2021.10.02

대한결핵 및 호흡기학회, 2021 기침연구회 개원의 연수강좌

가래를 조절하는 약제

문 지 용

한양대학교구리병원

Contents

주요 호흡기 증상들

- 기침
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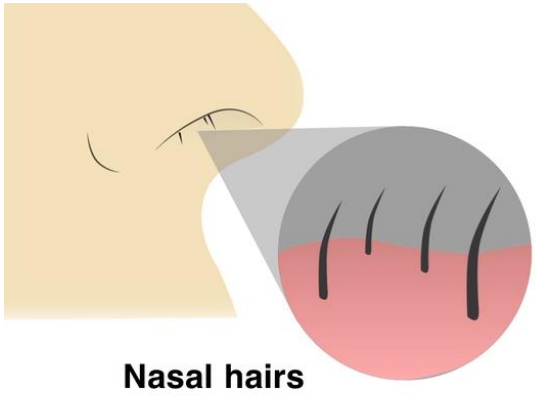
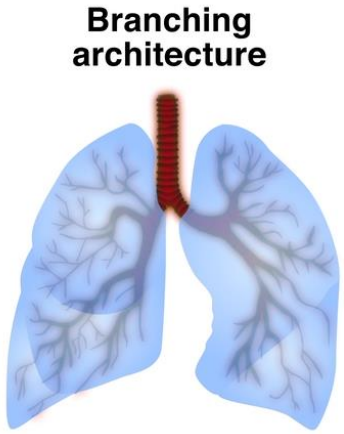
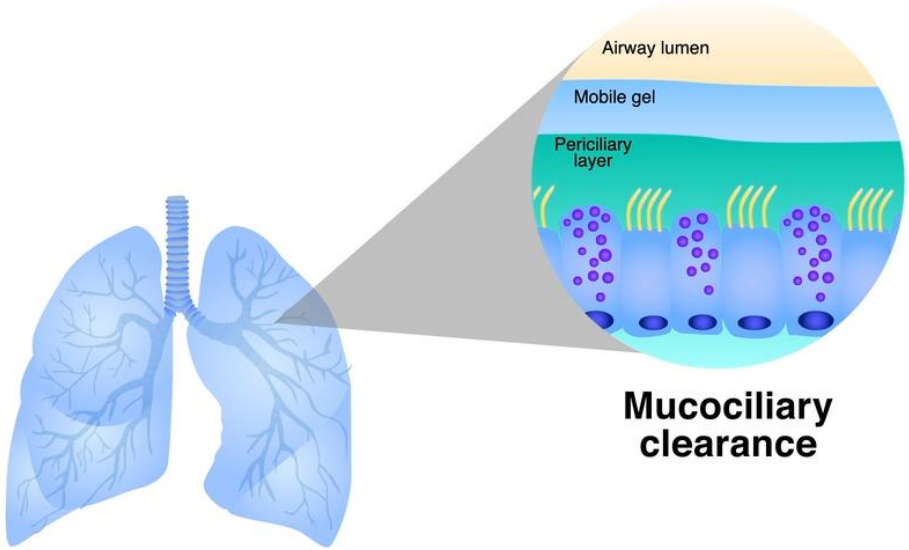
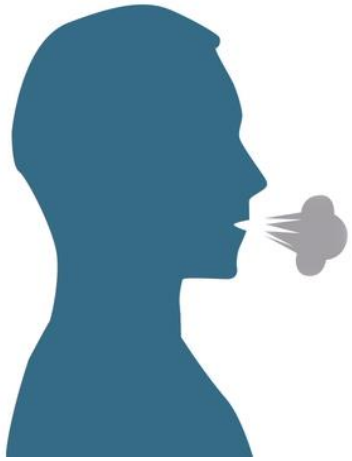
- 흉부불편감(가슴 답답함)
- 천명(쌕쌕거림)

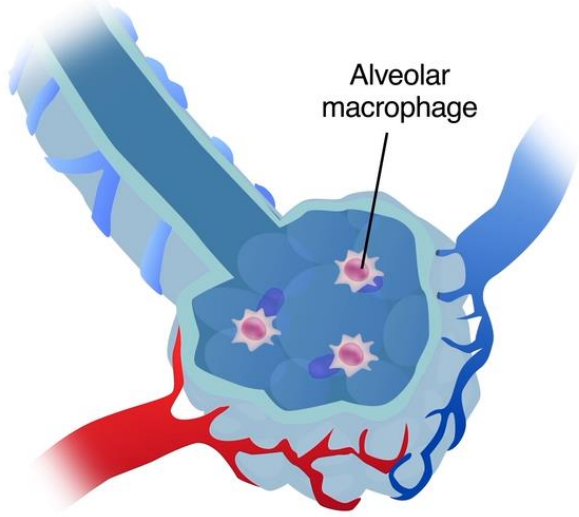
호흡기계(Respiratory System)를 보호하기 위한 작용들











Harrison's Principles of Internal Medicine, 20e > Pneumonia

Mucus

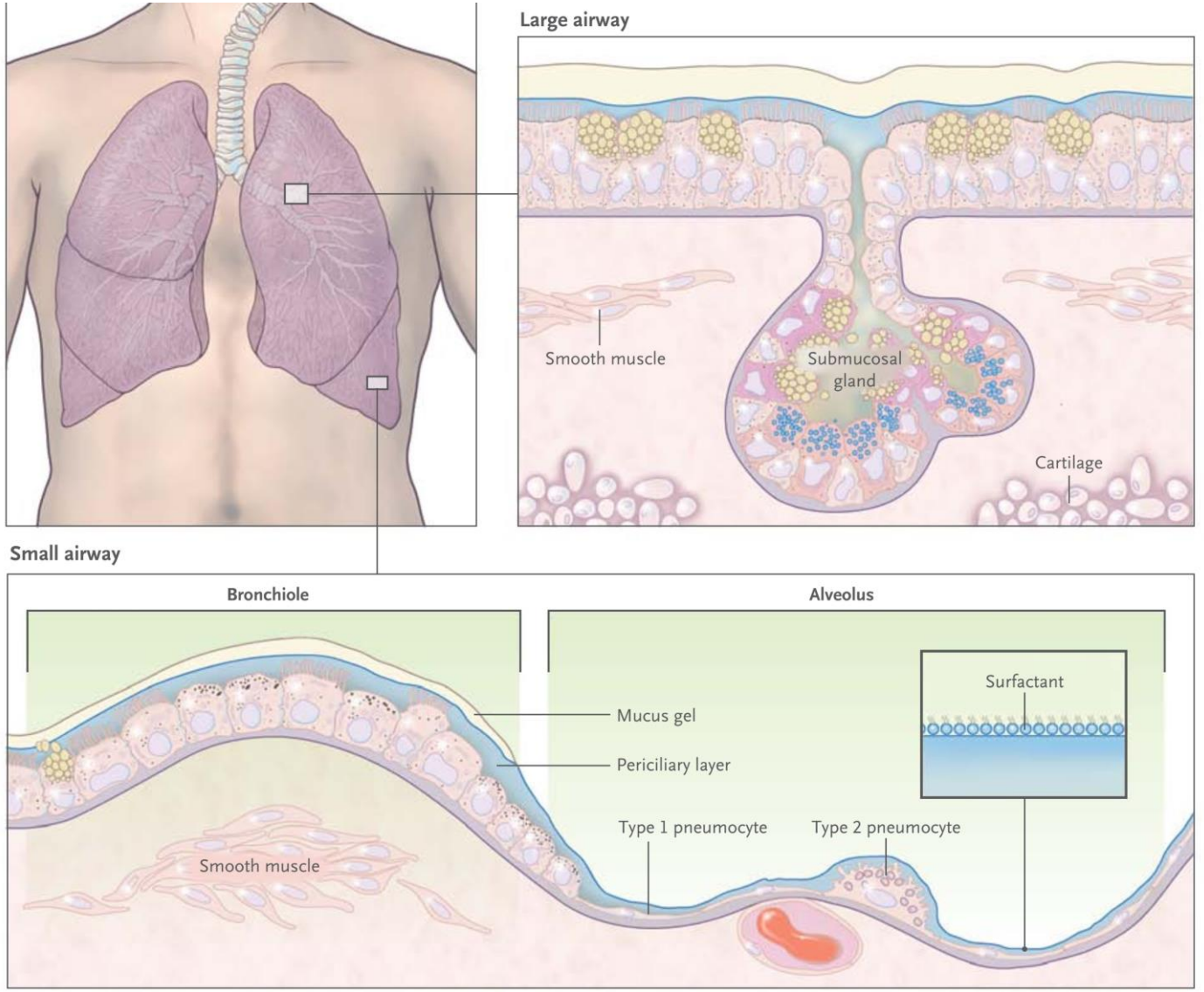
- Mucus = mucous secretion
  - Increased mucus = mucous hypersecretion
  - Mucus consists of **water (95%)**, most of which is bound in a **viscoelastic gel** containing **mucins**.
- Mucins: mucus의 주성분
  - 19 mucin (MUC) genes: two groups
    - **Membrane** associated mucins: *MUC1, MUC4*
    - **Gel-forming** secreted mucins: two are especially prominent in inflammatory airway diseases
      - ***MUC5AC*** in airway goblet cells (**large** [luminal diameter, >2 mm] and **small** airway)
      - ***MUC5B*** in submucosal gland mucous cells (**large airway**)
      - The gel-forming mucins in mucus are **high-molecular weight glycoproteins** that are key components of mucous cells and are rich in carbohydrates

Mucus

- Epithelial mucin production and secretion play major roles in **clearance** of inhaled "**invaders**" by **cough** and by **mucociliary clearance**.
- **Normally** mucin production is modest, and inhaled foreign substances are cleared **asymptomatically** and without obvious pathologic changes.
- Mucous hypersecretion in the **large conducting airways** is manifested in **symptoms**, predominantly **cough** and **sputum** production. Unlike the effects in the large airways, **bronchiolar hypersecretion** is generally **asymptomatic** early and consists of luminal **mucous plugging**, which can ultimately lead to **incapacitation** and death.

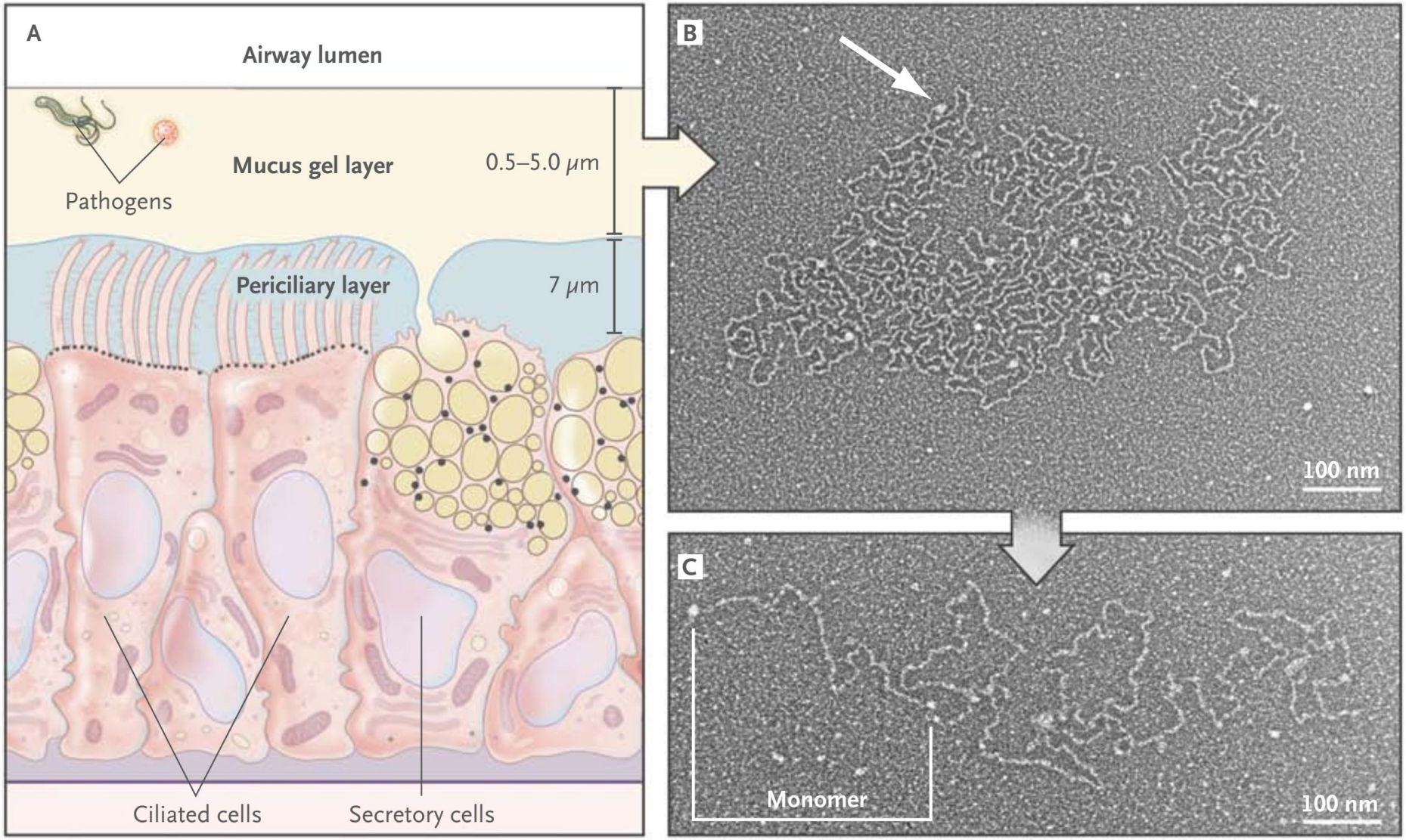
Murray 6th, Chapter 10 Airway Epithelium and Mucous Secretion

Mucus Clearance in Normal Airways



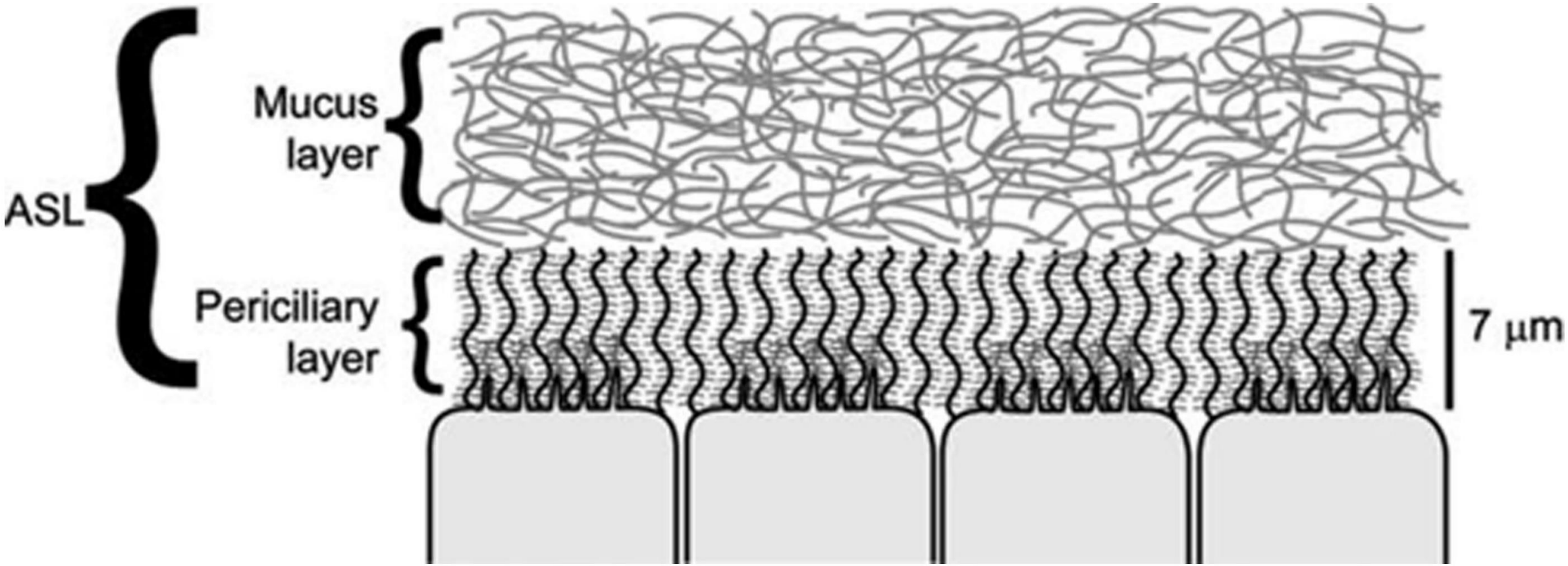
Fahy JV, N Engl J Med 2010;363:2233-47 [PMID 21121836]

Structure of Airway Mucus



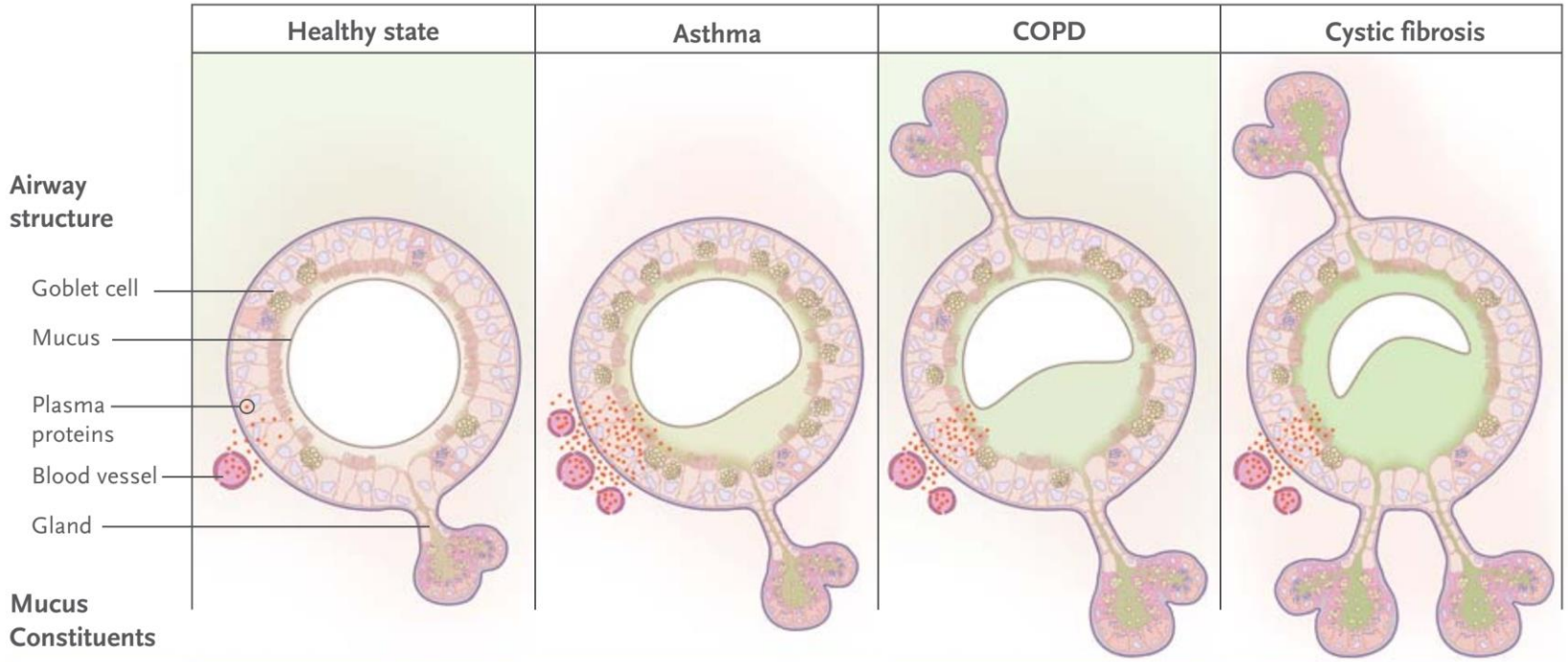
Fahy JV, N Engl J Med 2010;363:2233-47 [PMID 21121836]

