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Mucus Dynamics and Muco-active Treatment

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Contents

- Structure and function of mucin
- Pathogenesis of mucus dysfunction
- Osmotic agents for airway clearance
- Muco-active agents
- Summary

Contents

- **Structure and function of mucin**
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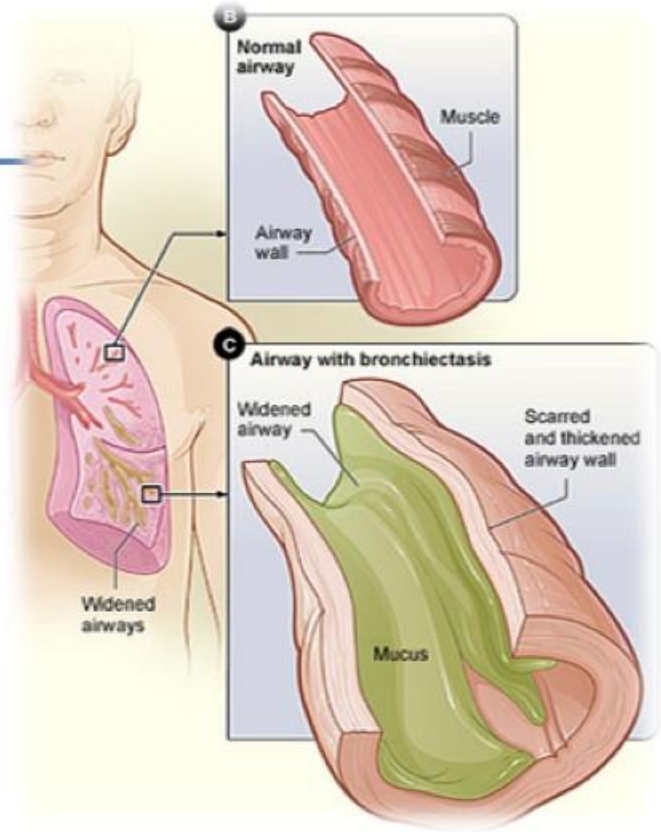
Mucus dysfunction in bronchiectasis

Bronchiectasis is characterized by

- ✓ abnormal and permanent dilatation of the bronchi
- ✓ a clinical syndrome of cough, sputum production and bronchial infection

Eur Respir J. 2017 Sep 9;50(3):1700629.



	COPD	Bronchiectasis
Main diagnostic criteria	Spirometry: post-bronchodilator $FEV_1/FVC < 0.7$	High-resolution chest CT: bronchial dilatation and wall thickening
Pathologic consequence	Alveolar wall destruction with loss of elastic recoil (emphysema) ➔ airflow limitation and air trapping	Irreversible bronchial dilatation with **impaired mucociliary clearance** ➔ mucus retention and bacterial colonization

Mucus composition and function

- **Mucus**
  - A hydrogel form mixture of **polypeptides(glycopeptides)**, cells, and debris
  - **Composition**

    : 97.5% water, 1% salt, 1% globular protein, **0.3~0.5% mucin**

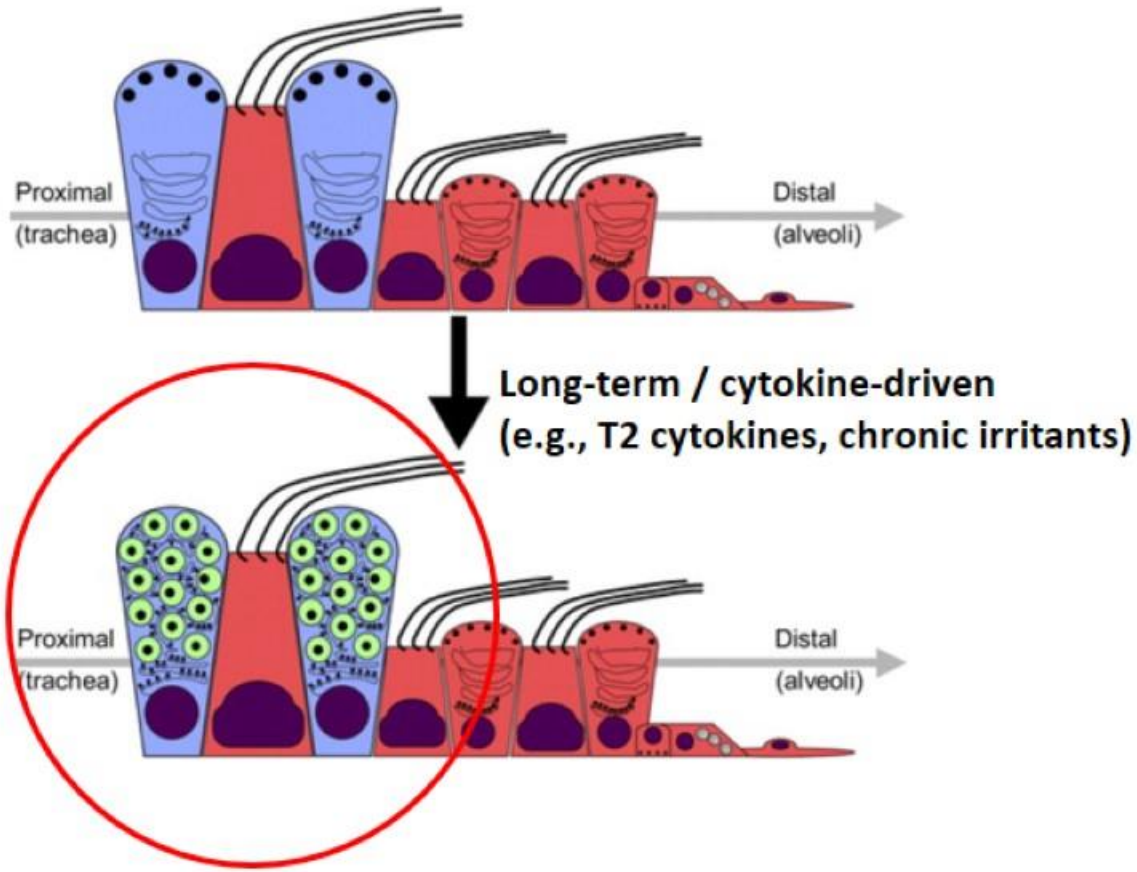
✓ **At baseline, low levels of mucus** present in the airways can **trap and eliminate inhaled particles** and **prevent desiccation** of airway surfaces.

✓ However, **mucus overproduction and retention** are closely tied to the **development and progression of a variety of airway diseases**.

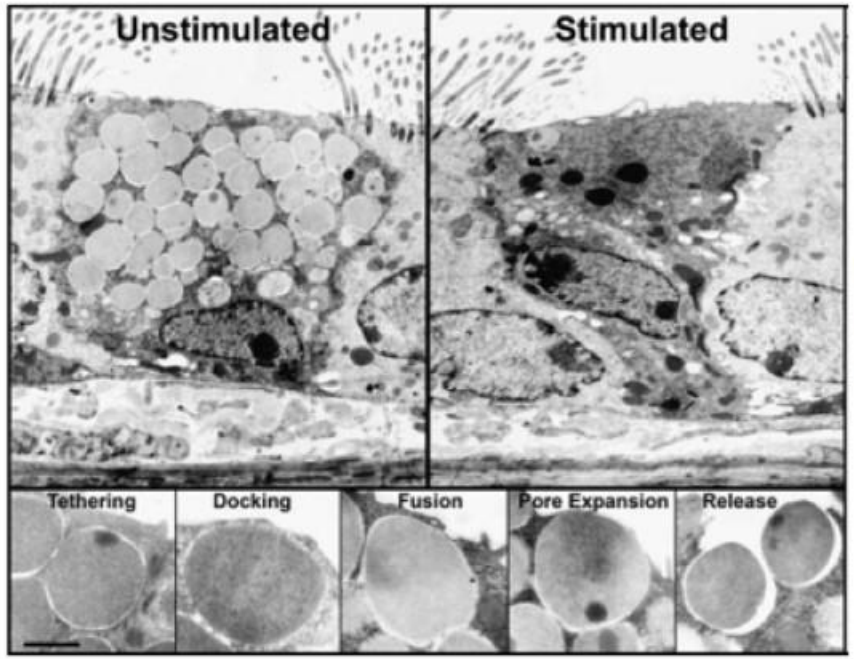
Physiol Rev. 2022 Jan 10;102(4):1757–1836

Regulation of mucin production and secretion

- Mucin synthesis and storage (production) and its extracellular release (secretion) in the airways are regulated by distinct signaling pathways and mechanisms.



Acute/ stimulus-driven
(e.g., ATP, acetylcholine, histamine)

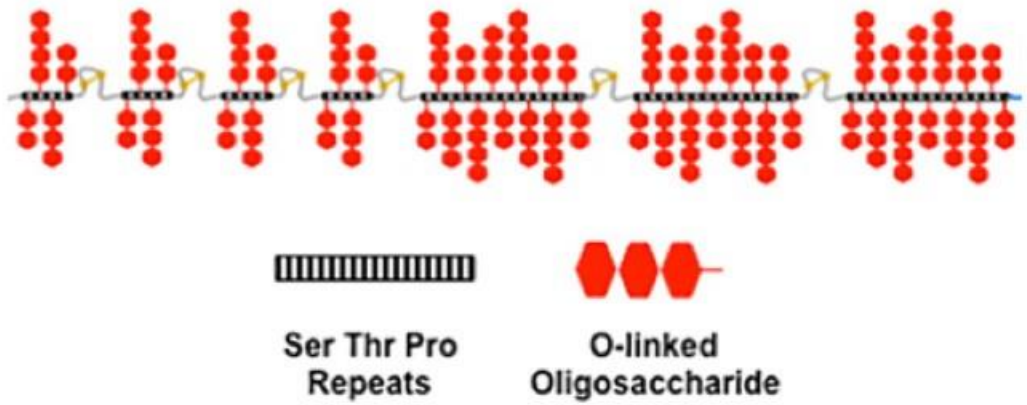


Mediated by MARCKS:
a switch for mucus secretion

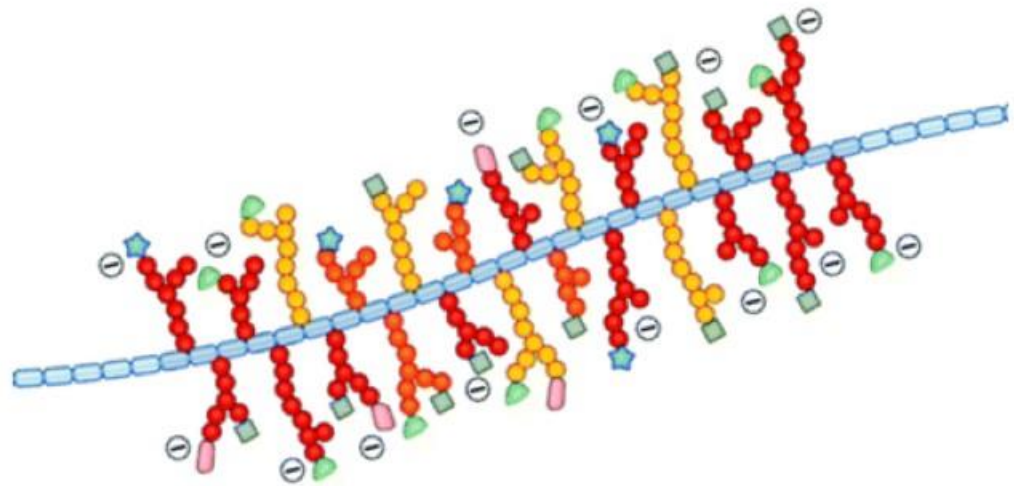
Am J Respir Cell Mol Biol. 2006 May;34(5):527-36.

Structure of mucin

- **Core protein**
  - ✓ A linear protein core with a **serine/threonine-rich tandem repeat** region, where **oligosaccharides** are attached via **O-glycosidic linkages**.



Core protein (Backbone protein)

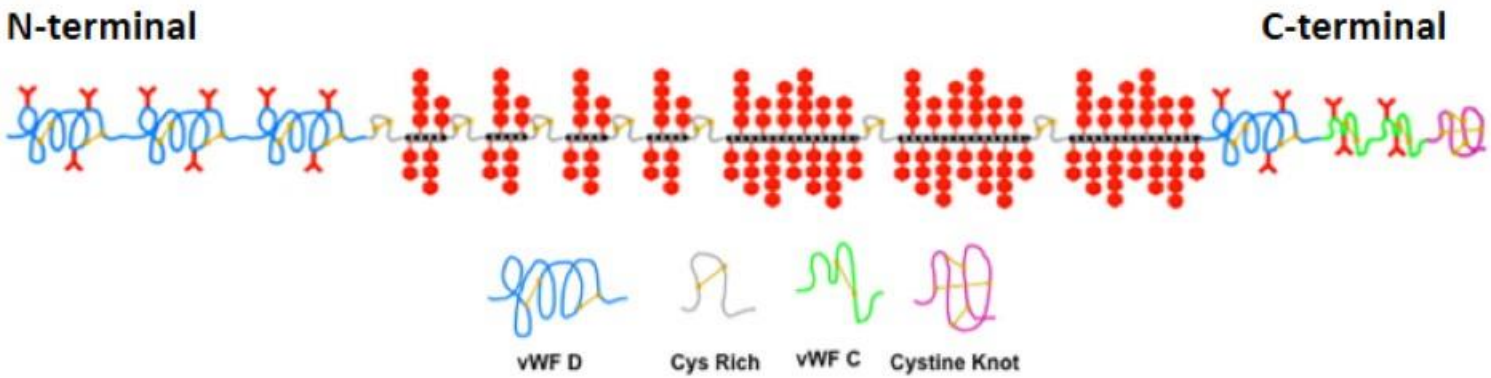


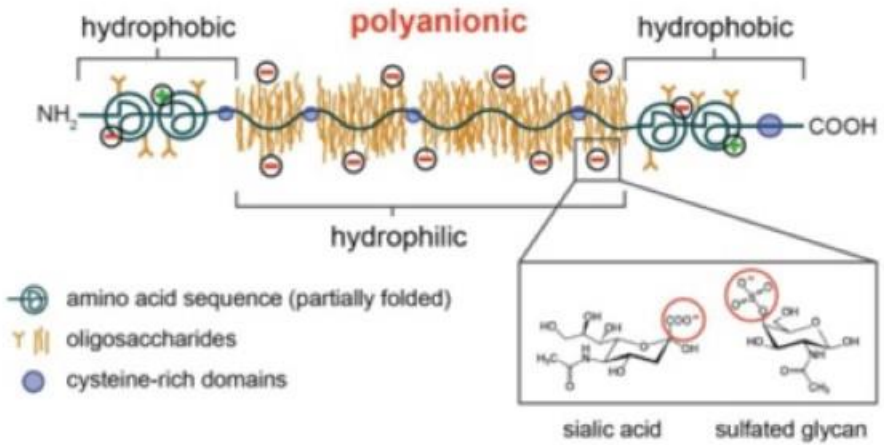
Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.; Biomater Sci. 2018 Aug 21;6(9):2282-2297.

Structure of mucin

- **N-terminal**
  - ✓ **Von Willebrand factor-like D-domain (vWF-D)**, Cys-rich domain

- **C-terminal**
  - ✓ vWF-D, vFW-C, **Cystine-knot domain (CK-domain, SS-bond of Cysteine residue)**

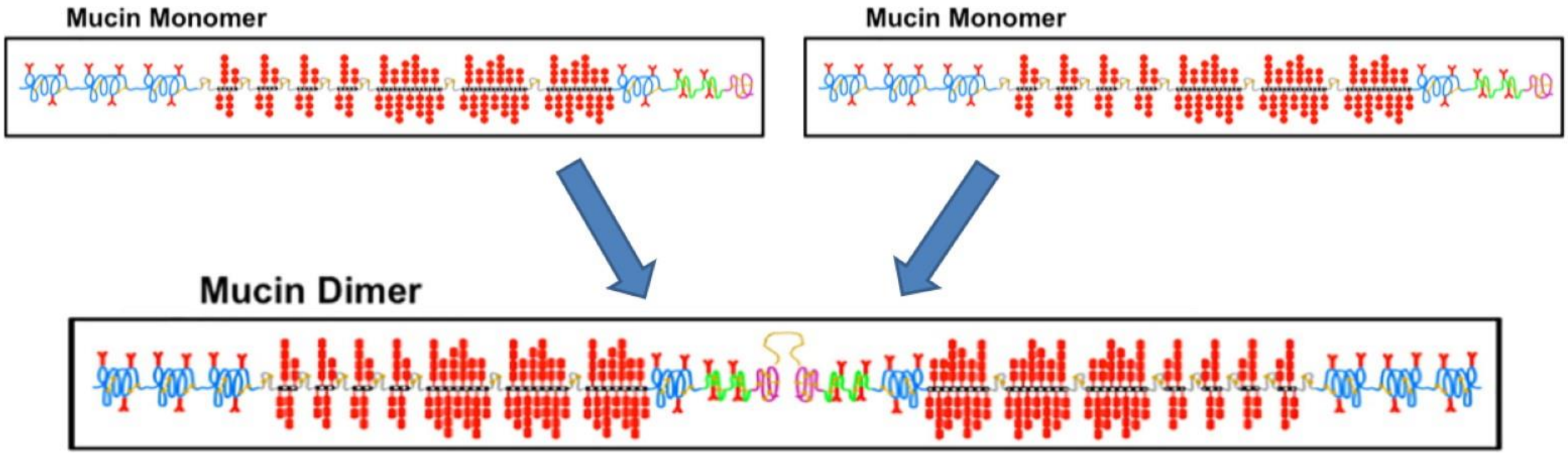




Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.; Colloids Surf B Biointerfaces. 2020 Mar:187:110614.

Mucin dimerization

- **Mucin monomer → Dimer via C-terminal SS bonds of cysteine groups**

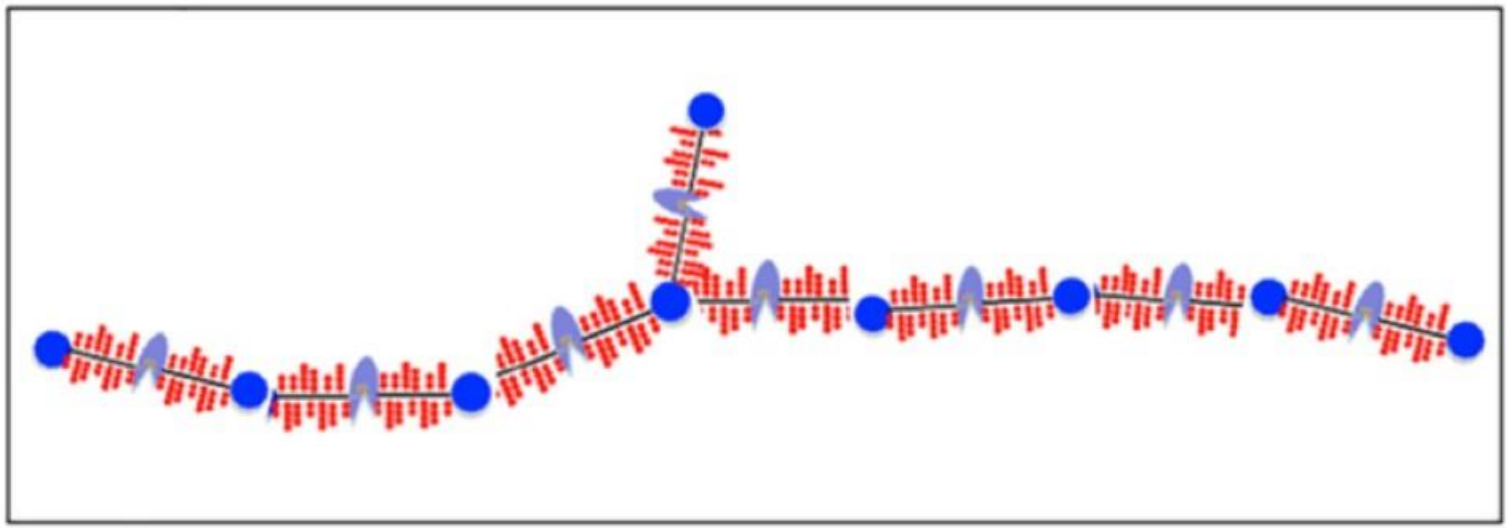


Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.

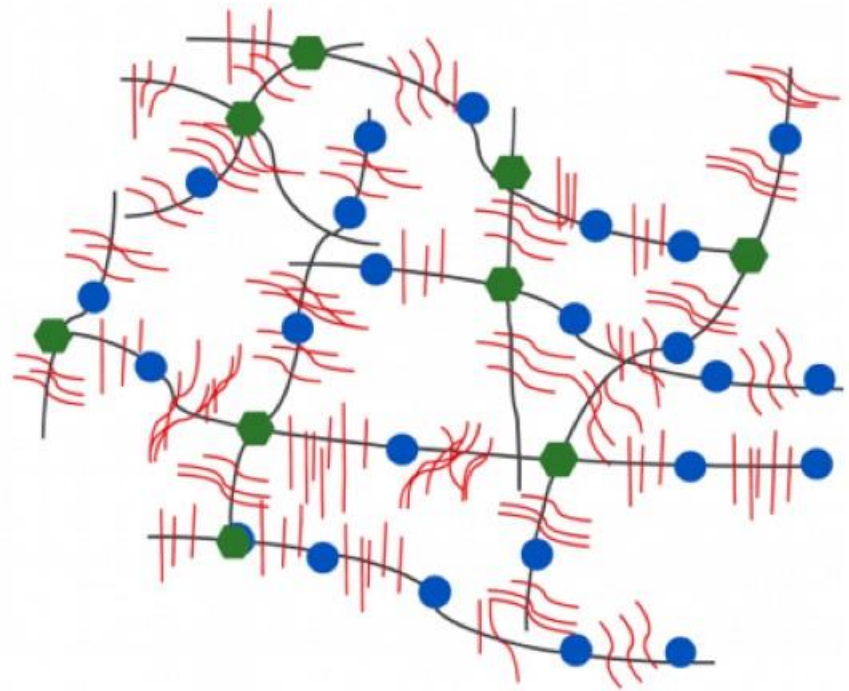
Mucin polymerization

- **Mucin polymer via N-terminal polymer branch**

Mucin multimer



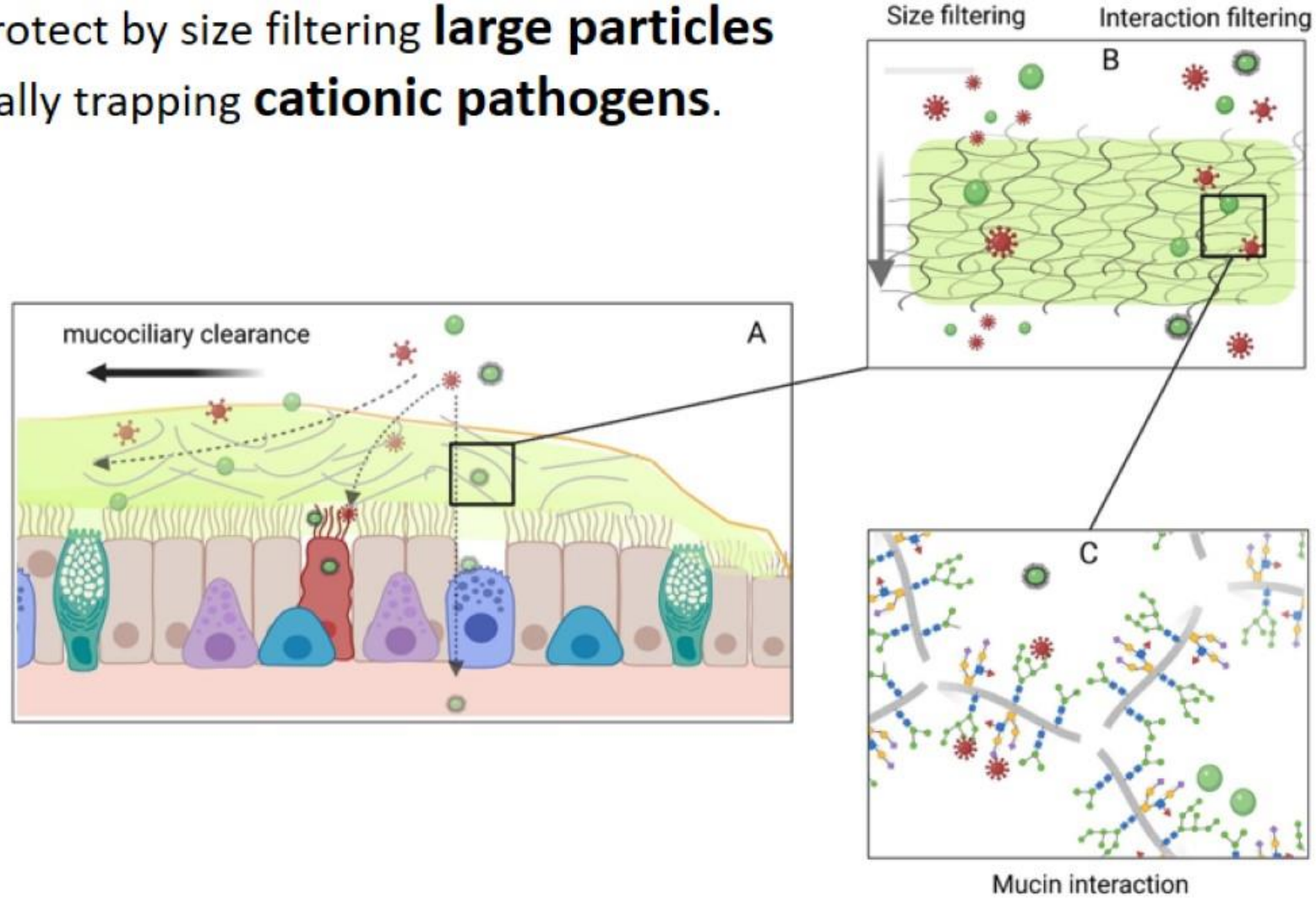
Mucin gel



Front Immunol. 2013 Oct 10:4:310.
Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.

