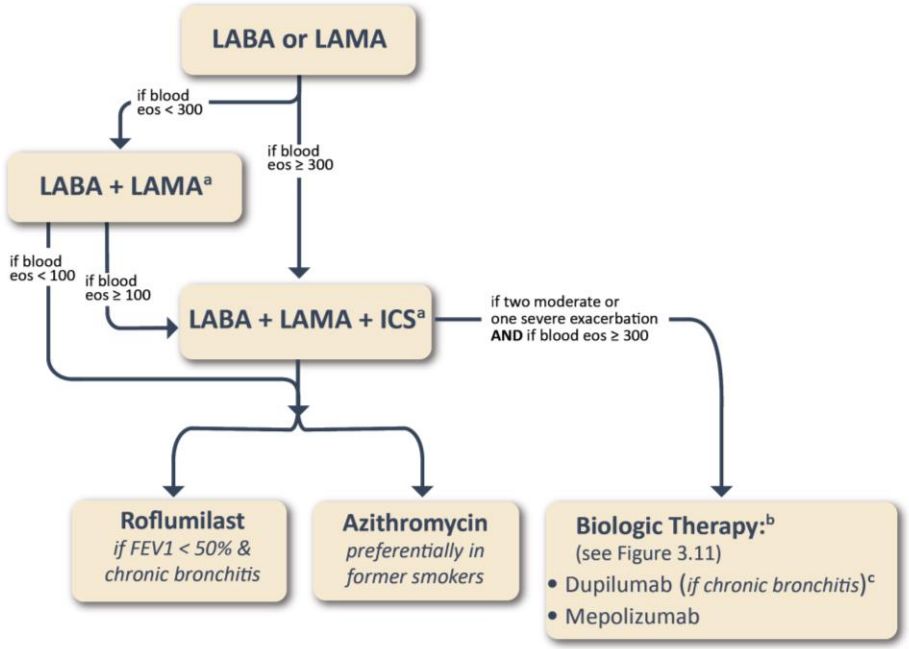
CONTINUE CURRENT TREATMENT

unless dyspnea or exacerbation(s) require optimization

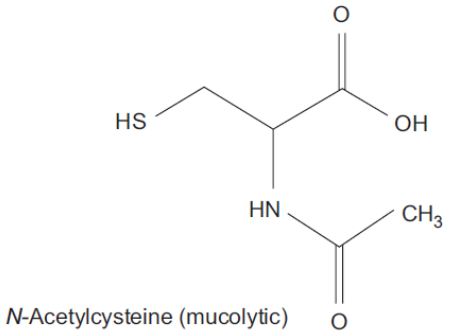
• IF PERSISTENT DYSPNEA



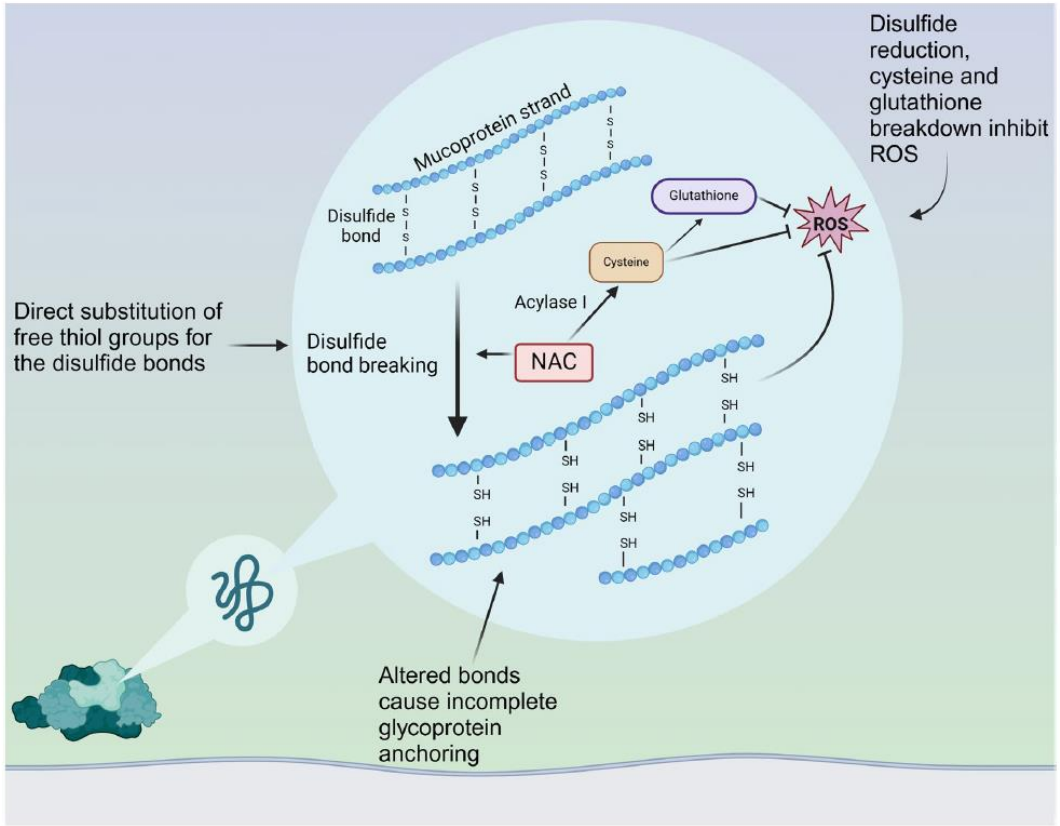
• IF ONE OR MORE MODERATE OR SEVERE EXACERBATION



N-acetylcysteine (NAC)



N-Acetylcysteine (mucolytic)



Mucolytic effect:
- breaking down disulphid bonds in mucus

Antioxidant effects:
- potent scavenging of NO_2 and HOX
- weak scavenging of H_2O_2 and superoxide
- GSH replenishment (cystein donor)
- Nrf2 stimulation

Anti-fibrotic effects:
- suppression of alveolar epithelial-mesenchymal transition
- decreased collagen, α-SMA and fibronectin production

NAC

Antidotum:
- paracetamol (acetaminophen) intoxication
- other poisonings (heavy metals, herbicides, mushrooms)

Anti-inflammatory effects:
- NF-κB, MAPK suppression
- COX-2, MMP-3, MMP-4, ICAM-1 suppression
- TNFα, IL-1β, IL-6, IL-8 suppression