Representation of the two layers that compose the airway surface layer (ASL)



Button B, Respir Physiol Neurobiol 2008;163:189-201 [PMID 18585484]

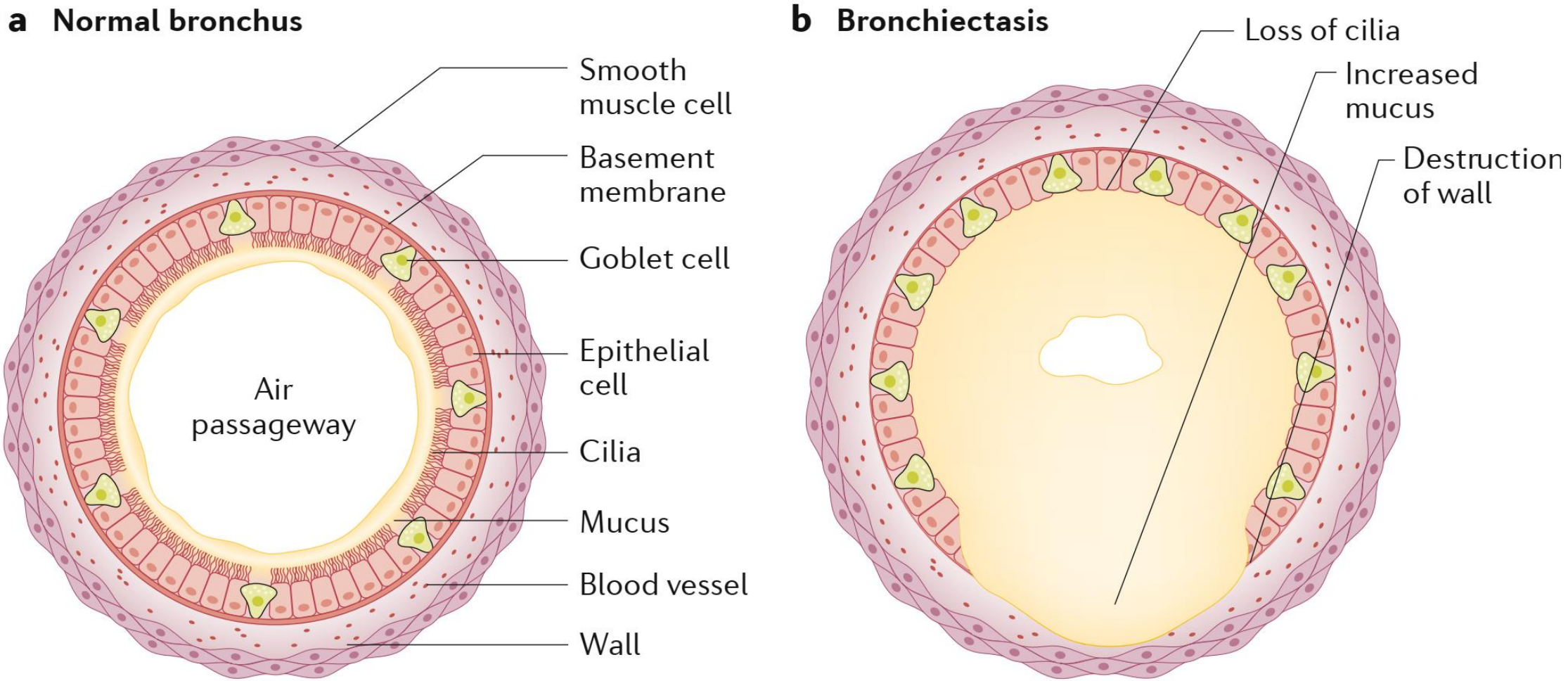
Airway Mucosal Disease and Mucus Characteristics



	Healthy state	Asthma	COPD	Cystic fibrosis
Mucin	X X	X X X X X	X X X X	X X X X
Plasma proteins	X	X X X X	X X	X X
Inflammatory cells	X	X X X	X X X	X X X X X
DNA		X	X X	X X X X X
Actin		X	X X	X X X X X
Bacteria			X X	X X X X X

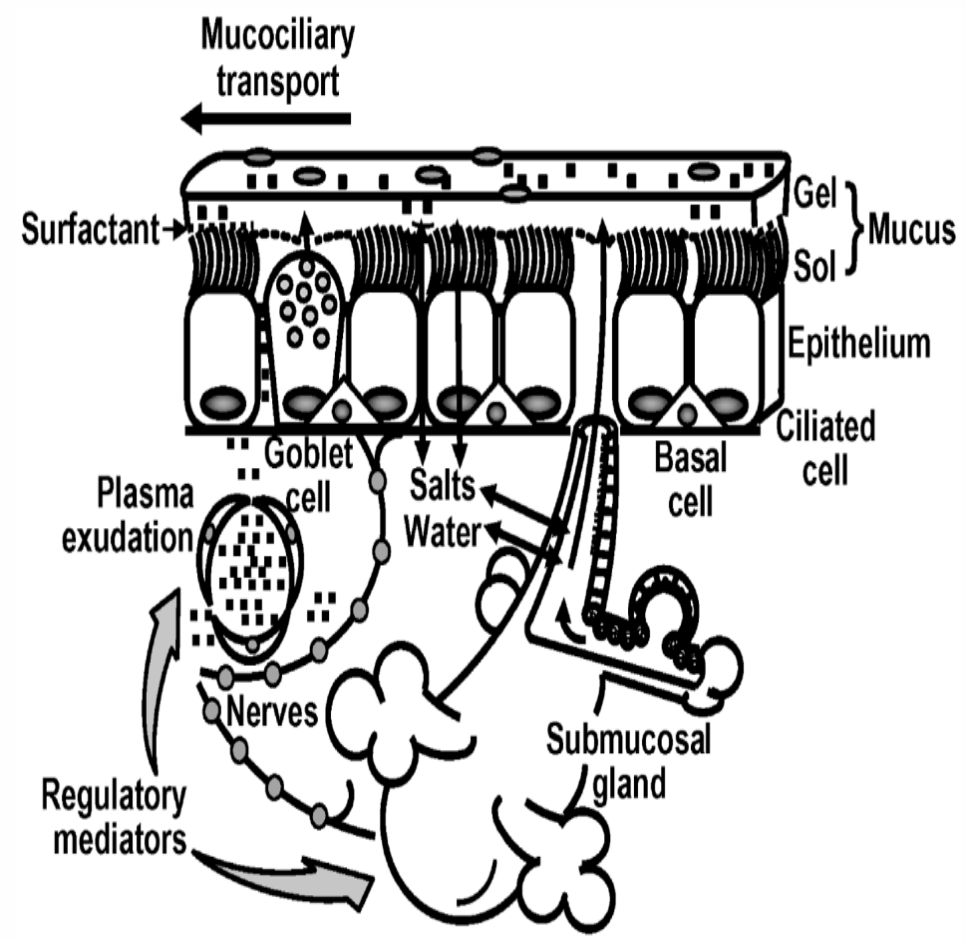
Fahy JV, N Engl J Med 2010;363:2233-47 [PMID 21121836]

Morphology of Healthy and Dilatated Bronchi



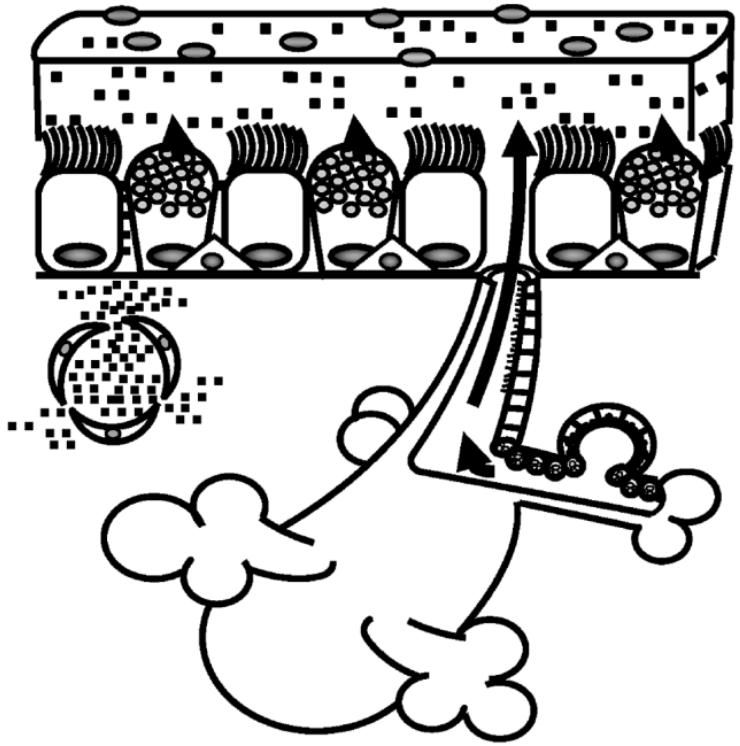
Chalmers JD, Nat Rev Dis Primers 2018;4:45 [PMID 30442957]

Airway Mucus Secretion and Hypersecretion



Inflammation

Asthma or COPD or (CF)



Rogers DF, Respir Care 2007;52:1134-46; discussion 46-9 [PMID 17716382]

Examples of Stimuli That Induce Mucin Synthesis *in vitro* or *in vivo* by EGFR Activation in Airways

In vitro experiments

- Bacterial products:
  - *P aeruginosa* supernatant[15]
  - Lipopolysaccharide (LPS)[15 16]
  - Lipoteichoic acid (LTA)[17]
- Phorbol 12-myristate 13-acetate (PMA)[16]
- Cigarette smoke[18]
- Inflammatory cells:
  - Neutrophils[19]
  - Eosinophils[20]
- Serine proteases:
  - Human neutrophil elastase[21]
  - Human airway trypsin-like protease[22]

In vivo experiments

- Th2 cells
  - Antigen (ovalbumin)[13]
  - IL-13[23]
- Mechanical damage of epithelium[24]
- Cigarette smoke[18]
- Leukotrienes[25]

Burgel PR, Thorax 2004;59:992-6 [PMID 15516478]

Mucous Hypersecretion

- **Asthma**
  - **Goblet cell** numbers in the conducting airways are **increased** even in mild asthma
  - A history of asthma with **chronic sputum** overproduction is associated with an **accelerated decline** in maximal **expiratory airflow** (indicative of airway obstruction)
- **COPD**
  - Increased expression of mucins in bronchioles in COPD and an increased number of **goblet cells** in peripheral airways.
  - Chronic mucous hypersecretion is often associated with **excessive decline** in pulmonary **function** and **increased risk** for **hospitalization**.
  - The **progression** of COPD was strongly associated with an increase in **inflammatory mucous exudates** in the lumens of small airways.

Lange P, N Engl J Med 1998;339:1194-200 [PMID 9780339]
Vestbo J, Am J Respir Crit Care Med 1996;153:1530-5 [PMID 8630597]

Impaired Mucociliary Clearance

- Conditions
  - **asthma**
  - chronic bronchitis/**COPD**
  - cystic fibrosis
  - **bronchiectasis**
  - primary ciliary dyskinesia
- Interventions
  - **Cough clearance** by physical therapy
  - **Mechanical** interventions
    - Flutter valves
    - Vibration vests
  - **Pharmaceutical** interventions

Lin VY, Eur Respir J 2020;55 [PMID 31672759]

Factors That Improve Mucociliary Transport

- increased **ciliary beat frequency**
- higher mucus **elasticity** (to store the transmitted energy)
- lower mucus **viscosity** (to reduce loss of energy)
- higher **adhesivity** (that hinders wave formation in the gel layer)
- increased **spinnability** (a measure of the thread forming ability of mucus)
- a thinner **mucus layer**
- a **periciliary (sol) layer** that is just less than the height of the cilia (to improve coupling with ciliary tips)

Rogers DF, Respir Care 2007;52:1176-93; discussion 93-7 [PMID 17716385]

Factors That Improve Cough Clearance

- lower mucus **elasticity** (to reduce recoil of cough-sheared mucus)
- higher mucus **viscosity**
- lower **adhesivity** (to promote wave formation in the gel)
- lower **spinnability** (ability to be spun into a thread)
- a thicker **mucus layer**
- a **periciliary layer** that is higher than the height of the cilia

Rogers DF, Respir Care 2007;52:1176-93; discussion 93-7 [PMID 17716385]

Mucoactive Drugs & Their Potential Mechanisms of Action

Mucoactive drugs	Potential mechanism of action
Expectorants	
Hypertonic saline (고장성 식염수)	Increases secretion volume and/or hydration
Guaifenesin	Stimulates secretion and reduces mucus viscosity
Mucoregulators	
Carbocisteine (OTC)	Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production
Anticholinergic agents (tiotropium etc.)	Decreases secretion volume
Glucocorticoids	Reduces airway inflammation and mucin secretion
Macrolide antibiotics	Reduces airway inflammation and mucin secretion

Balsamo R et al., Eur Respir Rev. 2010 Jun;19(116):127-33.

Mucoactive Drugs & Their Potential Mechanisms of Action

Mucoactive drugs	Potential mechanism of action
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 b_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
Bromhexine (OTC)	

#: also referred to as cough clearance promoters.

Balsamo R et al., Eur Respir Rev. 2010 Jun;19(116):127-33.

Contents

ERJ open research

ORIGINAL ARTICLE
COPD

Effect of hypertonic saline on mucociliary clearance and clinical outcomes in chronic bronchitis

William D. Bennett [1,2,4], Ashley G. Henderson[1,4], Agathe Ceppe[1], Kirby L. Zeman[2], Jihong Wu[2], Christine Gladman[3], Fred Fuller[1], Stephen Gazda[1], Brian Button[1], Richard C. Boucher[1] and Scott H. Donaldson[1]

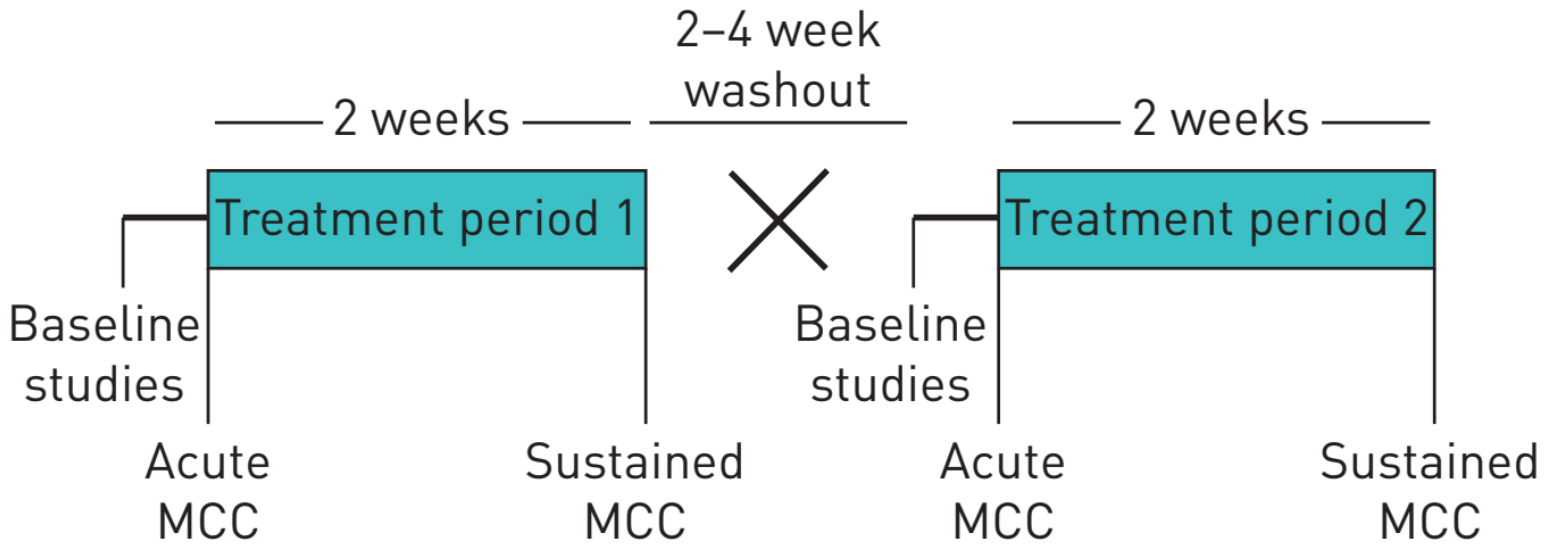


FIGURE 1 Study design. MCC: mucociliary clearance.

Bennett WD, ERJ Open Res 2020;6 [PMID 32802823]

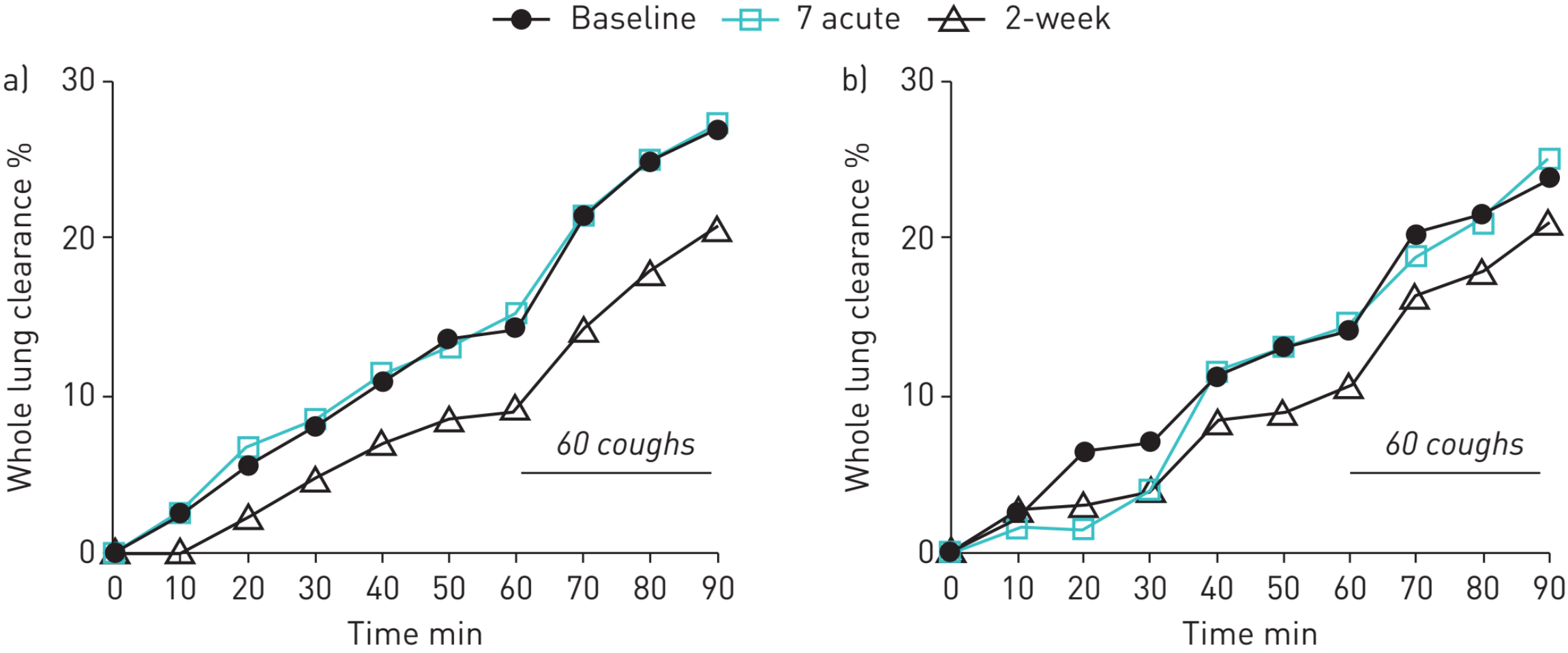


FIGURE 3 a) Mean whole lung mucus clearance for inhaled 7% hypertonic saline. b) Mean whole lung mucus clearance for inhaled 0.12% saline.