Mucin polymer is a meshwork as a barrier

- Airway mucins protect by size filtering **large particles** and electrostatically trapping **cationic pathogens**.



Int J Pharm. 2023 Mar 5:634:122661.

Two subtypes of mucin

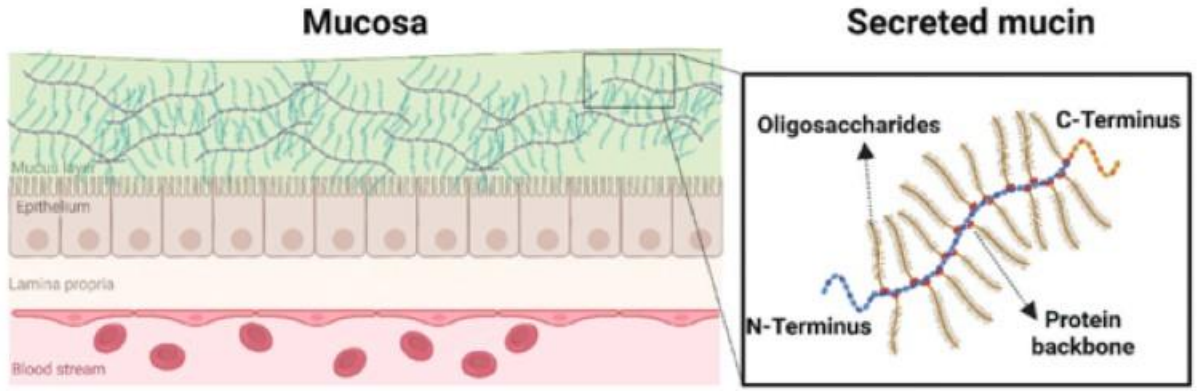
- **Secreted mucins**
  - Forming mucus gel & not membrane-bound
  - Provide **physical barrier** and enable **mucociliary clearance**

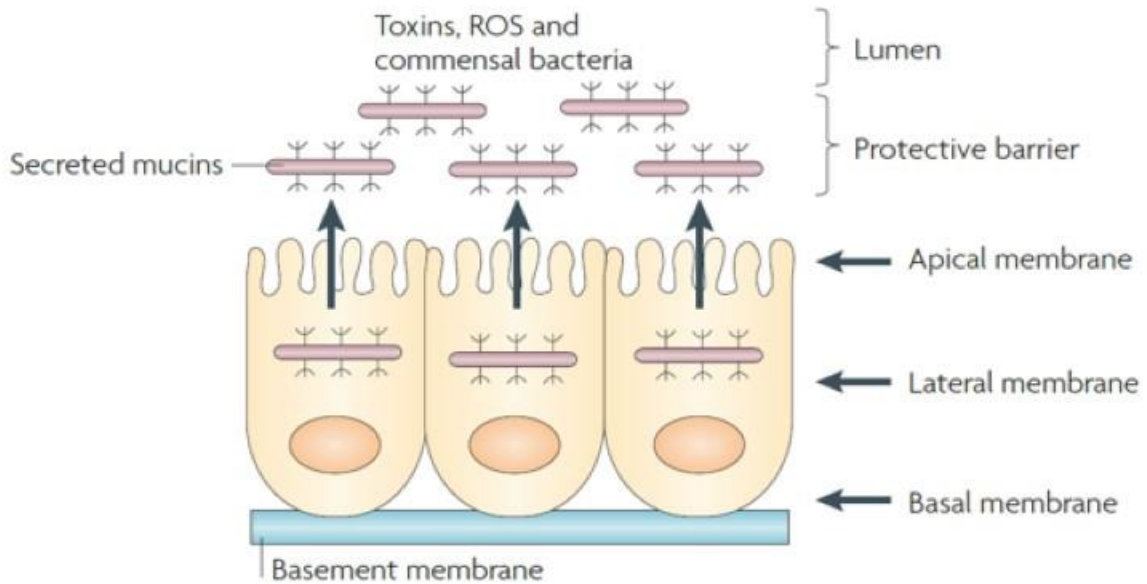
✓ **Types**

: **Gel-forming** / Nongel-forming type

✓ **MUC(=Mucin) gene / protein**

: MUC2, **MUC5AC, MUC5B**, MUC6, MUC7, MUC8, MUC9, and MUC19





Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.
Nat Rev Cancer. 2009 Dec;9(12):874-85.

Determinant of mucus characteristics

- Dominant **secreted mucins** in airway: **MUC5B** and **MUC5AC** mucins

MUC5B: Protective mucin

✓ Contributes to **gel formation**, maintaining structural **stability** and effective **mucus clearance**

✓ **Deceased proportion** → **Decreased airway protection and mucus clearance**

MUC5AC: Disease-related mucin

✓ Increases the **viscoelastic** properties of mucus, making it **thicker** and more **difficult to clear**

✓ **Increased proportion** → **Excessive mucus production** and **high viscosity of mucus**

Am J Respir Crit Care Med. 2022 Nov 1;206(9):1055-1057.
Physiol Rev. 2022 Oct 1;102(4):1757-1836.

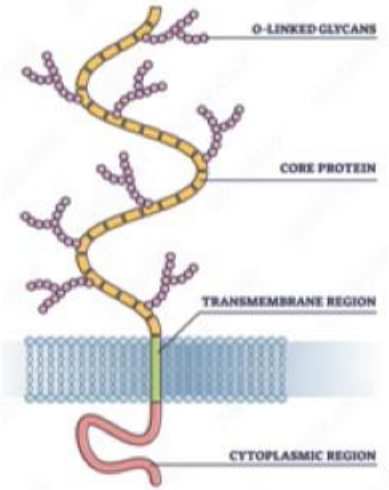
Two subtypes of mucin

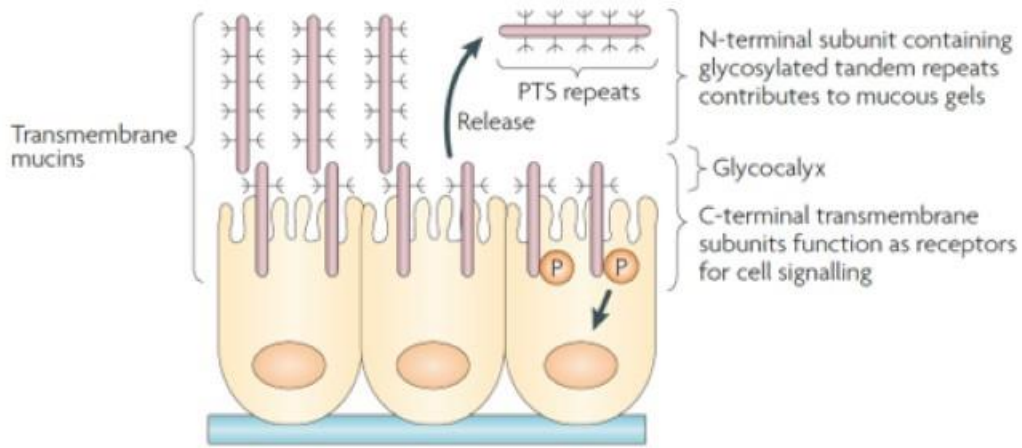
- **Transmembrane mucins**
  - Anchored to the cell membrane with extracellular, transmembrane, and cytoplasmic domains
  - Involved in **cell signaling,** **immune modulation**, and **pathogen interference**

✓ **MUC gene / protein**

: **MUC1**, MUC3, MUC4, MUC11/12, MUC13, MUC14, MUC15, MUC16, MUC17, MUC20, MUC21, and MUC22

Transmembrane mucin

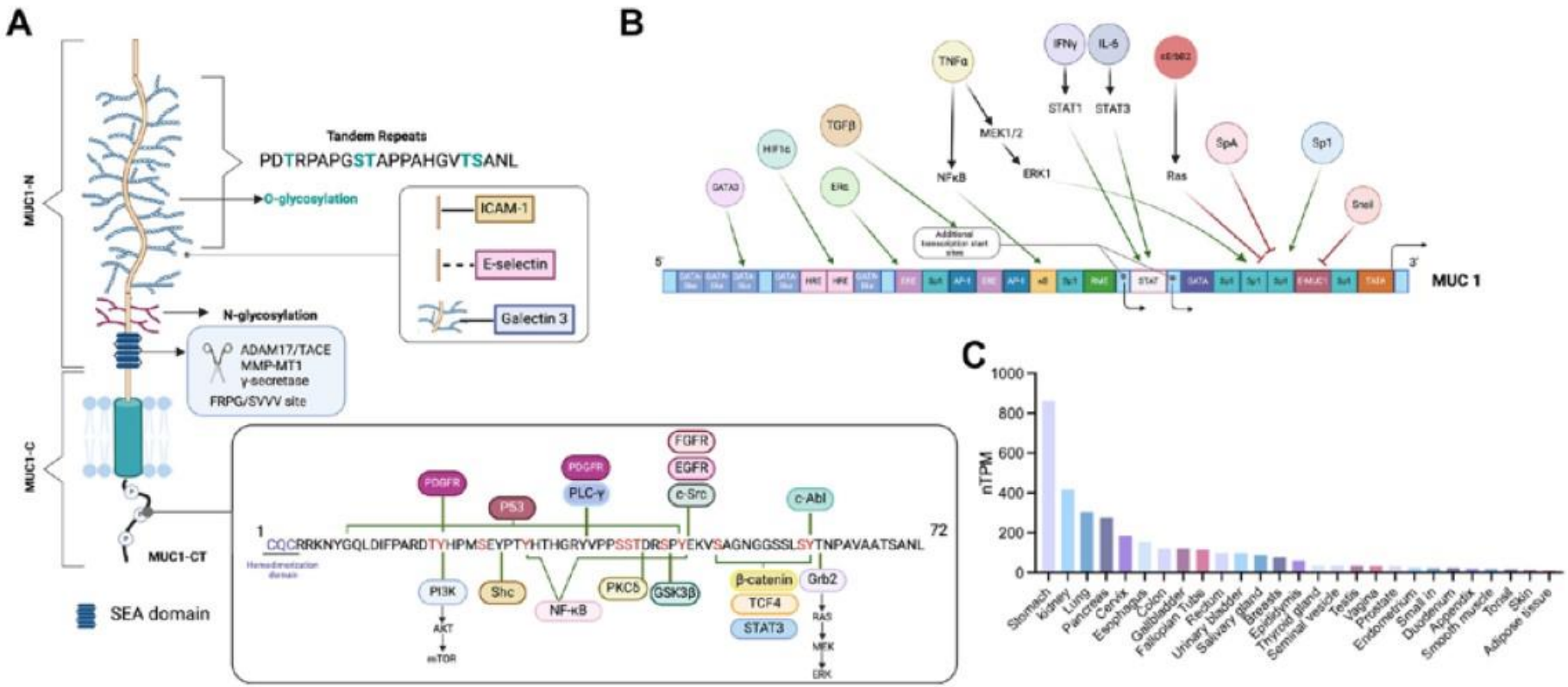




Adv Drug Deliv Rev. 2018 Jan 15:124:3-15.; Nat Rev Cancer. 2009 Dec;9(12):874-85.

MUC1 expression and functional role of CT

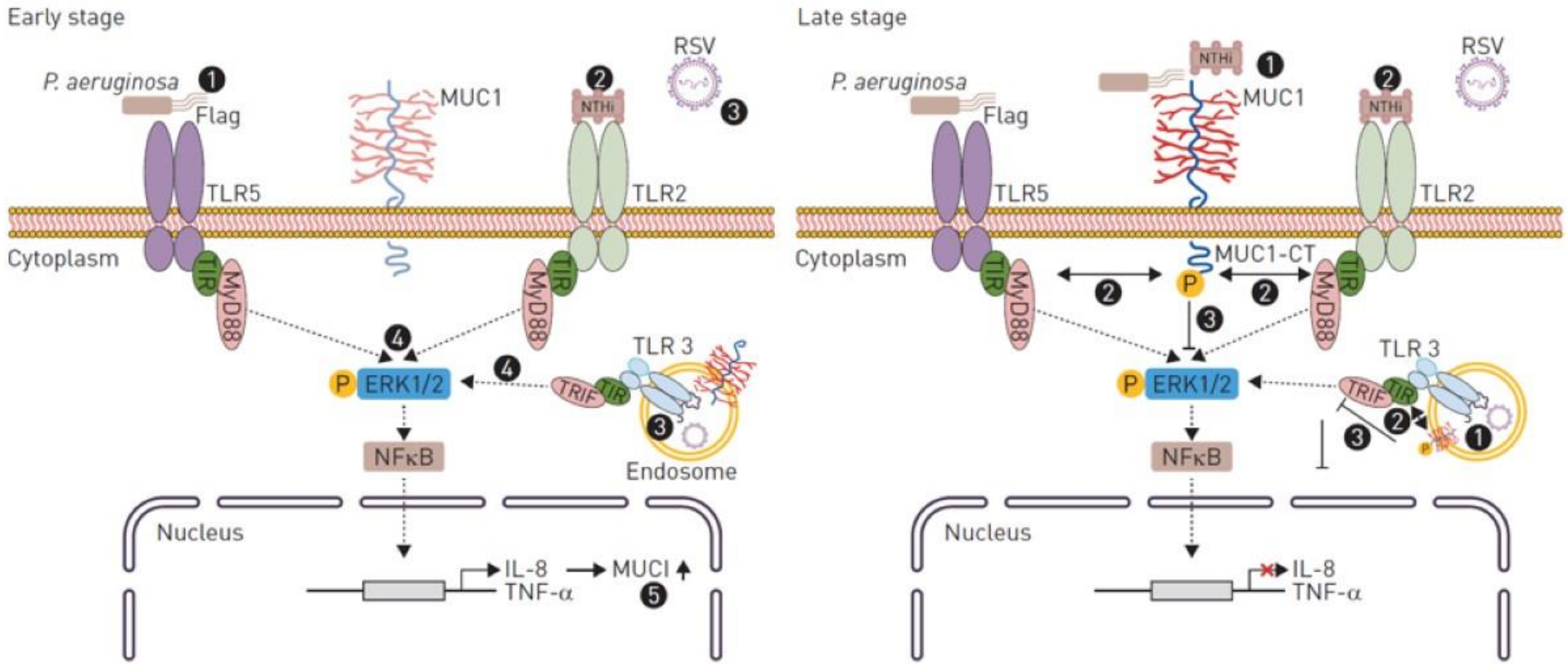
- **MUC1** is highly expressed in the lung, and its **cytoplasmic tail (CT)** interacts with various signaling proteins, **regulating cellular signaling** in a phosphorylation-dependent manner.



Physiol Rev. 2025;105(4):2233-2304

MUC1 regulates airway inflammation

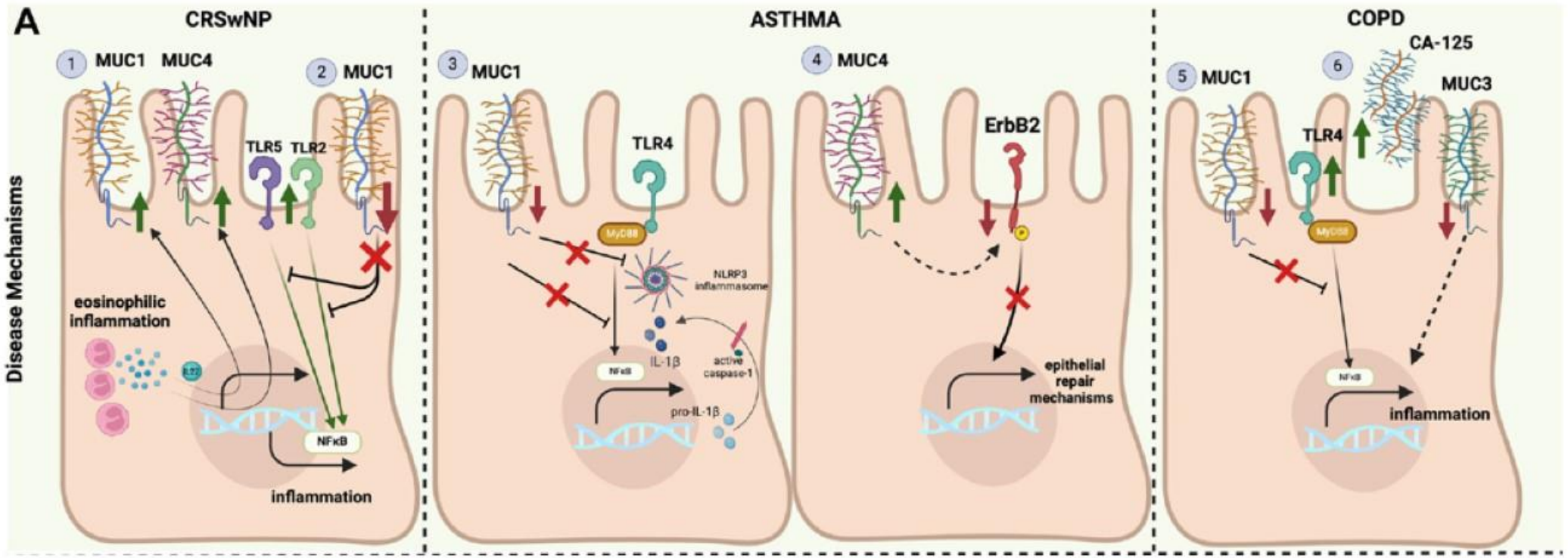
- The role of **MUC1** in airway infection/inflammation: **Regulating excessive inflammation**



Eur Respir Rev. 2021 Feb 3;30(159):200149.

MUC1 and chronic airway disease

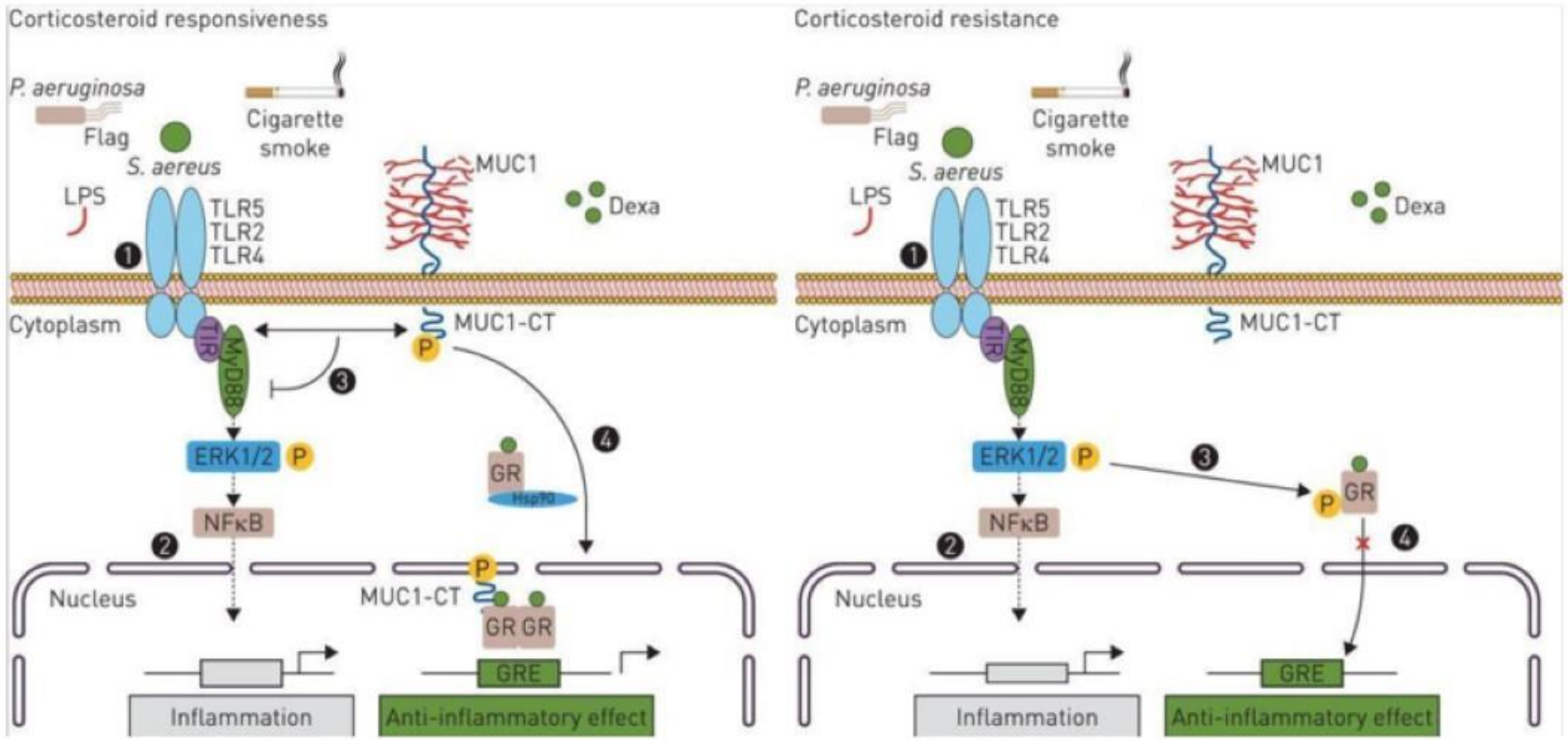
- Altered expression of transmembrane mucins (MUC1, MUC3, MUC4) disrupts anti-inflammatory and repair mechanisms via TLR and ErbB2 signaling, contributing to inflammation.