Other:
- cytoprotective effects
- neuroprotective effects
- vasoprotective effects

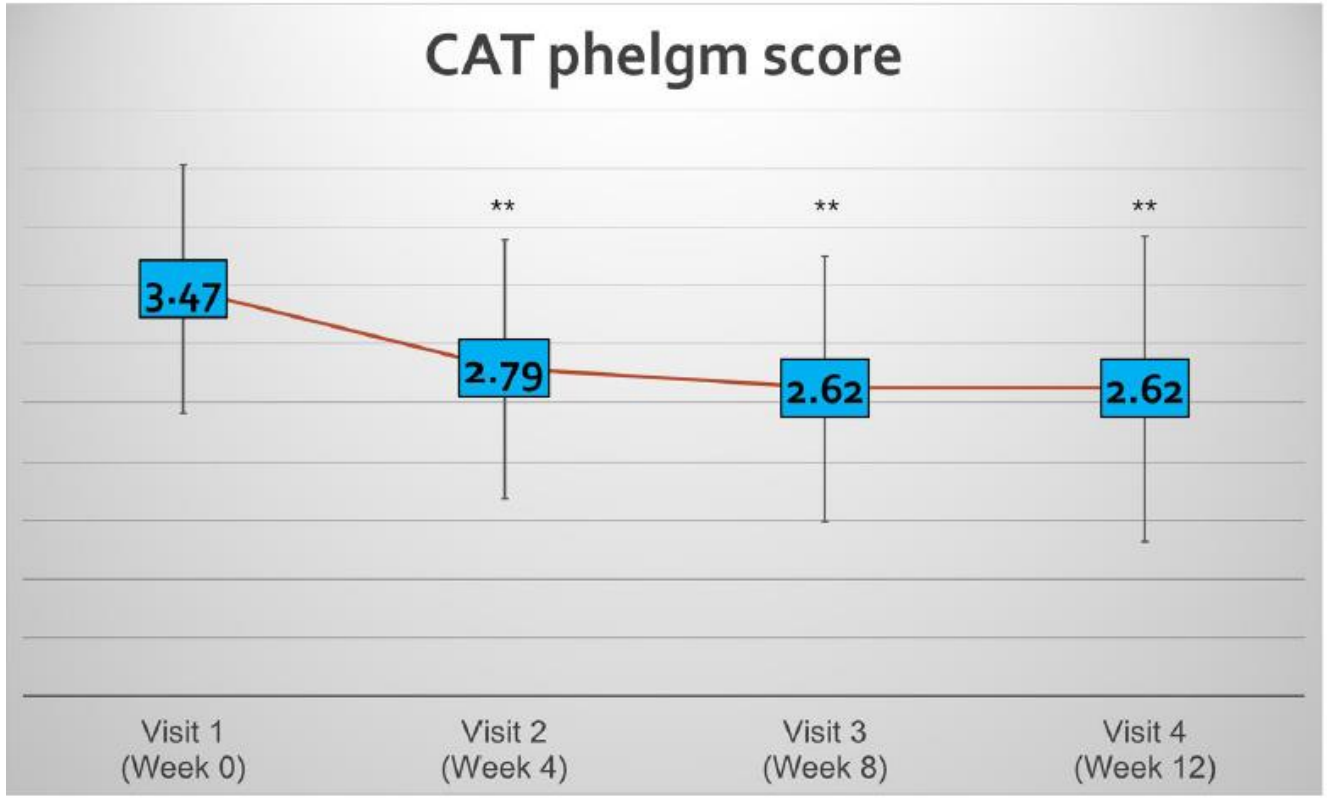
Critical Care (2025) 29:68

Antioxidants 2023, 12, 1713

RESEARCH Open Access

The effect of nebulized N-acetylcysteine on the phlegm of chronic obstructive pulmonary disease: the NEWEST study

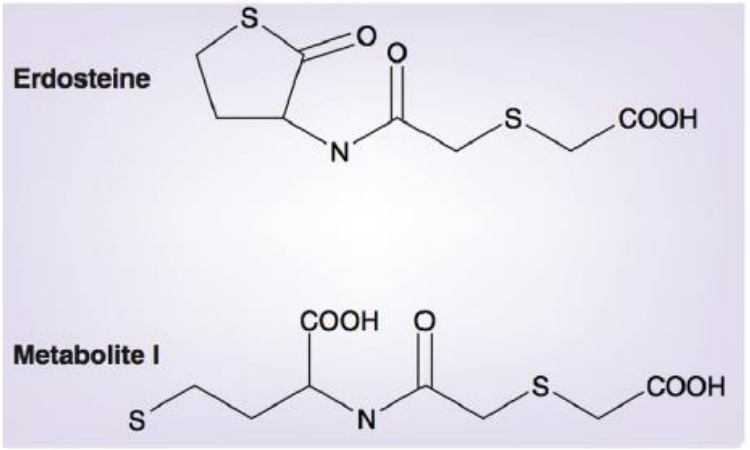
Chin Kook Rhee[1], Seong Yong Lim[2], Won-Yeon Lee[3], Ji Ye Jung[4], Yong Bum Park[5], Chang Youl Lee[6], Yong Il Hwang[7], Jin Woo Song[8], Won-Il Choi[9], Kwang Ha Yoo[10*], Ki Uk Kim[11], Yu-Il Kim[12], Tae-Hyung Kim[13], Seong Ju Park[14], Kyeong-Cheol Shin[15], Soo-Jung Um[16], Hyoung Kyu Yoon[17], Ho Sung Lee[18], Deog Kyeom Kim[19], Ah Young Leem[4] and on Behalf of the Korean Pulmonary Rehabilitation Study Group[20]



12-week, prospective, single-arm, open-label, Phase IV multi-center trial
NAC (Mucomyst®) via nebulizer.
Each vial (4 mL) of Mucomyst contains 0.8 g NAC, diluted with normal saline in a 1:1 ratio