Bennett WD, ERJ Open Res 2020;6 [PMID 32802823]

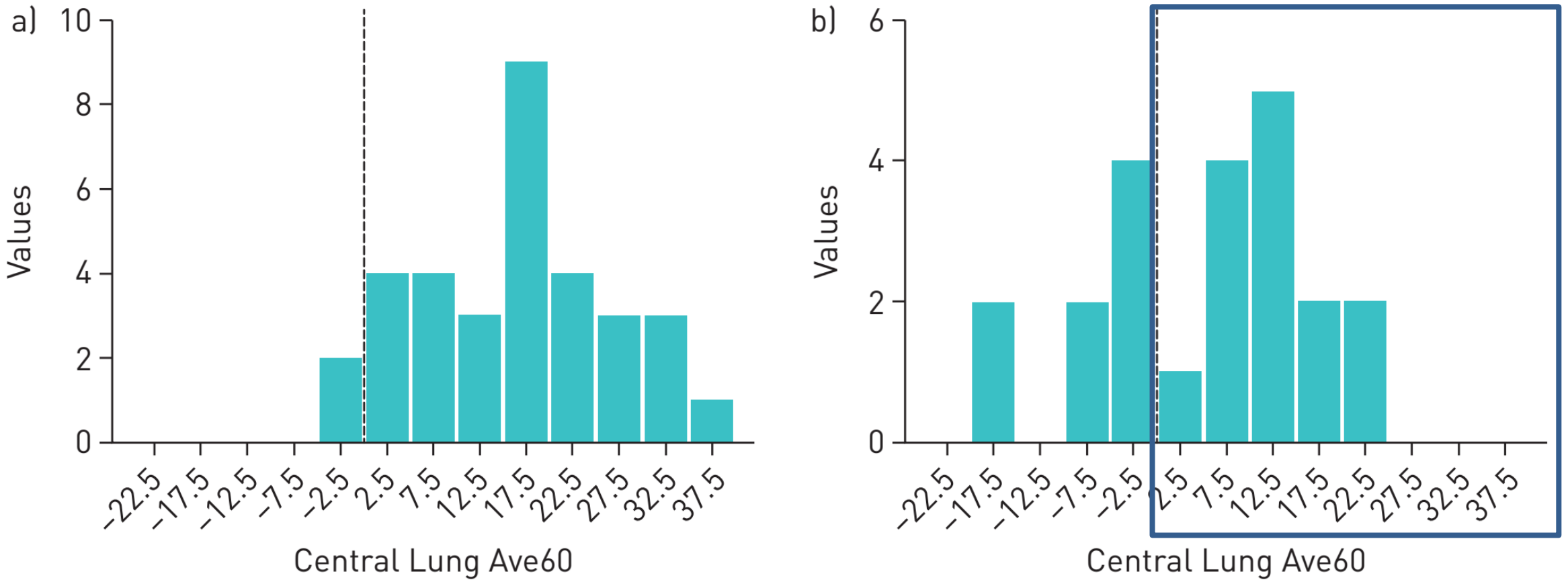


FIGURE 2 Distribution of Central Lung average clearance through 60 min (Ave60Clr) (%) values in a) healthy and b) chronic bronchitis (CB) subjects. Dotted line indicates zero net clearance over 60 min.

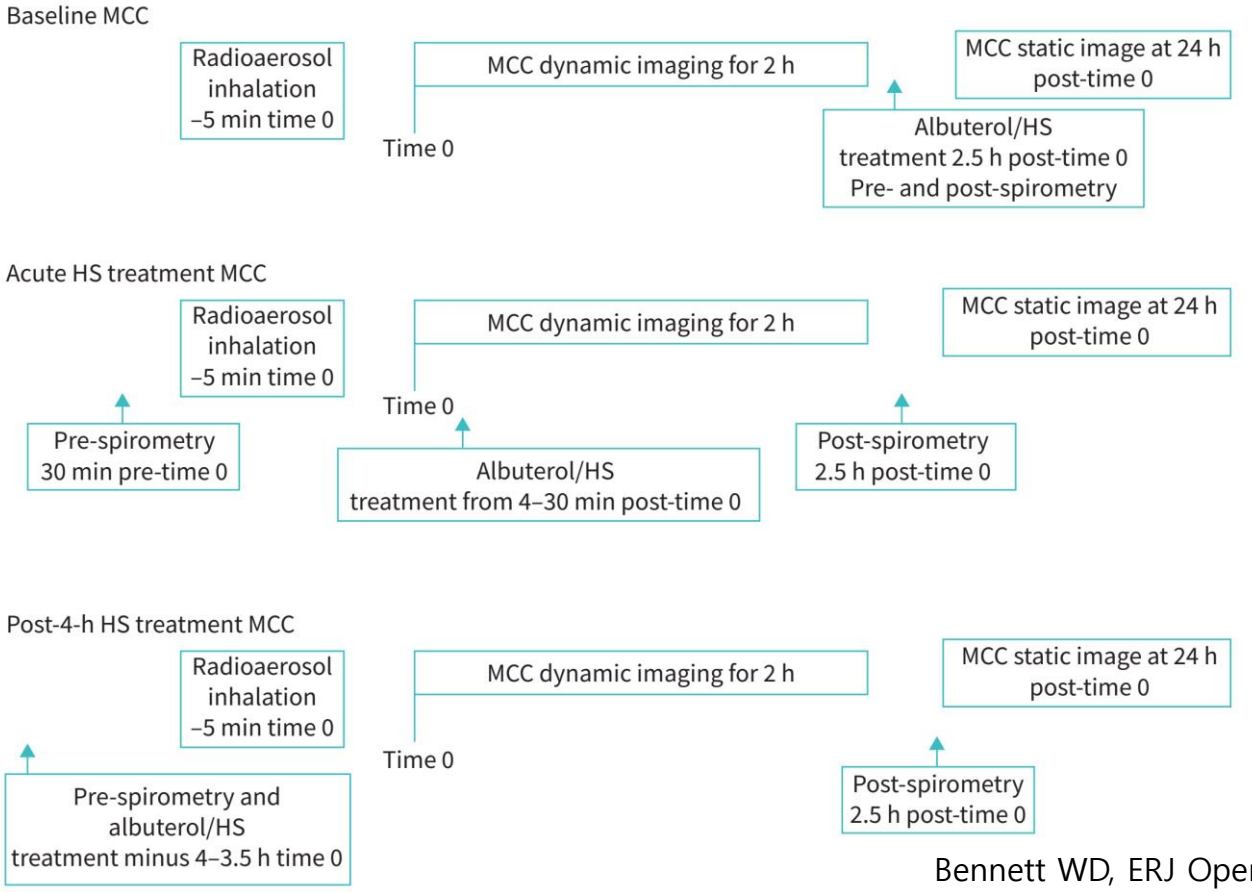
Bennett WD, ERJ Open Res 2020;6 [PMID 32802823]

ERJ open research

ORIGINAL ARTICLE
ASTHMA

Acute and durable effect of inhaled hypertonic saline on mucociliary clearance in adult asthma

William D. Bennett [1,2], Allison Burbank[1,3], Martha Almond[1], Jihong Wu[1], Agathe Ceppe[2], Michelle Hernandez[1,3], Richard C. Boucher[2] and David B. Peden [1,3]



Bennett WD, ERJ Open Res 2021;7 [PMID 34109248]

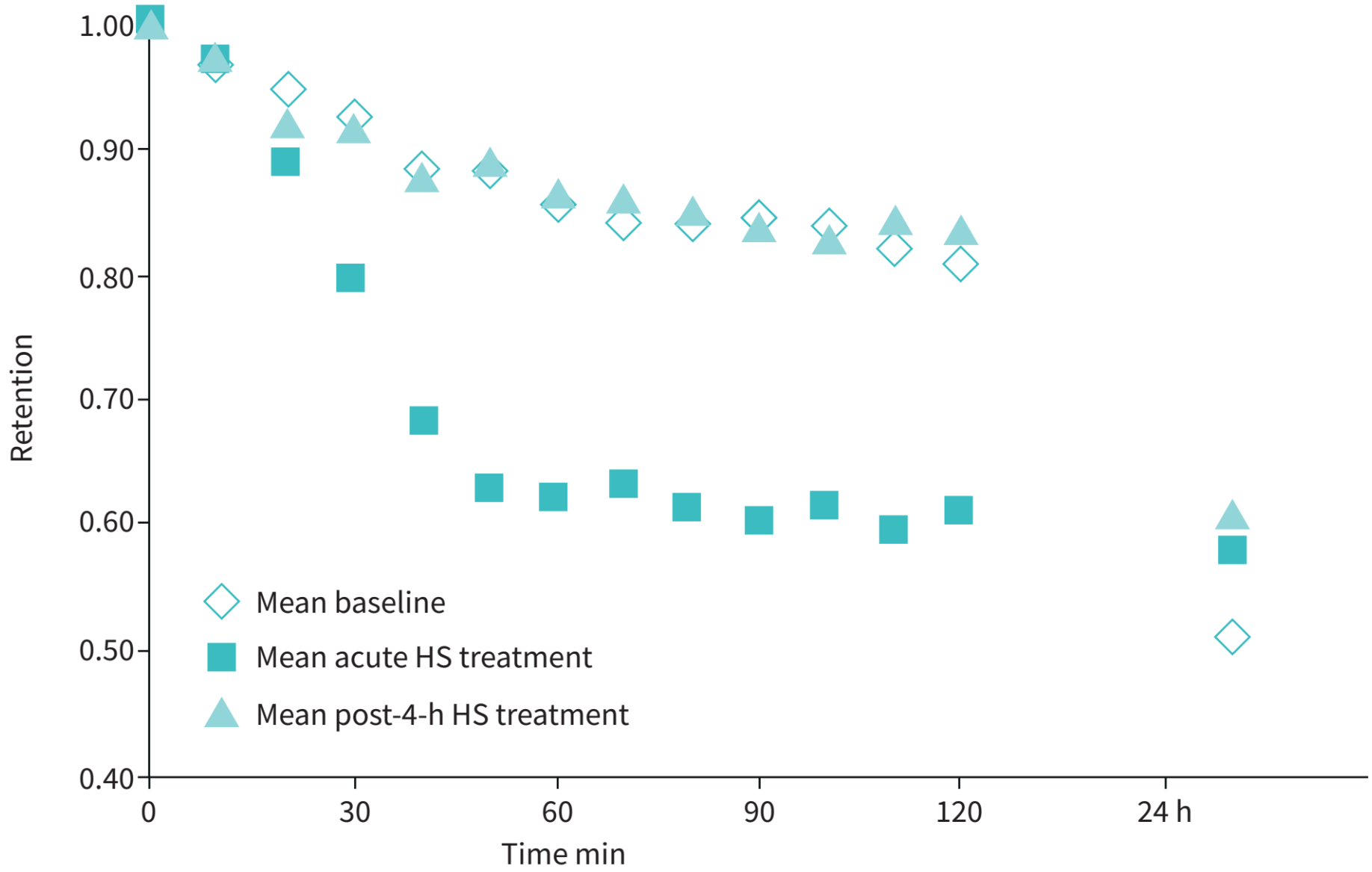


FIGURE 2 Mean retention *versus* time for the baseline, acute hypertonic saline (HS) treatment, and post-4-h HS treatment for eight adult female asthmatics.

Bennett WD, ERJ Open Res 2021;7 [PMID 34109248]

Table 1. Guaifenesin: Mechanism of Action and Effects on Mucus

Ref #	First Author (Year)	Study Design	Observed Mechanism of Action
23	Chodosh S (1964)	Double-blind.100 mg guaifenesin daily for 14 days versus placebo. In vivo	Decreased sputum surface tension
24	Chodosh S (1973)	Double-blind, crossover. 800 or 2400 mg/day guaifenesin for 4 weeks versus placebo. In vivo	Reduced surface tension and adhesiveness of mucus; Improved mucociliary clearance
25	Thomson ML (1973)	Double-blind, crossover study. 600 mg guaifenesin versus placebo. In vivo.	Increased mucociliary clearance
26	Dicpinigaitis PV (2003)	Randomized, single-blind study. Single dose of 400 mg guaifenesin versus placebo. In vivo.	Inhibition of cough reflex sensitivity through (1) a central antitussive effect (2) a peripheral effect whereby increased sputum volume shields cough receptors in the respiratory epithelium from tussive stimuli
27	Kagan L (2009)	Rat model PK study	Expectorant effect is mediated by stimulation of the gastrointestinal tract and not by systemic exposure
28	Seagrave J (2011)	In vitro	Suppressed mucin production; Increased mucociliary transport; Decreased mucus viscoelasticity
29	Seagrave J (2012)	In vitro	Inhibition of mucin [MUC5AC] production; Reduced viscosity and elasticity of mucus; Increased mucociliary transport rates

Ohar JA, Chronic Obstr Pulm Dis 2019;6:341-9 [PMID 31647856]

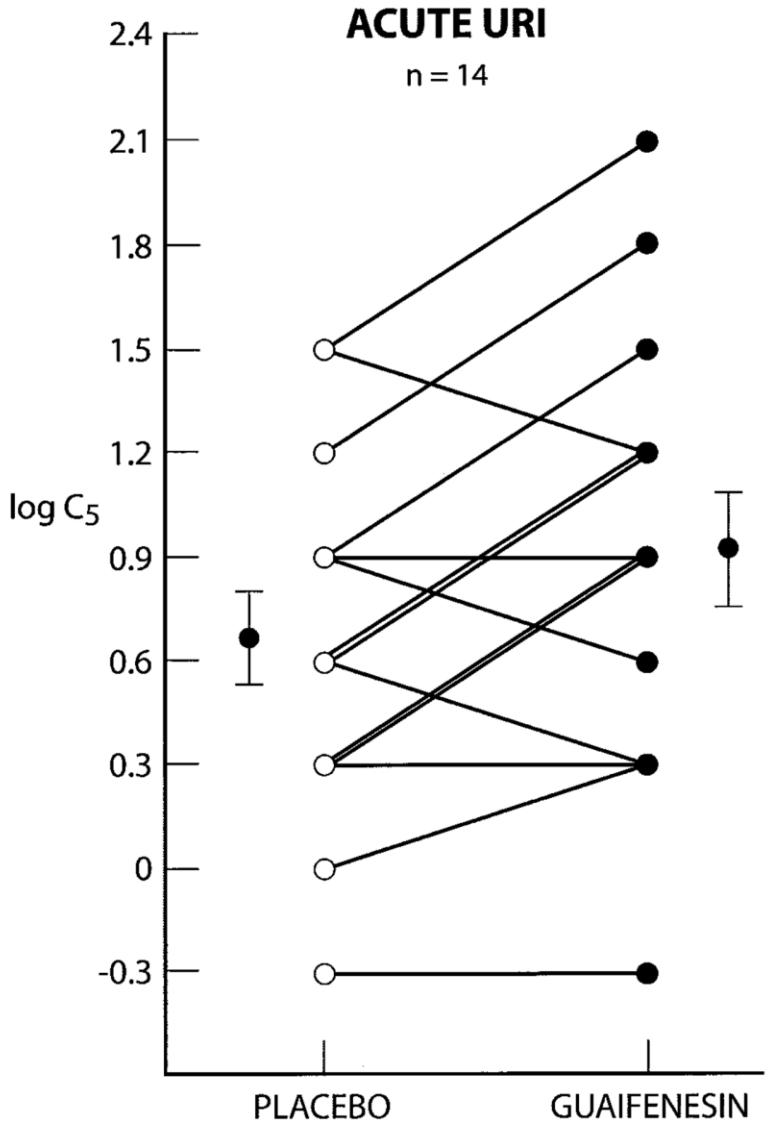


FIGURE 1. Effect of a single 400-mg dose of guaifenesin on cough reflex sensitivity to inhaled capsaicin compared to placebo in subjects with URI. Mean (± SEM) log C_5 after guaifenesin and placebo: 0.92 ± 0.17 and 0.66 ± 0.14, respectively ($p = 0.028$). Error bars indicate ± SEM.

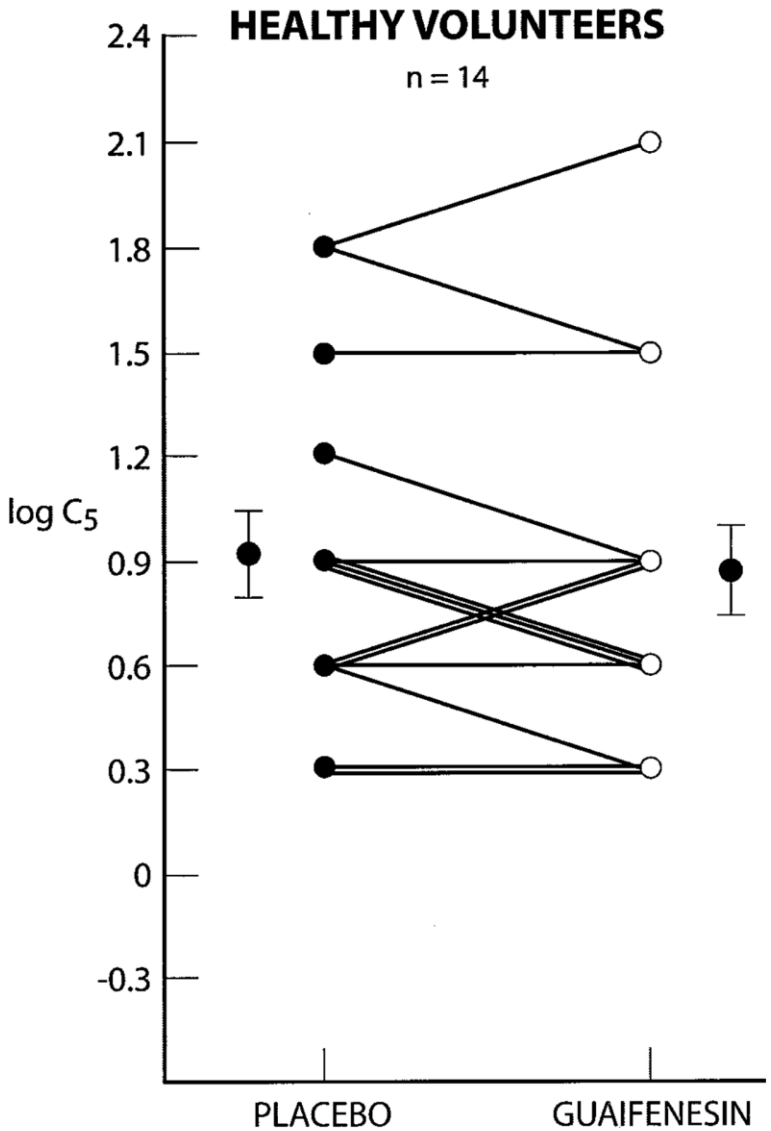


FIGURE 2. Effect of a single 400-mg dose of guaifenesin on cough reflex sensitivity to inhaled capsaicin compared to placebo in healthy volunteers. There was no significant difference in mean log C_5 between studies. Error bars indicate ± SEM.