Physiol Rev. 2025;105(4):2233-2304

MUC1 and corticosteroid resistance

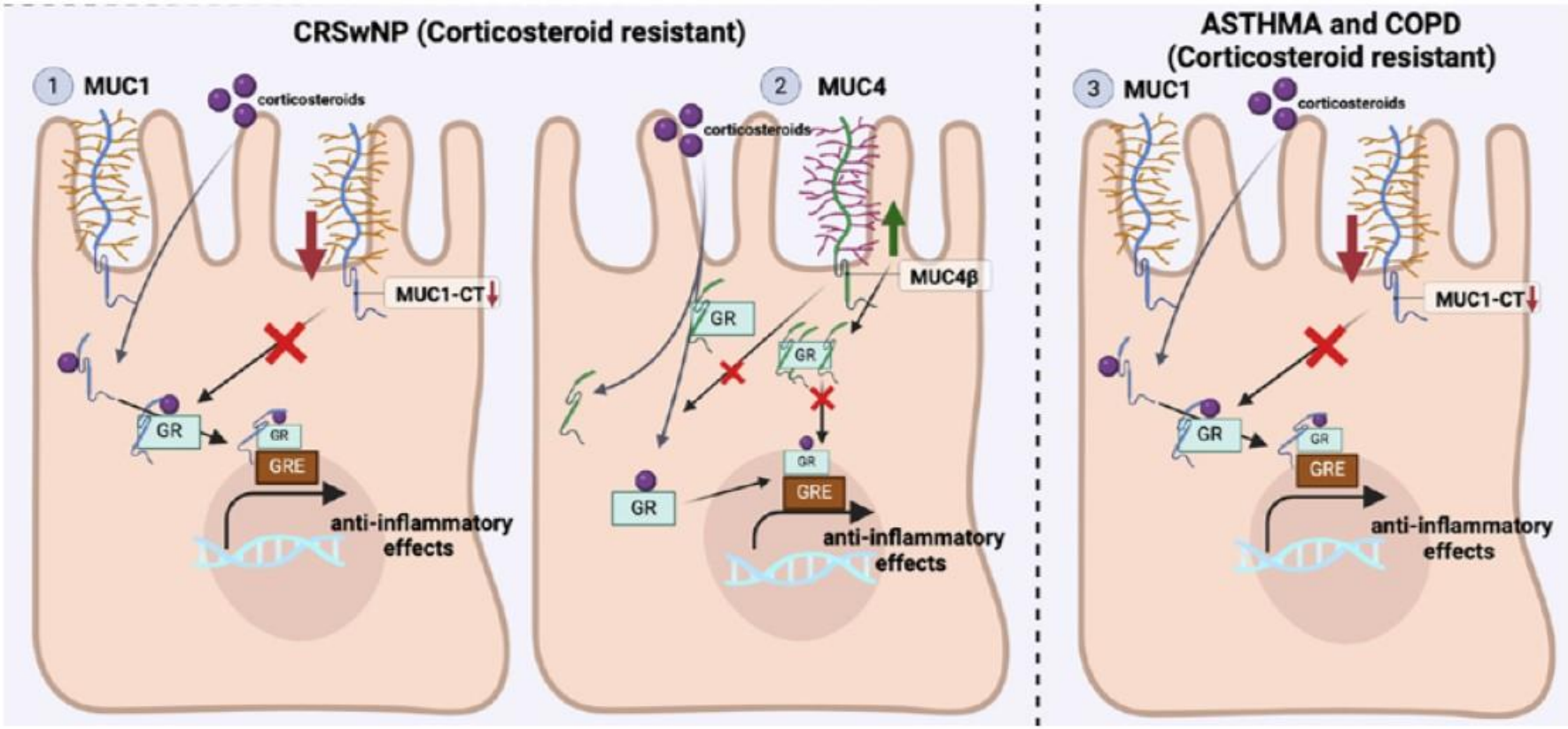
- Phosphorylated MUC1-CT enhances GR-mediated anti-inflammatory signaling in corticosteroid-responsive states, while its absence in resistance impairs GRE activation despite GR presence.



Eur Respir Rev. 2021 Feb 3;30(159):200149.

MUC1/4 and corticosteroid resistance

- Reduced MUC1-CT or increased MUC4β structural variant impairs GR–GRE–mediated anti-inflammatory signaling, contributing to corticosteroid resistance in CRSwNP, asthma, and COPD.



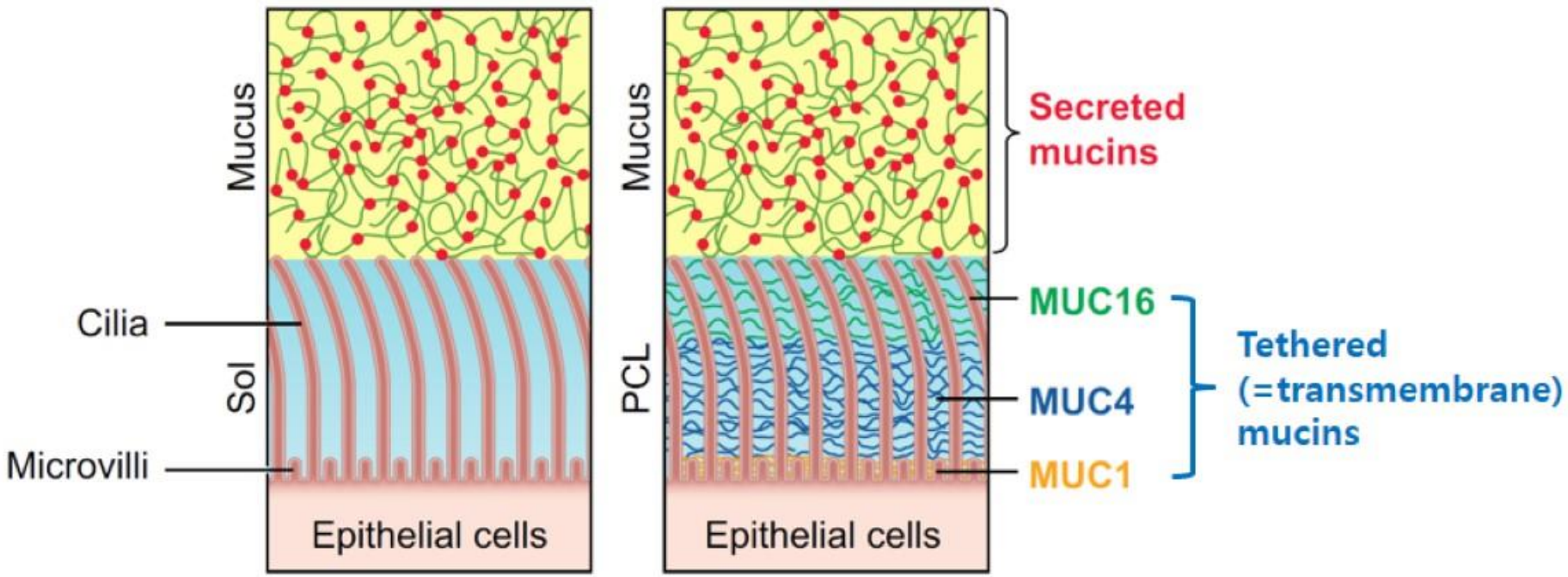
Physiol Rev. 2025;105(4):2233-2304

Structure of airway surface liquid (=mucus)

- **"Gel-on-brush"**

  The periciliary layer ("brush") is a thin liquid layer close to epithelial cells where cilia operate.

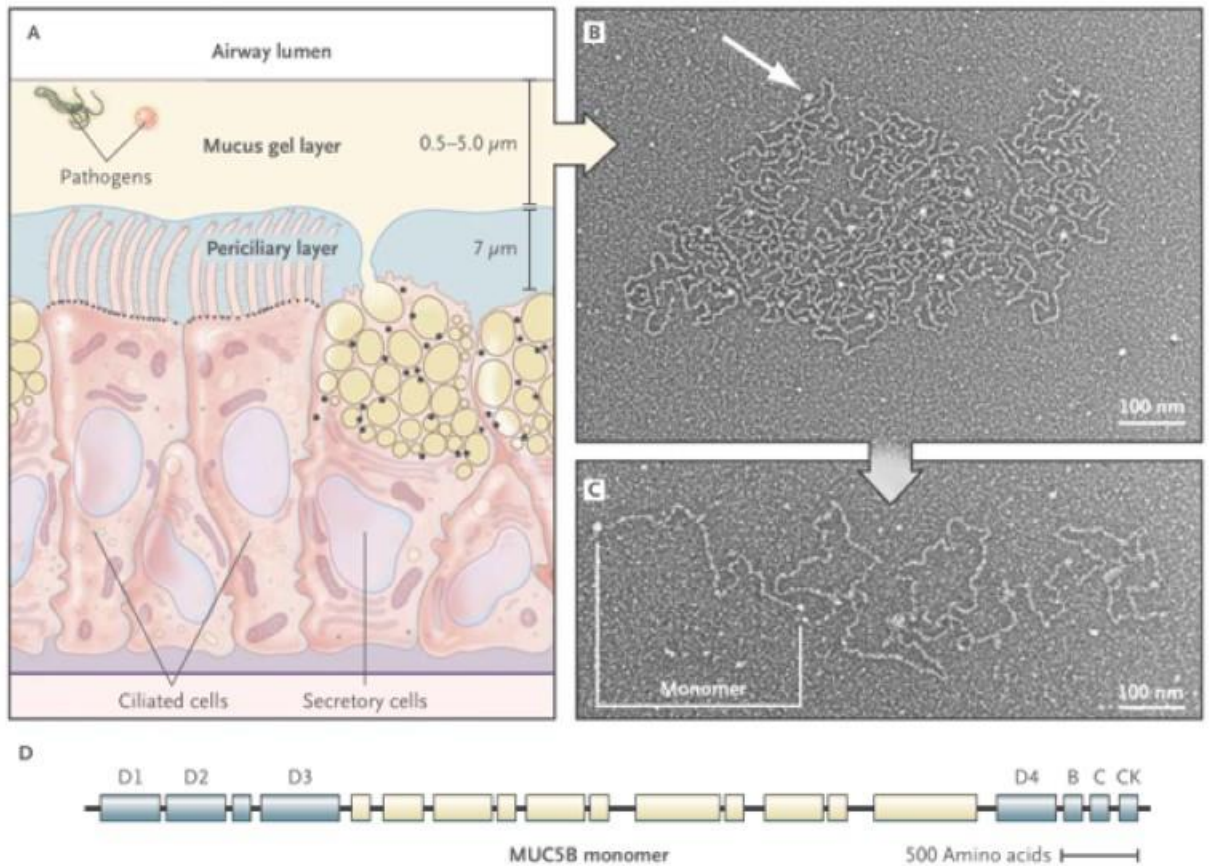
  A thicker "gel" layer above it traps pathogens, which are eliminated by immune cells.



Am J Respir Crit Care Med. 2022 Nov 1;206(9):1055-1057.
Physiol Rev. 2022 Oct 1;102(4):1757-1836.
Crit Care. 2025 Feb 7;29(1):68.

Mucus gel layer

- Airway surface liquid consists of a **mucus gel layer** and periciliary layer, with **MUC5B polymers** forming its **structural backbone through N–N and C–C terminal polymerization**.



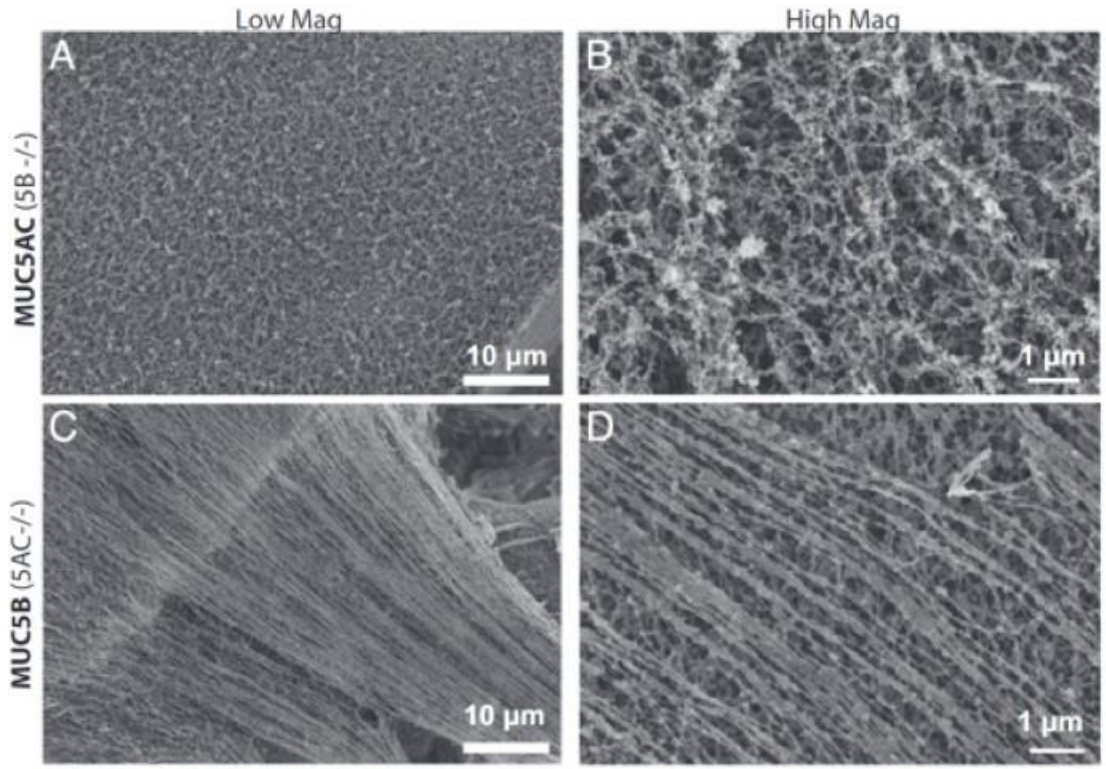
N Engl J Med. 2010 Dec 2;363(23):2233-47.

Difference between secreted mucins

- **Difference** between **MUC5B** and **MUC5AC** mucins

  1) Structure

  - MUC5B: Linear network
  - MUC5AC: Tightly organized & branched ➔ More rigid / viscoelastic/ hydrophobic



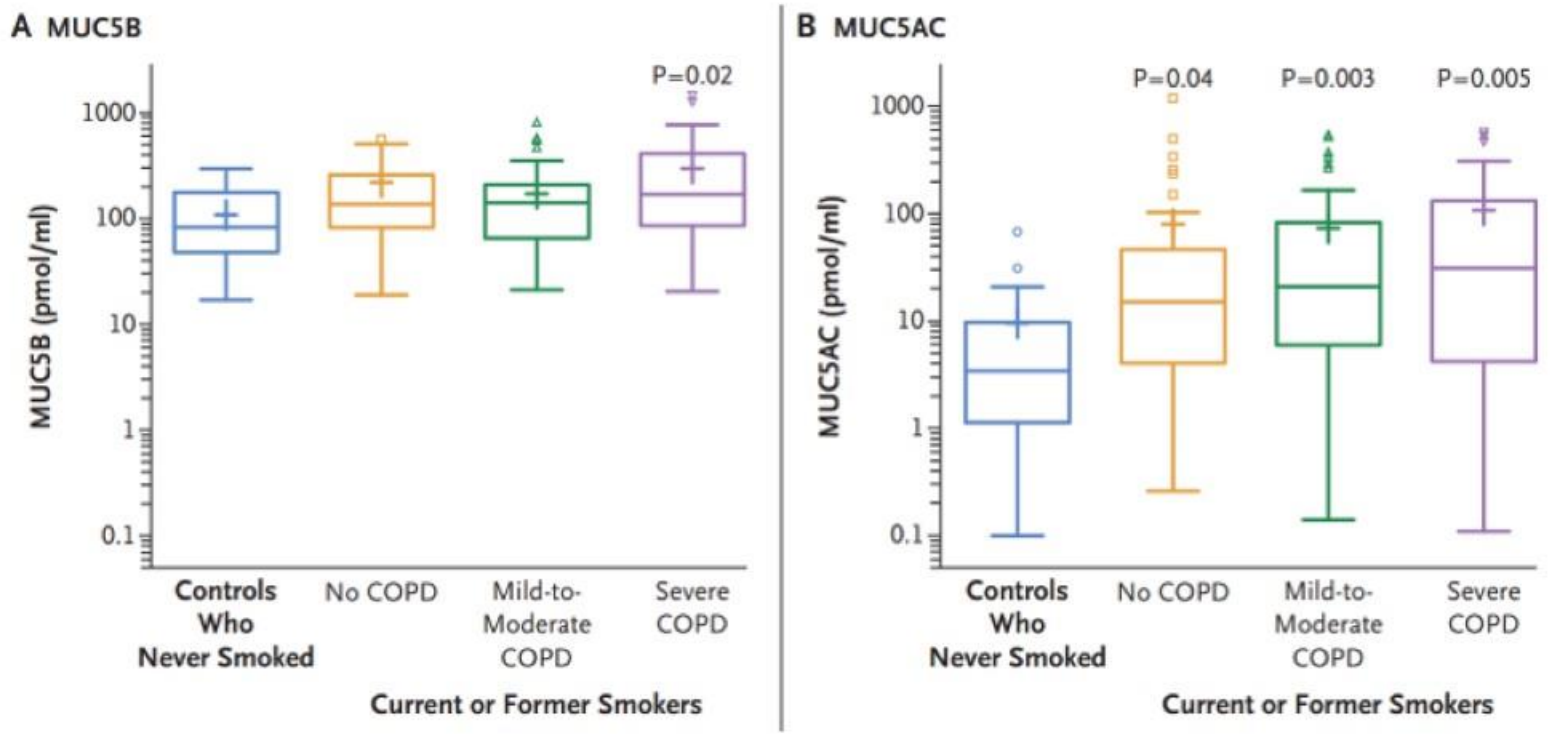
Proc Natl Acad Sci U S A. 2021 Sep 28;118(39):e2104490118

Difference between secreted mucins

- **Difference** between **MUC5B** and **MUC5AC** mucins

  2) Function

  - MUC5B: Lung homeostasis and defense
  - MUC5AC: Allergic airway response / mucus plugging



In **healthy** status,
MUC5B >> MUC5AC

In **diseased** status,
MUC5AC >> MUC5B

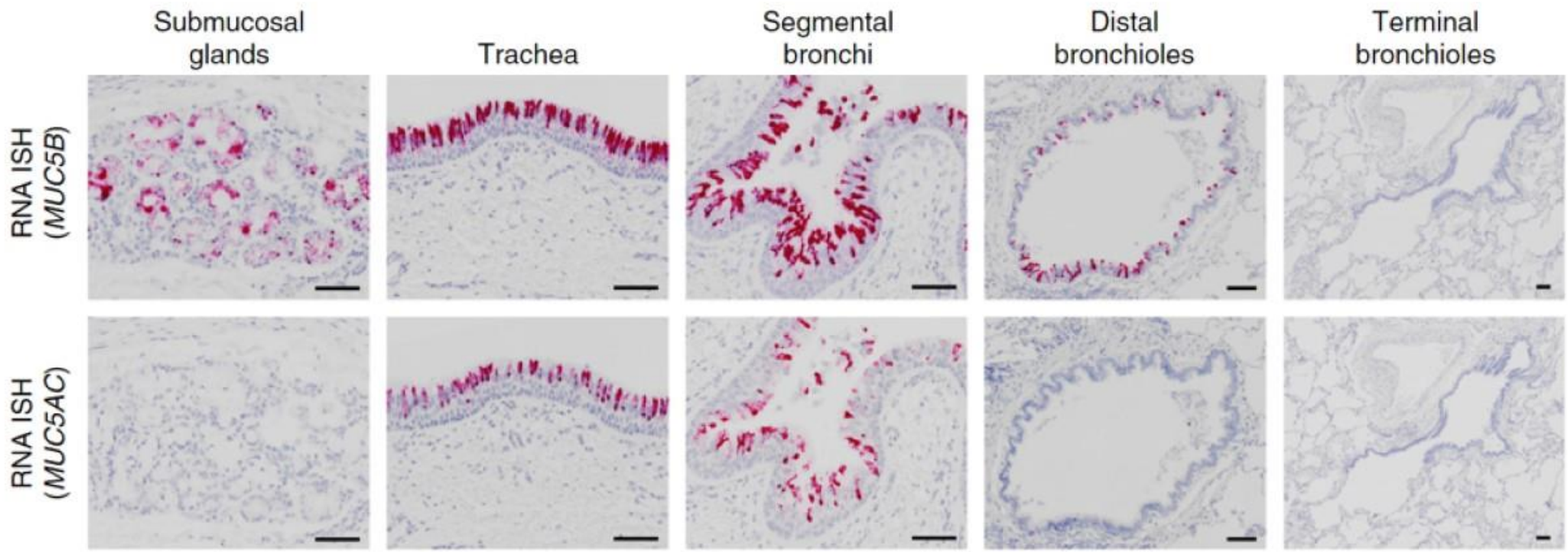
N Engl J Med. 2017 Sep 7;377(10):911-922.

Difference between secreted mucins

- **Difference** between **MUC5B** and **MUC5AC** mucins

  3) Regional distribution

  - MUC5B: Mainly submucosal gland in Trachea / Bronchi / Bronchiole
  - MUC5AC: Only superficial epithelium (Goblet cell) in Trachea / Bronchi



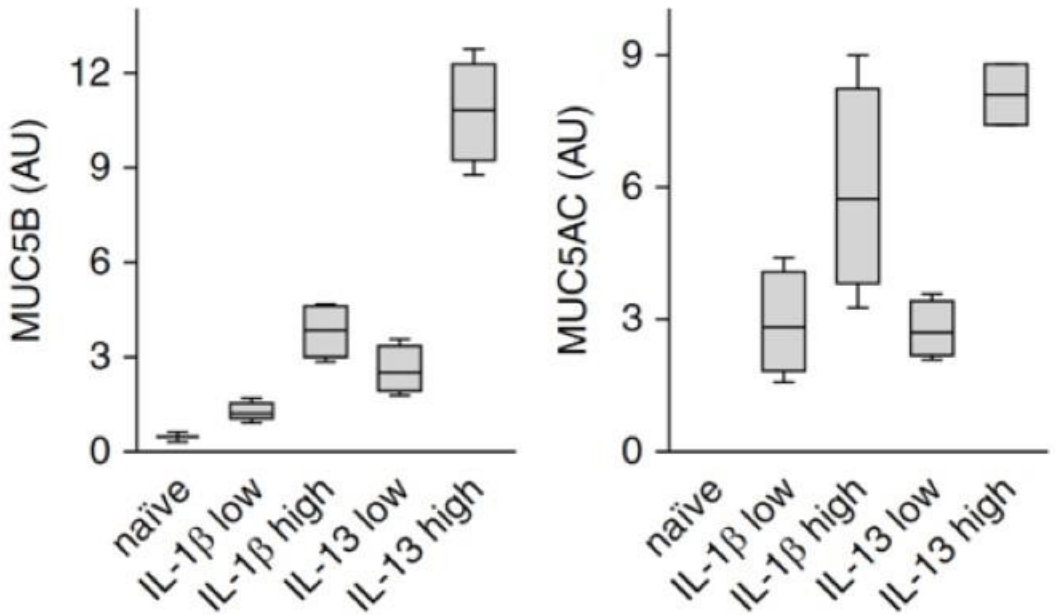
Am J Respir Crit Care Med. 2019 Mar 15;199(6):715-727.