BMC Pulmonary Medicine (2024) 24:434

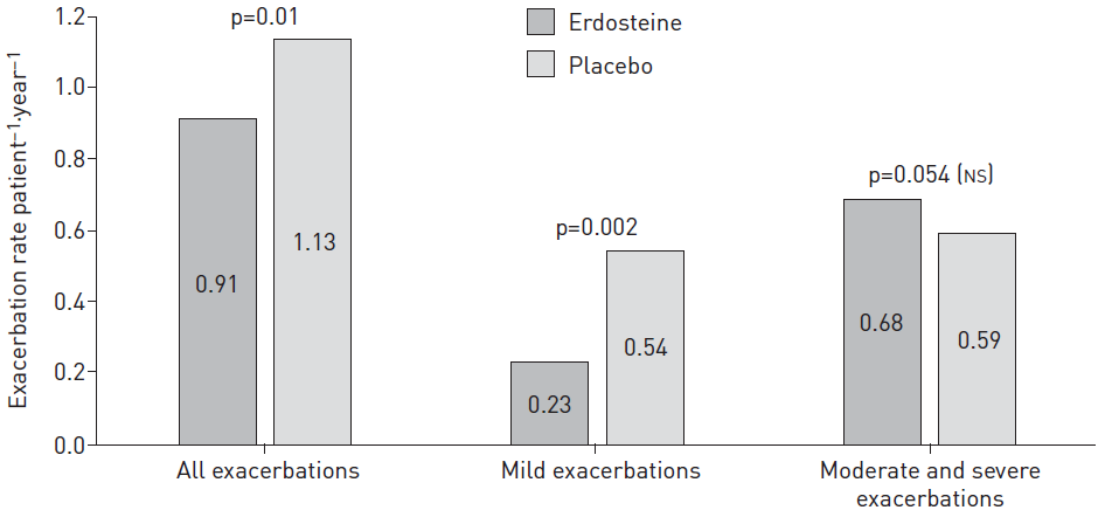
Erdosteine

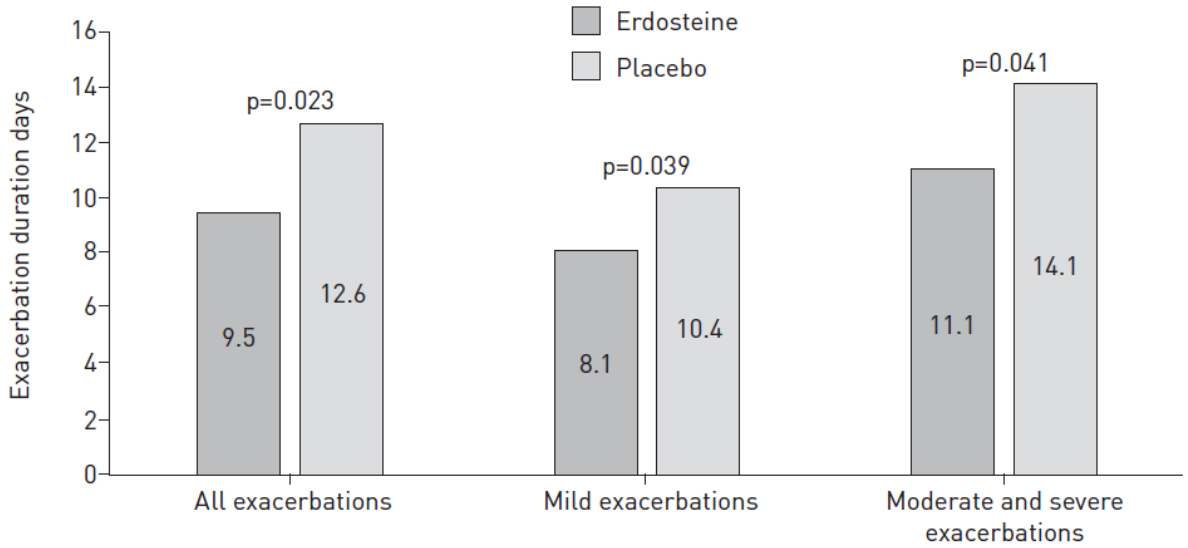


Antioxidant
Anti-inflammatory properties
Modulation of bacterial adhesiveness

Effect of erdosteine on the rate and duration of COPD exacerbations: the RESTORE study

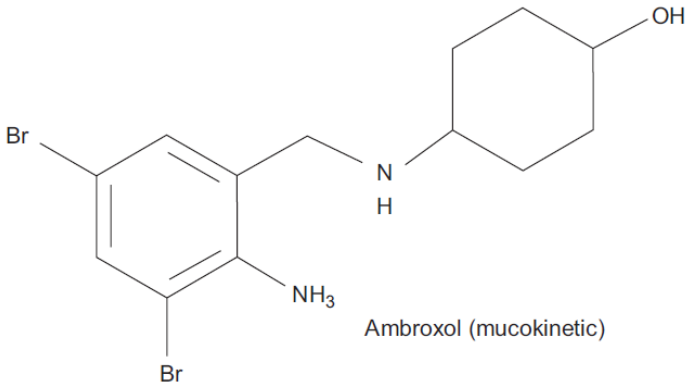
Roberto W. Dal Negro[1], Jadwiga A. Wedzicha[2], Martin Iversen[3], Giovanni Fontana[4], Clive Page[5], Arrigo F. Cicero[6], Edoardo Pozzi[7] and Peter M.A. Calverley[8] on behalf of the RESTORE group[9]