Dicpinigaitis PV, Chest 2003;124:2178-81 [PMID 14665498]

Albrecht *et al. Respiratory Research* 2012, **13**:118
http://respiratory-research.com/content/13/1/118

RESPIRATORY RESEARCH

RESEARCH Open Access

Patient-reported outcomes to assess the efficacy of extended-release guaifenesin for the treatment of acute respiratory tract infection symptoms

Helmut Albrecht[1*], Margaret Vernon[2] and Gail Solomon[3]

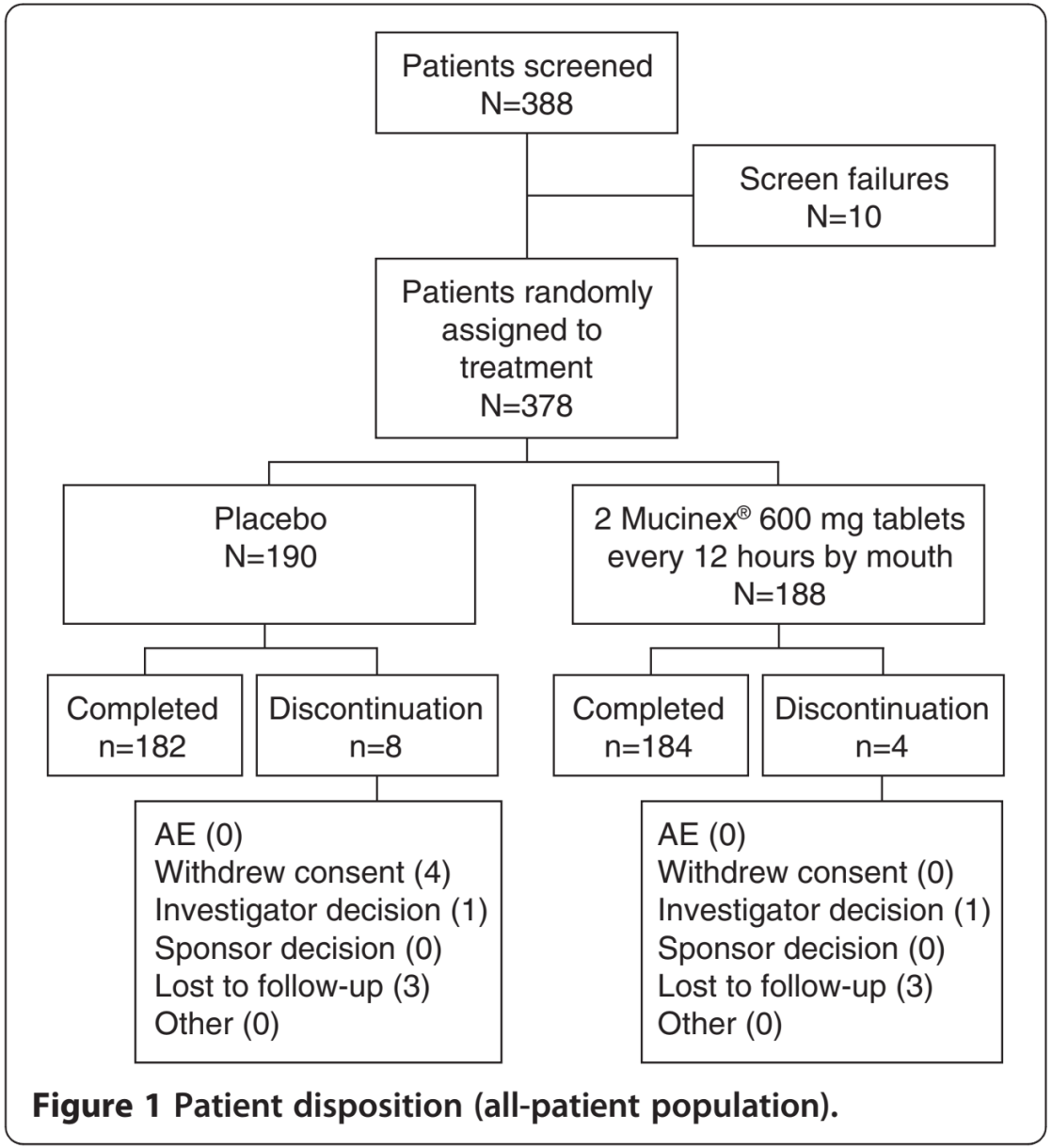


Figure 1 Patient disposition (all-patient population).

Albrecht H, Respir Res 2012;13:118 [PMID 23270519]

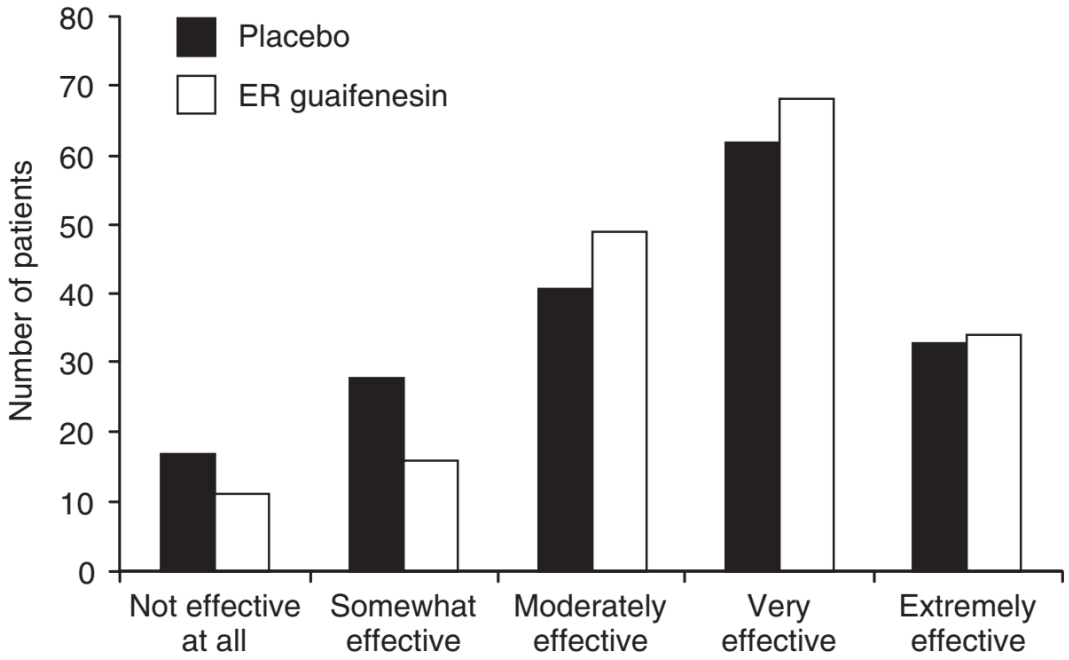


Figure 2 Patient's End-of-Treatment Assessment (mITT population) for the question "Was the study medication effective?".

Table 6 Internal consistency reliability symptom subscale (items 1, 2, 4, 5, 8, 9, 10 and 11) score at Days 1, 4, and 8 (Cronbach's Alpha)

Item	Cronbach's alpha			Cronbach's alpha with item deleted		
	Day 1	Day 4	Day 8	Day 1	Day 4	Day 8
Subscale score alpha	0.76 (n = 310)	0.87 (n = 305)	0.90 (n = 290)			
1. Bring up phlegm				0.73	0.84	0.88
2. Difficult to breathe				0.72	0.84	0.88
4. Annoyed by phlegm				0.71	0.83	0.87
5. Interference with ability to speak				0.71	0.84	0.88
8. Phlegm thickness				0.72	0.85	0.88
9. Difficulty bringing up phlegm				0.81	0.90	0.93
10. Cough when woke up				0.73	0.84	0.88
11. Cough during day				0.74	0.84	0.88

Albrecht H, Respir Res 2012;13:118 [PMID 23270519]

CHEST

Original Research

BRONCHIECTASIS

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

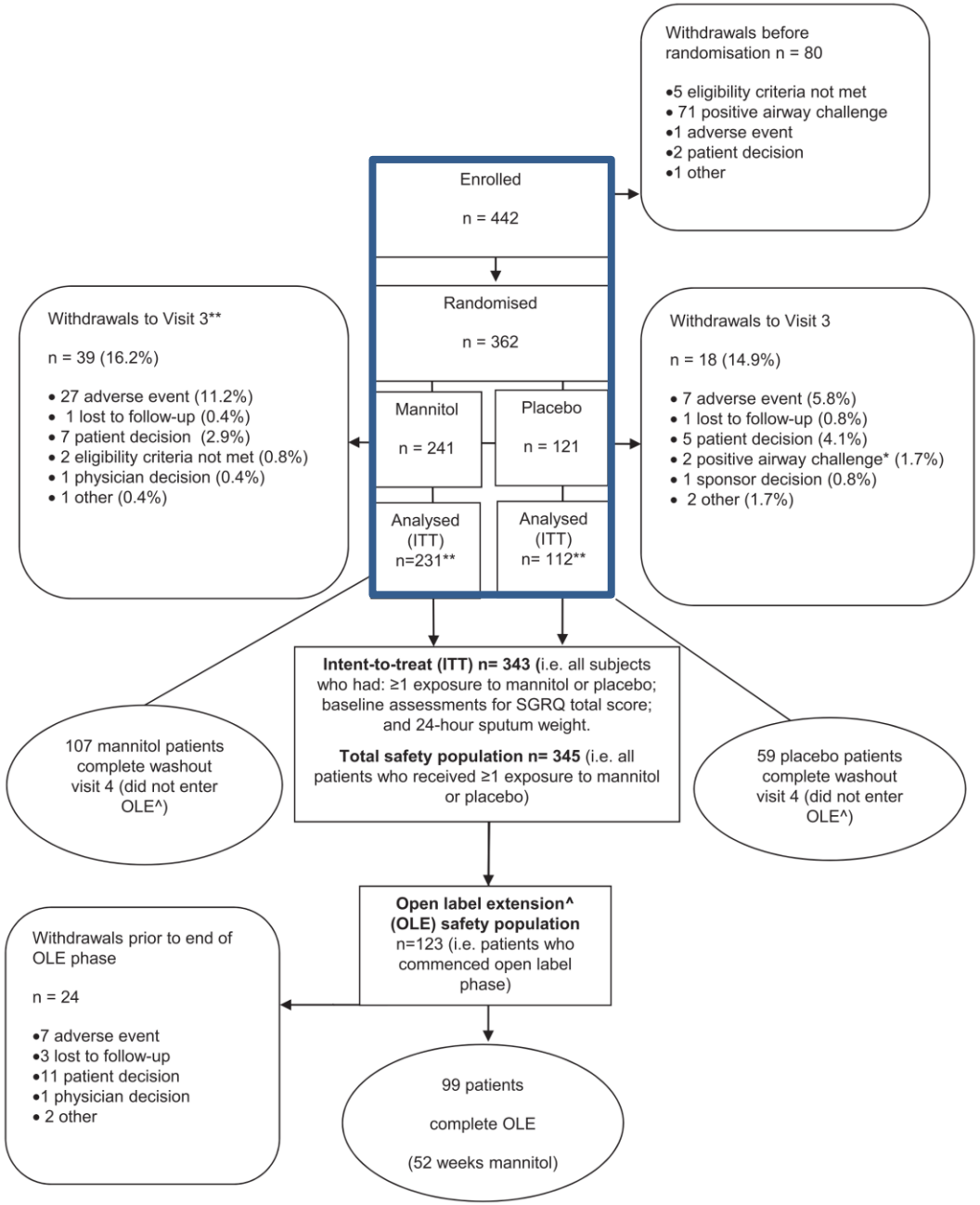
Diana Bilton, MD; Evangelia Daviskas, MBiomedE, PhD; Sandra D. Anderson, PhD, DSc; John Kolbe, MBBS; Gregory King, MBChB, PhD; Rob G. Stirling, MBBCh(Hons); Bruce R. Thompson, PhD; David Milne, MBChB; and Brett Charlton, PhD; for the B301 Investigators

Table 1—*Study Inclusion and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
Age 15-80 y	Bronchiectasis due to CF or focal endobronchial lesion
Bronchiectasis confirmed by HRCT scan	Terminally ill or listed for transplant
$FEV_1 \geq 50\%$ predicted and ≥ 1.0 L	Previous mannitol trial, or participating in any other trial, or used hypertonic saline within 4 wk prior to entry
Clinically stable (for ≥ 2 wk prior to study entry) and persistent cough (present for the majority of days during 3 mo prior to enrollment)	Hemoptysis (>60 mL) in previous 6 mo or IV antibiotics prescribed for an exacerbation within 4 wk prior to entry
Chronic sputum (>10 mL/d on the majority of days in the 3 mo prior to enrollment)	Active signs of asthma, malignancy, or TB, or uncontrolled hypertension
Chronic chest congestion (chronic excessive accumulation of mucus)	Smoking history (≥ 20 pack-y or >1 cigarette/wk within the previous 3 mo)
Ability to perform techniques necessary to measure lung function	MI, CVA, or ocular/abdominal/chest/brain surgery within the previous 3 mo
Provided written informed consent	Pregnancy or lactation
	Patient likely to develop bronchoconstriction, based on his/her clinical history (including medications) and a positive Aridol test, or the presence of any other condition likely to place the patient at risk

CF = cystic fibrosis; CVA = cerebral vascular accident; HRCT = high-resolution CT; MI = myocardial infarction.

Bilton D, Chest 2013;144:215-25 [PMID 23429964]



*Withdrawn post randomisation due to late notification
**Withdrawals were to visit 3
^Only 12/22 sites participated in the OLE (10 Australian & 2 New Zealand centres)

Table 3—*Baseline Demographics, Lung Function, SGRQ, Sputum Weight, and Small Airways Mucus Plugging and Function in ITT Population (N = 343)*

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
Small airways mucus plugging on HRCT scan[c]		
Mean (SD)	13.0 (21.3)	12.4 (20.2)
Range	0-80	0-85
Small airway function: nitrogen washout[d]		
Scond, per L		
Mean (SD)	0.09 (0.08)	0.09 (0.05)
Range	0-0.23	0.02-0.21
Sacin, per L		
Mean (SD)	0.38 (0.21)	0.37 (0.12)
Range	0.20-0.80	0.10-0.63

Bilton D, Chest 2013;144:215-25 [PMID 23429964]

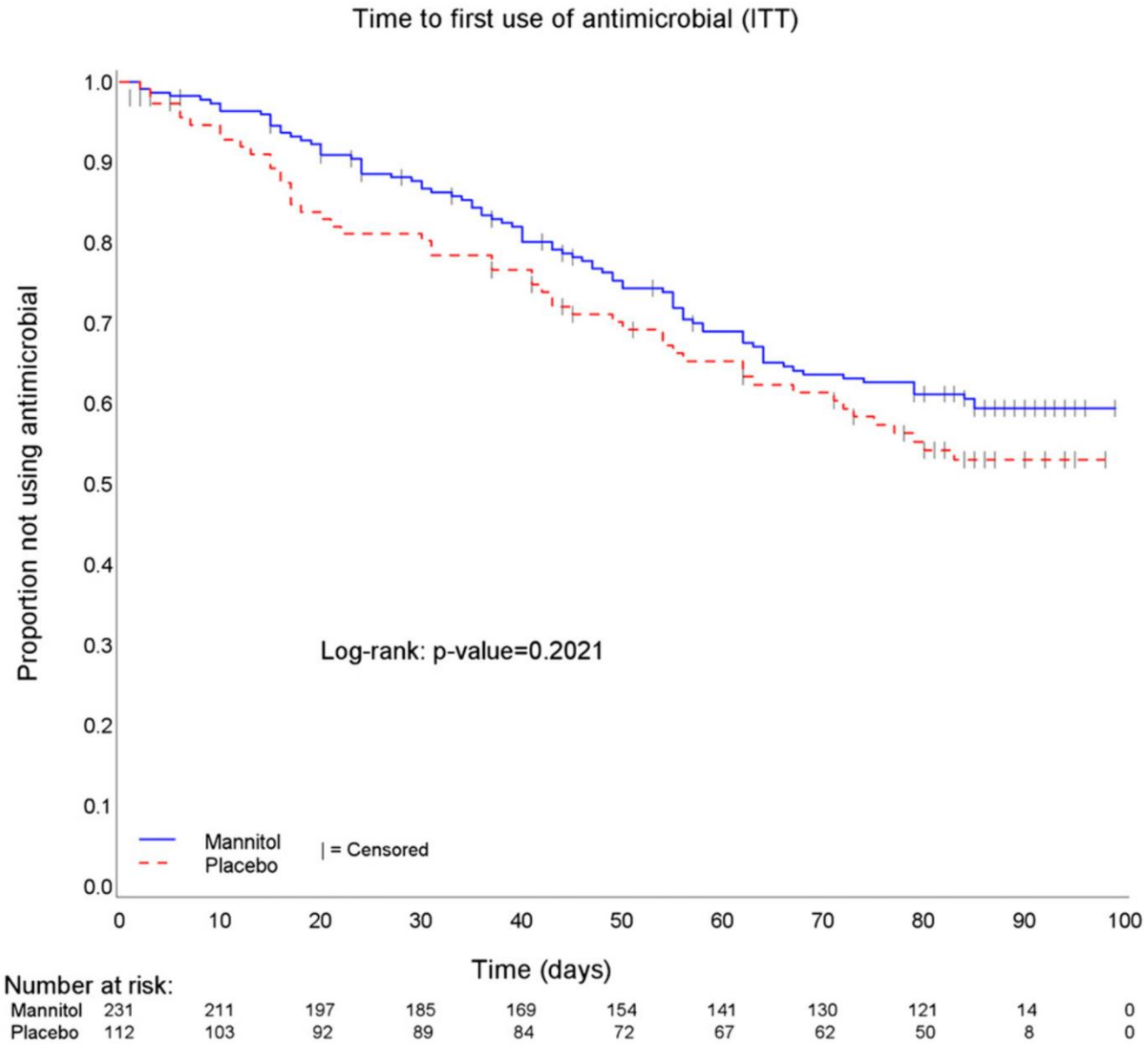
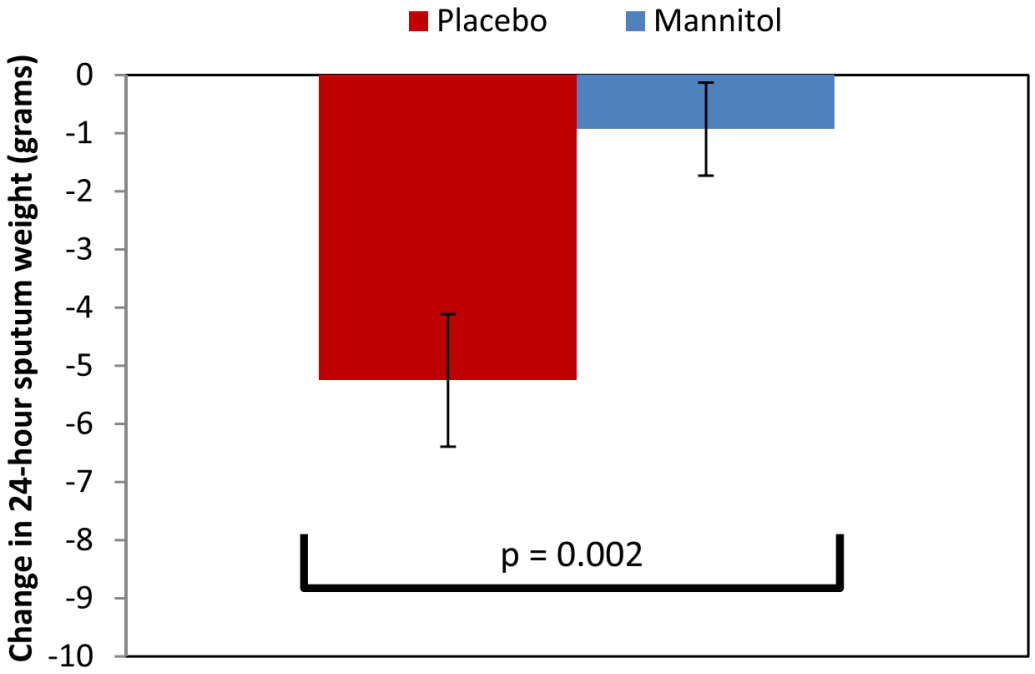
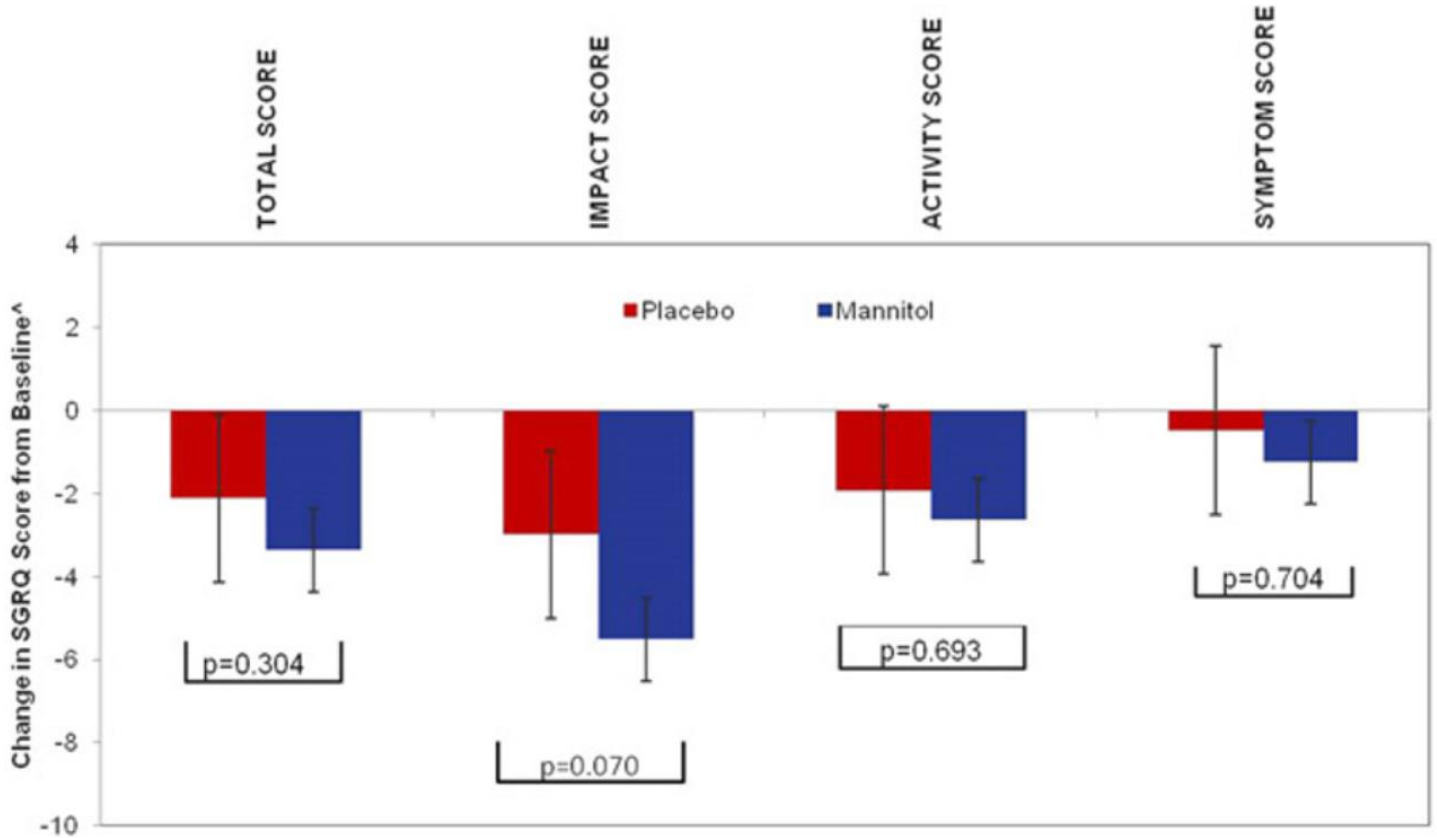


FIGURE 4. Kaplan-Meier plot for the time to first use of antimicrobials including week 12 (intention-to-treat).

