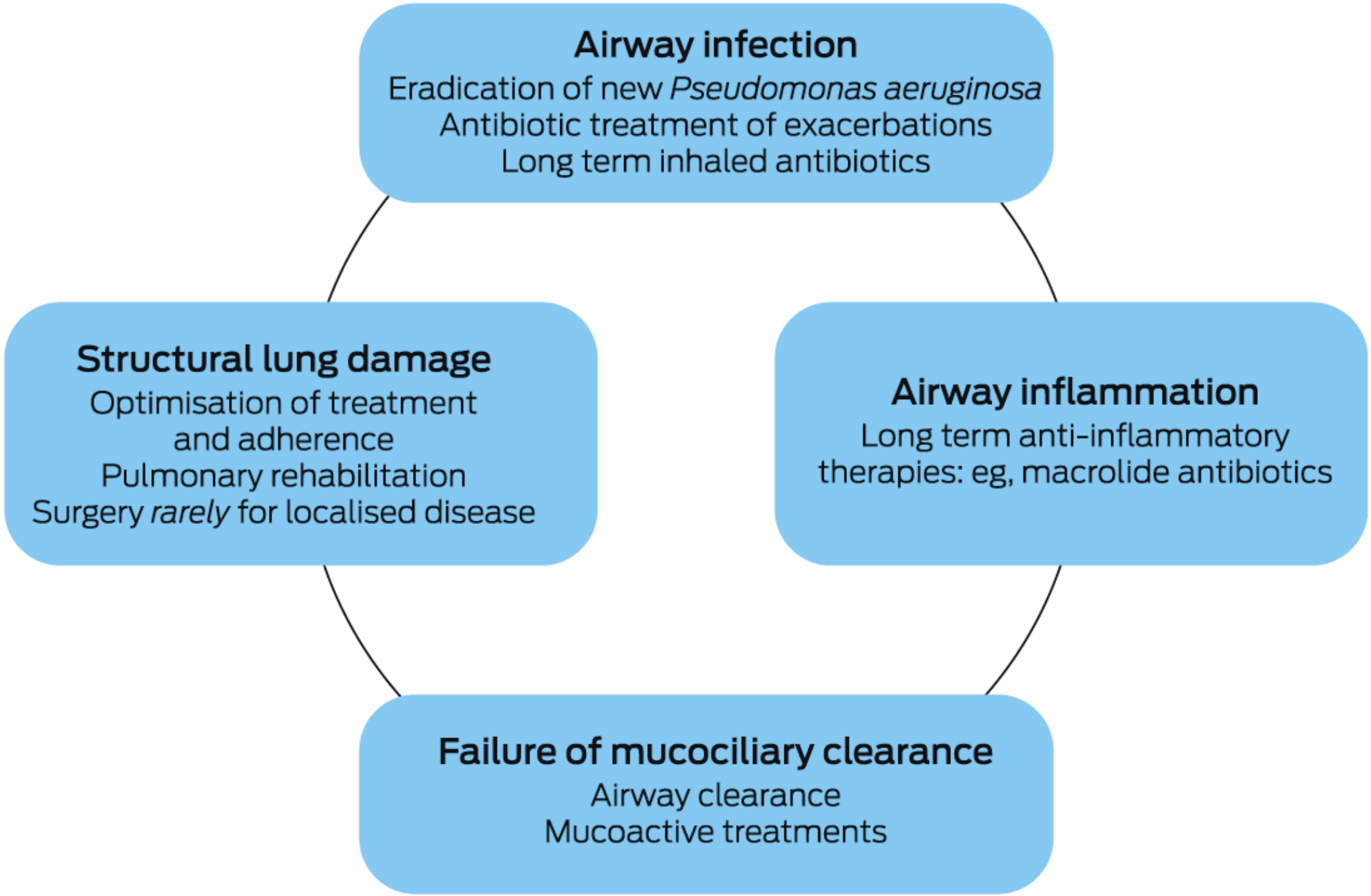
Pharmacological Management Of Bronchiectasis(including Cystic Fibrosis)