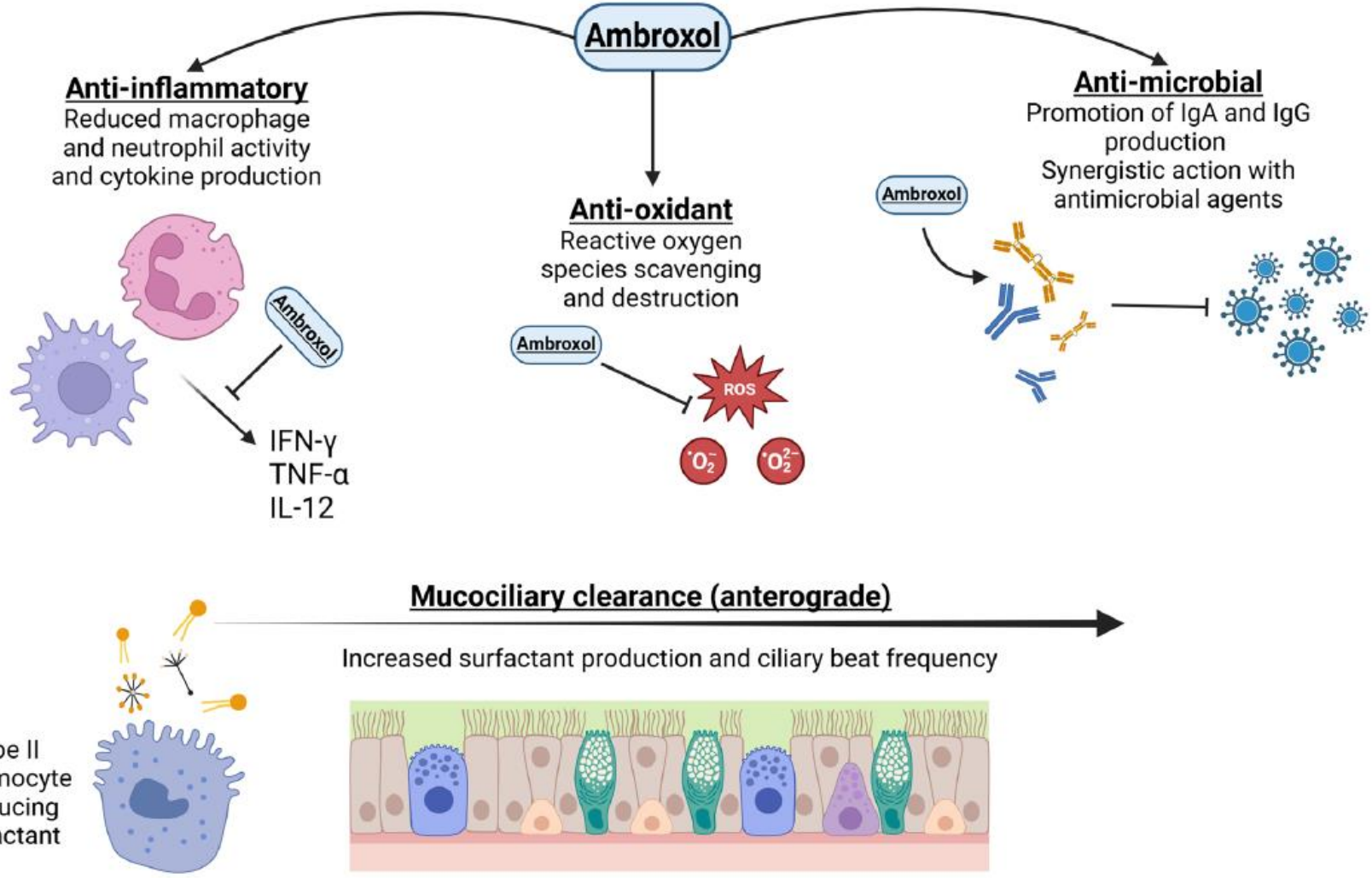


Pulm Pharmacol Ther 2008; 21: 304–308
Pulm Pharmacol Ther 2015; 33: 47–51.
Chemotherapy 2001; 47: 208–214.
Eur Respir J 2017; 50: 1700711

Ambroxol



Ambroxol (mucokinetic)



Critical Care (2025) 29:68

Pharmacodynamics activity

	Erdosteine	N-Acetylcysteine	Carbocysteine	Ambroxol
Mucolytic activity	YES	YES	WEAK	NO
Mucoregulatory activity	YES	YES	YES	YES
Anti-oxidant activity	YES	YES	WEAK	WEAK
Bronchial anti-inflammatory activity	YES	YES	WEAK	NO
Bacterial anti-adhesion activity	YES	WEAK	NO	NO
Activity on surfactant	NO	NO	NO	YES
Activity on mucociliary transport	YES	YES	WEAK	YES

Pulmonary Pharmacology & Therapeutics 53 (2018) 80–85

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
J.D. CHALMERS ET AL.

European Respiratory Society clinical practice guideline for the management of adult bronchiectasis

James D. Chalmers[1,33], Charles S. Haworth[2], Patrick Flume[3], Merete B. Long[1], Pierre-Régis Burgel[4], Katerina Dimakou[5], Francesco Blasi[6,7], Beatriz Herrero-Cortina[8,9], Raja Dhar[10], Sanjay H. Chotirmall[11,12], Felix C. Ringshausen[13,14,15], Josje Altenburg[16], Lucy Morgan[17], Mattia Nigro[18,19], Megan L. Crichton[1], Chayenne Van Meel[20], Oriol Sibila[21], Alan Timothy[22], Eliza Kompatsiari[22], Tanja Hedberg[22], Thomas Vandendriessche[20], Pamela J. McShane[23], Thomy Tonia[24], Kevin Winthrop[25], Michael R. Loebinger[26], Natalie Lorent[27,28], Pieter Goeminne[29], Michal Shteinberg[30,31], Eva Polverino[32] and Stefano Aliberti[19,20,33]

Eur Respir J 2025; 66: 2501126

Eur Respir J 2025; 66: 2501126

PICO Question 2: Mucoactive drugs

Should mucoactive drugs be used (compared with no mucoactive drugs) in adults with bronchiectasis?

Recommendations

We suggest to offer mucoactive treatments to patients with bronchiectasis where airway clearance has failed to control symptoms. *(Conditional recommendation for the intervention, very low certainty of evidence.)*

We suggest not to offer recombinant DNase to patients with bronchiectasis. *(Conditional recommendation against the intervention, very low certainty of evidence.)*

Remarks

- The choice of mucoactive treatment should be guided by the patient's comorbidities and concerns around treatment burden and tolerability.
- Mucoactive treatments are best delivered as part of a comprehensive airway clearance regimen, which includes personalised airway clearance instruction with or without devices, and regular physical exercise.

Interventional and surgical treatment for COPD

2026

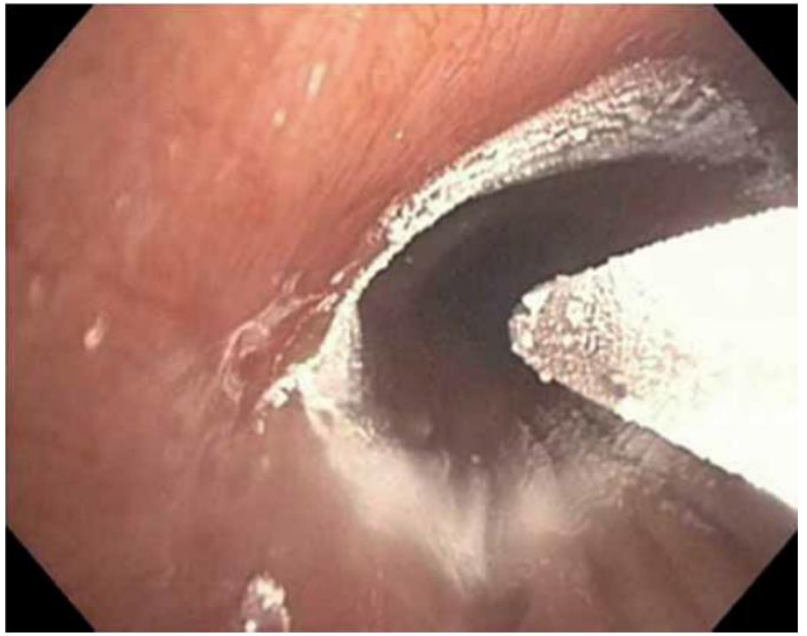
Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD