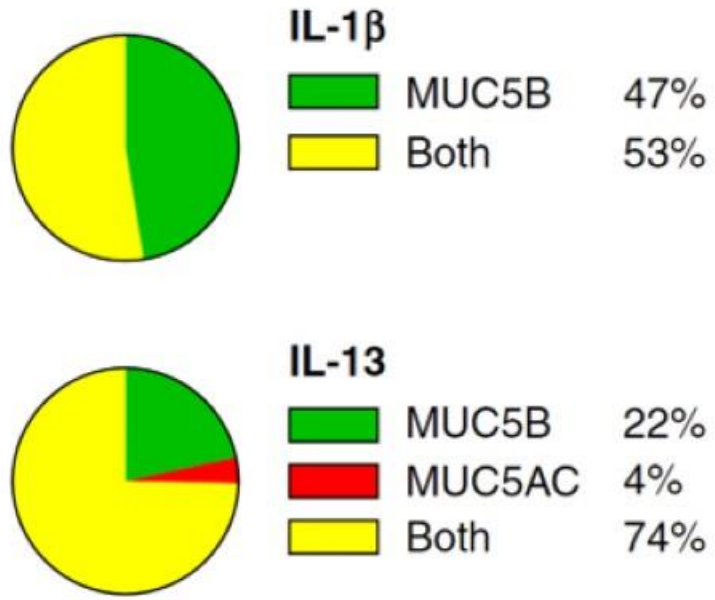
Difference between secreted mucins

- **Difference** between **MUC5B** and **MUC5AC** mucins

  4) Stimulated cytokines (for production)

  - MUC5B: IL-1β & IL-13
  - MUC5AC: IL-13 > IL-1β





Am J Respir Crit Care Med. 2022 Jul 1;206(9):1081–1095.

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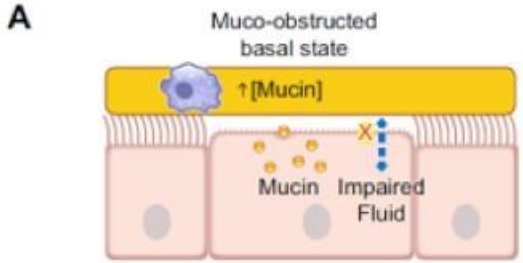
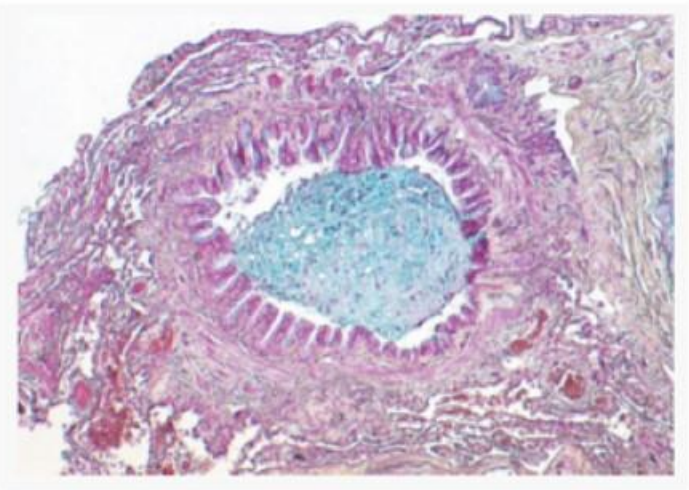
Pathogenesis of mucus dysfunction in bronchiectasis

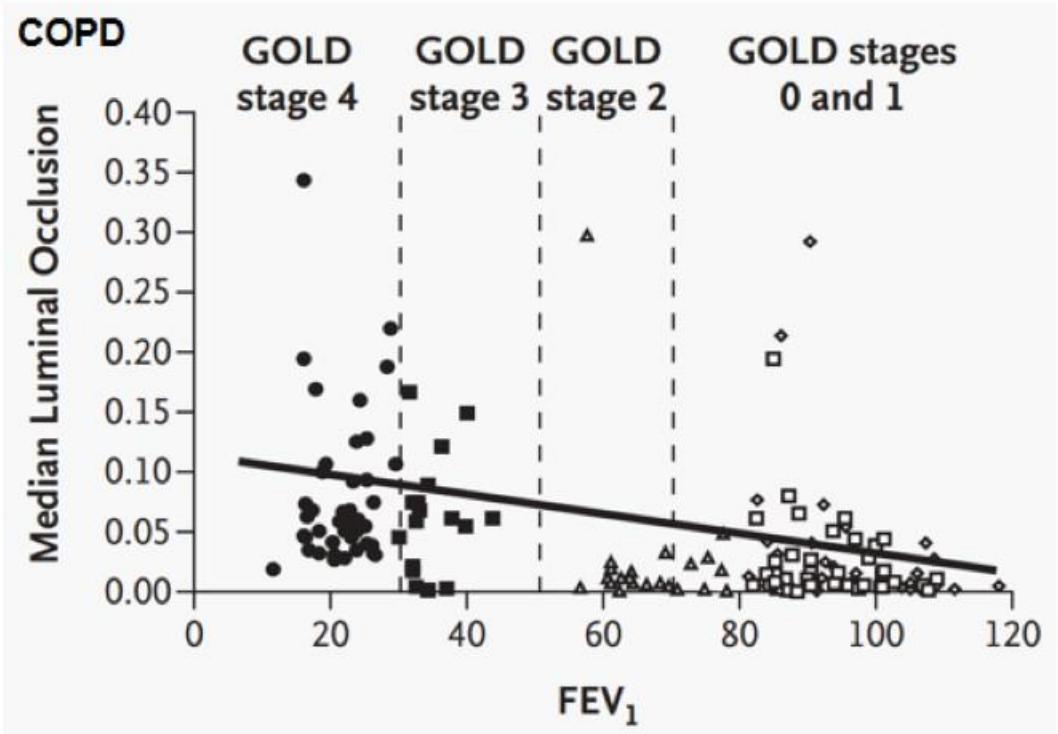
- **Abnormal mucin overproduction**
- **Abnormal osmolarity control**

Pathogenesis 1) abnormal mucin overproduction



Chronic airway injury produces a **muco-obstructed epithelium with impaired secretion clearance**



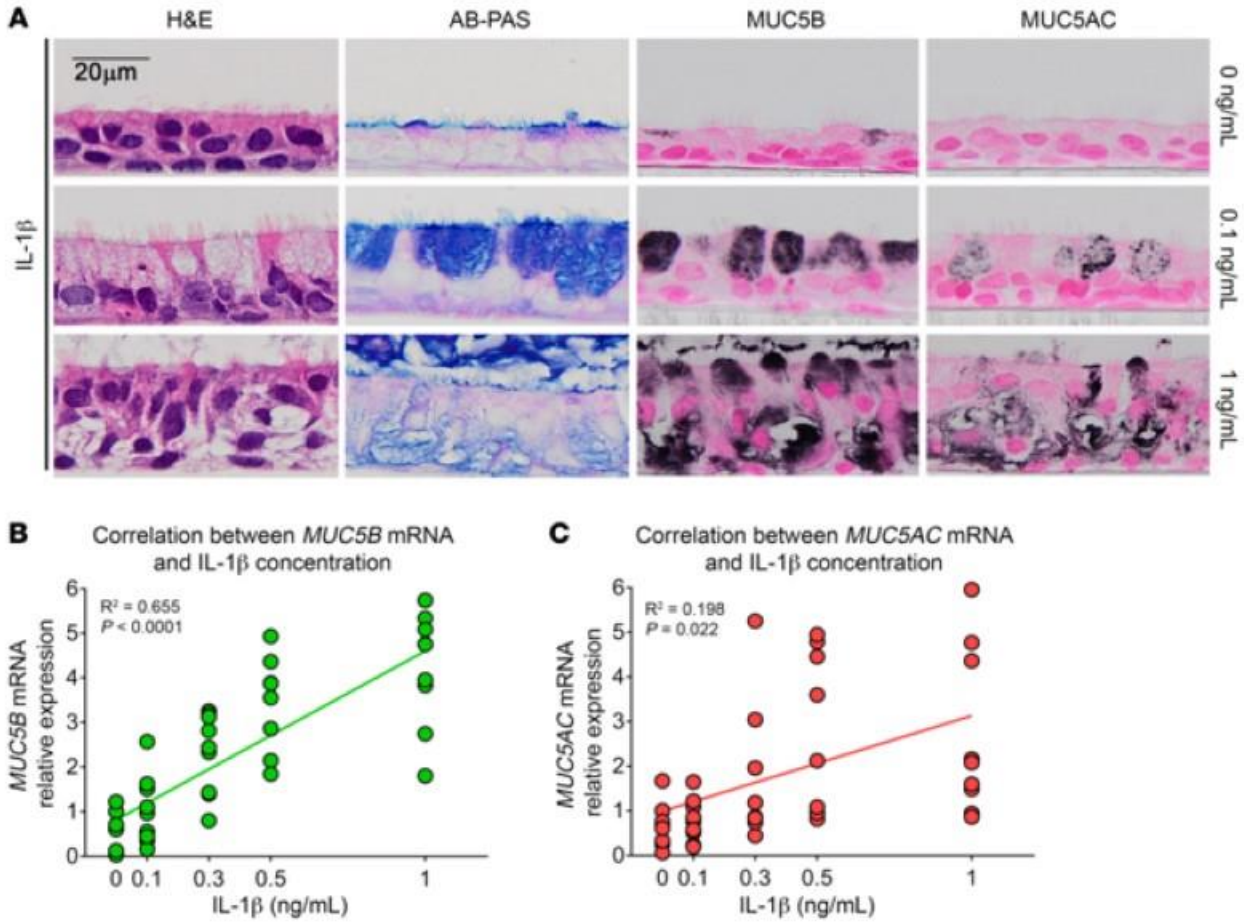


Bronchiectasis	FEV_1 (% *Predicted*)
Solids, %	−0.22 (−0.43 to −0.01)*
Total mucins, μg/ml	−0.08 (−0.29 to 0.13)
MUC5AC/MUC5B	−0.43 (−0.74 to −0.12)*
Sputum volume, g	−0.20 (−0.40 to 0.002)
Osmotic pressure, Pa	−0.01 (−0.22 to 0.21)
Complex viscosity, Pa · s	0.08 (−0.16 to 0.31)

N Engl J Med. 2004 Jun 24;350(26):2645-53
Am J Respir Crit Care Med. 2020 Mar 15;201(6):661-670.
Physiol Rev. 2022 Oct 1;102(4):1757-1836.

T1 inflammatory cytokines and mucin expression

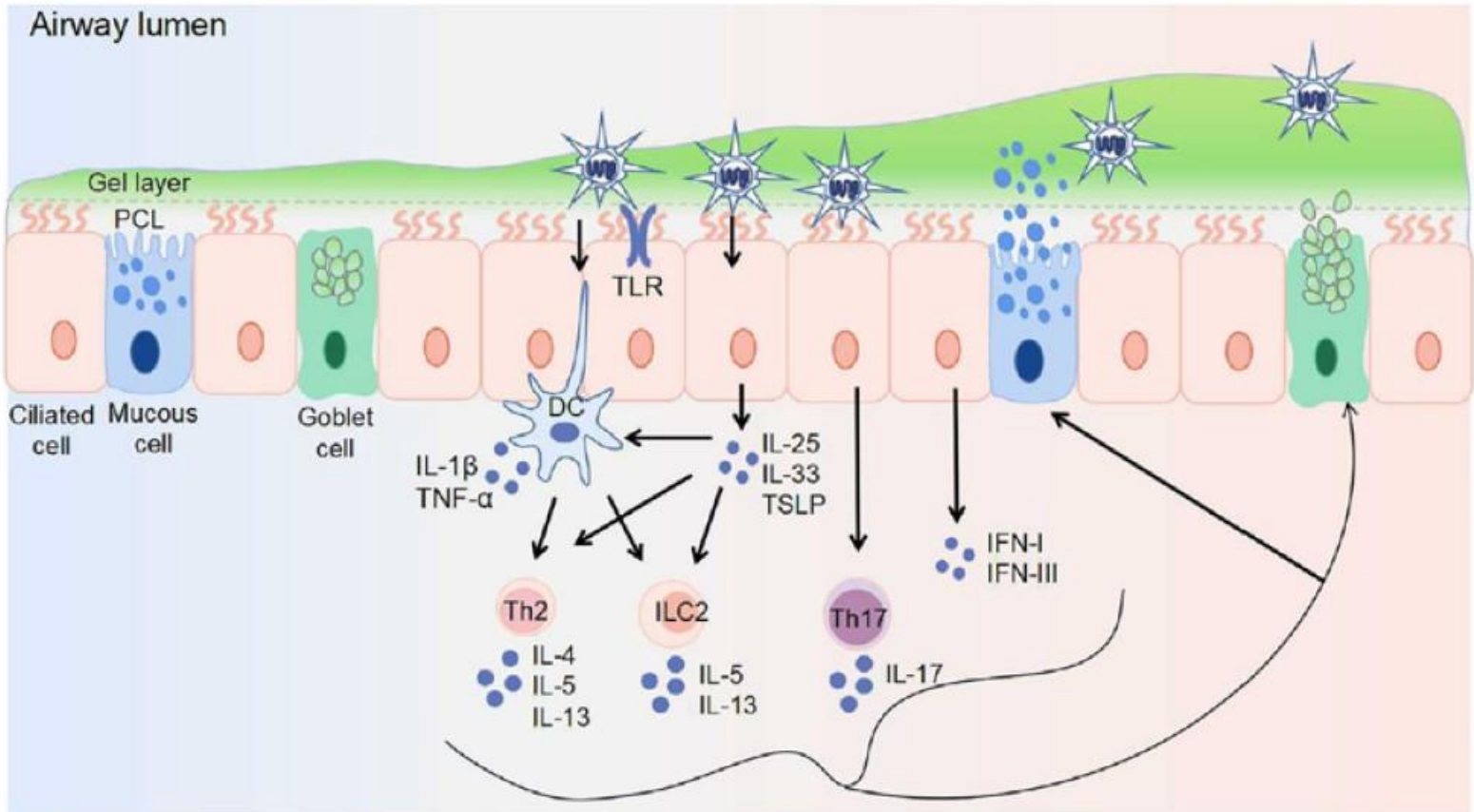
- In CF, **IL-1β strongly** induces **MUC5B** expression, while **MUC5AC** expression increases **modestly**.



J Clin Invest. 2019 Oct 1;129(10):4433-4450

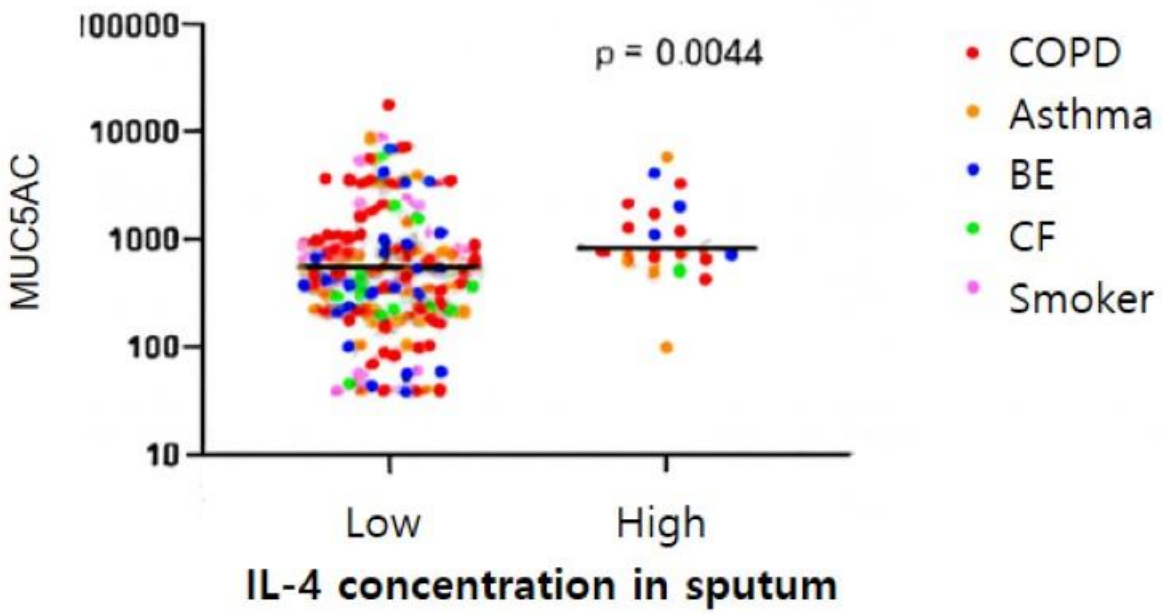
T2 inflammatory cytokines and mucin expression

- **Virus invasion** can induce abnormal airway mucus secretion through T2 inflammation



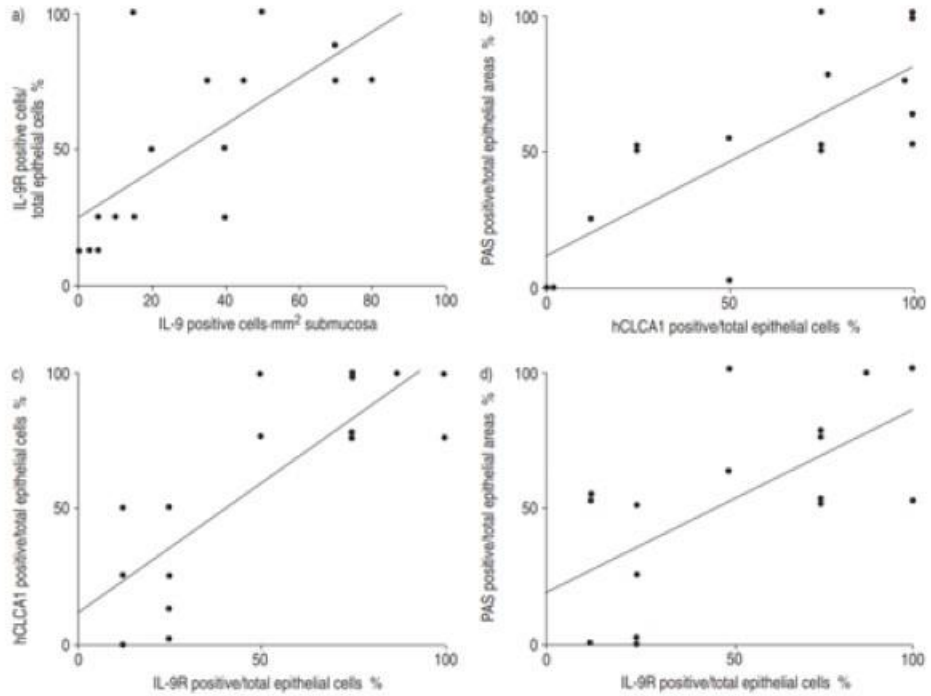
Front Immunol. 2021 Sep 28:12:701443

IL-4 & IL-9 increases expression of MUC5AC



Eur Respir J. 2022 60(suppl 66): 2958

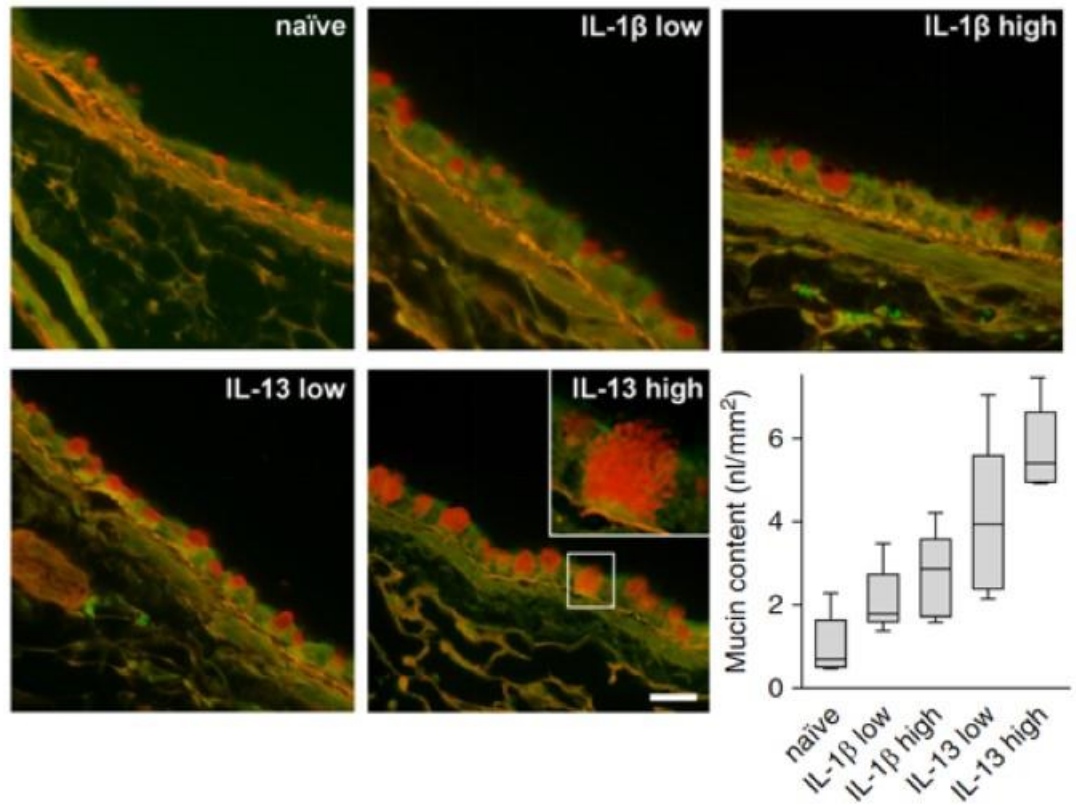
- **IL-9 ➔ hCLCA1 (Cl- channel)↑ ➔ MUC5AC ↑ ➔ Mucus overproduction in CF**



Eur Respir J. 2004 Jun;23(6):846-50.

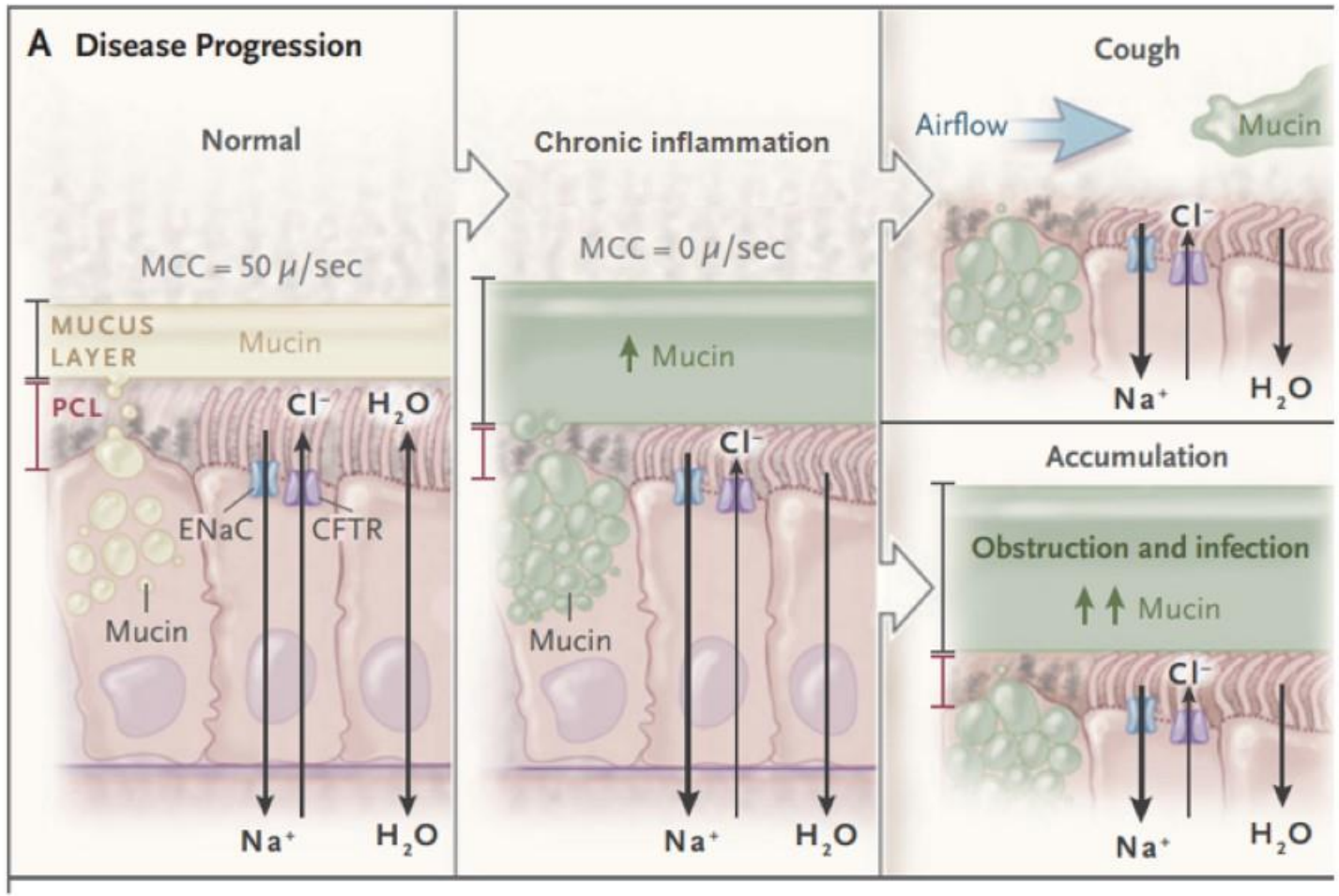
IL13 increases expression of MUC5AC

- In mouse airways, IL-1β and IL-13 differentially regulate MUC5B and MUC5AC expression with **high-dose IL-1β strongly inducing MUC5B** and **IL-13 favoring MUC5AC**



Am J Respir Crit Care Med. 2022 Jul 1;206(9):1081–1095.