G.Ratnakar

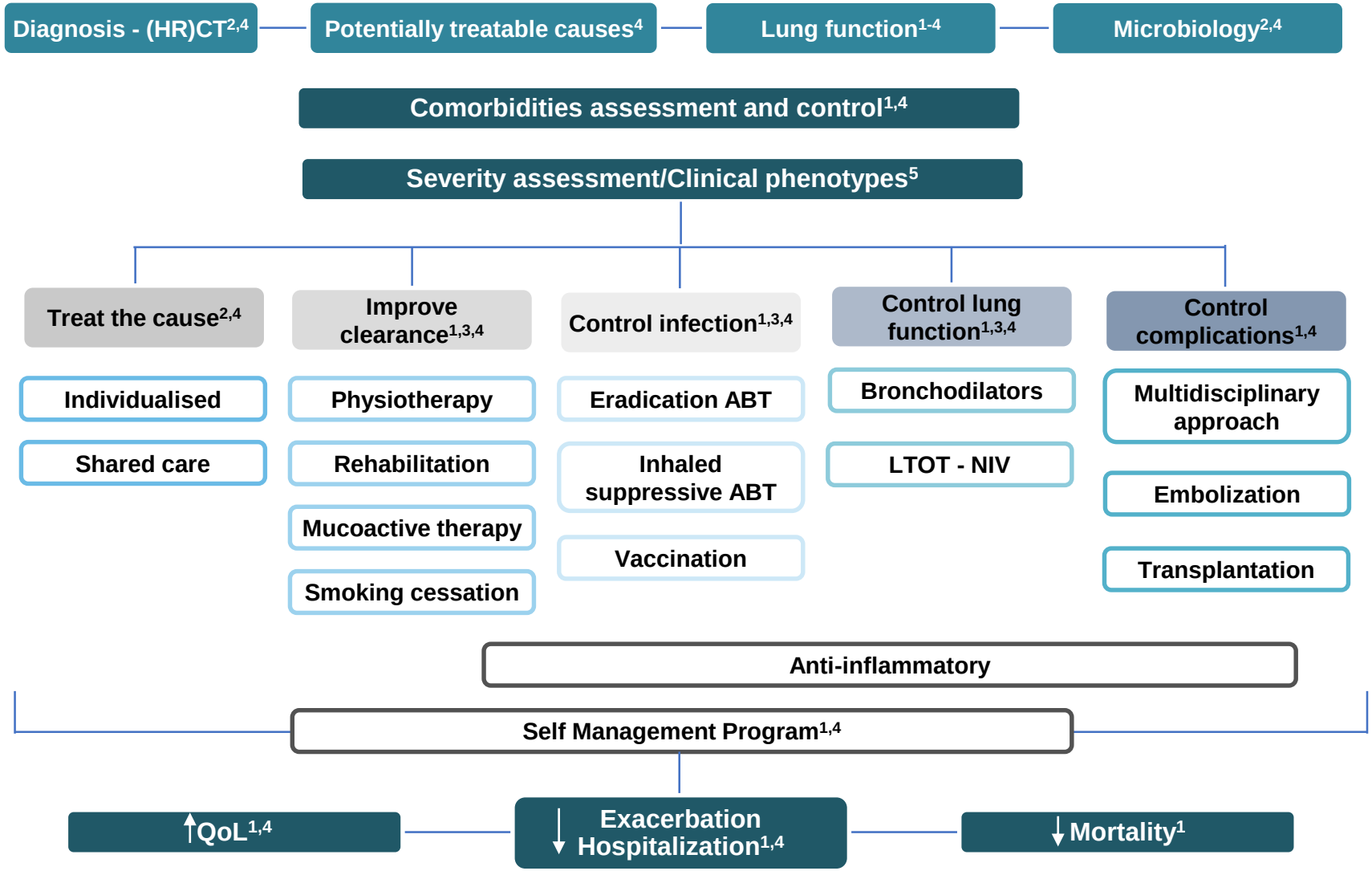
26-06-2020

Division

- Background
- Sputum importance
- Acute exacerbation management medications(Non-CF)
- Airway clearance-Mucoactive drugs(Non-CF)
- Long-term anti-inflammatory drugs(Non-CF)
- Cystic fibrosis management
- Treatable traits
- Newer approaches


Airway infection
Eradication of new *Pseudomonas aeruginosa*
Antibiotic treatment of exacerbations
Long term inhaled antibiotics
Structural lung damage
Optimisation of treatment and adherence
Pulmonary rehabilitation
Surgery *rarely* for localised disease
Airway inflammation
Long term anti-inflammatory therapies: eg, macrolide antibiotics
Failure of mucociliary clearance
Airway clearance
Mucoactive treatments

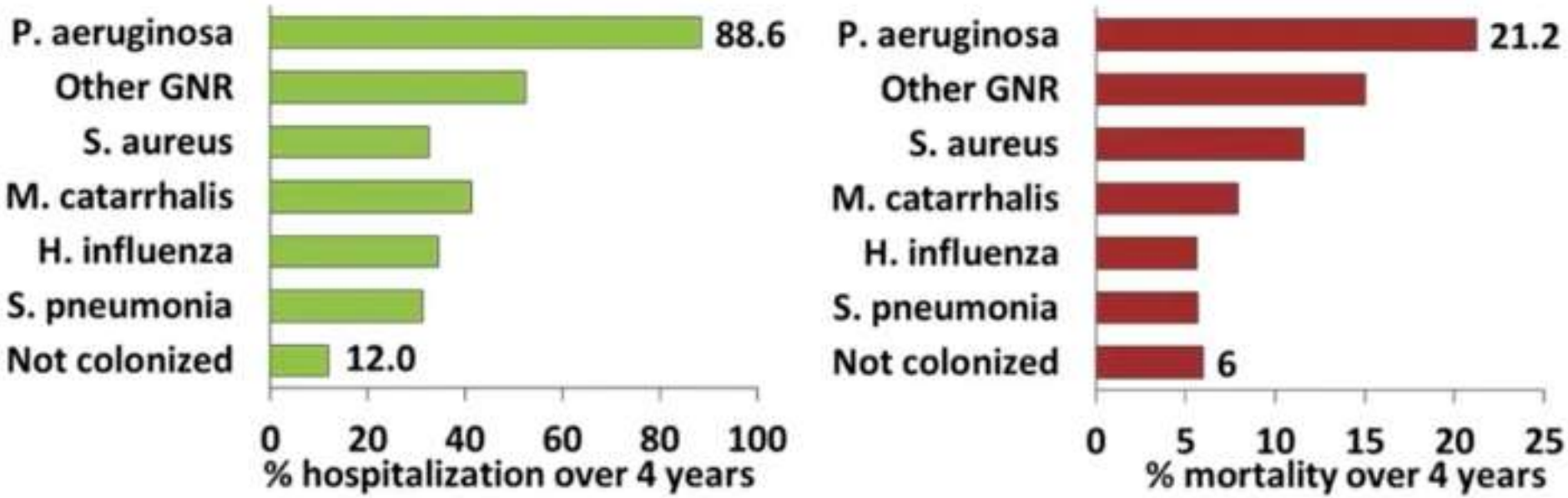
A general overview on bronchiectasis management



ABT, antibiotic therapy; HRCT, high resolution computed tomography; LTOT, long-term oxygen therapy; NIV, non-invasive ventilation.