Figure 3.21

Symptoms	Chronic Mucus Production	Exacerbations	Dyspnea
Disorders	• Chronic bronchitis	• Acute and chronic bronchitis • Bulla • Emphysema • Tracheobronchomalcia	• Bulla • Emphysema • Tracheobronchomalcia
Surgical and Bronchoscopic Interventions	• Nitrogen cryospray • Rheoplasty	• Targeted lung denervation	• Giant bullectomy • Large airway stenting • EBV • Coil • Thermal vapor ablation • Lung sealants • LVRS • Lung transplantation

A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD

Justin L. Garner[1,2,3], Tawimas Shaipanich[4], Jorine E. Hartman[5], Christopher M. Orton[1,2,3], Cielito Caneja[1,3], Karin Klooster[5], John Thornton[3], Don D. Sin[4], Dirk-Jan Slebos[5] and Pallav L. Shah[1,2,3]



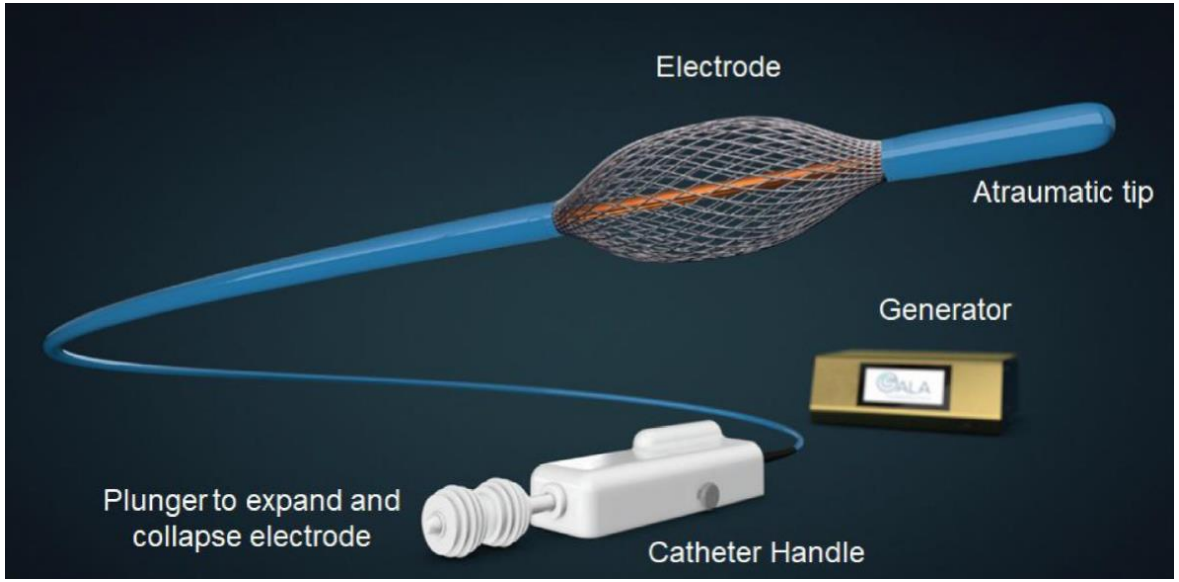
	RCT	Subjects	Time point	Result
Quality of life				
SGRQ total score change	No	34	3 months	**−6.4±14.4**
	No	31	12 months	−4.6±15.1
CAT total score change	No	34	3 months	**−3.8±7.1**
	No	31	12 months	−2.0±7.2
Chronic bronchitis symptoms				
LCQ total score change	No	34	3 months	**21.6±32.2**
	No	31	12 months	9.1±29.0
Lung function				
FEV_1 mL change	No	34	3 months	−33.2±167
	No	31	12 months	**−96.5±198**
Exercise capacity				
6MWD m change	No	34	3 months	1.1±55.4
	No	31	12 months	8.5±76.2

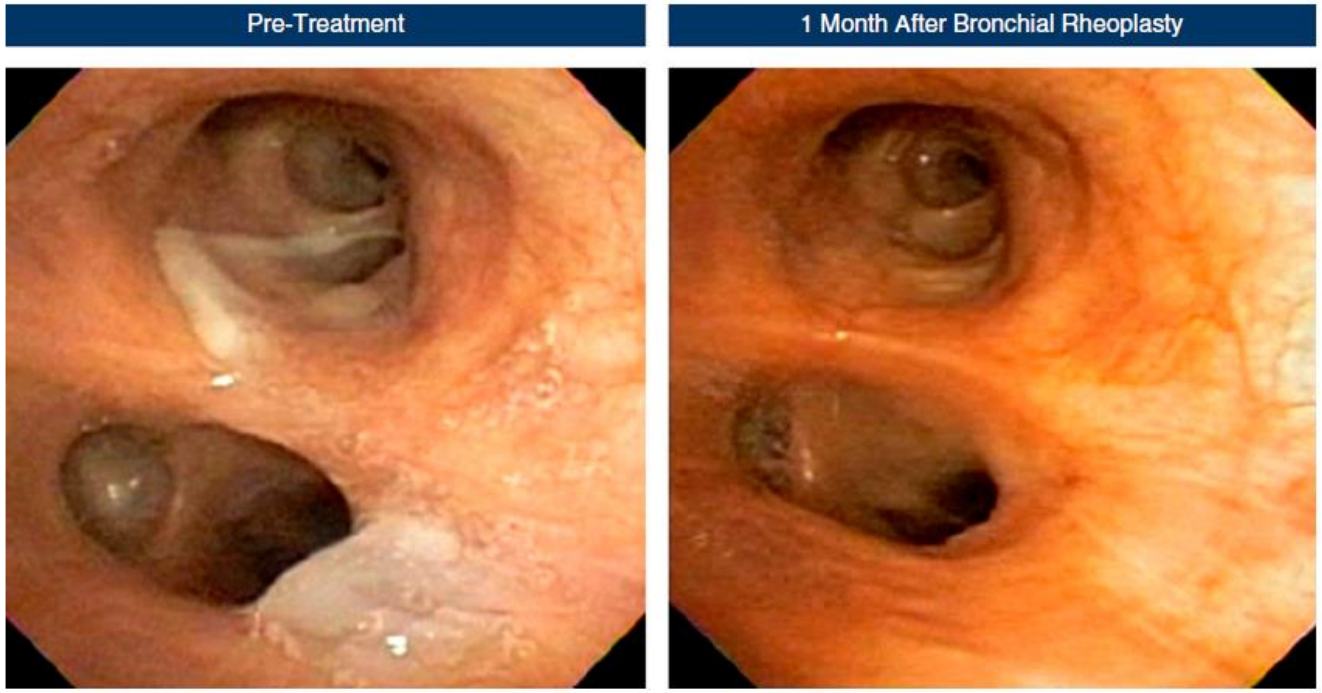
Eur Respir J2020; 56: 2000556.