Pathogenesis 2) abnormal osmolarity control



Modified from N Engl J Med. 2017 Sep 7;377(10):911-922.

Determinant of mucus osmolarity

- **Mucus osmolarity controlled by**

  ENaC (Na channel) & **CFTR** (Cl channel)

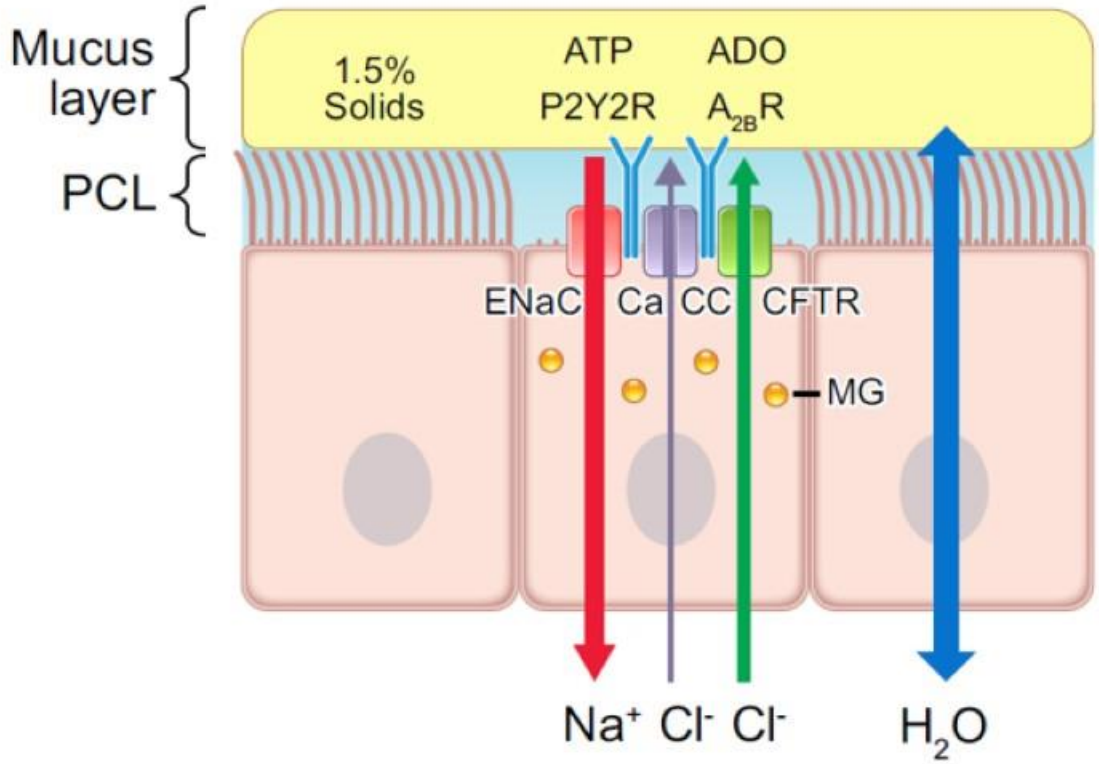
  Activated ENaC / Inactivated CFTR

  ➔ Decreased H_2O transport

  ➔ Increased mucin (mucus)

  & Increased osmolality of mucus layer

  (= Sticky mucus)



Am J Respir Crit Care Med. 2022 Nov 1;206(9):1055-1057.
Physiol Rev. 2022 Oct 1;102(4):1757-1836.

Strategy for mucociliary clearance

- **Activated ENaC / Inactivated CFTR**
  - ➔Imbalance of ion/fluid transport: Less H2O in mucus
  - ➔Accumulation of sticky mucus
  - ➔Inefficient mucociliary clearance

- **Treatment**
  1) Airway clearance ➔ Airway clearance technique
  2) Direct hydration (humidification) ➔ Hypertonic or isotonic saline / Mannitol inhalation
  3) Decrease viscosity ➔ Muco-active agents
  4) Inactivate ENaC ➔ ENaC inhibitor (Amiloride)
  5) Activate CFTR ➔ CFTR modulator [corrector/potentiator] (Elexacaftor-Tezacaftor-Ivacaftor)

Contents

- Structure and function of mucin
- Pathogenesis of mucus dysfunction
- **Osmotic agents for airway clearance**
- Muco-active agents
- Summary

Treatment for improving mucociliary clearance

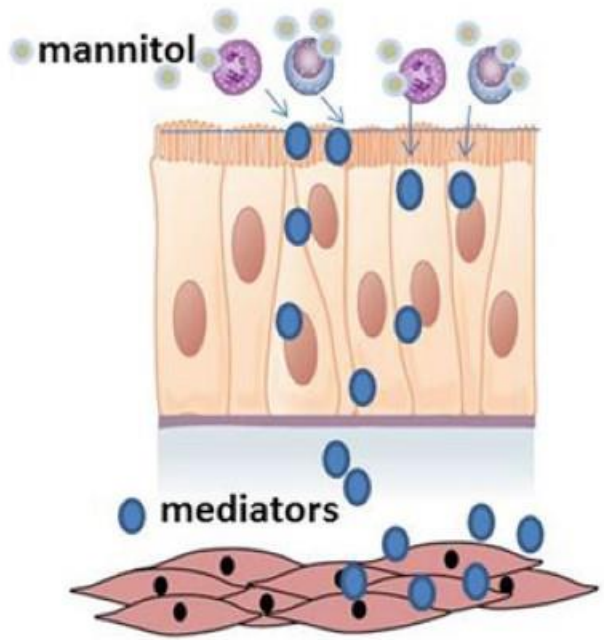
	Guideline		
	Thoracic Society of Australia and New Zealand, 2023	**British Thoracic Society, 2018**	**European Respiratory Society, 2017**
Airway clearance	**Airway clearance therapies** are recommended, should be on an individualized basis; taught preferably by a physiotherapist.	Patients with bronchiectasis should be taught **airway clearance** by physiotherapist.	Recommended for patients with chronic, **productive cough** or **difficulty producing sputum**; taught by physiotherapist.
Muco-active agents	Consider for patients with **>3 AEs per year despite use of long-term antibiotics**; **nebulized isotonic saline, hypertonic saline or mannitol**.	Consider for patients who have **difficulty with sputum expectoration**; **isotonic and hypertonic saline**.	Indicated for patients who have **difficulty with expectoration** and **decreased quality of life** despite using airway clearance.

JAMA. 2025 Jul 15;334(3):253-264.

Mechanism of inhaled mannitol

Inhaled mannitol for identifying asthma

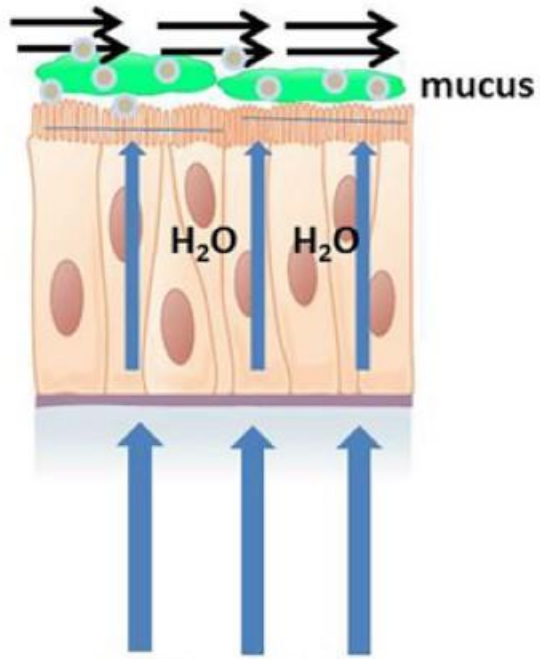
Mannitol dry powder increases osmolarity at the airway surface to cause mediator release from mast cells & eosinophils



Receptors on smooth muscle are stimulated by the mediators so it contracts & the airways narrow in those with currently active asthma

Inhaled mannitol for mucociliary dysfunction

Mannitol dry powder increases osmolarity of the periciliary fluid layer and water moves to the lumen enhancing clearance of mucus



H_2O from submucosa rehydrates airway surface liquid

Adv Drug Deliv Rev. 2018 Aug:133:45-56.

Inhaled mannitol in bronchiectasis

BRONCHIECTASIS

Phase 3 Randomized Study of the Efficacy and Safety of Inhaled Dry Powder Mannitol for the Symptomatic Treatment of Non-Cystic Fibrosis Bronchiectasis

Phase 3, Non-CF bronchiectasis

Inclusion: Age 18-80, FEV_1 ≥ 1L & ≥ 50%, persistent cough & chronic sputum >10 mL/d for 3m, chronic chest congestion

Exclusion: Previous use of mannitol or hypertonic saline, Hemoptysis >60ml in previous 6m, smoking history (>1 cigarette/wk), bronchoconstriction, asthma

Comparison: Inhaled mannitol 320mg bid (DPI) vs. placebo

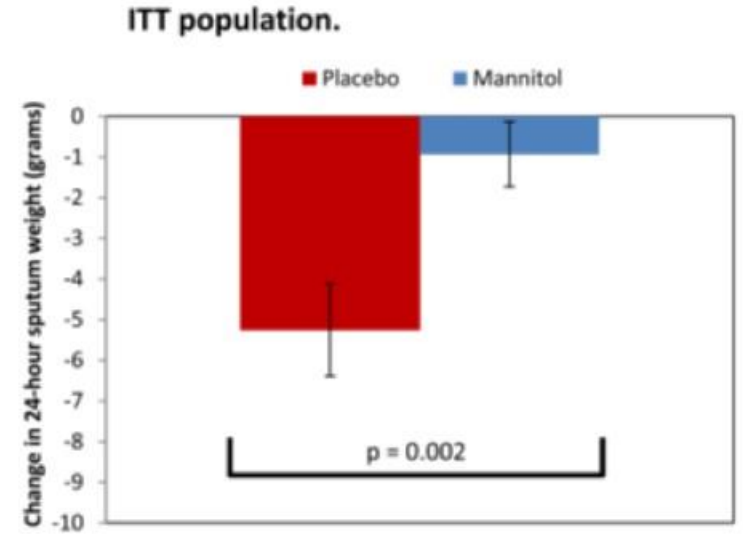
Primary outcome: Wet sputum weight, SGRQ at 12 weeks

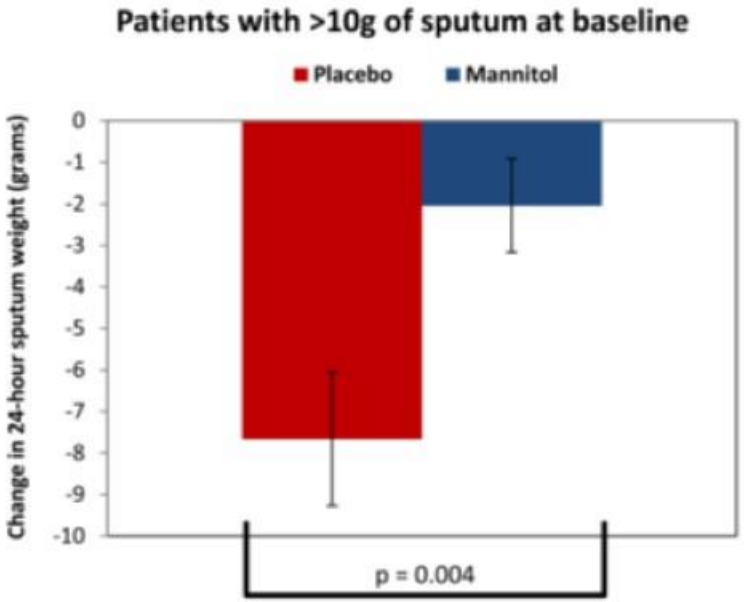
Duration: 12 weeks (Open label extension 52 weeks)

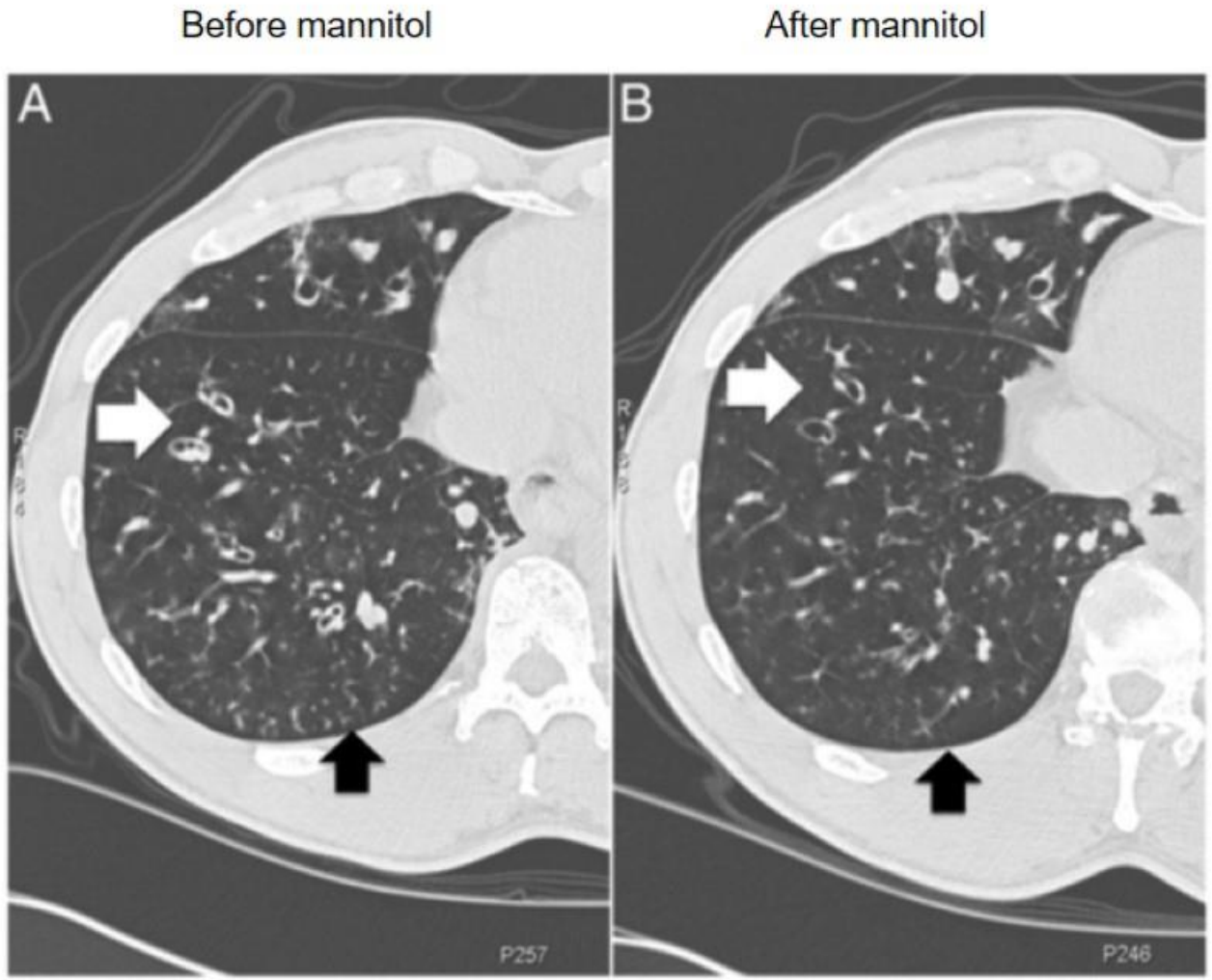
Demographics	Placebo (n = 112)	Mannitol (n = 231)
Age, y		
Mean (SD)	62.3 (8.9)	61.2 (10.4)
Range	38-78	18-79
Sex, No. (%)		
Female	72 (64.3)	152 (65.8)
Male	40 (35.7)	79 (34.2)
Race, No. (%)		
White	109 (97.3)	225 (97.4)
Other	3 (2.7)	6 (2.5)
Smoking history, No. (%)		
No[a]	94 (83.9)	203 (87.9)
Yes[b]	18 (16.1)	28 (12.1)
SGRQ total score		
Mean (SD)	37.6 (15.8)	37.0 (15.8)
Range	4-78	3-84
24-h sputum weight, g		
Mean (SD)	20.5 (18.1)	21.7 (27.1)
Range	0.3-92.9	0.0-307.8
FEV_1, L		
Mean (SD)	1.92 (0.56)	1.94 (0.55)
Range	1.00-3.73	1.01-4.49
FEV_1 % predicted		
Mean (SD)	74.6 (14.6)	74.9 (14.6)
Range	50-125	49-136

Chest. 2013 Jul;144(1):215-225.

Sputum burden and radiologic changes after 12wks

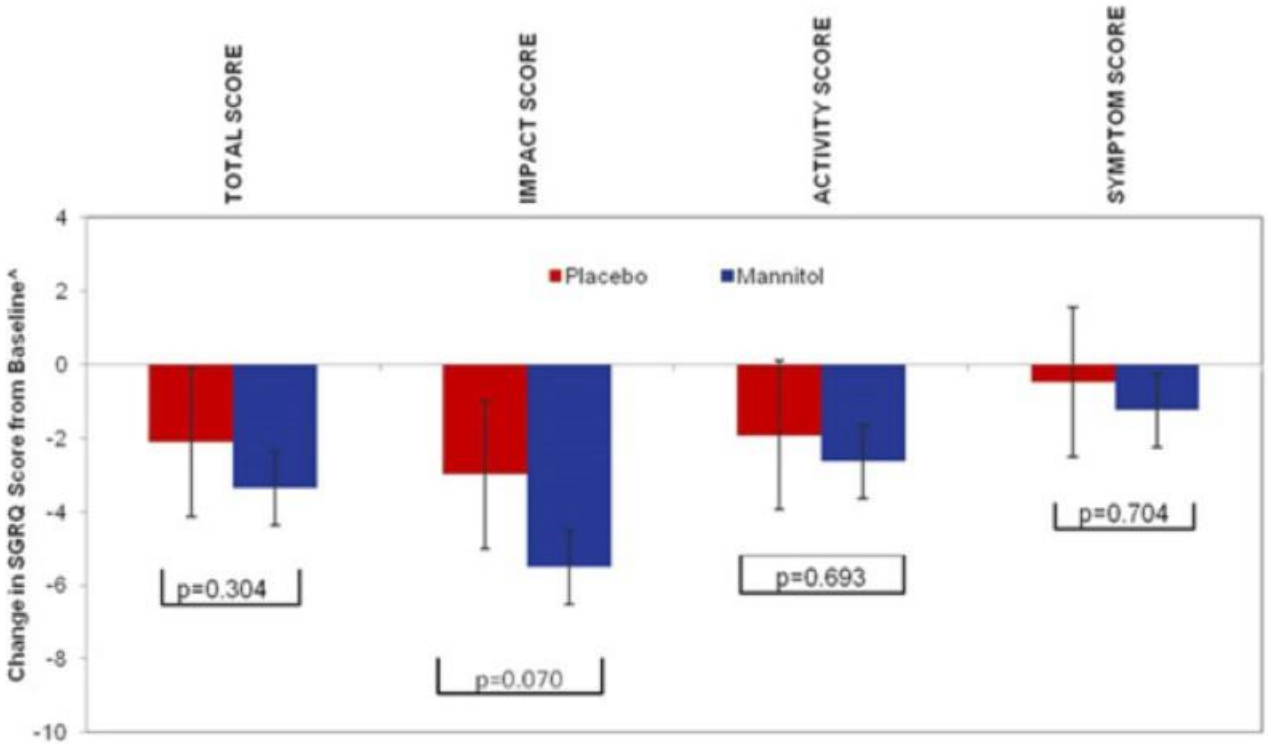


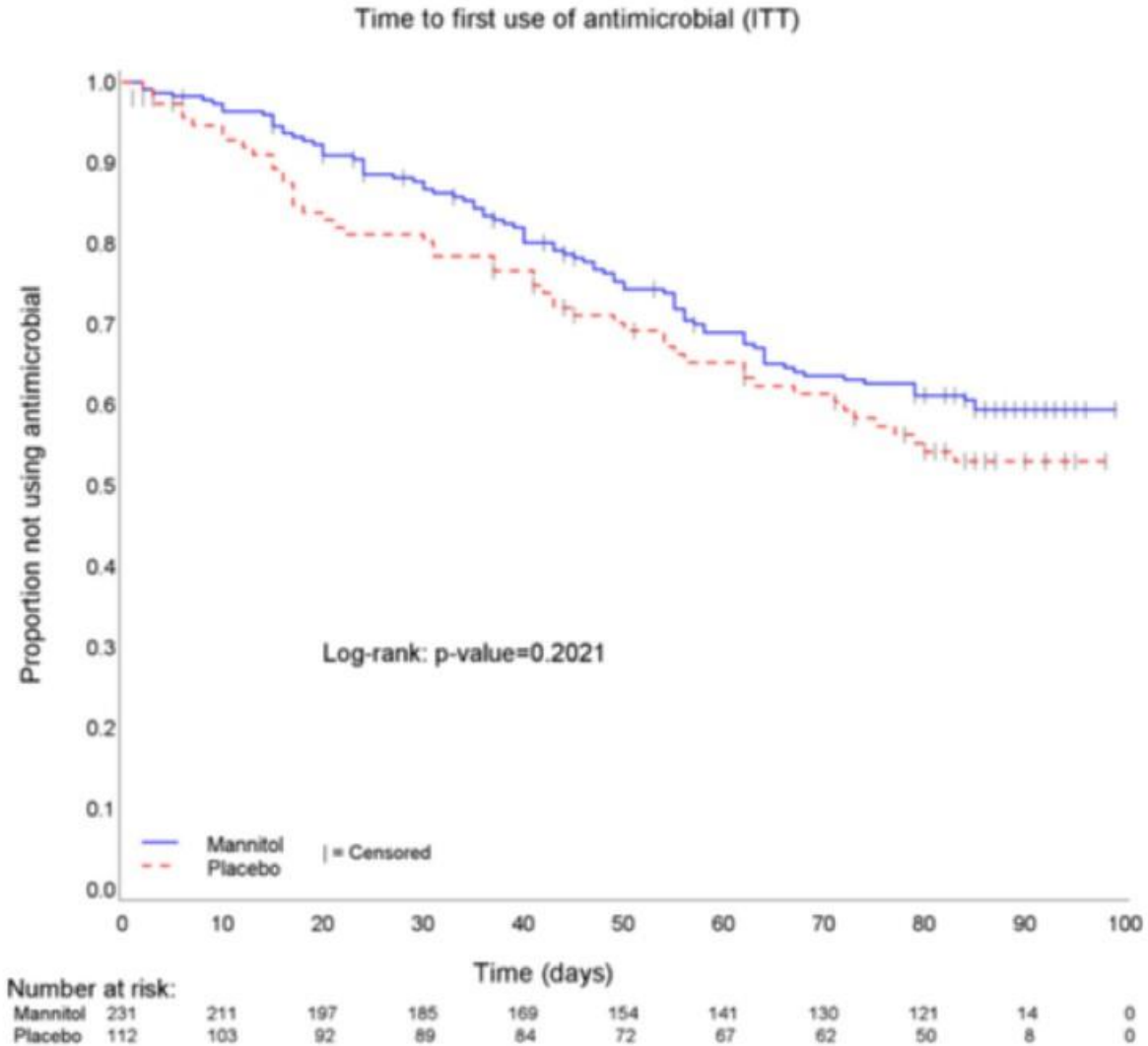




Chest. 2013 Jul;144(1):215-225.