1. Martinez-Garcia MA, et al. Arch Bronconeumol 2018; 54:88-98; 2. Drain M, Elborn JS. Eur Respir Monograph 2011; 52:32-43; 3. Polverino E, et al. Eur Respir J 2017; 50:1700629; 4. British Thoracic Society Guidelines for Bronchiectasis in adults. 2018; (https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guideline-for-bronchiectasis-in-adults-public-consultation/); 5. Chalmers JD, et al. Am J Respir Crit Care Med 2014; 189:576-85.

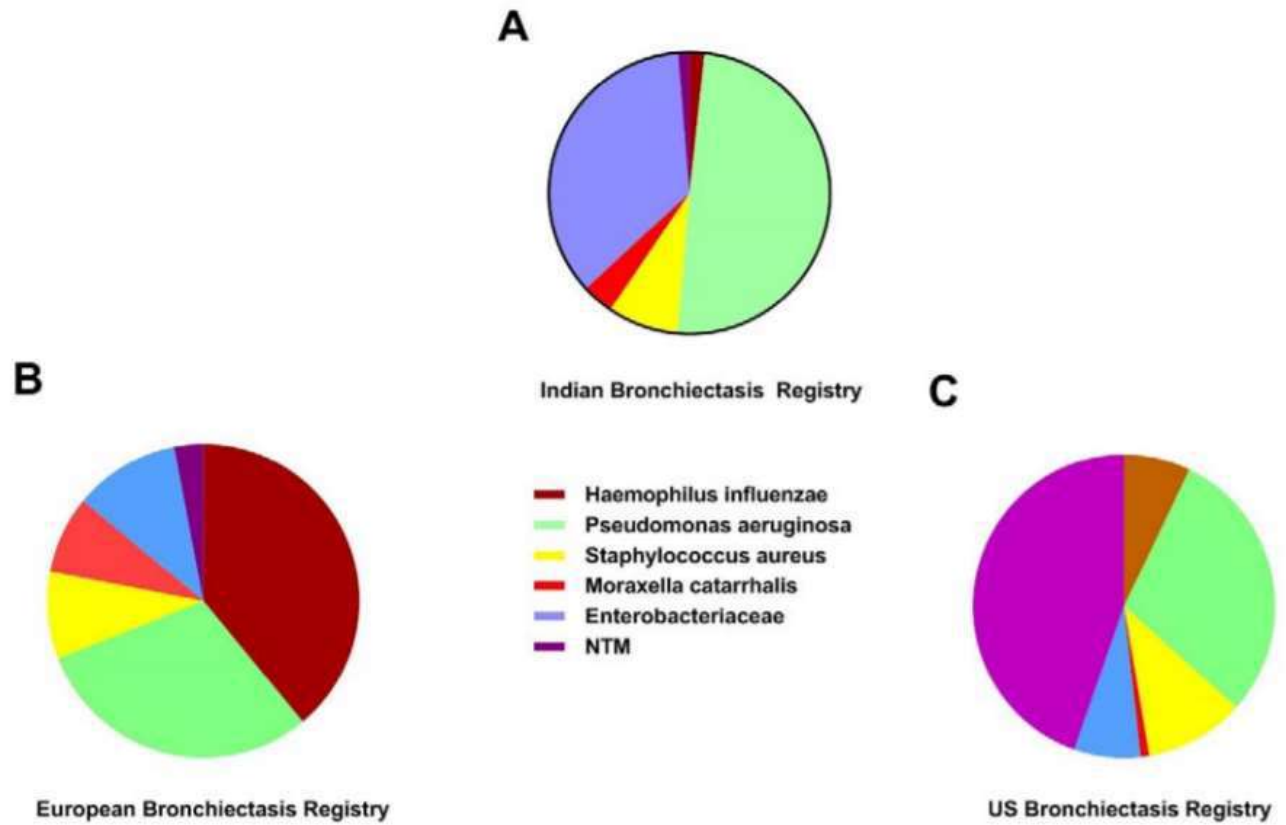
Sputum importance



N=608 patients, single centre UK study

Charmles et al.AJRCCM 2014

Microbiology	Indian	European	
Pseudomonas aeruginosa	301 (13·7%)	389 (15·0%)	0·2
Haemophilus influenzae	11 (0·5%)	569 (21·9%)	<0·0001
Staphylococcus aureus	50 (2·3%)	156 (6·0%)	<0·0001
Moraxella catarrhalis	22 (1·0%)	154 (5·9%)	<0·0001
Enterobacteriaceae	215 (9·8%)	158 (6·1%)	<0·0001



Sputum importance-BTS guidelines

Chronic colonisation with P. aeruginosa is independently associated with

- Higher mortality during follow-up (2++)
- Higher risk of admissions to hospital (2++)
- Increased exacerbations (2++)
- Poorer quality of life (2++)
- Worse radiological severity of disease (2+)
- Lower FEV1 and FVC cross-sectionally (2++)

Chronic colonisation with pathogens other than P. aeruginosa are associated with

- Hospital admissions (2++)
- Greater airway inflammation (2++)

Sputum bacterial load is associated with

- Greater airway inflammation (2++)
- More frequent exacerbations and hospital admissions (2+)