Bronchial Rheoplasty for Treatment of Chronic Bronchitis

Twelve-Month Results from a Multicenter Clinical Trial

Arschang Valipour[1], Sebastian Fernandez-Bussy[2,3], Alvin J. Ing[4], Daniel P. Steinfort[5,6], Gregory I. Snell[7], Jonathan P. Williamson[4], Tajalli Saghaie[4], Louis B. Irving[5,6], Eli J. Dabscheck[7], William S. Krimsky[8,9], and Jonathan Waldstreicher[9]

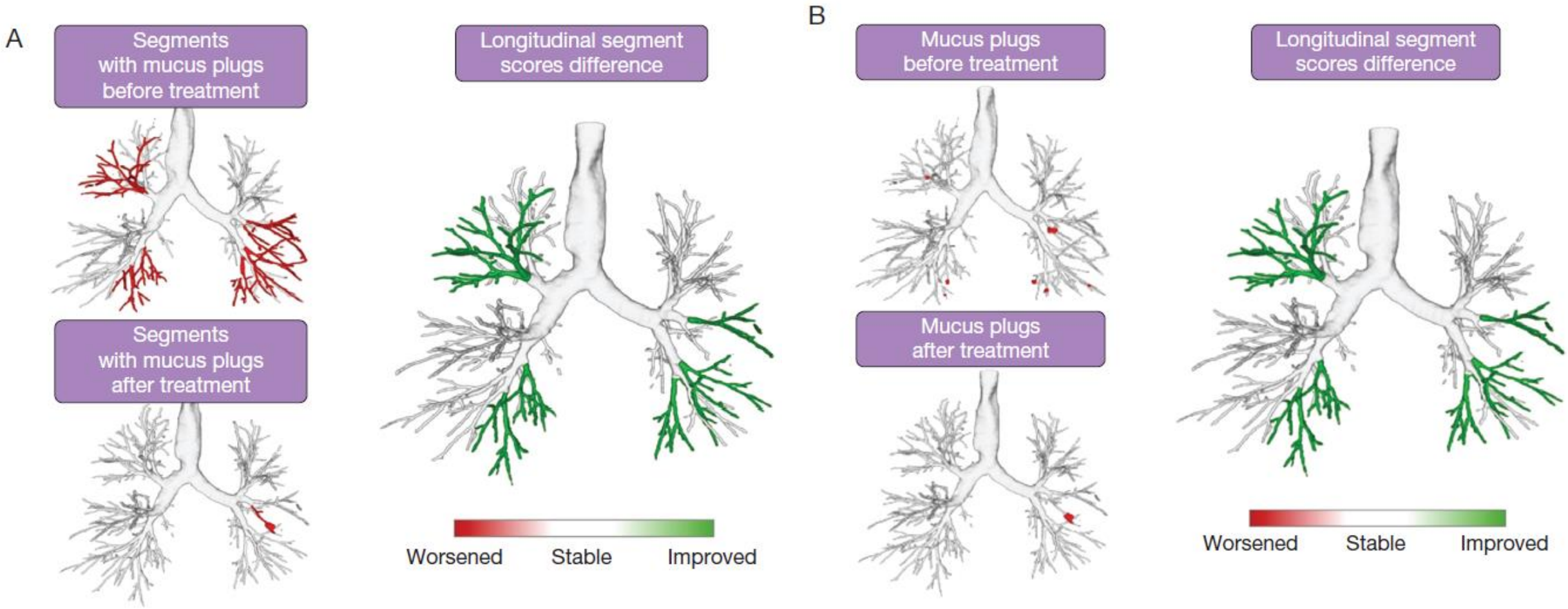




AJRCCM 2020; 202: 681–689

Airway Mucus Plugging in Chronic Bronchitis and the Impact of Bronchial Rheoplasty

William S. Krimsky, MD; Joseph G. Mammarappallil, MD, PhD; Victor Kim, MD; Brett Bannan, MS; Jean-Paul Charbonnier, PhD; Beryl A. Hatton, PhD; and Frank C. Sciurba, MD



CHEST 2026; 169(1):73-83

Targeted lung denervation

Physically interrupting parasympathetic pulmonary nerve input into the lung
Main bronchi using radiofrequency catheter blocks parasympathetic signaling within bronchial nerve branches, decreasing acetylcholine release and thus airway obstruction