SGRQ and time to antimicrobial use





Chest. 2013 Jul;144(1):215-225.

Adverse events of inhaled mannitol

Treatment-Related Adverse Events (≥1%) During the 12-Wk Double-Blind Phase

	Placebo (n = 112)				Mannitol (n = 233)			
Adverse Event	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Chest discomfort	1 (0.9)	1 (0.9)	…	2 (1.8)	1 (0.4)	…	…	<1%
Condition aggravated	…	1 (0.9)	1 (0.9)	2 (1.8)	…	1 (0.4)	1. (0.4)	<1%
Lower respiratory tract infection	2 (1.8)	1 (0.9)	…	3 (2.7)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.2)
Nasopharyngitis	…	…	…	0	1 (0.4)	2 (0.9)	…	3 (1.3)
FEV decreased	…	…	…	0	2 (0.9)	1 (0.4)	…	3 (1.3)
Headache	…	1 (0.9)	…	<1%	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.3)
Bronchospasm	…	…	…	0	…	2 (0.9)	2 (0.9)	4 (1.8)
Cough	1 (0.9)	4 (3.6)	1 (0.9)	6 (5.4)	5 (2.1)	4 (1.7)	1 (0.4)	10 (4.2)
Dyspnea	…	…	…	0	…	3 (1.3)	…	3 (1.3)
Hemoptysis	2 (1.8)	2 (1.8)	…	4 (3.6)	…	3 (1.3)	1 (0.4)	4 (1.7)
Pharyngolaryngeal pain	1 (0.9)	1 (0.9)	…	2 (1.8)	3 (1.3)	…	…	3 (1.3)
Throat irritation	…	…	…	0	2 (0.9)	1 (0.4)	…	3 (1.3)

Data are presented as No. (%). Adverse events were coded according to MedDRA System Organ Class.

Chest. 2013 Jul;144(1):215-225.

Long-term effect of inhaled mannitol

ORIGINAL ARTICLE

Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial

Diana Bilton,[1] Gregory Tino,[2] Alan F Barker,[3] Daniel C Chambers,[4,5] Anthony De Soyza,[6] Lieven J A Dupont,[7] Conor O'Dochartaigh,[8] Eric H J van Haren,[9] Luis Otero Vidal,[10] Tobias Welte,[11] Howard G Fox,[12] Jian Wu,[12] Brett Charlton,[12] for the B-305 Study Investigators

Phase3, Non-CF bronchiectasis

Inclusion: Age 18-85, FEV_1 ≥ 1L & 40-85%, **SGRQ ≥30,**

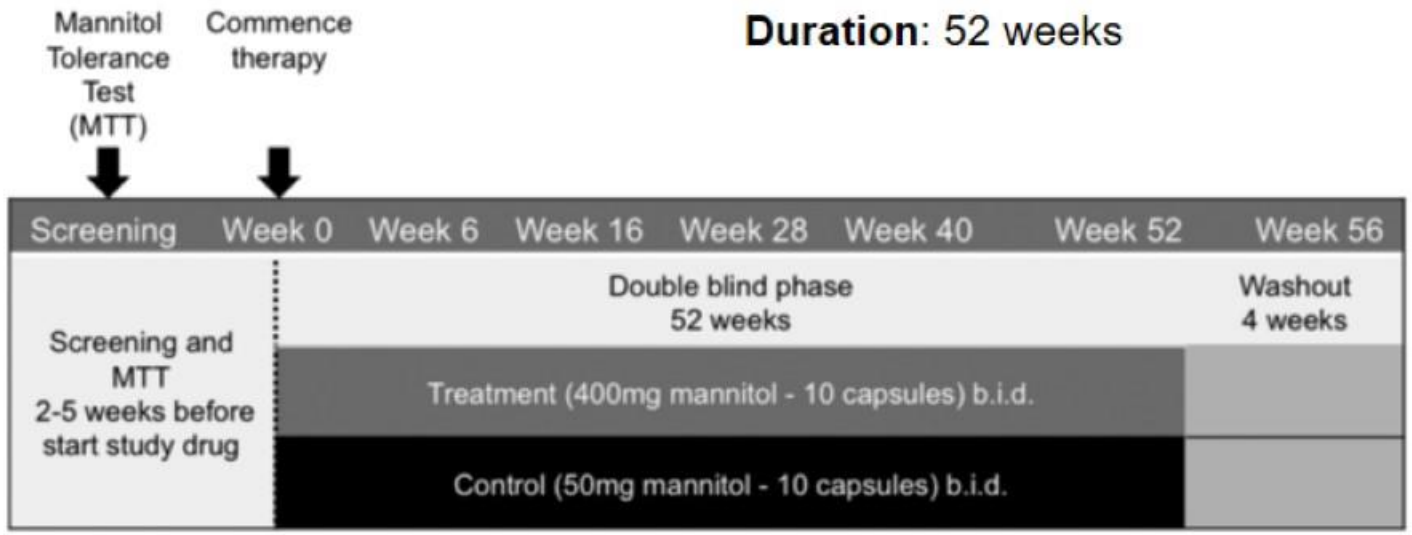
≥2 AE hx for 1yr and ≥4 AE hx for 2 yr

Exclusion: Intolerance to inhaled mannitol (bronchospasm), nebulized hypertonic saline user

Comparison: 400mg bid vs. 50mg bid inhaled mannitol (DPI)

Primary outcome: The annual rate of exacerbations

Duration: 52 weeks



Thorax. 2014 Dec;69(12):1073-9.

Study flow and baseline characteristics

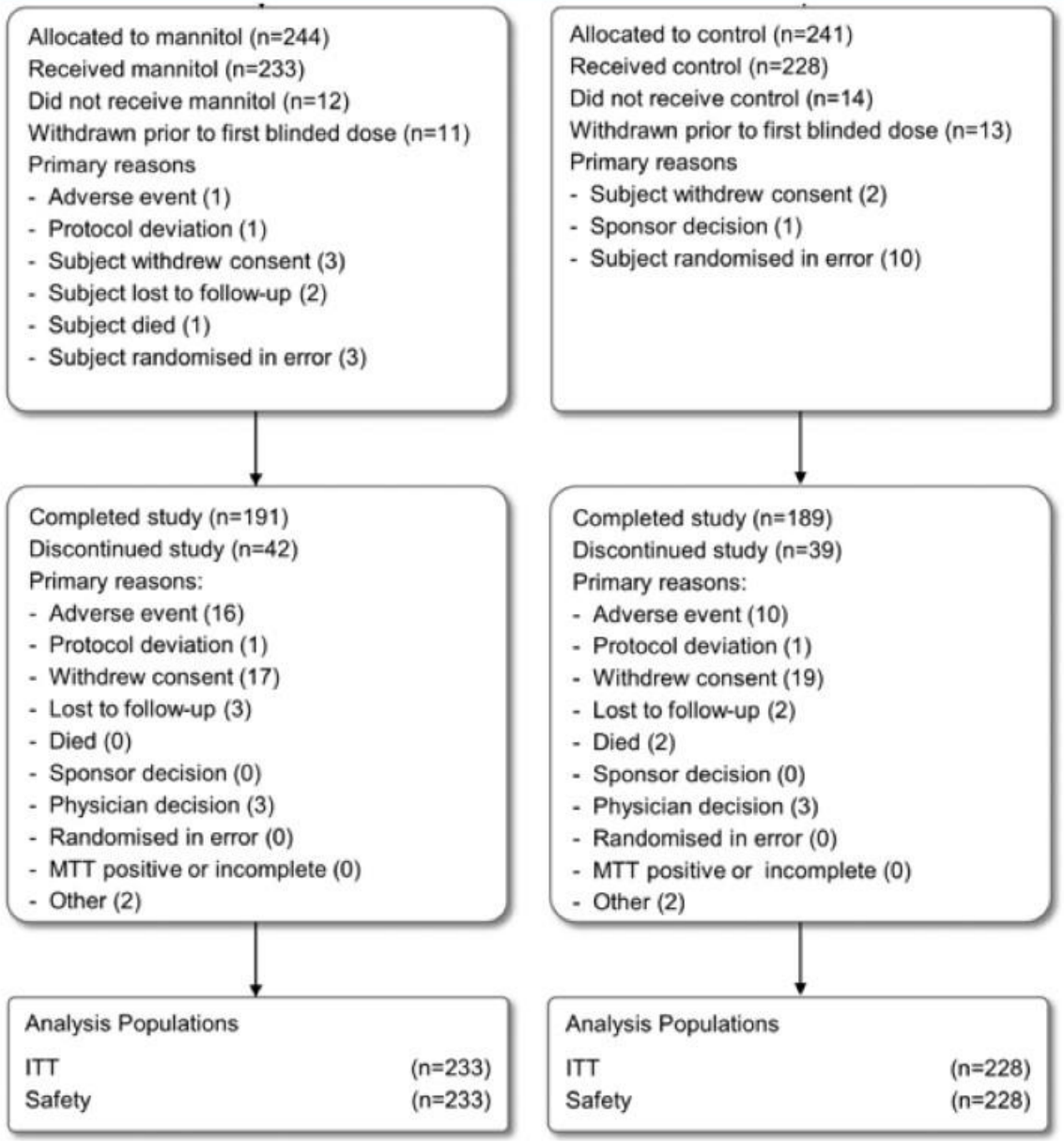


Table 1 Baseline characteristics of intention-to-treat population

Variable at screening/baseline (intention-to-treat population)	Inhaled mannitol n=233	Control n=228
Age years	59±14	60±13
Female sex (%)	63.1	62.3
Caucasian (%)	94.8	96.5
FEV_1		
Litres	1.76±0.59	1.67±0.51
% Predicted	63.0±13.6	61.5±13.4
FEV_1/FVC ratio (%)	65±11	65±11
Ex-smoker (%)	39.9	38.6
Exacerbation rate (events/year)	3.20±1.4	3.25±1.4
24 h sputum weight (g)	28.9±18.7	29.0±19.9
SGRQ total score	53.0±14.6	52.2±14.7
Macrolide use (%)	20.2	24.6
Pseudomonas aeruginosa positive (%)	17.7	20.6
Cause of bronchiectasis (%)		
Unknown	50.6	50.0
Infection	32.2	36.0
Primary ciliary dyskinesia	4.3	2.2
Other	12.9	11.8

Plus-minus values are means ±SD.
SGRQ, St George's Respiratory Questionnaire.

Thorax. 2014 Dec;69(12):1073-9.

Exacerbation, antibiotic use, and health status

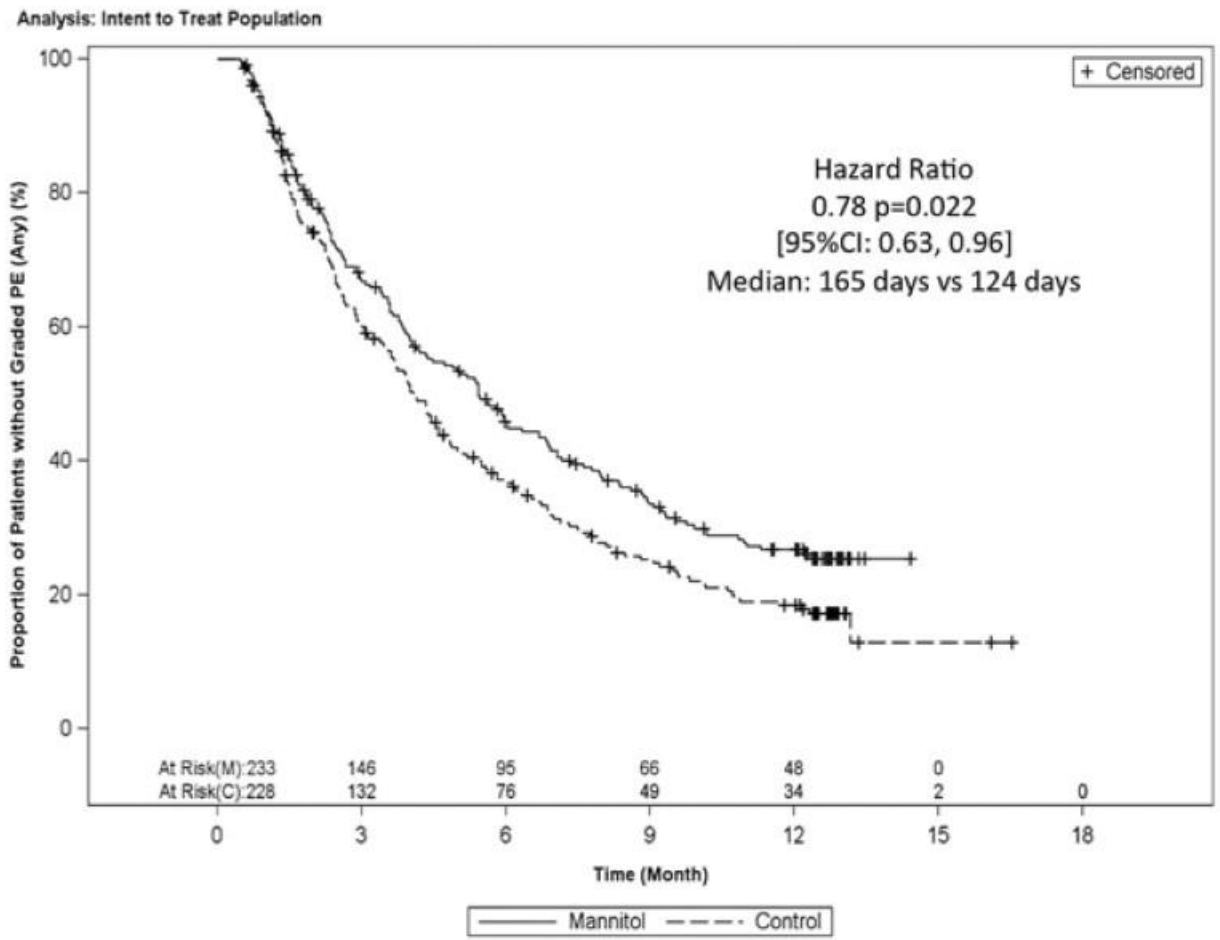
Primary endpoint: annual rate of exacerbation

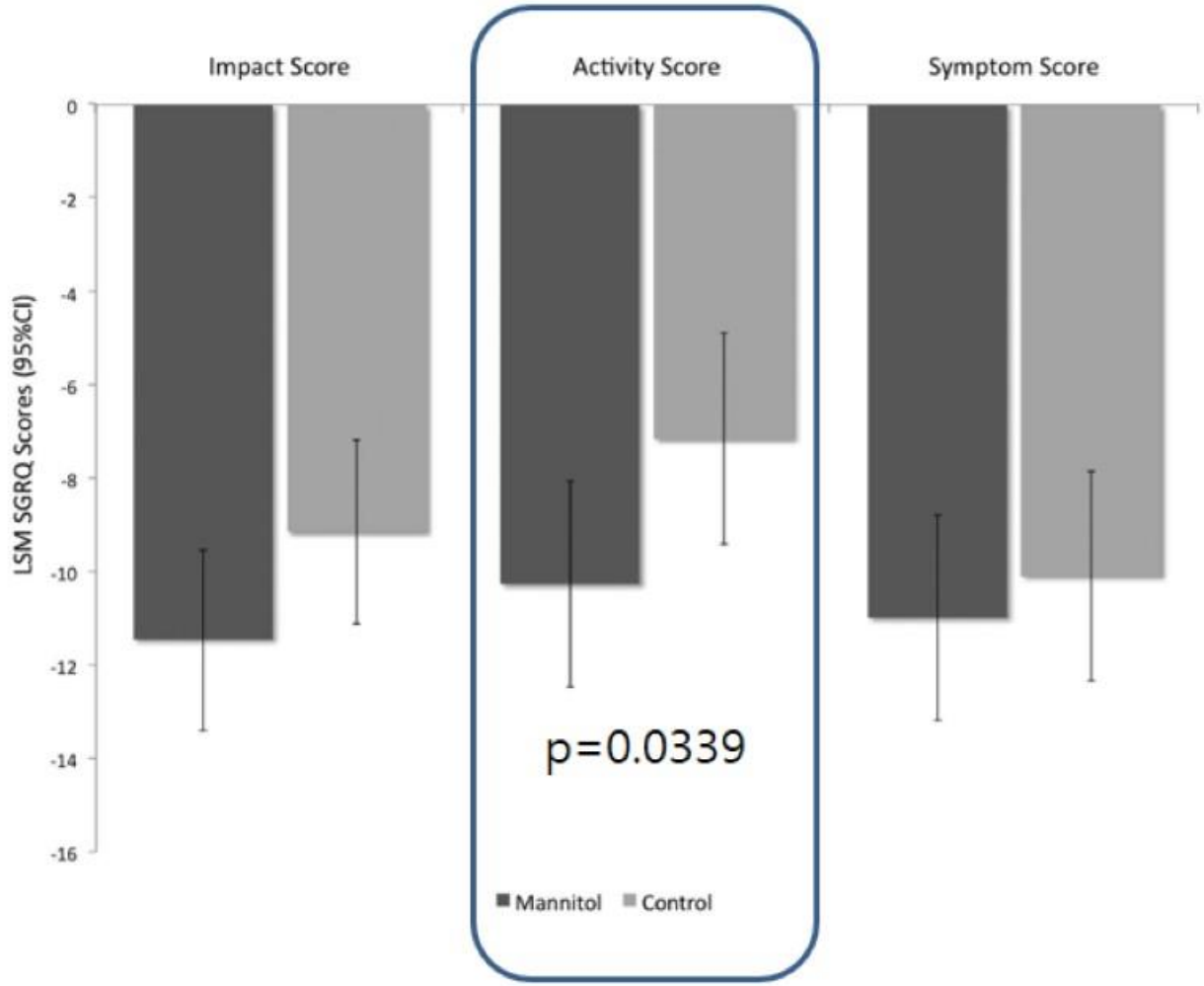
- The rate ratio was 0.92 (95% CI 0.78 to 1.08), P-value=0.31

	Mannitol (n=233)	Control (n=228)
Time to first exacerbation (days)		
Patients with event (%)	160 (68.7)	178 (78.1)
Median (95% CI)	165 (124, 204)	124 (107, 143)
p Value (stratified Log-rank Test)	0.0214	
HR (95% CI)	0.78 (0.63 to 0.96)	
p Value	0.0218	
Duration (days) of exacerbations*		
Mean days with GPE (any type) per year (95% CI)	31.49 (25.54 to 38.82)	35.74 (28.90 to 44.20)
Rate ratio (95% CI)	0.88 (0.67 to 1.16)	
p Value	0.3602	
Days on antibiotics for treatment of pulmonary exacerbations*		
Mean days on antibiotics for treatment of GPE (any type) per year (95% CI)	19.88 (16.12 to 24.51)	26.03 (21.11 to 32.09)
Rate ratio (95% CI)	0.76 (0.58 to 1.00)	
p Value	0.0496	
Absolute change in SGRQ total score from baseline†		
n used in analysis	228	219
All on-treatment period		
LS mean (95% CI)	−10.98 (−12.78 to −9.18)	−8.58 (−10.43 to −6.72)
Difference (95% CI)	−2.40 (−4.76 to −0.05)	
p Value	0.0457	

Thorax. 2014 Dec;69(12):1073-9.

Exacerbation and health status





Thorax. 2014 Dec;69(12):1073-9.

Adverse events of inhaled mannitol

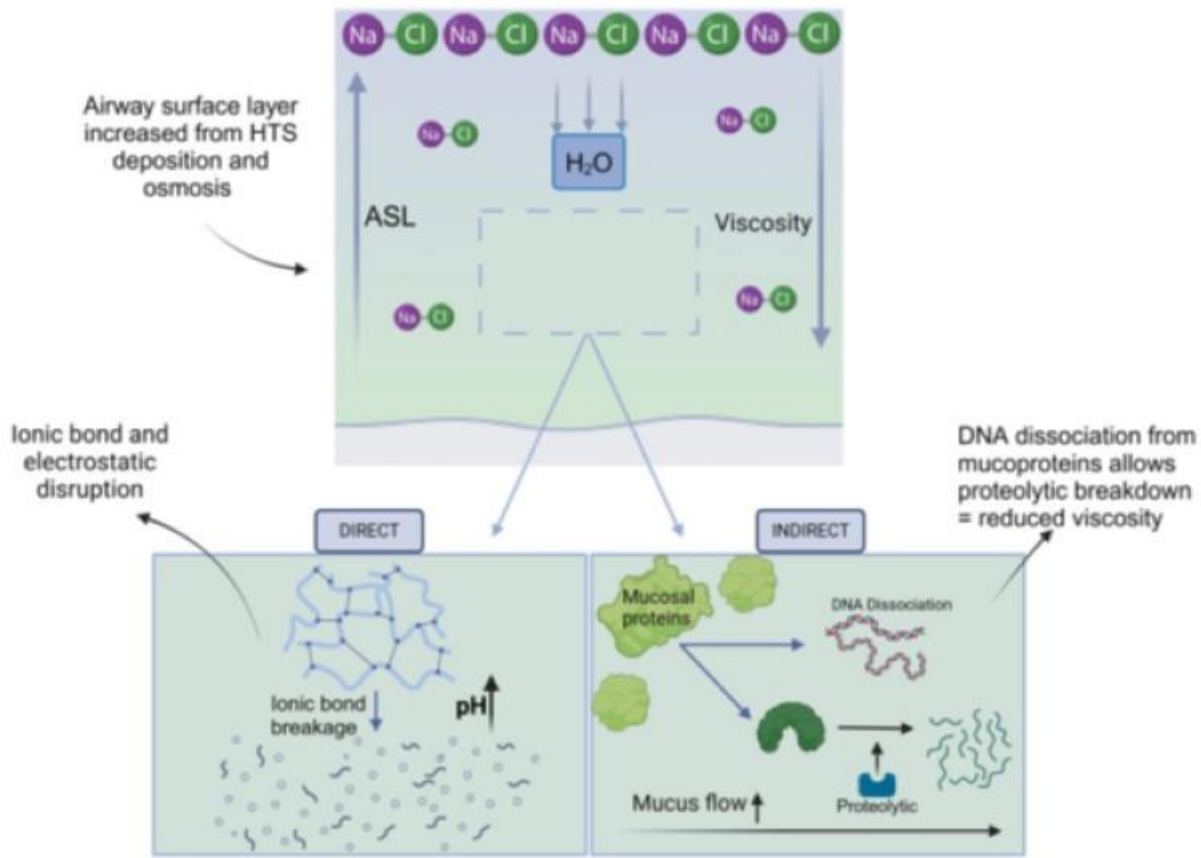
- Events possibly causally related to the inhaled mannitol were reported in 7.2%; cough (3.1%), fall in FEV_1 (2.2%), bronchospasm (0.5%), oxygen desaturation (0.7%), and self-reported wheeze (0.5%).