ERS bronchiectasis in adults guidelines-2017

	Strength of recommendation	Quality of evidence
Do a minimum bundle of tests, including differential blood count, serum immunoglobulins, and testing for ABPA in newly diagnosed patients	Conditional	Very low
Treat acute exacerbations of bronchiectasis with 14 days of antibiotics	Conditional	Very low
Patients with a new isolation of *Pseudomonas aeruginosa* should be offered eradication antibiotic treatment	Conditional	Very low
Do not offer eradication antibiotic treatment to patients after new isolation of pathogens other than *P aeruginosa*	Conditional	Very low
Do not offer inhaled corticosteroids for the treatment of bronchiectasis	Conditional	Low
Do not offer statins for the treatment of bronchiectasis	Strong	Low
Offer long-term antibiotic treatment for patients with three or more exacerbations per year*	Conditional	Moderate
Offer mucoactive treatment for patients with difficulty expectorating sputum and poor quality of life when standard airway clearance techniques have failed to control symptoms	Conditional	Low
Do not offer recombinant DNase for the treatment of bronchiectasis	Strong	Moderate
Do not routinely offer long-acting bronchodilators for patients with bronchiectasis	Conditional	Very low
Offer long-acting bronchodilators for patients with clinically significant breathlessness on an individual basis	Conditional	Very low
Do not offer surgical treatments, except to patients with localised disease and high exacerbation frequency despite optimum medical care	Conditional	Very low
Patients with chronic productive cough or difficulty expectorating should be taught airway clearance techniques	Conditional	Low
Patients with impaired exercise capacity should participate in pulmonary rehabilitation and take regular exercise	Strong	High

Only 3 strong recommendations

For remaining evidence is weak

Treatment Of Acute Exacerbations

Treatment Of Acute Exacerbations

- Aetiology (Bacterial>viral)
- Sputum is obtained for Gram stain and culture prior to antibiotic administration
- No RCT evaluating the efficacy of antibiotics in exacerbations in adults
- No RCT which route is better
- No RCT for pathogen based therapy
- Bronchiectasis patients are typically given prolonged courses of antibiotics of 14 days’ duration for infective exacerbations

Treatment Of Acute Exacerbations

- It is based on expert consensus and studies that documented good clinical outcomes with such treatment regimens.
- However, evidence base for this duration is poor
- ERS task force panel suggests that mild exacerbations, exacerbations in mild patients, those associated with pathogens more sensitive to antibiotics (e.g. S. pneumoniae), or patients with a rapid return to baseline state may benefit from shorter courses, but evidence supporting shorter course treatment is lacking

Addition of Inhaled Tobramycin to Ciprofloxacin for Acute Exacerbations of *Pseudomonas aeruginosa* Infection in Adult Bronchiectasis*

Diana Bilton, MD; Noreen Henig, MD, FCCP; Brian Morrissey, MD, FCCP; and

Objectives: This study tested the effect of adding inhaled tobramycin solution to oral ciprofloxacin (Cip) for the treatment of acute exacerbations of non-CF bronchiectasis in patients with *P aeruginosa* infection.

Methods: A double-blind, randomized, active comparator, parallel-design study conducted at 17 study centers (5 in the United Kingdom, and 12 in the United States) compared 2 weeks of therapy with Cip with either an inhaled tobramycin solution or placebo in 53 adults with known *P aeruginosa* infection who were having acute exacerbations of bronchiectasis.

Measurements: Clinical symptoms, pulmonary function, clinical efficacy, and sputum microbiology were investigated prospectively.

Main results: An inhaled solution of Cip with tobramycin, compared to placebo, achieved greater microbiological response but no statistically significant difference in clinical efficacy at days 14 or 21. Clinical and microbiological outcomes at the test of cure (*ie*, the clinical outcome assessment at day 21) were concordant when an inhaled tobramycin solution was added to therapy with Cip and compared to placebo ($p = 0.01$). Both subject groups had similar overall adverse event rates, but subjects receiving therapy with an inhaled tobramycin solution reported an increased frequency of wheeze (50%; placebo group, 15%).

Treatment Of Acute Exacerbations

- Absence of any direct data comparing longer and shorter courses of antibiotics, we suggest continuing the usual practice of treating acute exacerbations of bronchiectasis with 14 days of antibiotics