Bilton D, Chest 2013;144:215-25 [PMID 23429964]





Bilton D, Chest 2013;144:215-25 [PMID 23429964]

Table 6—*Changes From Baseline at Week 12 in Small Airways Mucus Plugging and Function With Treatment in the ITT Population*

Parameter	Placebo		Mannitol		Group Differences: Mannitol-Placebo	
	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value
HRCT scans[a]						
Small airways mucus plugging	2.20 (−3.28-7.68)	.425	−4.39 (−8.15 to −0.63)	.023	−6.59 (−13.11 to −0.07)	.048
Small airway function: nitrogen washout[b]						
Scond, per L	0.02 (−0.04-0.08)	.465	0.03 (−0.01-0.06)	.095	0.01 (−0.06-0.08)	.809
Sacin, per L	−0.01 (−0.09-0.07)	.801	−0.10 (−0.15 to −0.05)	.0004	−0.09 (−0.18-0.00)	.061

See Table 1 and 3 legends for expansion of abbreviations.

[a]Baseline: placebo n = 28; mannitol n = 54; week 12: placebo n = 18; mannitol n = 45; both baseline and week 12: placebo n = 18; mannitol n = 42.

[b]Baseline: placebo n = 7; mannitol n = 17; week 12: placebo n = 8; mannitol n = 18; both baseline and week 12: placebo n = 5; mannitol n = 15.

Bilton D, Chest 2013;144:215-25 [PMID 23429964]

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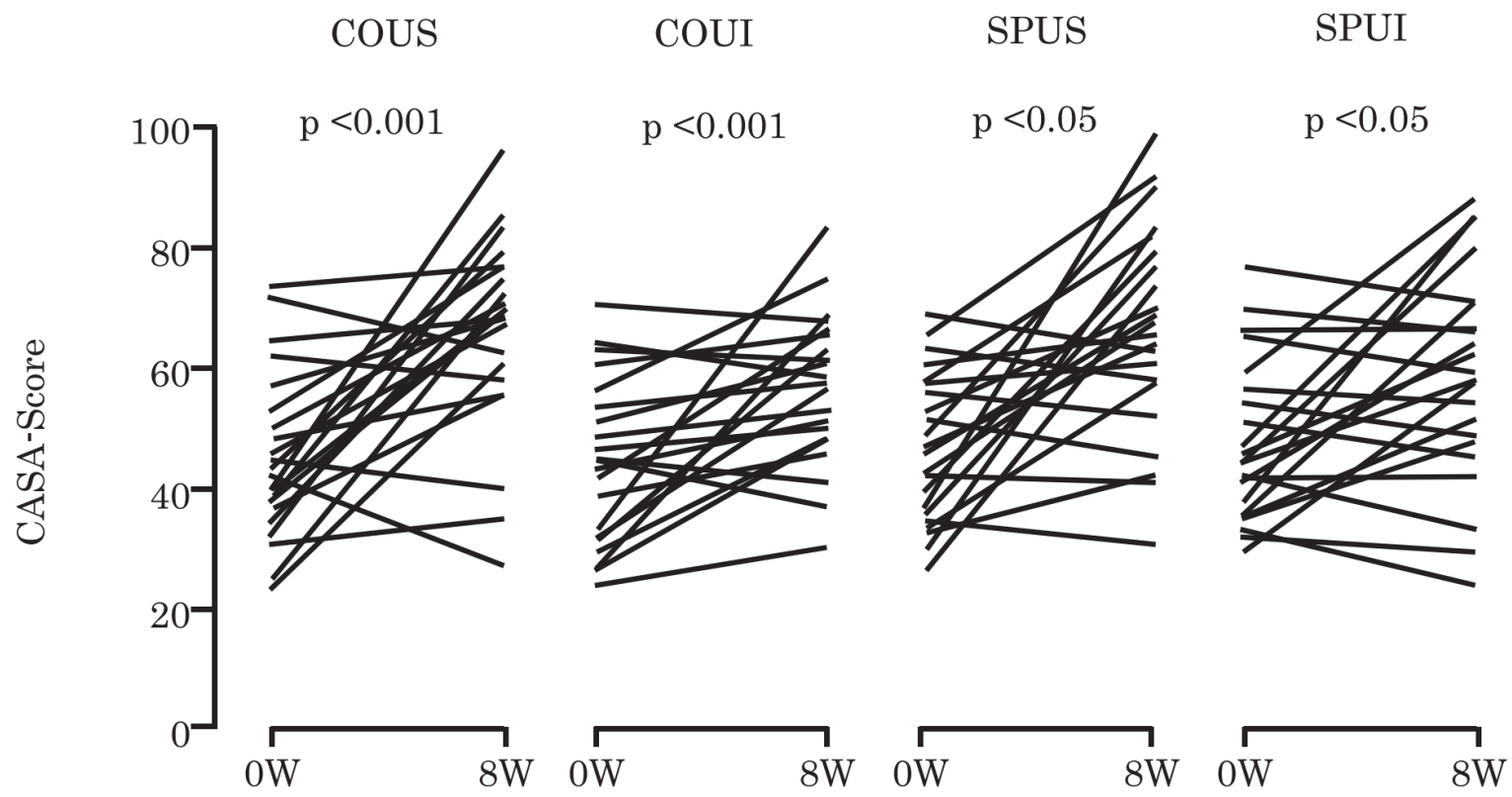
Effect of tiotropium on mucus hypersecretion and airway clearance in patients with COPD☆

Etsuko Tagaya, Osamitsu Yagi, Akitoshi Sato, Ken Arimura, Kiyoshi Takeyama, Mitsuko Kondo, Jun Tamaoki*

First Department of Medicine, Tokyo Women's Medical University, Tokyo, Japan

- 26 patients with COPD complaining of sputum and cough at least for 8 weeks who had not been treated with anticholinergic agents
- Cough and Sputum Assessment Questionnaire (CASA-Q)

Tagaya E, Pulm Pharmacol Ther 2016;39:81-4 [PMID 27350218]



	COUS	COUI	SPUS	SPUI
Greatly improved (n)	7	3	6	5
Improved (n)	7	6	6	6
No change (n)	8	13	10	11
Worse (n)	0	0	0	0

Fig. 1. Individual change of CASA-Q domain score in patients with COPD before and after 8-week treatment with tiotropium. COUS, cough symptom domain; COUI, cough impact domain; SPUS, sputum symptom domain; SPUI, sputum impact domain.

Tagaya E, Pulm Pharmacol Ther 2016;39:81-4 [PMID 27350218]

Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study

Jin-Ping Zheng, Jian Kang, Shao-Guang Huang, Ping Chen, Wan-Zen Yao, Lan Yang, Chun-Xue Bai, Chang-Zheng Wang, Chen Wang, Bao-Yuan Chen, Yi Shi, Chun-Tao Liu, Ping Chen, Qiang Li, Zhen-Shan Wang, Yi-Jiang Huang, Zhi-Yang Luo, Fei-Peng Chen, Jian-Zhang Yuan, Ben-Tong Yuan, Hui-Ping Qian, Rong-Chang Zhi, Nan-Shan Zhong*

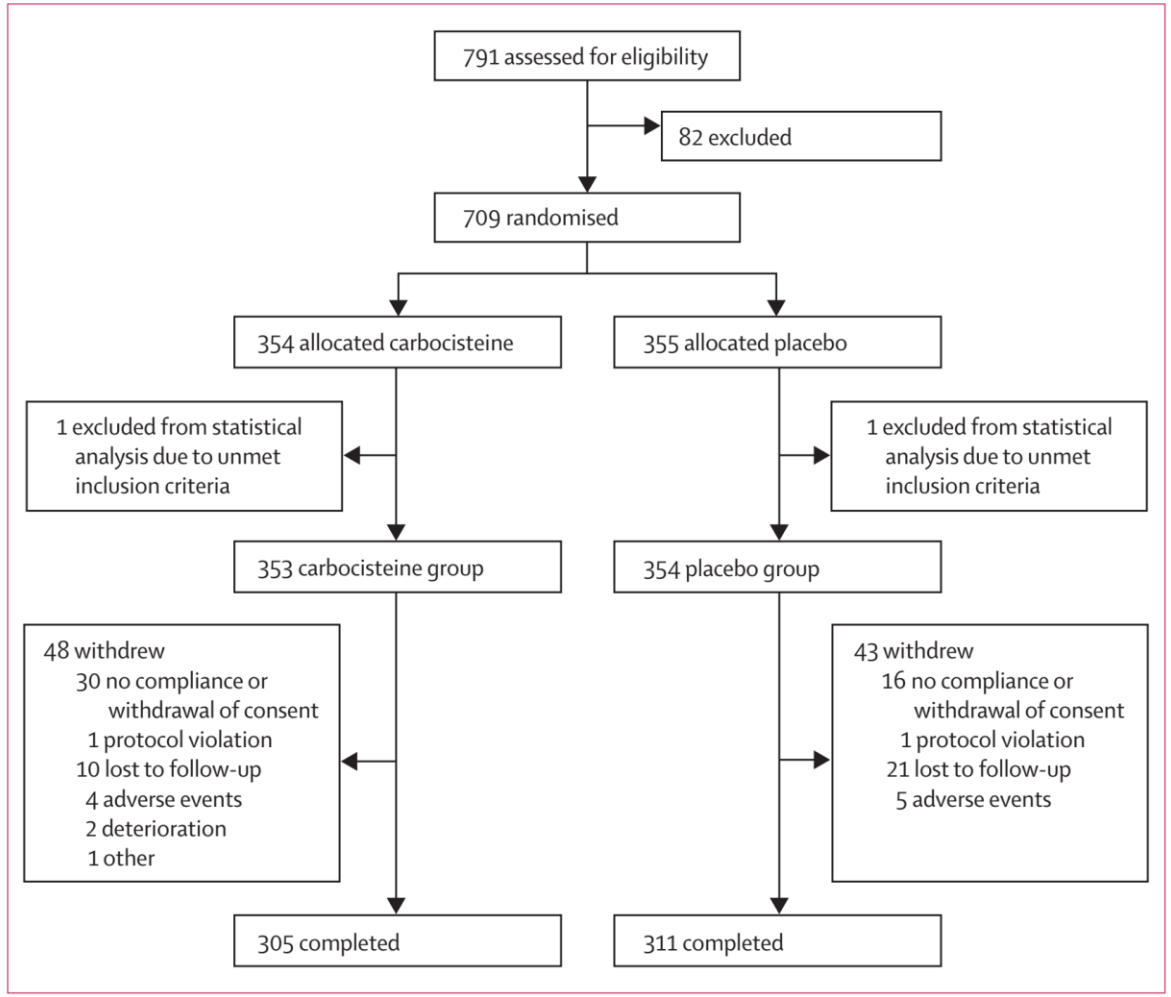


Figure 1: **Trial profile**

	Carbocisteine n=353	Placebo n=354
Men	273 (77·3%)	282 (79·7%)
Age in years, mean (SD)	65·40 (9·17)	64·95 (8·58)
Duration of COPD in years, mean (SD)	8·76 (8·71)	9·61 (9·19)
Ever smokers	265 (75·1%)	262 (74·0%)
Baseline spirometry, mean (SD)		
FEV_1, L	1·07 (0·41)	1·12 (0·43)
FEV_1 percentage of predicted value	43·93%(15·40)	45·10%(15·23)
FVC, L	2·20 (0·74)	2·28 (0·75)
FEV_1/FVC	49·61% (12·75)	50·11%(12·57)
GOLD stages		
II	167 (47·2%)	177 (50·0%)
III	139 (39·4%)	140 (39·6%)
IV	47 (13·3%)	37 (11·4%)
SGRQ total score, mean (SD)	41·57 (19·05)	42·83 (19·34)
Medications for COPD before study		
β_2 agonists	76 (21·53%)	61 (17·23%)
Anticholinergic agents	40 (11·33%)	36 (10·17%)
Inhaled corticosteroids	64 (18·13%)	54 (15·25%)
Xanthines	113 (30·01%)	95 (26·84%)

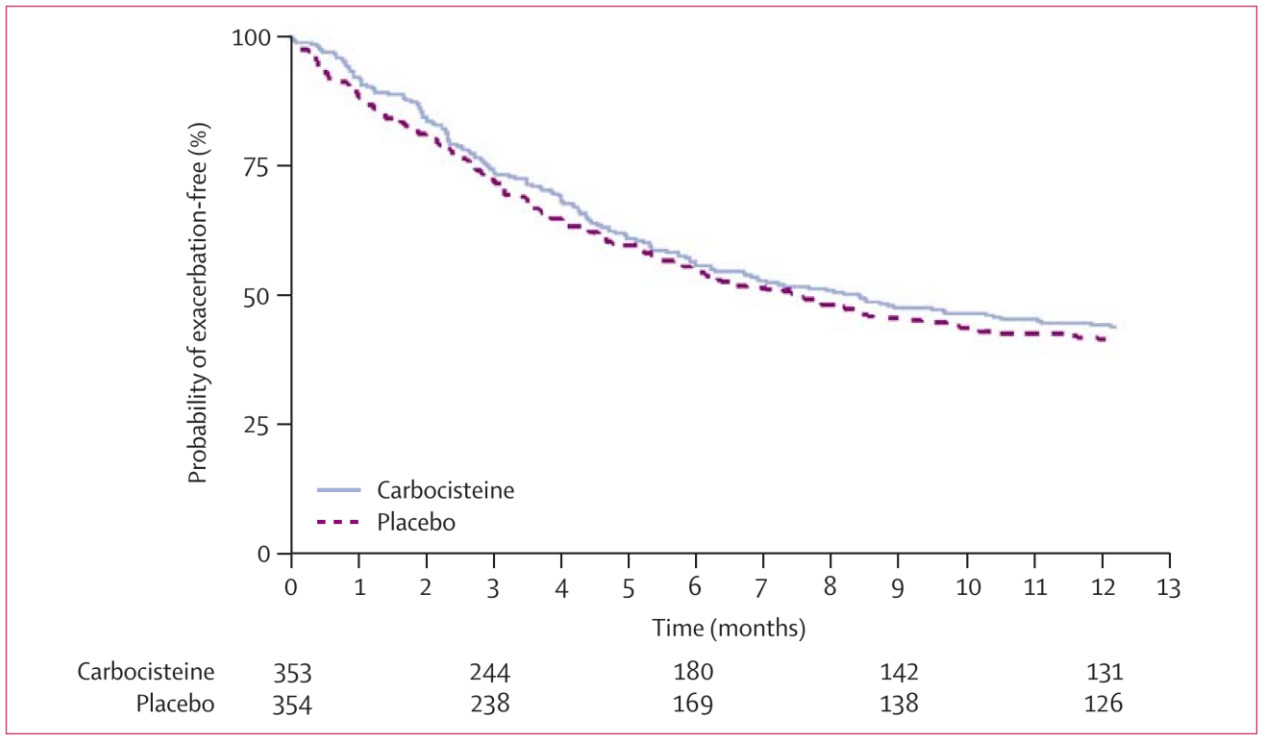
Data are number (%) unless otherwise specified. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease. SGRQ=St George's Respiratory Questionnaire.

Table 1: **Patient demographics and baseline characteristics**

Zheng JP, Lancet 2008;371:2013-8 [PMID 18555912]

Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study

Jin-Ping Zheng, Jian Kang, Shao-Guang Huang, Ping Chen, Wan-Zen Yao, Lan Yang, Chun-Xue Bai, Chang-Zheng Wang, Chen Wang, Bao-Yuan Chen, Yi Shi, Chun-Tao Liu, Ping Chen, Qiang Li, Zhen-Shan Wang, Yi-Jiang Huang, Zhi-Yang Luo, Fei-Peng Chen, Jian-Zhang Yuan, Ben-Tong Yuan, Hui-Ping Qian, Rong-Chang Zhi, Nan-Shan Zhong*



- FEV1 between 25% and 79%
- Risk ratio 0·75 (95% CI 0·62–0·92, p=0·004)

Zheng JP, *et al. Lancet 2008;371:2013-8.*

	Risk ratio	95% CI	p
COPD stage			
Stage IV/stage II	1·44	1·07–1·94	0·015
Stage III/stage II	1·24	1·01–1·53	0·037
Treatment			
Carbocisteine/placebo	0·74	0·61–0·89	0·002

Table 2: **Risk ratio of exacerbation affected by GOLD-defined COPD severity and treatment with carbocisteine**

	Carbocisteine	Placebo	p
Total			
Baseline	41·57 (19·05)	42·83 (19·34)	0·430
After treatment	37·51 (21·39)*	42·78 (22·91)	0·046
Change	−4·06 (16·43)	−0·05 (19·01)	0·130
Symptoms			
Baseline	50·30 (20·80)	49·19 (23·25)	0·564
After treatment	38·96 (20·88)*	45·65 (26·02)	0·015
Change	−11·34 (22·52)	−3·54 (23·49)	0·004
Activity			
Baseline	51·27 (20·08)	50·24 (22·04)	0·994
After treatment	47·94 (23·14)*	50·04 (24·29)	0·428
Change	−3·33 (19·42)	−0·20 (21·50)	0·321
Impacts			
Baseline	33·93 (21·59)	35·25 (21·70)	0·511
After treatment	33·44 (24·44)	35·61 (26·59)	0·562
Change	−0·49 (21·18)	0·36 (23·19)	0·830

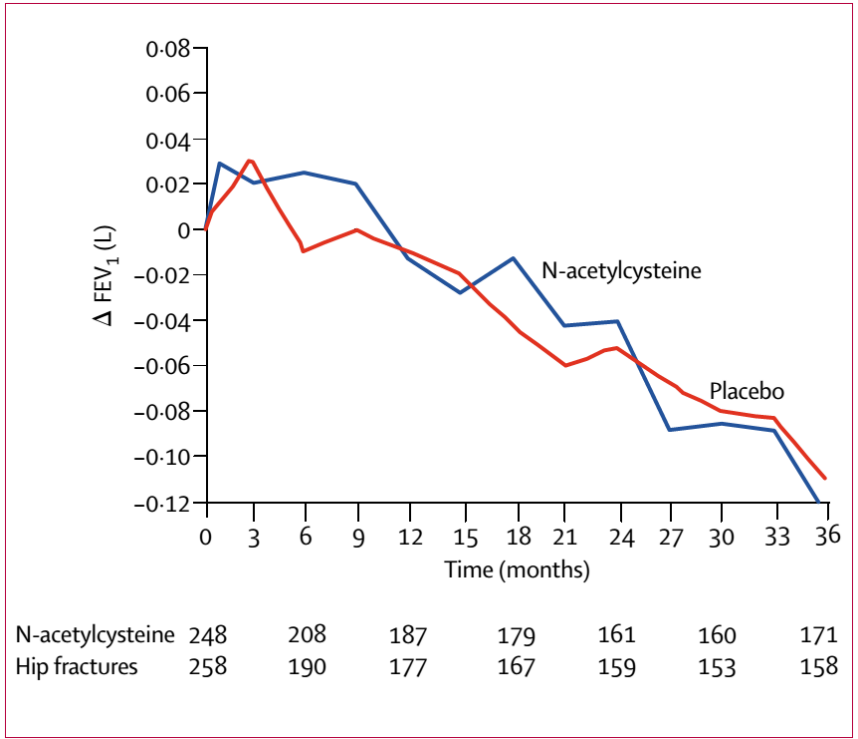
Data are mean (SD). *p<0·001 compared with baseline.