Preferred term	Mannitol (n=233) n (%)	Control (n=228) n (%)
Condition aggravated	149 (63.9)	159 (69.7)
Nasopharyngitis	36 (15.5)	30 (13.2)
Bacteria sputum identified	30 (12.9)	30 (13.2)
Cough	30 (12.9)	22 (9.6)
Headache	27 (11.6)	32 (14.0)
Haemoptysis	24 (10.3)	23 (10.1)
Dyspnoea	20 (8.6)	16 (7.0)
Back pain	19 (8.2)	13 (5.7)
Sinusitis	17 (7.3)	14 (6.1)
Lower respiratory tract infection	28 (12.1)	30 (13.2)
Diarrhoea	15 (6.4)	21 (9.2)
Nausea	14 (6.0)	18 (7.9)

Thorax. 2014 Dec;69(12):1073-9.

Mechanism of hypertonic saline

- Hypertonic saline hydrates the airway and disrupts mucus structure, reducing viscosity and improving mucus clearance.

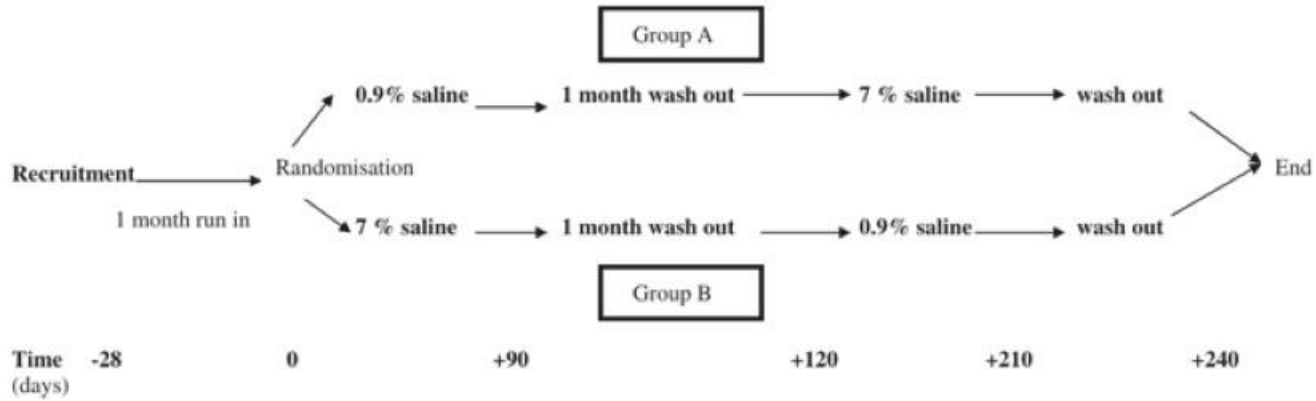


Crit Care. 2025 Feb 7;29(1):68.

Hypertonic saline and lung function and AE

Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis

Fiona Kellett [a,*], Niven M. Robert [b]

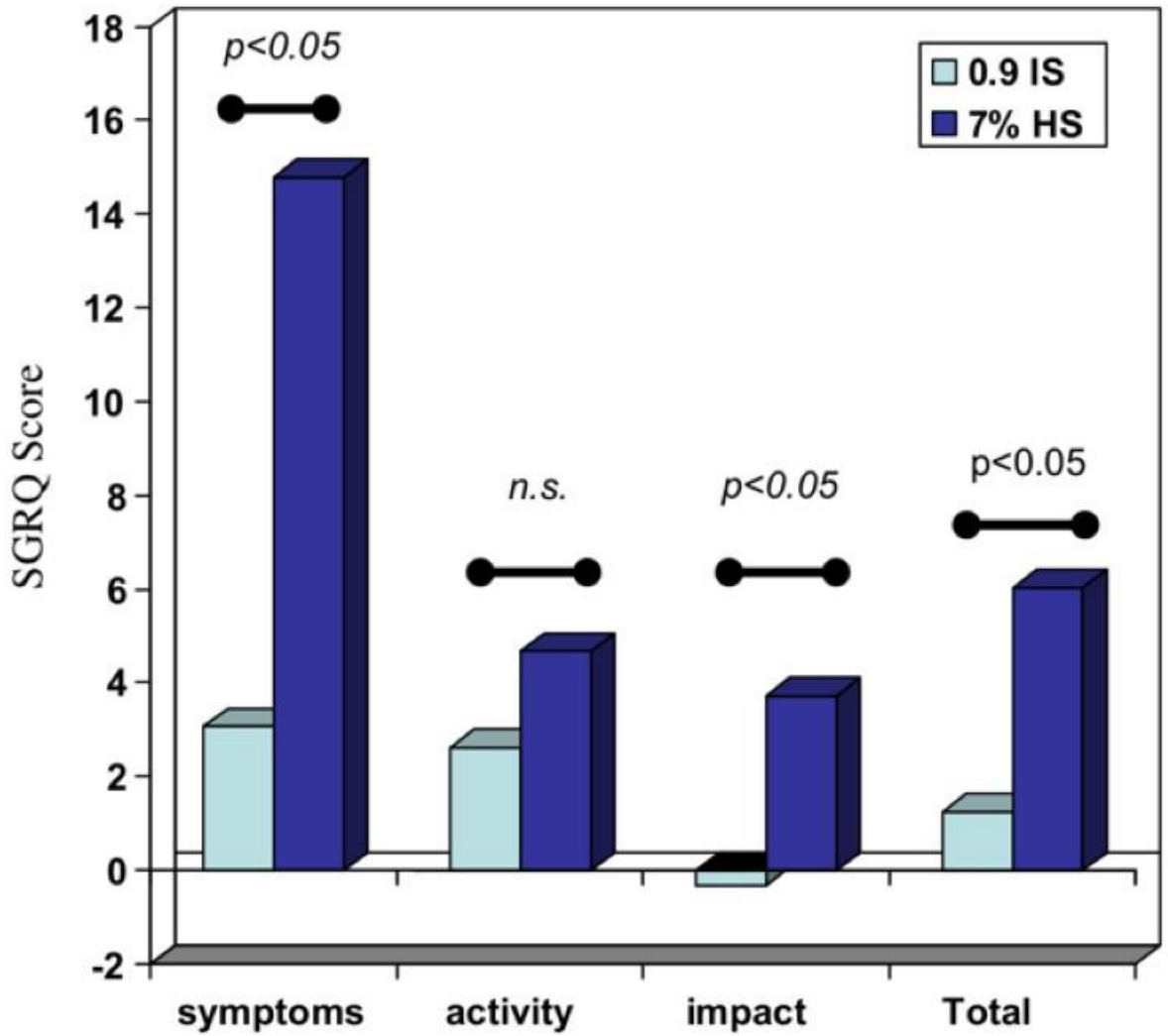


Phase	Active (HS)	Placebo (NS)	*P* value
FEV_1% change (95% C.I.)	15.1 (8.2;22.0)	1.8 (−8.9;10.7)	<0.01
FVC % change (95% C.I.)	11.23 (8.6;13.9)	0.72 (−7.4;8.9)	<0.01

	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

Respir Med. 2011 Dec;105(12):1831-5.

Hypertonic saline and SGRQ



Respir Med. 2011 Dec;105(12):1831-5.

Long-term effect of hypertonic saline

The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis

Caroline H.H. Nicolson [a,*], Robert G. Stirling [b], Brigitte M. Borg [c], Brenda M. Button [b], John W. Wilson [b], Anne E. Holland [d]

	IS (0.9%)	HTS (6%)
Age (years)	56 (15)	58 (15)
Gender (M/F)	8/12	7/13
BMI (kg/m^2)	28.2 (5.0)	27.9 (5.4)
FEV_1 (% pred)	80.4 (21.1)	84.8 (20.5)
FVC (% pred)	97.1 (18.0)	98.5 (17.8)
$FEF_{25-75\%}$ (% pred)	49.0 (24.8)	57.7 (25.4)
FEV_1/FVC (% pred)	0.67 (0.11)	0.69 (0.11)
Self reported exacerbations		
Median (IQR)	5.5 (3.1)	5.0 (3.9)
Range	10.0	13.0
Previous physiotherapy (%)		
Nil	7.5	7.5
ACBT	32.5	42.5
PEP therapy	22.5	32.5
Postural drainage	25.0	17.5

Phase3, Non-CF bronchiectasis
Inclusion: Adults ≥18 yr, **≥2 exacerbations/year in prior 2 yr**, clinically stable, FEV1 ≥1 L
Exclusion: FEV1 drop >15% after HTS challenge
Comparison: Inhaled hypertonic saline 6% (5 ml) vs. isotonic saline 0.9% (5 ml), twice daily via nebulizer, both preceded by salbutamol 200 µg
Primary outcome: Number of exacerbations over 12 months
Duration: 52 weeks

	IS (0.9%)	HTS (6%)	*p* value
Exacerbations	1.0 (0–4)	3.0 (0–6)	0.24
Exacerbations requiring antibiotics	0.5 (0–3)	1.0 (0–2.5)	0.99
Exacerbation days	2.0 (0–26)	12.0 (1–26)	0.57
Exacerbation days requiring antibiotics	1.0 (0–19.5)	2.0 (0–7)	0.77

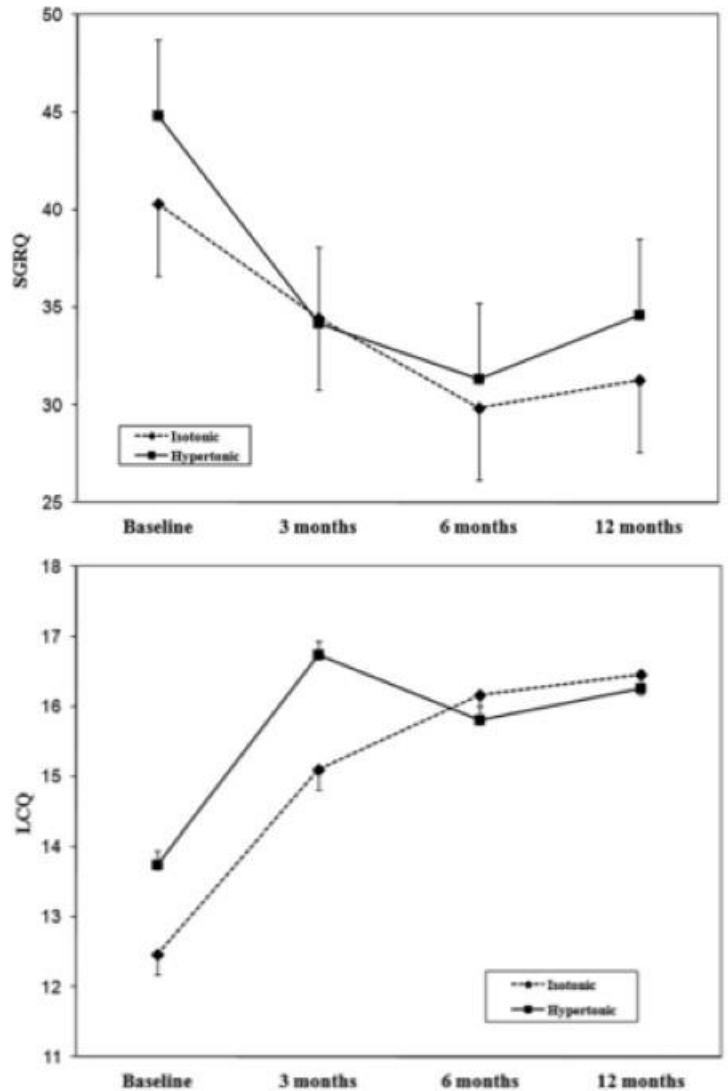
Respir Med. 2012 May;106(5):661-7.

Long-term effect of hypertonic saline

SGRQ	Baseline	3 m	6 m	12 m	*p* value[a]
Symptom					0.18
IS	64.1 (16.1)	57.0 (17.5)[b]	51.2 (19.8)[b]	50.7 (22.7)[b]	
HTS	64.3 (14.2)	48.5 (21.0)[b]	57.6 (20.0)[b]	52.3 (22.9)[b]	
Activity					0.18
IS	39.4 (22.2)	35.4 (22.4)[b]	31.0 (21.3)[b]	34.7 (25.1)[b]	
HTS	50.1 (24.4)	39.8 (28.5)[b]	33.6 (25.2)[b]	37.4 (25.9)[b]	
Impact					0.60
IS	33.5 (17)	27.2 (17.9)[b]	22.8 (15.2)[b]	23.3 (19.1)[b]	
HTS	35.6 (16.9)	26.8 (19.6)[b]	22.0 (13.5)[b]	27.7 (19.3)[b]	

LCQ	Baseline	3 m	6 m	12 m	*p* value[a]
Physical					0.21
IS	4.2 (1.7)	4.9 (1.0)[b]	5.1 (1.4)[b]	5.3 (1.3)[b]	
HTS	4.4 (1.0)	5.3 (1.0)[b]	5.0 (1.1)[b]	5.1 (1.1)[b]	
Psychological					0.06
IS	3.9 (1.5)	5.0 (1.4)	5.4 (1.4)[b]	5.5 (1.6)[b]	
HTS	4.7 (1.3)	5.9 (1.1)[b]	5.3 (1.0)[b]	5.7 (1.0)[b]	
Social					0.17
IS	4.4 (1.4)	5.2 (1.3)[b]	5.6 (1.3)[b]	5.7 (1.4)[b]	
HTS	4.6 (1.2)	5.7 (1.4)[b]	5.5 (1.0)[b]	5.6 (1.0)[b]	

No significant difference between groups at any time point
Significantly improved at 12 months compared to baseline



Respir Med. 2012 May;106(5):661-7.

Long-term effect of hypertonic saline

	Baseline	3 months	6 months	12 months	*p* value
FEV_1					0.70
IS	2.16 (0.75)	2.23 (0.89)	2.24 (0.95)	2.18 (0.92)	
HTS	2.28 (0.87)	2.36 (0.91)	2.41 (0.88)	2.37 (0.90)	
FVC					0.62
IS	3.23 (0.95)	3.26 (1.07)	3.22 (1.1)	3.14 (1.12)	
HTS	3.27 (1.00)	3.31 (1.11)	3.32 (1.07)	3.25 (1.06)	
$FEF_{25-75\%}$					0.41
IS	1.39 (0.85)	1.61 (1.07)	1.71 (1.20)	1.57 (0.98)	
HTS	1.62 (1.02)	1.73 (0.98)	1.87 (1.14)	1.86 (1.08)	

No significant difference between groups at any time point
FEF25-75 significantly improved at 12 months compared to baseline

- There were three adverse events in the HTS group and no adverse events in the IS group.
- Self reported adherence to therapy over 12 months was not significantly different between groups (p=0.86).

Respir Med. 2012 May;106(5):661-7.

Inhaled hypertonic vs. isotonic saline

- In a meta-analysis, the efficacy of inhaled hypertonic saline was compared to isotonic saline as the placebo in bronchiectasis.

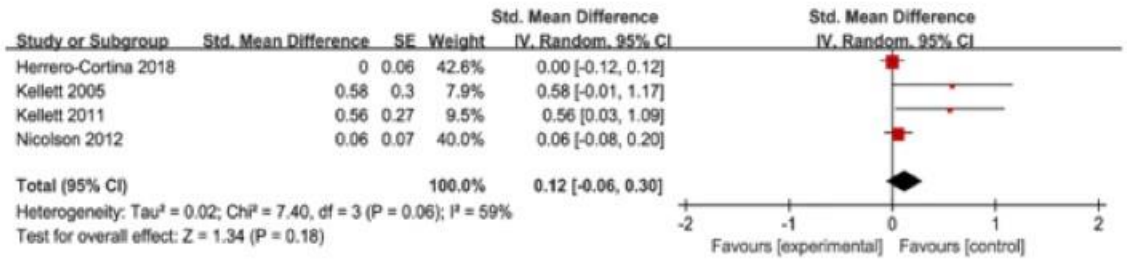


Fig. 2. Forest plot for the meta-analysis of FEV1.

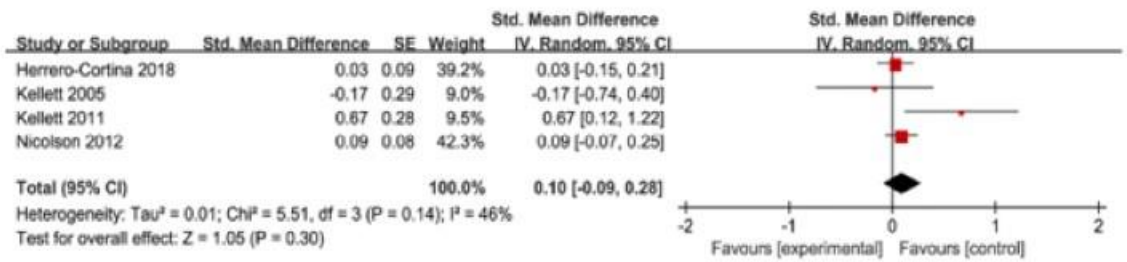


Fig. 3. Forest plot for the meta-analysis of FVC.

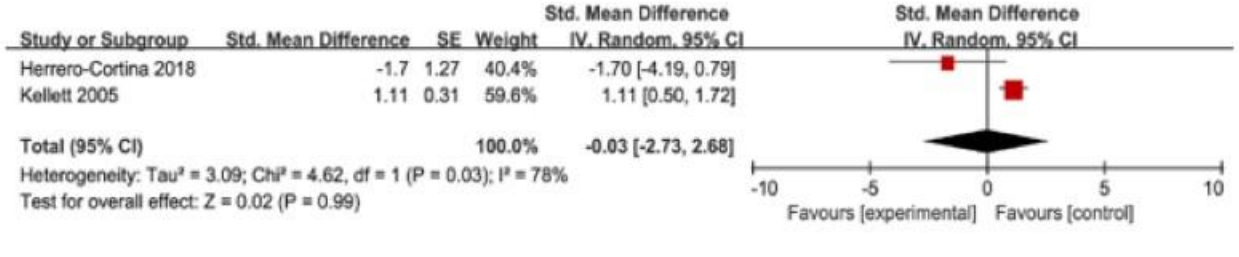


Fig. 4. Forest plot for the meta-analysis of sputum expectorated.

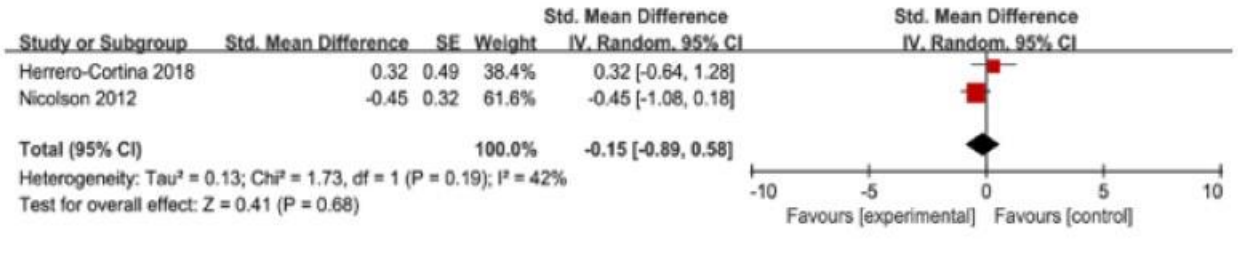


Fig. 5. Forest plot for the meta-analysis of LCQ score.

Am J Emerg Med. 2020 Dec;38(12):2713-2717

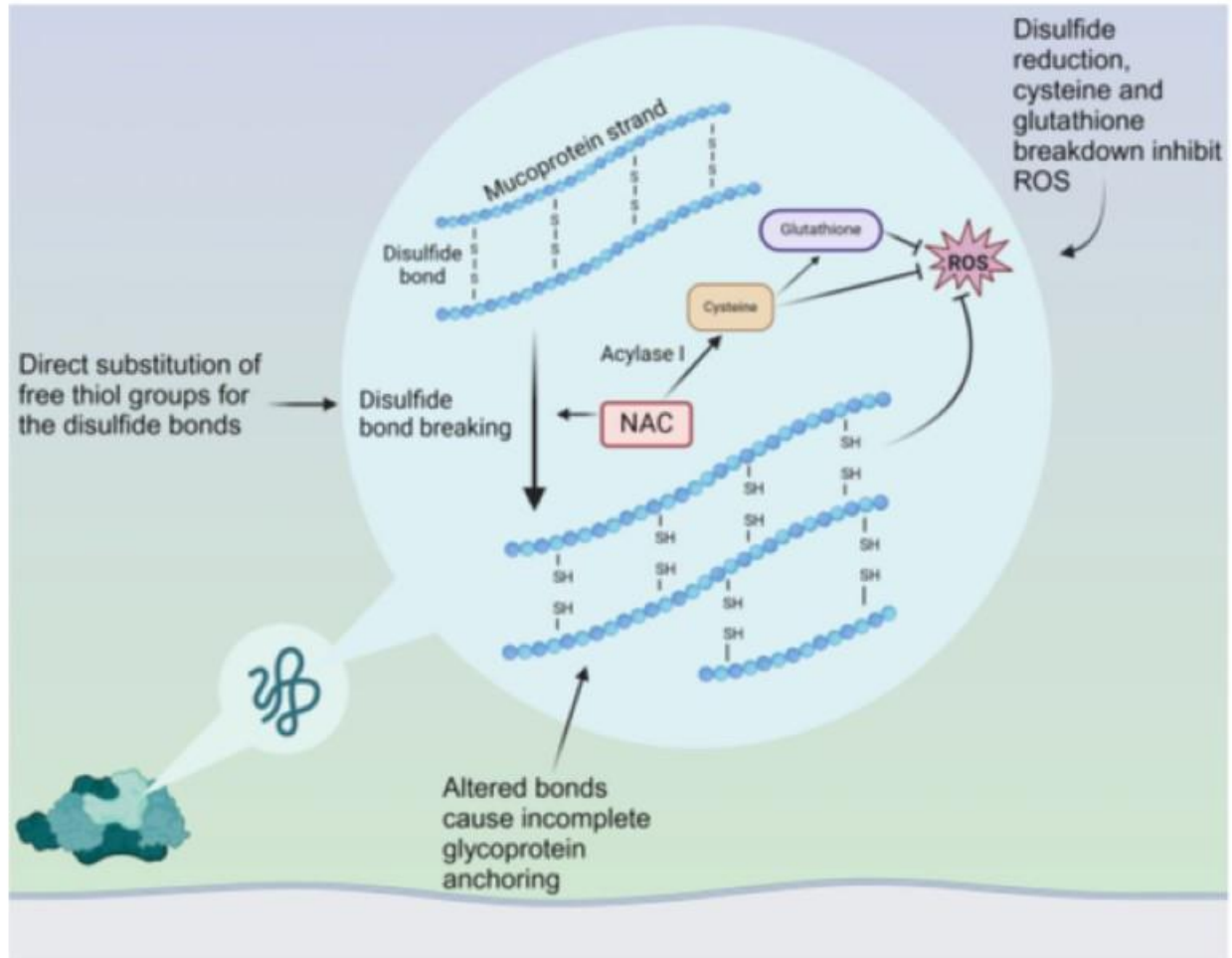
Contents

- Structure and function of mucin
- Pathogenesis of mucus dysfunction
- Osmotic agents for airway clearance
- **Muco-active agents**
- Summary

Muco-active agents

- **Oral N-acetylcysteine**
- **Erdosteine**
- **Recombinant human DNase**

Mechanism of N-acetylcystein / Erdosteine



Crit Care. 2025 Feb 7;29(1):68.