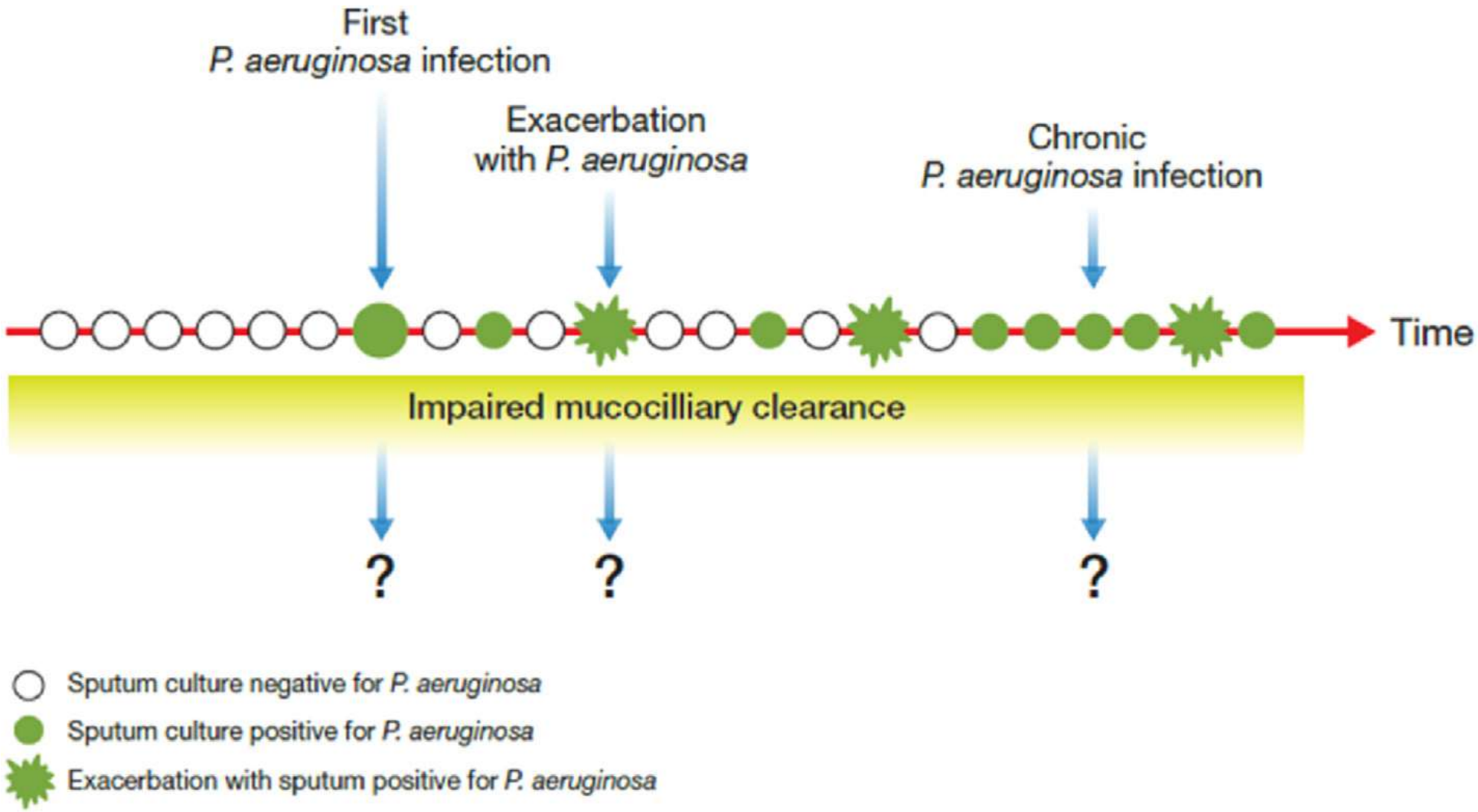
BTS guidelines 2019

Table 6 Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents- adults

Organism	Recommended first line treatment	Length of treatment	Recommended second line treatment	Length of treatment
Streptococcus pneumoniae	Amoxicillin 500 mg Three times a day	14 days	Doxycycline 100 mg BD	14 days
Haemophilus influenzae- beta lactamase negative	Amoxicillin 500 mg Three times a day Or Amoxicillin 1G Three times a day Or Amoxicillin 3G BD	14 days	Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Haemophilus influenzae- beta lactamase positive	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Doxycycline 100 mg bd Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Moraxella catarrhalis	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD	14 days
Staphylococcus aureus (MSSA)	Flucloxacillin 500 mg Four times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days

Staphylococcus aureus (MRSA) Oral preparations	Doxycycline 100 mg BD Rifampicin (<50 Kg) 450 mg OD Rifampicin (>50 Kg) 600 mg OD Trimethoprim 200 mg BD	14 days	Third line Linezolid 600 mg BD	14 days
Staphylococcus aureus (MRSA) Intravenous preparations	Vancomycin 1 gm BD* (monitor serum levels and adjust dose accordingly) or Teicoplanin 400 mg OD	14 days	Linezolid 600 mg BD	14 days
Coliforms for example, Klebsiella, enterobacter	Oral Ciprofloxacin 500 mg or 750 mg BD	14 days	Intravenous Ceftriaxone 2G OD	14 days
Pseudomonas aeruginosa	Oral Ciprofloxacin 500 mg bd (750 mg bd in more severe infections)	14 days	**Monotherapy:** Intravenous Ceftazidime 2G TDS or Piperacillin with tazobactam 4.5G TDS or Aztreonam 2G TDS or Meropenem 2G TDS **Combination therapy** The above can be combined with gentamicin or tobramycin or Colistin 2MU TDS (under 60 kg, 50 000–75 000 Units/kg daily in 3 divided doses) Patients can have an *in vivo* response despite in vitro resistance. Caution with aminoglycosides as highlighted below but also if previous adverse events, particularly previous ototoxicity/acute kidney injury due to aminoglycosides	14 days

Concept of eradication



Eradication therapy

- Definitions of chronic airway infection in bronchiectasis are not established but a systematic review identified that the most frequent definition used in bronchiectasis studies is two or more isolates of the same organism at least 3 months apart in 1 year
- P. aeruginosa eradication was considered successful if all (and at least three) bacteriologic cultures from respiratory samples collected during the 6-month period following the eradication attempt were negative for P. aeruginosa
- No clear evidence to support one regimen over another

Eradication Therapy against *Pseudomonas aeruginosa* in Non-Cystic Fibrosis Bronchiectasis

Ramon Orriols[a, b, e, g] Rosana Hernando[b, e, f] Adelaida Ferrer[c]