Table 3: **SGRQ scores in carbocisteine and placebo groups**

Zheng JP, Lancet 2008;371:2013-8 [PMID 18555912]

Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial

- 523 patients, GOLD II – III with frequent AE (at least two per year for 2 years)
- Oral **NAC** (anti-oxidant, anti-inflammatory agent) **600 mg/d** versus placebo, 3 years
- Primary end point: yearly reduction in forced expiratory volume in 1 s (**FEV1**) and the number of **exacerbations** per year



Decramer M, *et al. Lancet 2005;365:1552-60.*

Group	Number of exacerbations with N-acetylcysteine	Number of exacerbations with placebo	Risk ratio (95% CI)	p
All patients (n=506)	693	658	0·990 (0·889–1·101)	0·847
Inhaled corticosteroids (n=351)	563	471	1·059 (0·937–1·197)	0·359
No inhaled corticosteroids (n=155)	130	187	0·790 (0·631–0·989)	0·040

***Table 3*: Exacerbation rate in patients allocated N-acetylcysteine or placebo**

- Subgroup analysis suggested that the exacerbation rate might be reduced with N-acetylcysteine in patients not treated with inhaled corticosteroids

Decramer M, *et al. Lancet 2005;365:1552-60.*

Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial

Jin-Ping Zheng, Fu-Qiang Wen, Chun-Xue Bai, Huan-Ying Wan, Jian Kang, Ping Chen, Wan-Zhen Yao, Li-Jun Ma, Xia Li, Luca Raiteri, Marco Sardina, Yi Gao, Bai-Song Wang, Nan-Shan Zhong, on behalf of the PANTHEON study group

- 1297 patients with postBD FEV1 30-70 %, 1-year treatment

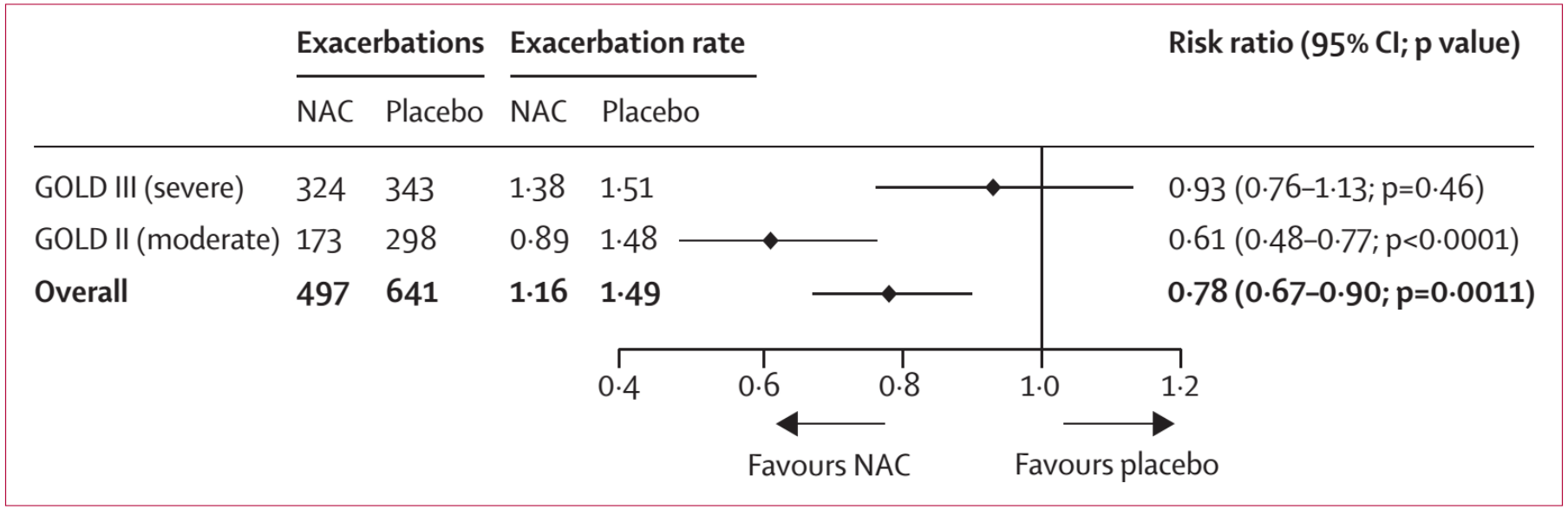


Figure 2: **Forest plot of exacerbations in all patients, and stratified by GOLD moderate and GOLD severe disease**

- Chinese patients with moderate-to-severe COPD, long-term use of N-acetylcysteine 600 mg twice daily can prevent exacerbations, especially in disease of **moderate severity**

Zheng J-P, *et al. The Lancet Respiratory Medicine 2014;2:187-94.*

THE EFFECT OF LONG-TERM TREATMENT WITH ERDOSTEINE ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE EQUALIFE STUDY

MORETTI M.,[1] BOTTRIGHI P.,[2] DALLARI R.,[3] DA PORTO R.,[4] DOLCETTI A.,[5] GRANDI P.,[6] GARUTI G.,[7] GUFFANTI E.,[8] ROVERSI P.,[1] DE GUGLIEMO M.,[1] POTENA A.[9] FOR THE EQUALIFE STUDY GROUP

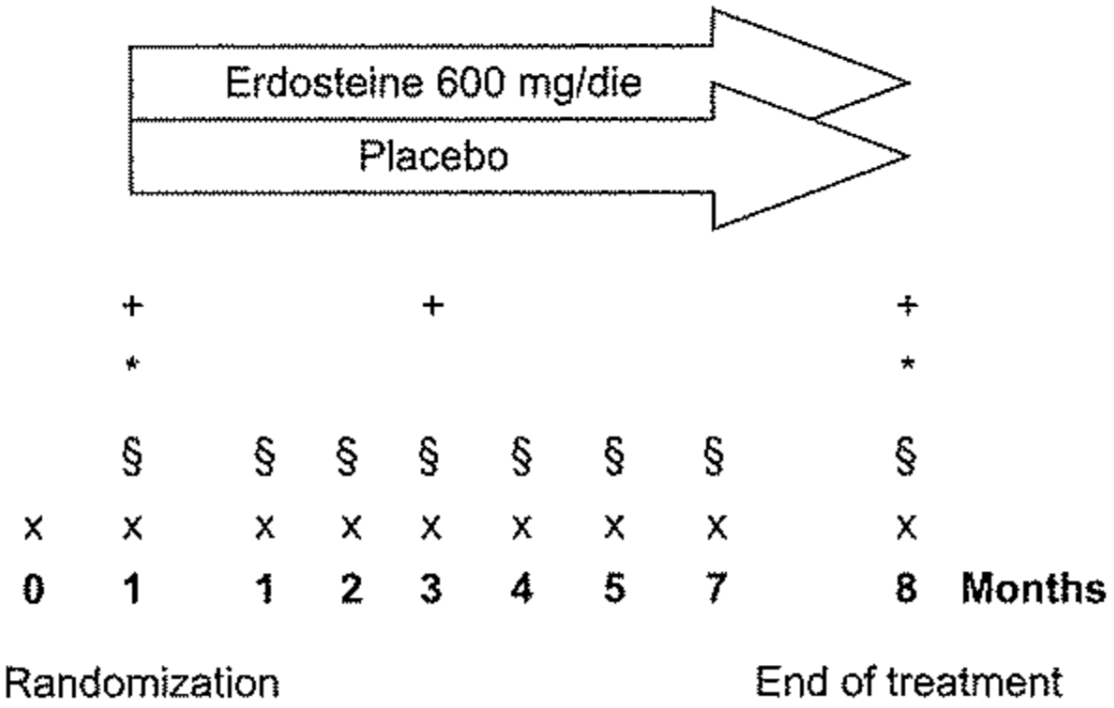


Fig. 1 Flow-chart of the study protocol. x: indicates clinical evaluation; *: indicates lung function test, 6-minute walking test; §: indicates Short Form 36; +: indicates St. George's Respiratory Questionnaire.

Moretti M, Drugs Exp Clin Res 2004;30:143-52 [PMID 15553660]

Table I *Baseline characteristics of the patients recruited*

Characteristics	Erdosteine	Placebo
Patient number	79	76
Age years	67.4 (8.3)	67.5 (8.3)
Male %	84.8	75.0
Current smokers %	31.6	34.2
FEV_1 l	1.61 (0.31)	1.54 (0.28)
FEV_1 % predicted	59.4 (7.29)	59.0 (5.1)
FEV_1 l after salbutamol	1.68 (0.31)	1.59 (0.29)

Data are presented as mean (SD), numbers or % where indicated.
FEV_1 = forced expiratory volume in 1 second.

Table III *Exacerbations, hospitalization admissions and workdays lost in the erdosteine and the placebo group*

	Erdosteine (n = 63)	Placebo (n = 61)
Number of patients with exacerbation	37	48
Number of exacerbations	59	84
Exacerbation per person*	0.94 (1.12)	1.38 (1.39)**
Number of hospitalizations	10	19
Number of hospitalization days	70	163
Hospitalization per person*	0.16 (0.57)	0.31 (0.74)***
Individuals losing workdays	7	10
Workdays lost per person*	0.8 (0.3)	1.1 (0.4)

*Data presented as mean (SD); **$p < 0.01$; ***$p < 0.05$.

- 30 % reduction in exacerbations
- 58 % reduction in hospital days
- improved health status
- lower COPD-related diseases costs

Moretti M, Drugs Exp Clin Res 2004;30:143-52 [PMID 15553660]

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]

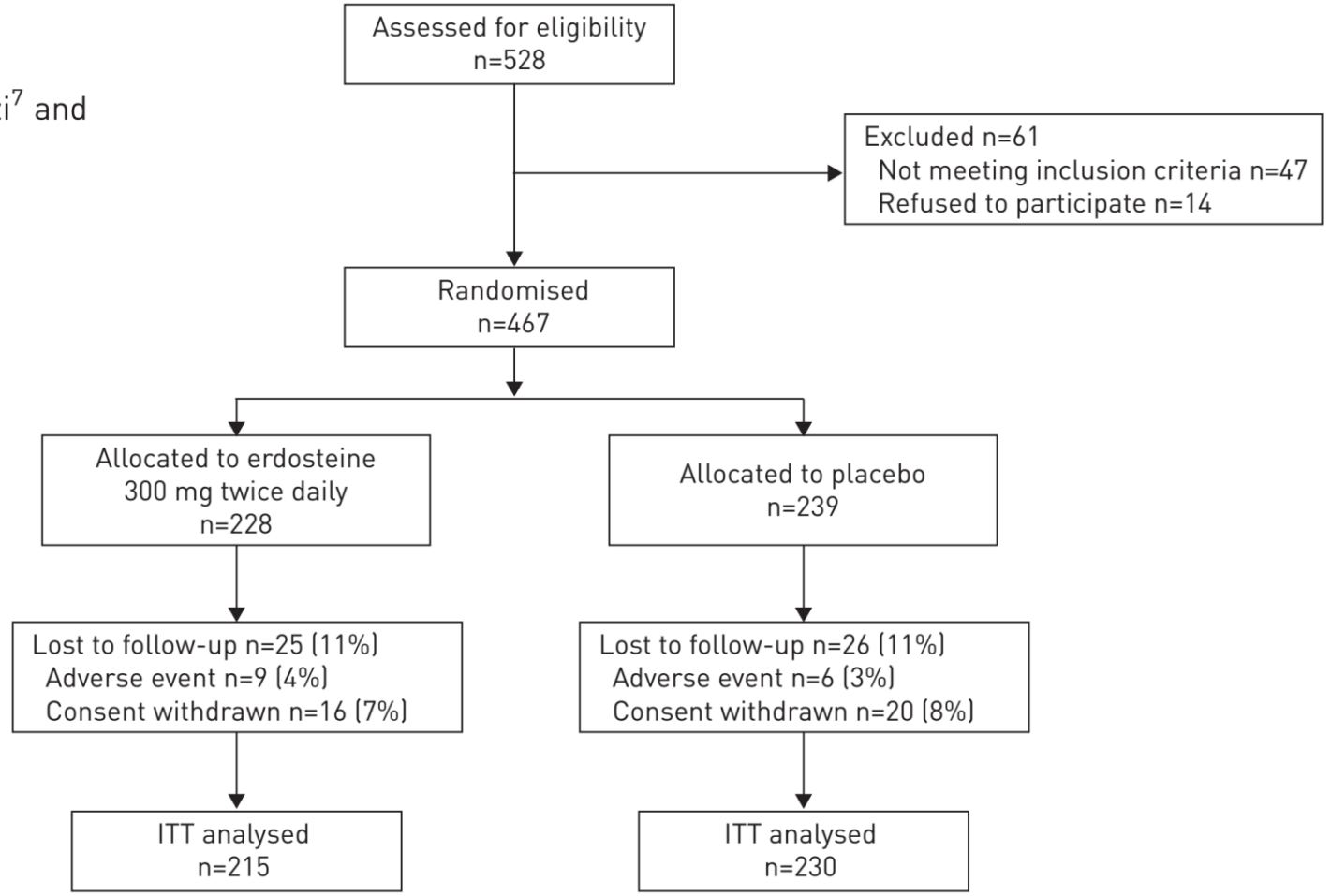


FIGURE 1 Trial profile. Percentages are based on the number of randomised patients in the single treatment group. ITT: intention to treat.

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

TABLE 1 Demographics and baseline characteristics

	Erdosteine group	Placebo group	Total
Patients	228	239	467
Age years	64.3±8.4	65.1±8.2	64.8±8.3
Male	166 (72.8)	179 (74.9)	345 (73.9)
BMI kg·m^{-2}	27.3±5.2	27.9±5.6	27.6±5.4
Smoking status			
Current smoker	66 (28.9)	69 (28.8)	135 (28.8)
Ex-smoker	162 (71.1)	170 (71.2)	332 (71.2)
FEV_1 L	1.39±0.3	1.43±0.4	1.41±0.4
FEV_1 % pred	51.39±11.5	52.17±12.1	51.79±11.8
FVC L	2.75±0.7	2.72±0.7	2.74±0.7
Post-bronchodilator FEV_1/FVC ratio %	52.91±10.9	54.52±10.9	53.74±10.9
Concomitant medication[#] for COPD[¶]			
Short-acting β_2-agonists (inhalant)	215 (94)	217 (91)	432 (93)
Anticholinergics	172 (75)	183 (77)	355 (76)
Adrenergics in combination with corticosteroids	102 (45)	102 (43)	204 (44)
Xanthines	71 (31)	86 (36)	157 (34)
Glucocorticoids	63 (28)	71 (30)	134 (29)
Adrenergics in combination with anticholinergics	13 (6)	11 (5)	24 (5)
Selective β_2-adrenoreceptor agonists (oral)	1 (0.4)	5 (2)	6 (1.3)
Other systemic drugs for obstructive airway diseases	2 (0.9)	1 (0.4)	3 (0.6)

Data are presented as n, mean±SD or n (%). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease. [#]: concomitant treatments have been categorised according to Anatomical Therapeutic Chemical code; [¶]: patients could have received more than one of these medications.

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

TABLE 2 Baseline characteristics of patients who completed or did not completed the trial

	Patients completing the trial			Dropouts		
	Erdosteine group	Placebo group	p-value	Erdosteine group	Placebo group	p-value
Age years	63.8±8.3	64.1±8.2	NS	65.1±8.5	65.5±8.9	NS
Male	71.8	74.6	NS	73.1	75.2	NS
BMI kg·m^{-2}	27.2±5.3	28.0±5.4	NS	27.4±5.4	27.9±5.9	NS
Smoking status						
Current smoker	27.1	28.0	NS	29.6	28.8	NS
Ex-smoker	72.9	72.0	NS	70.4	71.2	NS
FEV_1 L	1.43±0.40	1.46±0.47	NS	1.36±0.38	1.43±0.41	NS
FEV_1 % pred	51.45±12.8	54.38±13.3	NS	51.36±11.2	50.34±11.7	NS
FVC L	2.74±0.93	2.74±0.94	NS	2.74±0.71	2.73±0.73	NS
Post-bronchodilator FEV_1/FVC ratio %	54.01±11.3	53.26±10.8	NS	51.88±11.1	52.39±10.1	NS

Data are presented as mean±SD or %, unless otherwise indicated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; NS: not significant.

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

TABLE 3 Analysis of exacerbations

	Exacerbation rate patient^{-1}·year^{-1}#		Rate ratio (95% CI)	Effect size#	
	Erdosteine¶	Placebo+		Difference *versus* placebo %	p-value§
Overall	0.91	1.13	0.81 (0.68–0.92)	−19.4	0.01
ICS use	0.93	1.16	0.80 (0.67–0.94)	−19.5	0.02
No ICS use	0.89	1.10	0.81 (0.65–0.93)	−19.3	0.01

ICS: inhaled corticosteroid. #: Poisson regression estimates; ¶: n=215; +: n=230; §: two-sided p-value for between-treatment difference (significance level <5%, Wilcoxon rank-sum test).