Oral N-acetylcystein in bronchiectasis

RESEARCH

Effect of N-acetylcysteine on exacerbations of bronchiectasis (BENE): a randomized controlled trial

Phase 3, Idiopathic or **post-infective bronchiectasis**

Inclusion: Age 18-80, **≥2 AE hx for 1yr**

Exclusion: FEV_1 ≤30%, Current/Recent smoker, prior macrolide use

Comparison: Oral NAC 600mg bid vs. as-needed therapy (control)

Primary outcome: Incidence of exacerbations

Duration: 12 months

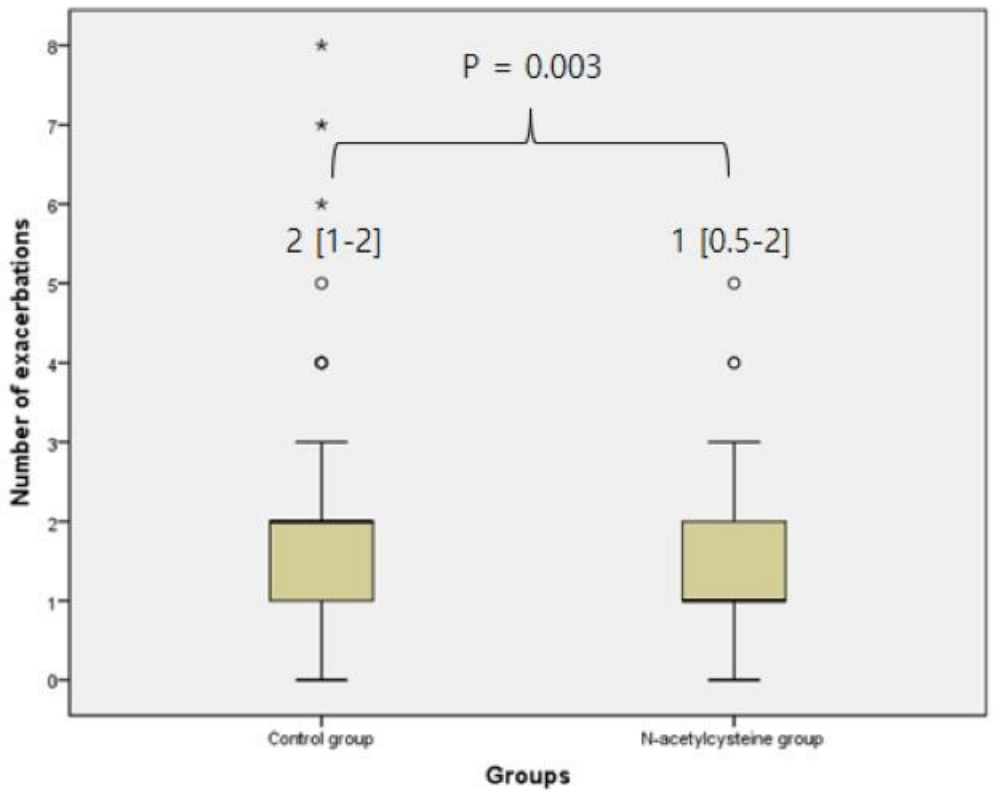
Characteristic	Group	
	Control group (*N* = 80)	N-acetylcysteine group (*N* = 81)
Gender		
Female, n (%)	52 (65.0)	45 (55.6)
Age, years	56.56 ± 12.41	53.28 ± 11.90
Body mass index, kg/m^2	22.16 ± 4.22	22.72 ± 3.57
Ex-smoker, n (%)	8 (10.0)	6 (7.4)
mMRC score(≥2)	48 (60.0)	45 (55.6)
CAT score	19.55 ± 7.26	19.15 ± 7.12
24-h sputum volume, mL	28.84 ± 40.94	29.74 ± 41.35
Etiology of bronchiectasis		
Postinfectious	38 (47.5)	30 (37.0)
Idiopathic	42 (52.5)	51 (63.0)
Pseudomonas aeruginosa positive, n (%)	20 (25.0)	27 (33.3)
Medications, n (%)		
Inhaled corticosteroids and long-acting β-agonist	45 (56.2)	56 (69.1)
Inhaled short-acting β-agonist	20 (25.0)	15 (18.5)
Inhaled anticholinergics	22 (27.5)	24 (29.6)
Inhaled corticosteroids	17 (21.2)	11 (13.6)
Pulmonary function		
FVC, L	2.42 ± 0.94	2.32 ± 0.74
FEV_1, L	1.56 ± 0.81	1.62 ± 0.73
Predicted FEV_1, %	63.63 ± 26.28	60.23 ± 27.32
FEV_1/FVC, %	64.39 ± 14.63	67.44 ± 16.49
Number of exacerbations in the last year	2 (2–3)	2 (2–3)
Bronchiectasis Severity Index	8.00 ± 4.27	8.43 ± 4.68

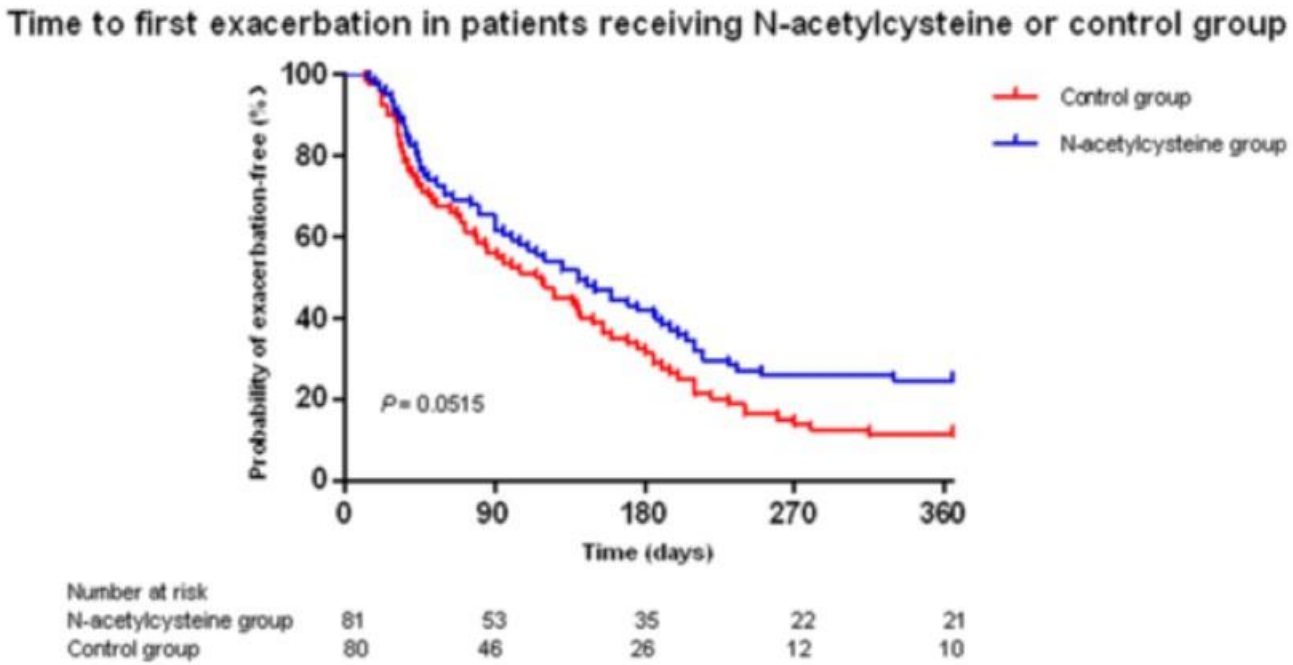
Respir Res. 2019 Apr 11;20(1):73.

Incidence of exacerbation

- **Incidence of exacerbations within 1 year**

- Significantly lower in the NAC group than the control group (1.31 vs. 1.98 exacerbations per patient-year; risk ratio, 0.41; 95% CI, 0.17–0.66; P = 0.0011)





Respir Res. 2019 Apr 11;20(1):73.

Oral erdosteine in bronchiectasis

Brief Report

Effectiveness of Erdosteine in Elderly Patients with Bronchiectasis and Hypersecretion: A 15-Day, Prospective, Parallel, Open-Label, Pilot Study

Ernesto Crisafulli, MD[1]; Orietta Coletti, MD[1]; Stefania Costi, RT[2]; Emanuela Zanasi, MD[1]; Cristina Lorenzi, RT[1]; Sasa Lucic, MD[1]; Leonardo M. Fabbri, MD[2]; Marco Bertini, MD[3]; and Enrico M. Clini, MD[1,2]

Open-label, elderly bronchiectasis with hypersecretion

Inclusion: Age >55, no current smoking, daily sputum >30 mL, stable condition, no change in chronic medication in past 4 weeks

Exclusion: Use of antibiotics, mucolytics, systemic steroids, or antitussives within 4 weeks; hypersensitivity to erdosteine; diabetes; liver failure; cancer

Comparison: Oral erdosteine 225 mg bid + chest physiotherapy (**Group 1**) vs. chest physiotherapy alone (**Group 2**)

Primary outcome: Change in sputum characteristics (density, purulence, volume) on a semiquantitative 3-point scale

Duration: 15days

Clin Ther. 2007 Sep;29(9):2001-9.

Oral erdosteine in bronchiectasis

- **Erdosteine plus physiotherapy improved all sputum measures (including mucus purulence)**, while physiotherapy alone improved only density and volume.

Table II. Time course of the mucus scores in elderly patients with bronchiectasis and hypersecretion treated with physiotherapy and erdosteine (group 1) or physiotherapy alone (group 2). Data are mean (SD).

	Day 0 (Baseline)	Day 5	Day 10	*P**	Day 15	*P**
Group 1						
MD	1.67 (0.48)	1.60 (0.48)	1.13 (0.51)	0.005	0.80 (0.56)	<0.001
MP	1.20 (0.56)	1.00 (0.53)	0.60 (0.63)	0.003	0.33 (0.48)	<0.001
MVP	0.33 (0.48)	0.47 (0.64)	1.07 (0.59)	0.001	1.33 (0.48)	0.001
Group 2						
MD	1.60 (0.50)	1.67 (0.48)	1.40 (0.63)	NS	1.07 (0.45)	0.005
MP	1.00 (0.37)	1.03 (0.37)	0.80 (0.41)	NS	0.80 (0.41)	NS
MVP	0.47 (0.51)	0.60 (0.73)	0.87 (0.74)	0.01	0.93 (0.70)	0.008

MD = mucus density; MP = mucus purulence; MVP = mucus volume production.

Clin Ther. 2007 Sep;29(9):2001-9.

Oral erdosteine in bronchiectasis

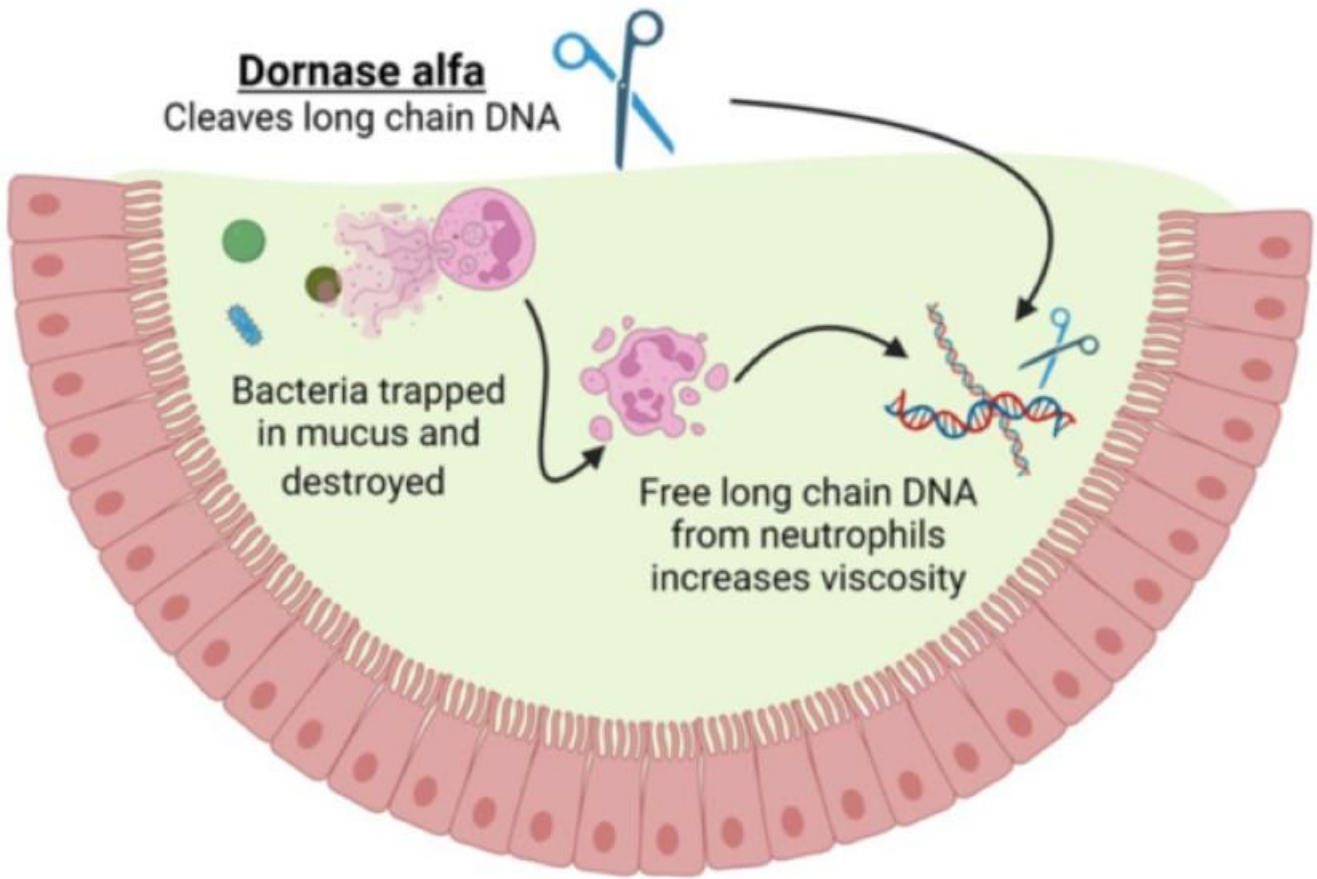
- **Erdosteine plus physiotherapy** improved exercise capacity, symptoms, **lung function**, respiratory muscle strength, and **oxygenation**, whereas physiotherapy alone improved only exercise capacity, symptoms, and expiratory muscle strength

Table III. Functional outcome changes (day 15 vs baseline) in elderly patients with bronchiectasis and hypersecretion treated with physiotherapy and erdosteine (Group 1) or physiotherapy alone (Group 2).

	Group 1	P*	Group 2	P*	P†
6MWT,[2] m	67.3 (43.0)	0.001	68.3 (60.2)	0.001	NS
VAS dyspnea, %	-14.2 (3.7)	0.001	-0.6 (0.9)	0.01	NS
VAS cough, %	-11.0 (12.0)	0.001	-0.4 (0.6)	0.04	NS
FEV_1, L	0.2 (0.3)	0.02	0 (0.1)	NS	0.05
Predicted, %	5.8 (13.3)	NS	1.3 (7.0)	NS	NS
FVC, L	0.3 (0.5)	0.02	0 (0.2)	NS	0.05
Predicted, %	9.5 (20.8)	NS	0.6 (8.9)	NS	NS
PEF, L/s	0.3 (1.1)	NS	0 (0.5)	NS	NS
Predicted, %	3.5 (16.5)	NS	0.7 (7.8)	NS	NS
MEF, L/s	0 (0.1)	NS	0 (0.1)	NS	NS
Predicted, %	-0.3 (7.3)	NS	0.5 (4.1)	NS	NS
MIP, cm H_2O	8.9 (9.4)	0.002	3.9 (12.3)	NS	NS
Predicted, %	7.1 (11.0)	0.01	3.4 (11.3)	NS	NS
MEP, cm H_2O	8.4 (21.1)	0.03	9.7 (16.4)	0.04	NS
Predicted, %	6.4 (23.6)	0.03	10.8 (17.5)	0.03	NS
PaO_2, mm Hg	5.1 (7.3)	0.01	0.3 (6.1)	NS	NS
$PaCO_2$, mm Hg	0.1 (2.5)	NS	0.4 (3.5)	NS	NS

Clin Ther. 2007 Sep;29(9):2001-9.

Mechanism of recombinant human DNase



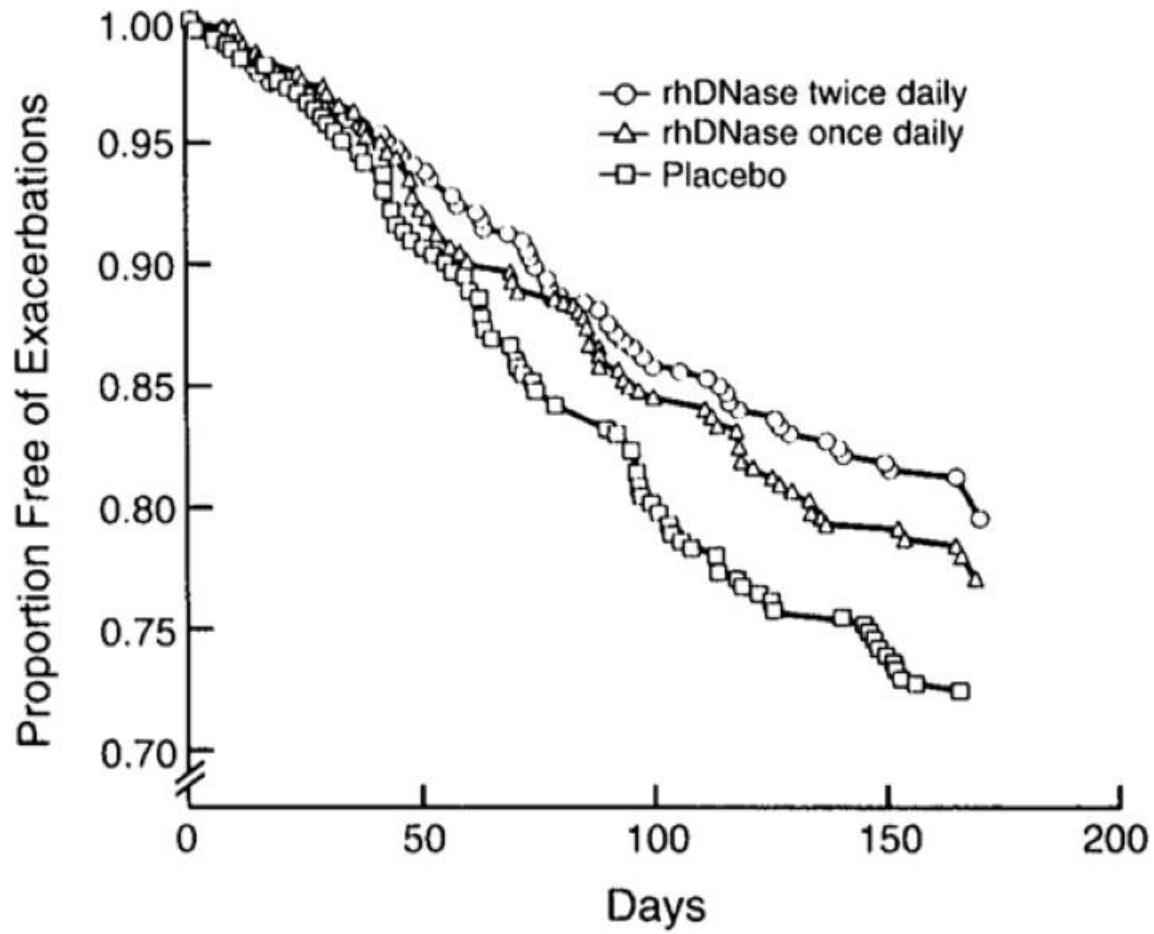
Crit Care. 2025 Feb 7;29(1):68.

rhDNase in cystic fibrosis

EFFECT OF AEROSOLIZED RECOMBINANT HUMAN DNase ON EXACERBATIONS OF RESPIRATORY SYMPTOMS AND ON PULMONARY FUNCTION IN PATIENTS WITH CYSTIC FIBROSIS

Henry J. Fuchs, M.D., Drucy S. Borowitz, M.D., David H. Christiansen, Dr.P.H., Edward M. Morris, Pharm.D., Martha L. Nash, R.N., Bonnie W. Ramsey, M.D., Beryl J. Rosenstein, M.D., Arnold L. Smith, M.D., and Mary Ellen Wohl, M.D., for the Pulmozyme Study Group*

Variable	Placebo (N=325)	Inhaled rhDNase 2.5mg	
		Once Daily (N=322)	Twice Daily (N=321)
No. (%) of patients with ≥1 exacerbations	89 (27%)	71 (22%)	61 (19%)
Relative risk (vs. placebo)	—	0.78	0.66
95% confidence interval	—	0.57–1.06	0.48–0.91
P value (vs. placebo)	—	0.11	0.01



N Engl J Med. 1994 Sep 8;331(10):637-42.

rhDNase in non-CF bronchiectasis

- **Pulmonary exacerbations**: The **rhDNase group had higher rates of PDE** (0.66 vs 0.56) and NPDE (0.29 vs 0.14), with the combined PDE+NPDE rate significantly increased (RR=1.35).
- **Lung function**: rhDNase treatment led to a **significant decline in FEV_1** (−3.6% vs −1.7%, p≤0.05) and **FVC** (−3.4% vs +0.3%, p≤0.01) compared with placebo.
- **Other outcomes**: Antibiotic use (56.9 vs 44.1 days, p≤0.05), steroid use (29.4 vs 23.4 days, p≤0.05), and hospitalization rate (0.39 vs 0.21, RR=1.85) were all higher in the rhDNase group.

	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

Chest. 1998 May;113(5):1329-34

Why outcomes were worse in non-CF BE?

Disease factors:

- Idiopathic bronchiectasis is often diffuse/lower lobe predominant, making airway clearance harder.
- CF has upper lobe disease, higher sputum DNA, and more frequent physiotherapy, enhancing benefit.

Patient factors:

- Older age in idiopathic bronchiectasis reduced muscle strength, impaired immunity, decreased mucociliary clearance, and reduced elastic recoil.
- Thinned secretions may pool distally and worsen infection.

Chest. 1998 May;113(5):1329-34

Summary

- **Structure and function of mucin**
  - ✓ Mucins, including MUC5B and MUC5AC, play key roles in structural **stability** of mucus, **mucociliary clearance**, **pathogen trapping**, and **airway protection**.

- **Pathogenesis of mucus dysfunction**
  - ✓ Mucus dysfunction arises from **abnormal mucin overexpression** driven by **inflammatory cytokines** and **altered osmolarity** due to **ENaC activation** and **CFTR inhibition**, leading to accumulation of viscous mucus and impaired airway clearance.

Summary

- **Osmotic agents for airway clearance**
  - ✓ **Mannitol** and **hypertonic saline** and hydrate the airway, disrupt mucus structure, reduce viscosity, and facilitate mucus clearance
  - ➔ Improved **sputum burden, exacerbation risk**, **QoL,** and **lung function** (*Controversial*)

- **Muco-active agents**
  - ✓ **N-acetylcysteine** and **erdosteine** may reduce mucus viscosity, enhance clearance, remove ROS
  - ➔ Decreased **sputum burden** and **exacerbation** (*Controversial*)
  - ✓ **Against suggestion: rhDNase**
  - ➔ Worsened **exacerbation** and **lung function** in non-cystic fibrosis bronchiectasis

Thank you for your attention