Abstract

Background: No prospective study has assessed eradication treatment of early *Pseudomonas aeruginosa* colonisation in bronchiectasis not due to cystic fibrosis (CF). ***Objectives:*** To evaluate the efficacy of 3 months of nebulised tobramycin after a short course of intravenous antibiotics in the eradication of *P. aeruginosa* and its clinical consequences in non-CF bronchiectasis following initial *P. aeruginosa* infection. ***Methods:*** A 15-month, single-masked, randomised study including 35 patients was conducted in a tertiary university hospital. Following the isolation of *P. aeruginosa* and a 14-day intravenous treatment with ceftazidime and tobramycin, patients received 300 mg nebulised tobramycin twice daily or placebo during 3 months, and were followed up for 12 months thereafter. ***Results:*** The median time to recurrence of *P. aeruginosa* infection was higher in the tobramycin than in the placebo group (p = 0.048, log-rank test). At the end of the study 54.5% of the patients were free of *P. aeruginosa* in the tobramycin group and 29.4% in the placebo group. The numbers of exacerbations (p = 0.044), hospital admissions (p = 0.037) and days of hospitalisation (p = 0.034) were lower in the tobramycin than in the placebo group. A global, non-significant trend to improvement in the tobramycin group was observed in most of the other studied parameters on comparing the two groups. Bronchospasm in the tobramycin group was remarkable. ***Conclusions:*** Our study shows that 3 months of nebulised tobramycin following a short course of intravenous antibiotics may prevent bronchial infection with *P. aeruginosa* and has a favourable clinical impact on non-CF bronchiectasis.

Outcomes of *Pseudomonas* eradication therapy in patients with non-cystic fibrosis bronchiectasis

Laura White, Ghazi Mirrani, Mark Grover, Judith Rollason, Adam Malin,

bronchiectasis. It is unknown whether early eradication improves outcomes. This retrospective study assessed clinical and microbiological outcomes of eradication therapy following initial *Pseudomonas* infection.

All patients undergoing *Pseudomonas* eradication therapy from 2004 to 2010 were identified retrospectively and assessed for microbiological eradication, exacerbation frequency, hospital admissions, clinical symptoms and lung function.

30 patients were identified with median follow-up time 26.4 months. Eradication therapy involved intravenous antibiotics ($n = 12$), intravenous antibiotics followed by oral ciprofloxacin ($n = 13$) or ciprofloxacin alone ($n = 5$), combined with 3 months of nebulised colistin. *Pseudomonas* was initially eradicated from sputum in 24 patients (80.0%). 13/24 patients remained *Pseudomonas*-free and 11/24 were subsequently reinfected (median time 6.2 months). Exacerbation frequency was significantly reduced from 3.93 per year pre-eradication and 2.09 post-eradication ($p = 0.002$). Admission rates were similar, at 0.39 per year pre-eradication and 0.29 post-eradication ($p =$ NS). 20/30 patients reported initial clinical improvement, whilst at one-year follow up, 19/21 had further improved or remained stable. Lung function was unchanged.

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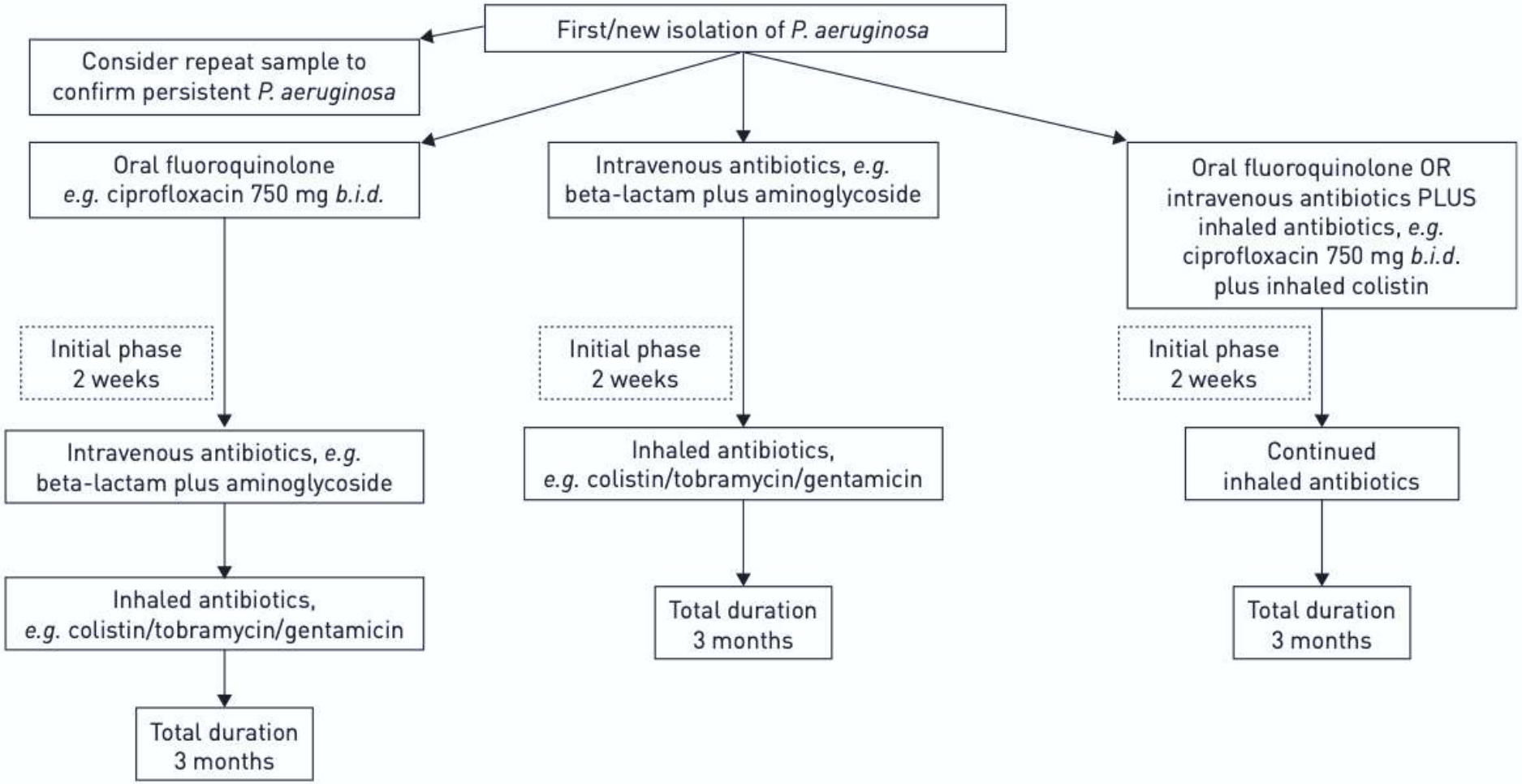
ERS guidelines