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

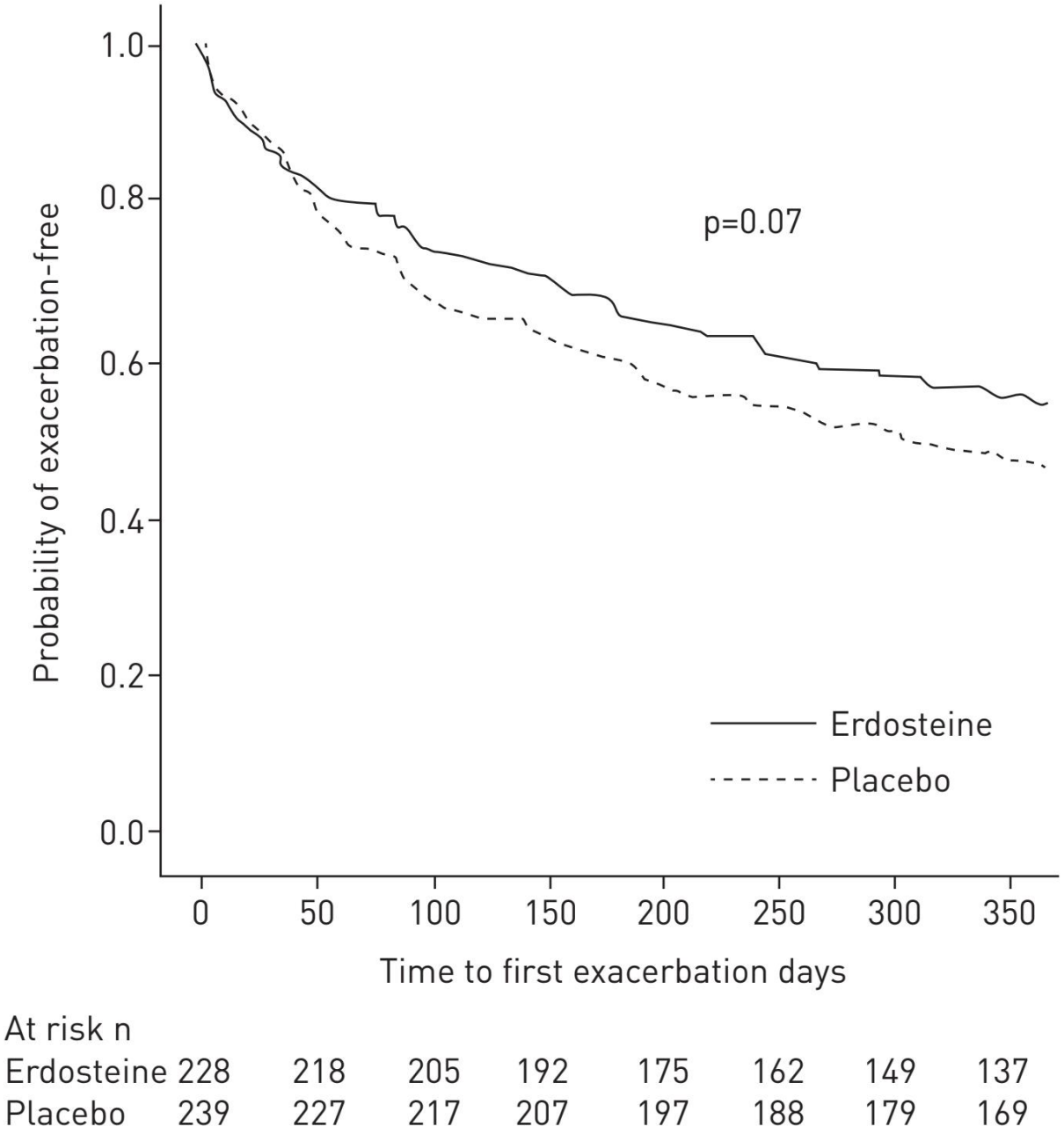


FIGURE 4 Kaplan–Meier plot of probability of being exacerbation-free at each point through the study. Numbers show remaining patients at randomisation and during treatment at 50, 100, 150, 200, 250, 300 and 350 days.

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

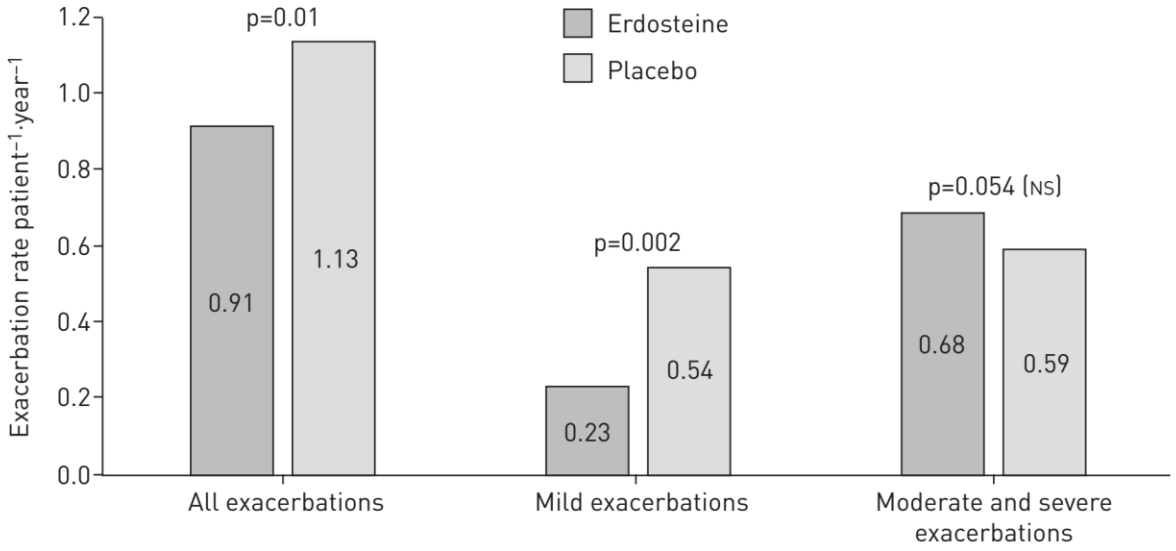


FIGURE 2 Mean exacerbation rate in the study period (1 year). NS: not significant.

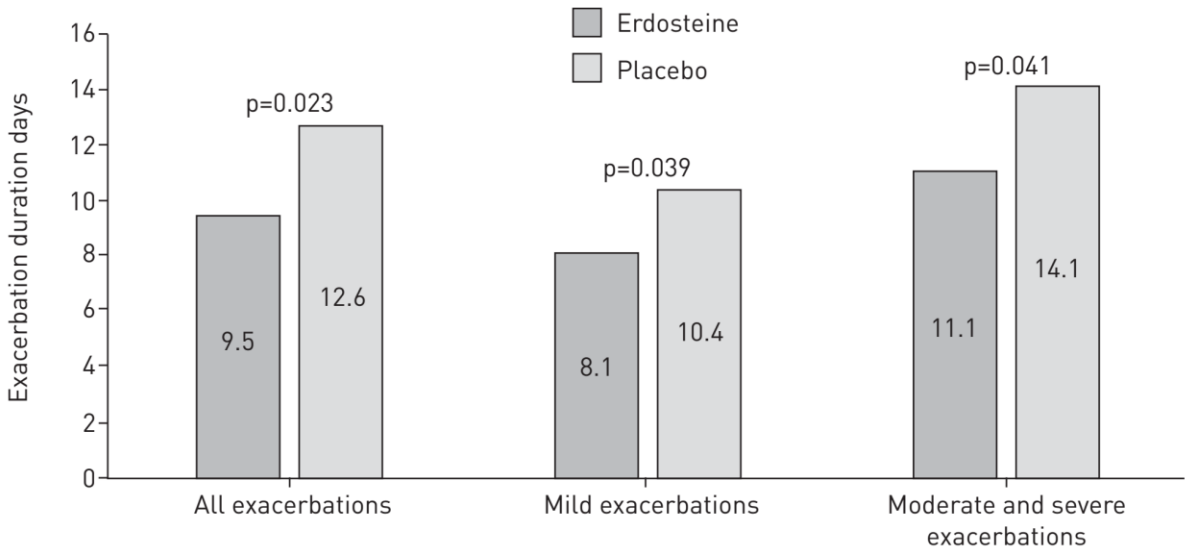


FIGURE 3 Mean exacerbation duration in the study period (1 year).

Lazaar AL, Respir Res 2020;21:149 [PMID 32532258]

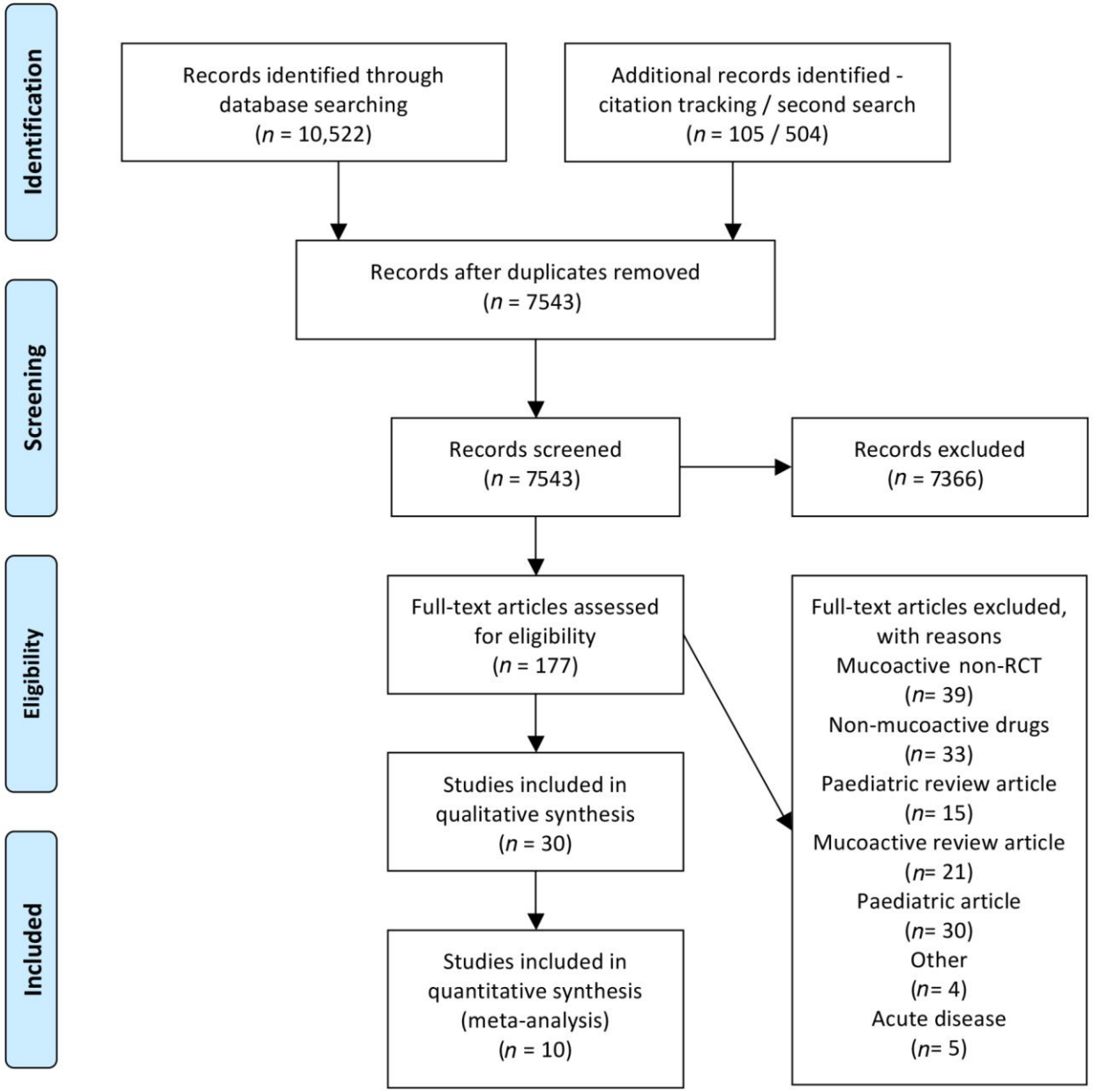
Official Journal of the Asian Pacific Society of Respirology
Respirology

SYSTEMATIC REVIEW

Mucoactive agents for chronic, non-cystic fibrosis lung disease: A systematic review and meta-analysis

BENJAMIN J. TARRANT,[1,2] CAITLIN LE MAITRE,[1] LORENA ROMERO,[3] RANJANA STEWARD,[1] BRENDA M. BUTTON,[1,4] BRUCE R. THOMPSON[4,5] AND ANNE E. HOLLAND[1,2]

[1]Department of Physiotherapy, [3]Ian Potter Library, [5]Department of Allergy, Immunology and Respiratory Medicine, Alfred Health, [2]Department of Rehabilitation, Nutrition and Sport, La Trobe University and [4]Department of Allergy, Immunology and Respiratory Medicine (AIRmed), Monash University, Melbourne, Victoria, Australia



Tarrant BJ, Respirology 2017;22:1084-92 [PMID 28397992]

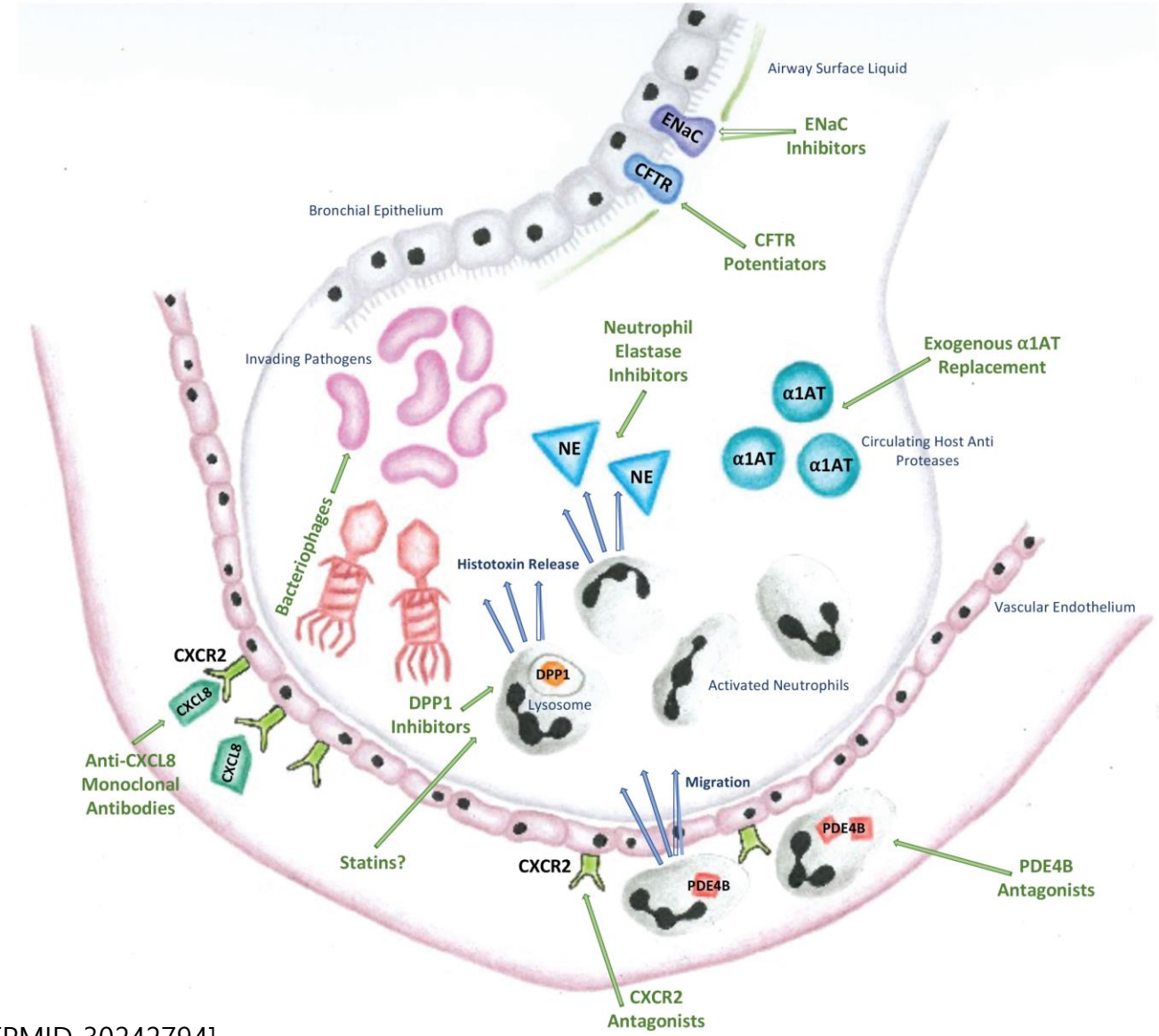
Table 1 Summary of benefit

Strength of findings[†]	Low	Unclear	High	No benefit
Bronchiectasis		Mannitol[6,7,11–14]	HS[18,19,23,33] NS[23,33]	Dornase alfa[‡24,35]
COPD	NS[20,21,25,26,34] Mesna[§9,29,31]	NAC[15,27,32]		HS[9,34]
Asthma	Dornase alfa[¶30]	HS[12] NAC[8,17] Mannitol[10]		

[†]Strength of findings defined according to Higgins and Green.[5]
[‡]Detrimental.
[§]Single study, single outcome.
[¶]Sub-study significance only.

Benefit, one or more trials show positive results in one or more outcomes; dornase alfa, recombinant human deoxyribonuclease/rhDNase; HS, hypertonic saline; NAC, N-acetylcysteine; No benefit, lack of positive results in any trial; NS, normal saline.

Emerging Therapies in Bronchiectasis



Regan KH, Respirology 2018;23:1127-37 [PMID 30242794]

Lazaar *et al. Respiratory Research* (2020) 21:149
https://doi.org/10.1186/s12931-020-01401-4

Respiratory Research

RESEARCH Open Access

CXCR2 antagonist for patients with chronic obstructive pulmonary disease with chronic mucus hypersecretion: a phase 2b trial

Aili L. Lazaar[1*], Bruce E. Miller[1], Alison C. Donald[1], Thomas Keeley[2], Claire Ambery[2], John Russell[1], Henrik Watz[3], Ruth Tal-Singer[1] and for 205724 Investigators

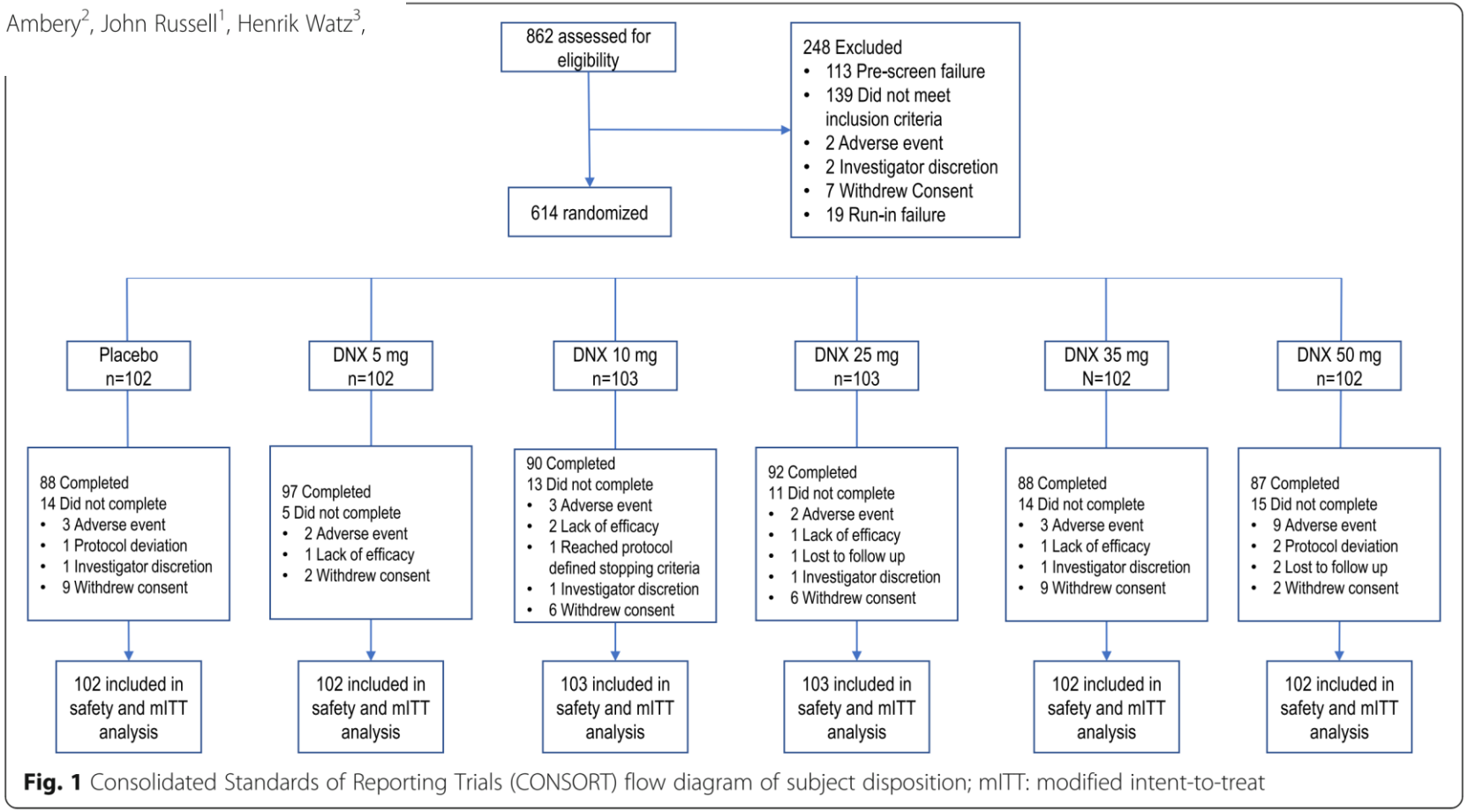


Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of subject disposition; mITT: modified intent-to-treat