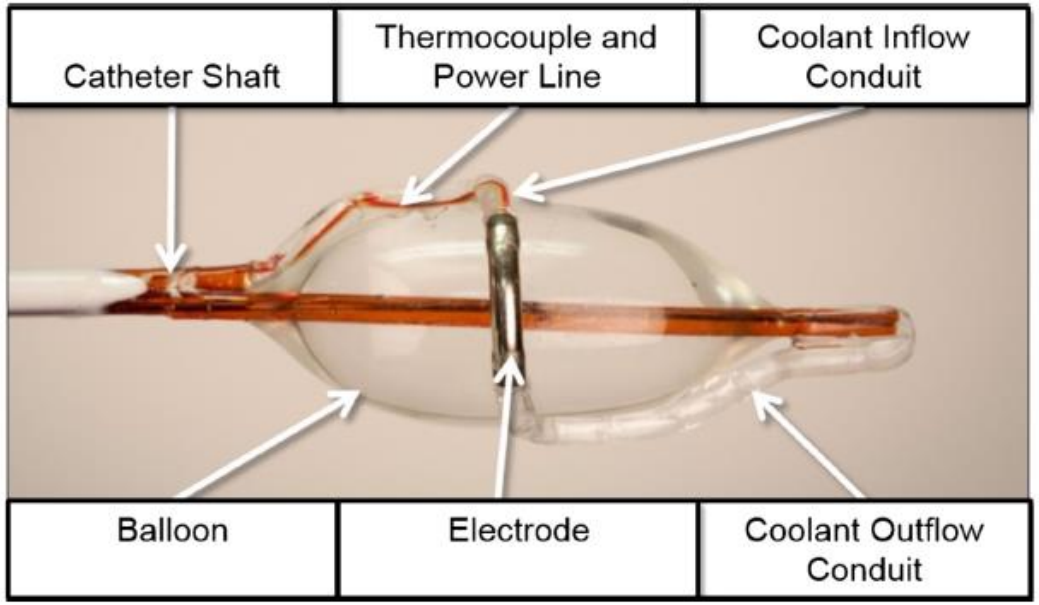
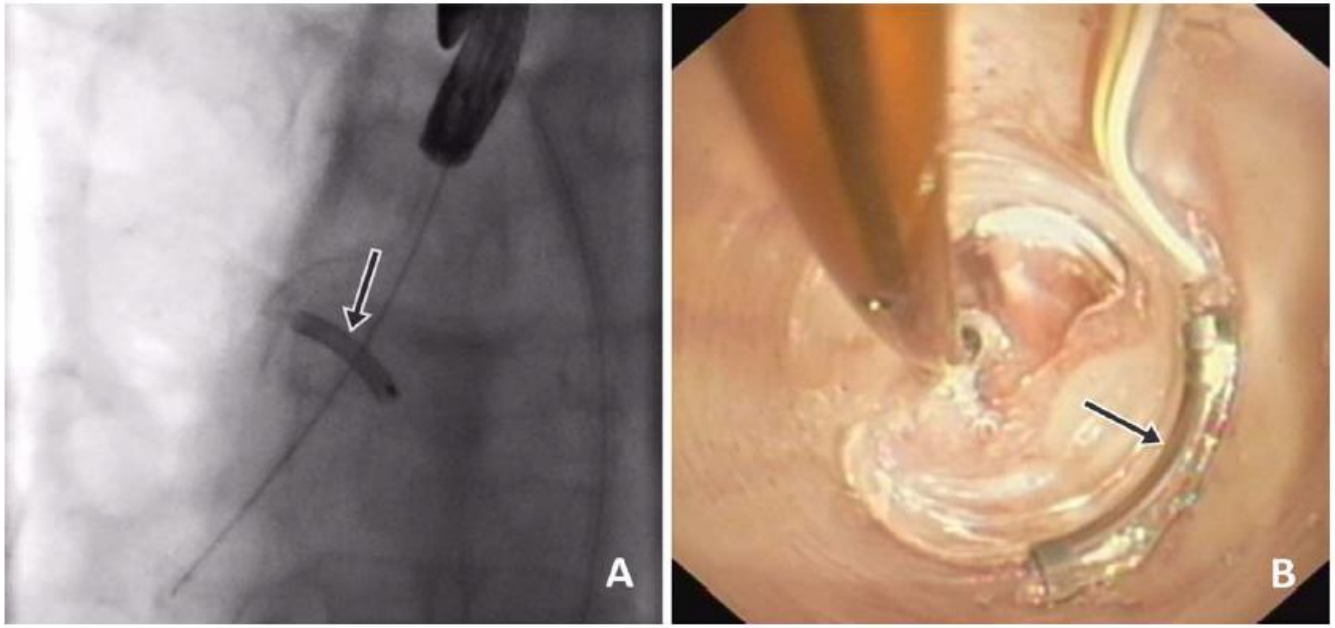


Figure 1 Description of the key components of the targeted lung denervation (TLD) catheter.