Long term therapies

- Antibiotics
- Statins
- ICS
- Bronchodilators
- Others

Long term antibiotics therapy(>=3 months)

Options available

- Oral
  - Macrolides
  - Non-macrolides
- Intravenous
- Inhalational

In addition to reducing bacterial burden, macrolides have well established immunomodulatory effects that include suppression of neutrophil mediated lung damage and enhancement of cilia function to promote mucociliary clearance

MRC study - 1957 involved 122 bronchiectasis patients from seven centres randomised to receive penicillin 500 mg QID or oxytetracycline 500 mg QID or identical placebo for 2 days per week for 1 year	Oxytetracycline-most efficacious with least exacerbations,50% reduction in sputum purulence, markedly less days confined to bed and less days off work. Penicillin arm-marginal treatment response compared with placebo

- In a study 38 bronchiectasis patients looked at the use of daily oral amoxicillin 3 g bd over 32 weeks. In this study CTs were not performed and no reduction in exacerbations was demonstrated, but some improvement in sputum volume, diary card symptom improvement and less time away from work
- Tetracycline based regimens may reduce exacerbation frequency, duration of illness and improve symptoms in patients wit bronchiectasis, with penicillin based regimens being less effective

Study (year)	Treatment	Study duration	Number of patients	Patient characteristics	Significant results and outcomes
BAT study (2013)[65]	250 mg daily azithromycin v. placebo	12-mo treatment 90-d run-out	83	≥ x 3 exacerbations/yr ≥ 1 sputum culture with pathogens in preceding yr	With azithromycin v. placebo: -Fewer exacerbations (0[0 – 1] v. 2[1 – 3]) -Improvement in FEV_1% predicted (+1.03% v. –0.1%) -Improved HRQL -Well tolerated, despite increased relative risk of diarrhea -Increased macrolide resistance: 35% in 8 patients at baseline increased to 88% in 20 patients v. 26% in 22 patients
BLESS study (2013)[66]	400 mg twice daily erythromycin v. placebo	48-wk treatment 4-wk washout	117	≥ x 2 exacerbations/yr	With erythromycin v. placebo: -Fewer exacerbations (76 v. 114) -Significant reduction in 24-h sputum weight (–5.4 g v. –1.7 g reduction) -Less decline in postbronchodilator FEV_1% predicted (–1.6% v. –4.0%) -Increased macrolide resistance: 27.7% v. 0.04% -Well tolerated; 28.8% v. 25.9% reporting AEs
EMBRACE study (2012)[67]	500 mg azithromycin 3 times per wk v. placebo	6-mo treatment 6-mo follow-up	141	≥ x 1 exacerbation/yr	With azithromycin v. placebo: -62% relative reduction in exacerbation rate during treatment and 42% annually -Annually, longer time to first exacerbation 239 (190–331) d v. 85 (52–113) d -Well tolerated, with 59 reported AEs v. 65 -No macrolide resistance testing performed

Note: AE = adverse event, FEV_1 = forced expiratory volume in the first second, HRQL = health-related quality of life.

Meta-analysis of macrolide maintenance therapy for prevention of disease exacerbations in patients with noncystic fibrosis bronchiectasis

Donghai Wang, MS[a,b], Wenlong Fu, MS[a], Jihong Dai, MD[a,b,*]

Results: A total of 10 studies involving 602 patients were included in the analysis. Pooled results showed that macrolide therapy significantly reduced the number of patients who suffered from exacerbations (RR=1.56, 95% CI=1.14–2.14, P=.006, I^2=72%), number of patients who experienced at least 3 exacerbations (RR=0.55, 95% CI=0.39–0.77, P=.0005, I^2=40%), average exacerbations per patient during the observation time (SMD=−0.69, 95% CI=−1.06 to −0.32, P=.0002, I^2=60%), and bronchiectasis exacerbation-related admissions (RR=0.46, 95% CI=0.23–0.96, P=.04, I^2=0%). Specified subgroup analyses of the number of patients free from exacerbations were further performed; macrolide therapy showed a significant benefit in both children (RR 5.03, 95% CI 2.02–12.50, P=.0005, I^2=45%) and adults (RR=1.66, 95% CI=1.37–2.02, P<.00001, I^2=79%); azithromycin showed a significant reduction on the number of patients who suffered from exacerbations (RR=2.25, 95% CI=1.67–3.02, P<.00001, I^2=0%), was different from erythromycin (RR=1.33, 95% CI=0.92–1.94, P=.13, I^2=0%) and roxithromycin (RR=1.14, 95% CI=0.97–1.35, P=.11, I^2=0%). The pooled results also showed no higher risk of adverse events (RR=0.98, 95% CI=0.85–1.13, P=.80, I^2=8%), even a lower risk of severe adverse events (RR=0.53, 95% CI=0.33–0.85, P=.009, I^2=0%). However, a higher risk of macrolide resistance (RR=3.59, 95% CI 2.6–4.96, P<.00001, I^2=0%) was observed.