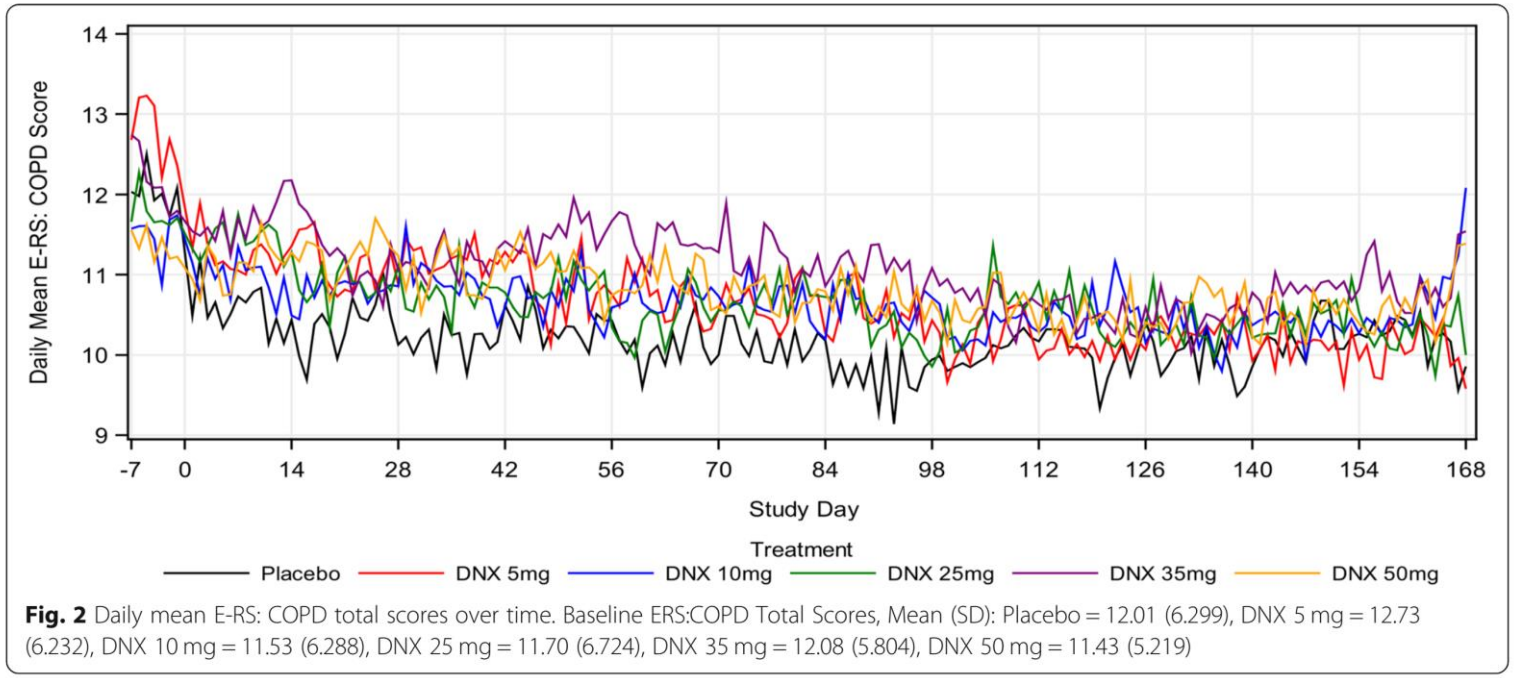


Fig. 2 Daily mean E-RS: COPD total scores over time. Baseline ERS:COPD Total Scores, Mean (SD): Placebo = 12.01 (6.299), DNX 5 mg = 12.73 (6.232), DNX 10 mg = 11.53 (6.288), DNX 25 mg = 11.70 (6.724), DNX 35 mg = 12.08 (5.804), DNX 50 mg = 11.43 (5.219)

Table 3 Bayesian Analysis of Change from Baseline SGRQ Score up to Month 6

	Placebo	DNX 5 mg	DNX 10 mg	DNX 25 mg	DNX 35 mg	DNX 50 mg
N	101	102	100	103	100	99
Baseline SGRQ Total Score	46.21 (17.426)	47.16 (16.057)	45.97 (14.991)	48.47 (17.514)	47.18 (15.871)	46.19 (16.669)
n	85	96	86	90	86	85
Mean Change from Baseline (90% CI)	−4.11 (−6.25,-2.00)	−3.44 (−5.51,-1.38)	−4.19 (−6.28,-2.12)	−4.94 (−7.03,-2.91)	−4.12 (−6.22,-1.99)	−3.41 (−5.55,-1.26)
Mean Difference from Placebo (90% CI)		0.68 (−2.26,3.67)	−0.08 (− 3.05,2.84)	−0.83 (− 3.81,2.09)	−0.01 (− 3.06,2.97)	0.70 (−2.33,3.76)

N Number enrolled, *n* Number of subjects with analysable data at the current time point; *CI* Credible interval

Contents

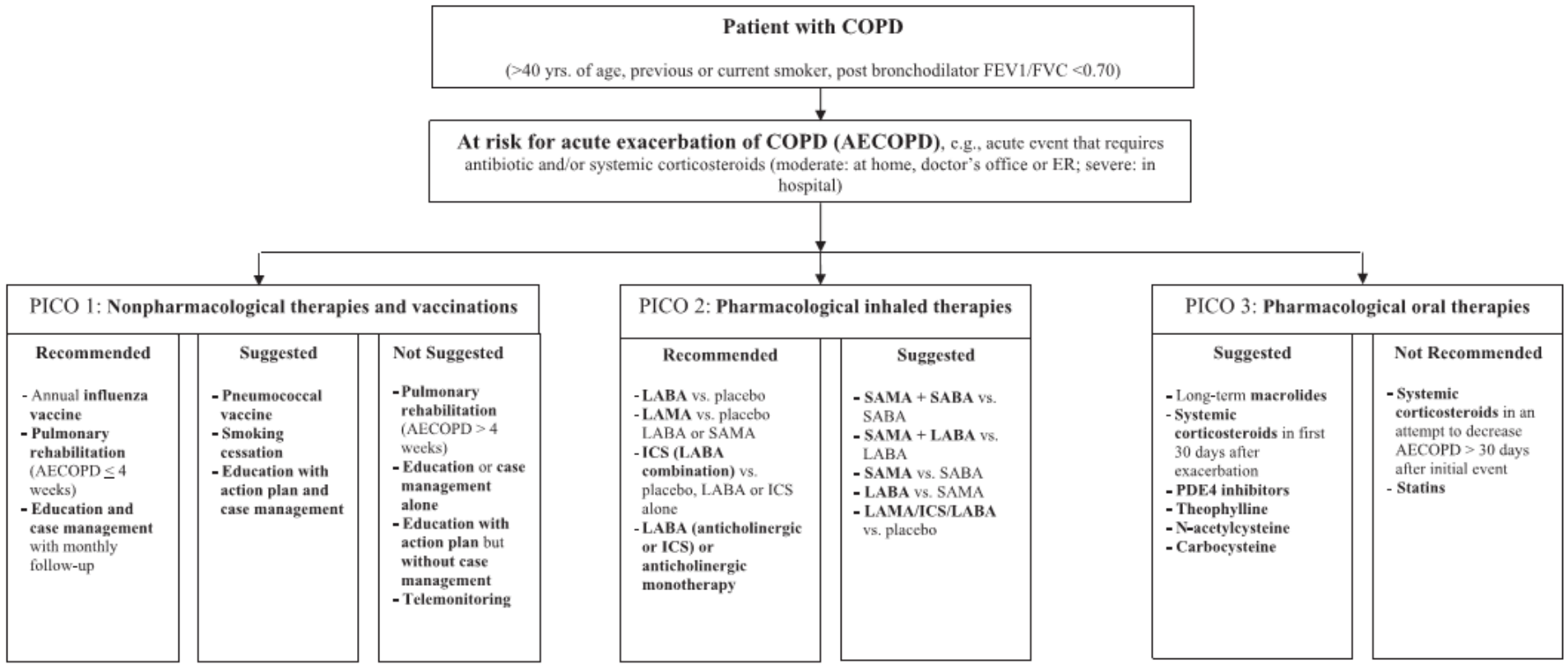
COPD: NICE guideline [NG115]

- Oral mucolytic therapy
  - 1.2.40 Consider **mucolytic drug** therapy for people **with a chronic cough productive of sputum**. [2004]
  - 1.2.41 Only **continue** mucolytic therapy if there is symptomatic **improvement** (for example, reduction in frequency of cough and sputum production). [2004]
  - 1.2.42 Do **not routinely use mucolytic** drugs to prevent exacerbations in people with stable COPD. [2010]
- Last updated: 26 July 2019

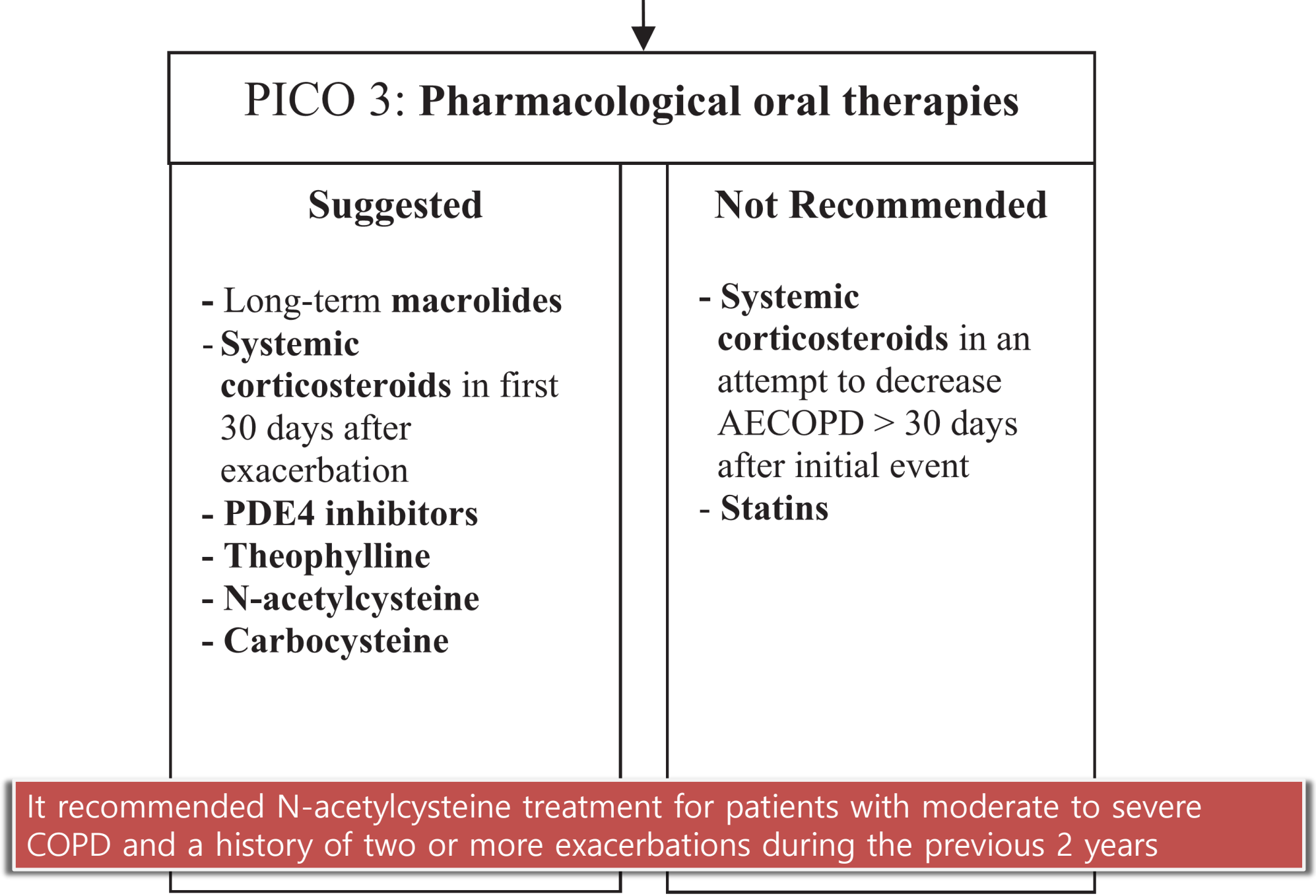
https://www.nice.org.uk/guidance/ng115/chapter/Recommendations#managing-stable-copd

Executive Summary

Prevention of Acute Exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline



Criner GJ, *et al. Chest 2015;147:883-93.*



Criner GJ, *et al. Chest 2015;147:883-93.*

Prevention of COPD exacerbations: a European Respiratory Society/ American Thoracic Society guideline

Jadwiga A. Wedzicha (ERS co-chair)[1], Peter M.A. Calverley[2], Richard K. Albert[3], Antonio Anzueto[4], Gerard J. Criner[5], John R. Hurst[6], Marc Miravitlles[7], Alberto Papi[8], Klaus F. Rabe[9], David Rigau[10], Pawel Sliwinski[11], Thomy Tonia[12], Jørgen Vestbo[13], Kevin C. Wilson[14] and Jerry A. Krishnan (ATS co-chair)[15]

1) Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?

2) Are long-acting β-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) preferable in patients with stable COPD to prevent COPD exacerbations?

3) Should roflumilast be prescribed to patients with COPD associated with chronic bronchitis and exacerbations to prevent subsequent exacerbations?

4) Should fluoroquinolones be prescribed to patients with stable COPD to prevent COPD exacerbations?

5) Should macrolides be prescribed to patients with stable COPD to prevent COPD exacerbations?

Wedzicha JA, Eur Respir J 2017;50 [PMID 28889106]

1) Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?

- ERS/ATS recommendation
  - For patients who have COPD with moderate or severe airflow obstruction and **exacerbations despite optimal inhaled therapy**, we **suggest** treatment with an oral **mucolytic** agent to prevent future exacerbations (conditional recommendation, low quality of evidence)

- Remarks
  - Moderate or severe airflow obstruction is defined as a post-bronchodilator FEV1/FVC <0.70 and an FEV1 % pred of 30–79%. The beneficial effect of mucolytic therapy on the rate of COPD exacerbations was driven by trials that administered **high-dose mucolytic therapy** (e.g. N-acetylcysteine 600 mg twice daily)

Wedzicha JA, Eur Respir J 2017;50 [PMID 28889106]

GOLD 2021

- Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (**N-acetylcysteine, carbocysteine, erdosteine**) In COPD patients not receiving inhaled corticosteroids, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC**) may reduce exacerbations** and modestly improve health status.
- In contrast, it has been shown that **erdosteine** may have a significant effect on (mild) exacerbations **irrespective of concurrent treatment with ICS.**
- Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow one to identify precisely the potential target population for antioxidant agents in COPD

European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino[1], Pieter C. Goeminne[2,3], Melissa J. McDonnell[4,5,6], Stefano Aliberti[7], Sara E. Marshall[8], Michael R. Loebinger[9], Marlene Murris[10], Rafael Cantón[11], Antoni Torres[12], Katerina Dimakou[13], Anthony De Soyza[14,15], Adam T. Hill[16], Charles S. Haworth[17], Montserrat Vendrell[18], Felix C. Ringshausen[19], Dragan Subotic[20], Robert Wilson[9], Jordi Vilaró[21], Bjorn Stallberg[22], Tobias Welte[19], Gernot Rohde[23], Francesco Blasi[7], Stuart Elborn[9,24], Marta Almagro[25], Alan Timothy[25], Thomas Ruddy[25], Thomy Tonia[26], David Rigau[27] and James D. Chalmers[28]

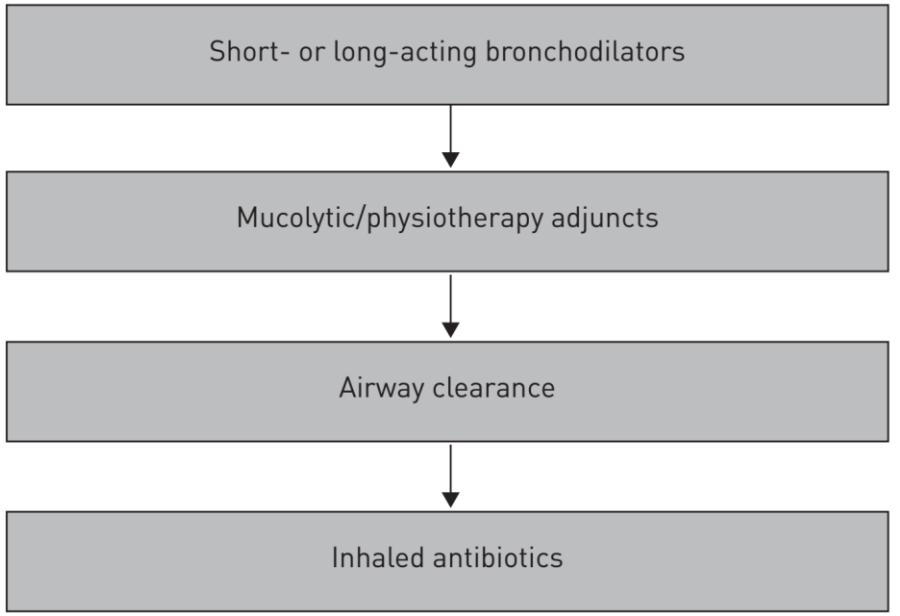


FIGURE 5 Flowchart of multiple sequential airways treatment administration in adult patients with bronchiectasis.

Polverino E, Eur Respir J 2017;50 [PMID 28889110]

Question 6: Is long-term mucoactive treatment (⩾3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?

- Recommendation
  - We suggest **offering long-term mucoactive treatment** (⩾3 months) in adult patients with bronchiectasis who have **difficulty in expectorating sputum** and poor quality of life and where standard airway clearance techniques have failed to control symptoms (weak recommendation, low quality evidence).
  - We recommend **not to offer recombinant human DNase** to adult patients with bronchiectasis (strong recommendation, moderate quality evidence)

Polverino E, Eur Respir J 2017;50 [PMID 28889110]

Mucoactives in Bronchiectasis

- Recommendations

➢ Do **not** routinely **use** recombinant human **DNase** in adults with bronchiectasis. (A)

➢ Consider the use of **humidification** with sterile water or normal **saline** to facilitate airway clearance. (D)

- Good practice points

✓ Consider a **trial of mucoactive treatment** in patients with bronchiectasis who have difficulty in sputum expectoration.

✓ Perform an airway **reactivity challenge test when inhaled mucoactive treatment** is first administered.

✓ Consider **pre-treatment with a bronchodilator** prior to inhaled or nebulised mucoactive treatments especially in individuals where bronchoconstriction is likely (patients with asthma or bronchial hyper-reactivity and those with severe airflow obstruction FEV1 <1 litre).

✓ If **carbocysteine** is prescribed, **a 6-month trial** should be given and continued if there is ongoing clinical benefit.

Hill AT, Thorax 2019;74:1-69 [PMID 30545985]

감사합니다.