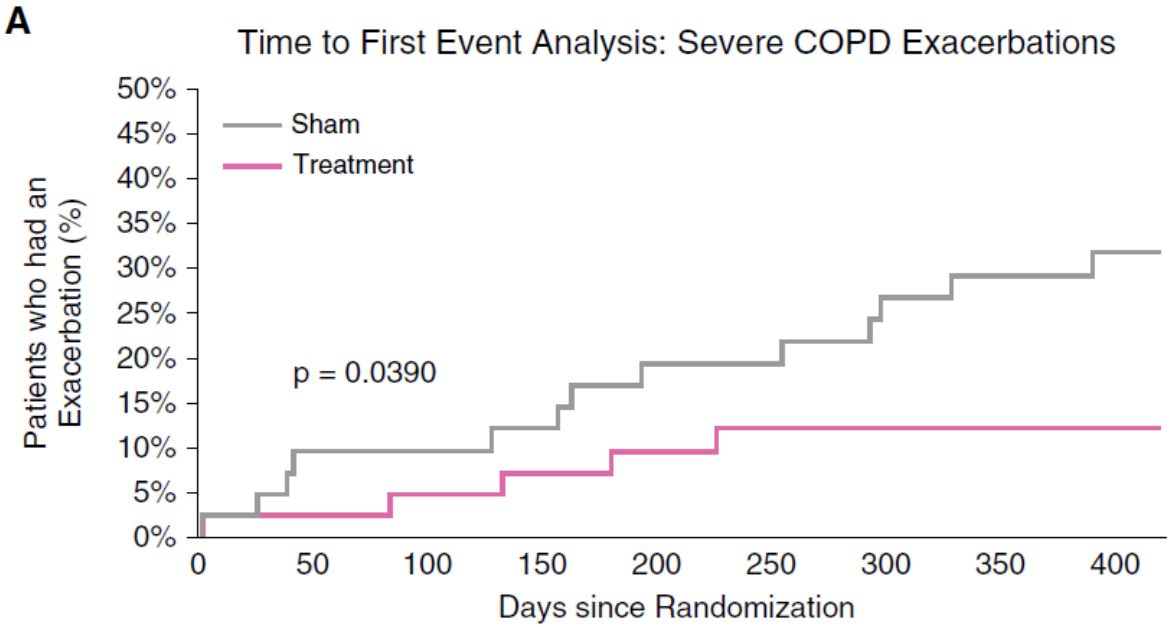


Thorax 2015;70:411–419

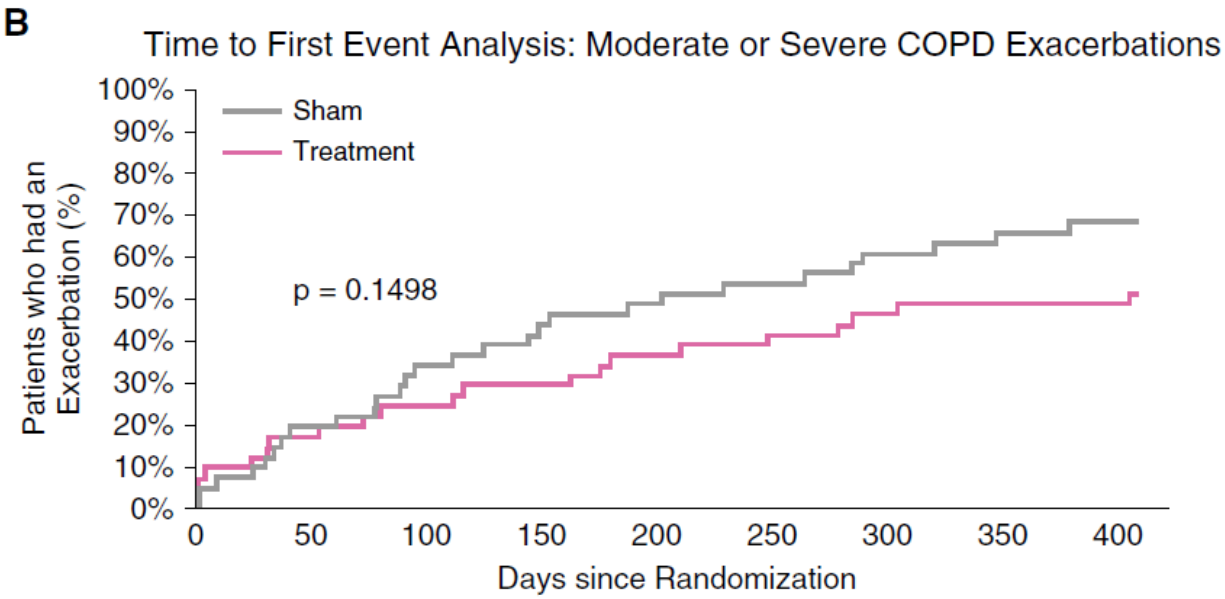
Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW)

A Multicenter Randomized Controlled Clinical Trial

A



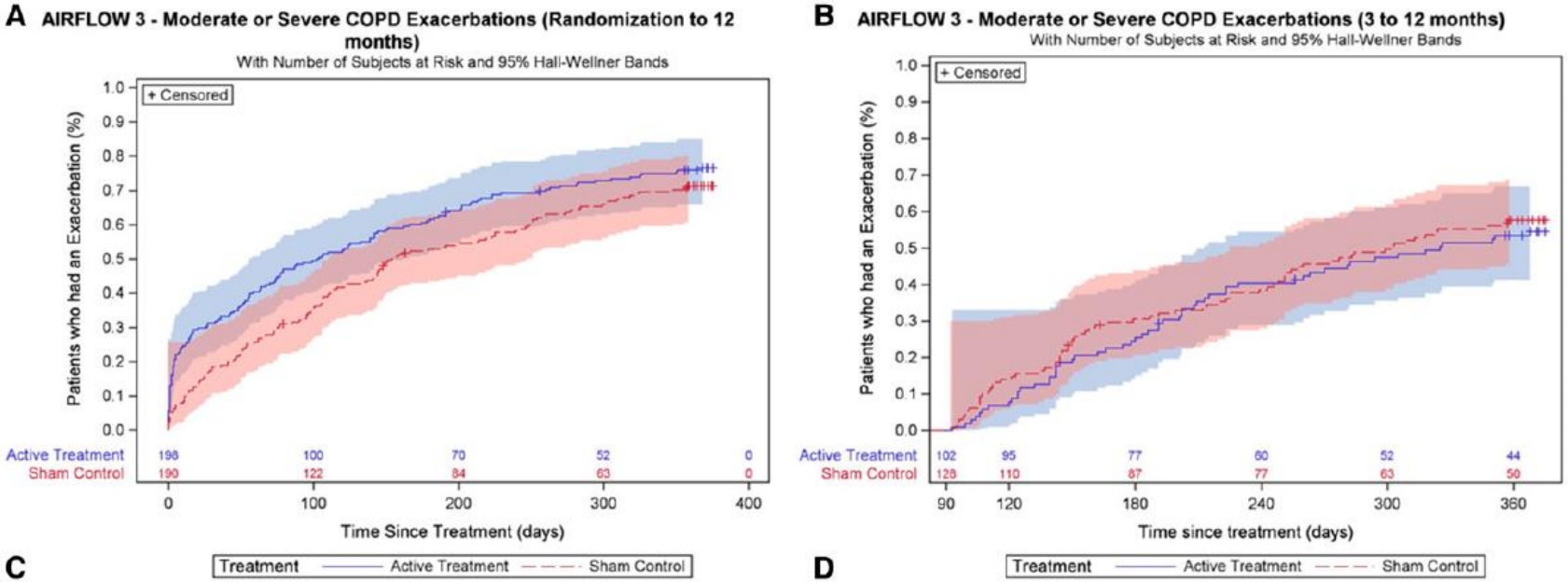
B



AJRCCM 2019; 200: 1477-1486

Randomized Sham-controlled Trial of Targeted Lung Denervation in Patients with Chronic Obstructive Pulmonary Disease (AIRFLOW-3)

Pallav L. Shah[1], Dirk-Jan Slebos[2], Richard Sue[3], Surya P. Bhatt[4], Christian Ghattas[5], Charlie Strange[6], Bruno Degano[7], Arschang Valipour[8], Stephan Eisenmann[9], Jose De Cardenas[10], Charles-Hugo Marquette[11], Jose Soto-Soto[12], Frank C. Sciurba[13], Francesca Conway[1], James Tonkin[1], Anand Tana[1], Nathaniel Marchetti[15], Jorine E. Hartman[2], Valentin Heluain[14], Nicolas Guibert[14], and Gerard J. Criner[15]; for the AIRFLOW-3 Study Group



AJRCCM 2025; 211: 2318-2329

Summary

- Mucus plugging: Clinical significance
- Mucin expression and CFTR dysfunction
- Physiotherapy
- Use of mucoactive drugs
- Bronchoscopic intervention
- Still unmet need in clinical practice

경청해주셔서 감사합니다