Study or Subgroup	microlide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Koh Y.Y 1997	13	13	10	12	17.2%	1.19 [0.90, 1.59]	1997
Tsang KW 1999	11	11	8	10	16.2%	1.24 [0.88, 1.75]	1999
Cymbala AA 2005	9	11	3	11	6.6%	3.00 [1.10, 8.19]	2005
JF Liu 2012	21	22	18	21	18.6%	1.11 [0.91, 1.36]	2012
Wong C 2012	27	71	12	70	11.7%	2.22 [1.22, 4.02]	2012
Masekela R 2013	3	17	0	14	1.1%	5.83 [0.33, 104.22]	2013
Serisier DJ 2013	20	59	16	58	12.5%	1.23 [0.71, 2.13]	2013
Altenburg J 2013	23	43	8	40	10.4%	2.67 [1.36, 5.28]	2013
Valery PC 2013	9	45	4	44	5.8%	2.20 [0.73, 6.62]	2013
Total (95% CI)		**292**		**280**	**100.0%**	**1.56 [1.14, 2.14]**	
Total events	136		79				

Heterogeneity: Tau² = 0.13; Chi² = 28.23, df = 8 (P = 0.0004); I² = 72%

Test for overall effect: Z = 2.76 (P = 0.006)

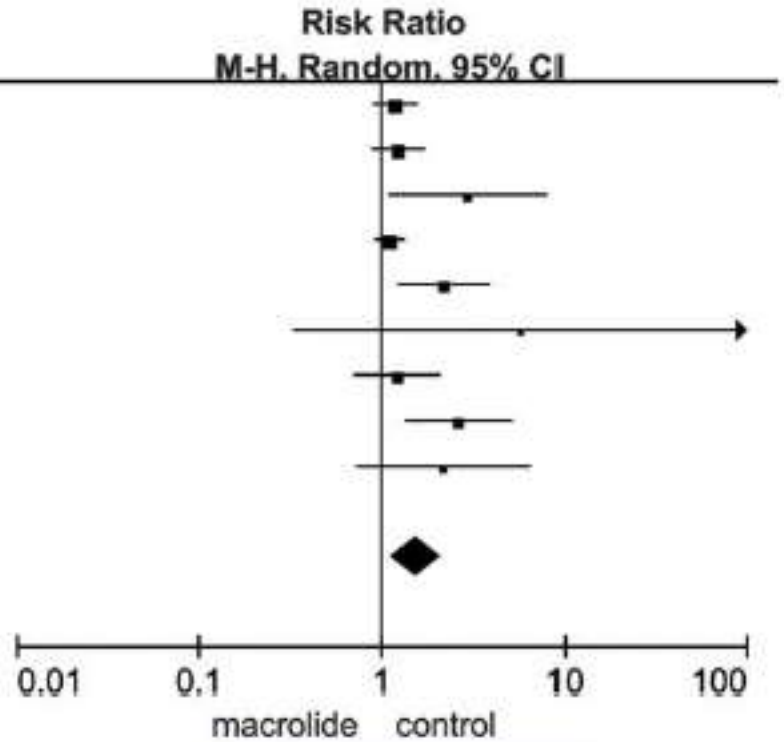


Figure 1. Effects of macrolide therapy on the number of patients with non-CF bronchiectasis free from exacerbations.

1.6.3 Azithromycin							
Cymbala AA 2005	9	11	3	11	1.7%	3.00 [1.10, 8.19]	2005
Wong C 2012	49	71	24	70	13.6%	2.01 [1.40, 2.88]	2012
Valery PC 2013	9	45	4	44	2.3%	2.20 [0.73, 6.62]	2013
Altenburg J 2013	23	43	8	40	4.6%	2.67 [1.36, 5.28]	2013
Subtotal (95% CI)		**170**		**165**	**22.2%**	**2.25 [1.67, 3.02]**	
Total events	90		39				
Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 5.35 (P < 0.00001)							
1.6.4 Erythromycin							
Tsang KW 1999	11	11	8	10	5.0%	1.24 [0.88, 1.75]	1999
Masekela R 2013	3	17	0	14	0.3%	5.83 [0.33, 104.22]	2013
Serisier DJ 2013	20	59	16	58	9.0%	1.23 [0.71, 2.13]	2013
Subtotal (95% CI)		**87**		**82**	**14.3%**	**1.33 [0.92, 1.94]**	
Total events	34		24				
Heterogeneity: Chi² = 1.26, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 1.50 (P = 0.13)							
1.6.5 Roxithromycin							
Koh Y.Y 1997	13	13	10	12	6.1%	1.19 [0.90, 1.59]	1997
JF Liu 2012	21	22	18	21	10.3%	1.11 [0.91, 1.36]	2012
Subtotal (95% CI)		**35**		**33**	**16.4%**	**1.14 [0.97, 1.35]**	
Total events	34		28				
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%							
Test for overall effect: Z = 1.61 (P = 0.11)							
Total (95% CI)		**584**		**561**	**100.0%**	**1.76 [1.54, 2.00]**	
Total events	316		172				
Heterogeneity: Chi² = 71.01, df = 17 (P < 0.00001); I² = 76%							
Test for overall effect: Z = 8.45 (P < 0.00001)							
Test for subgroup differences: Chi² = 25.79, df = 4 (P < 0.0001), I² = 84.5%							

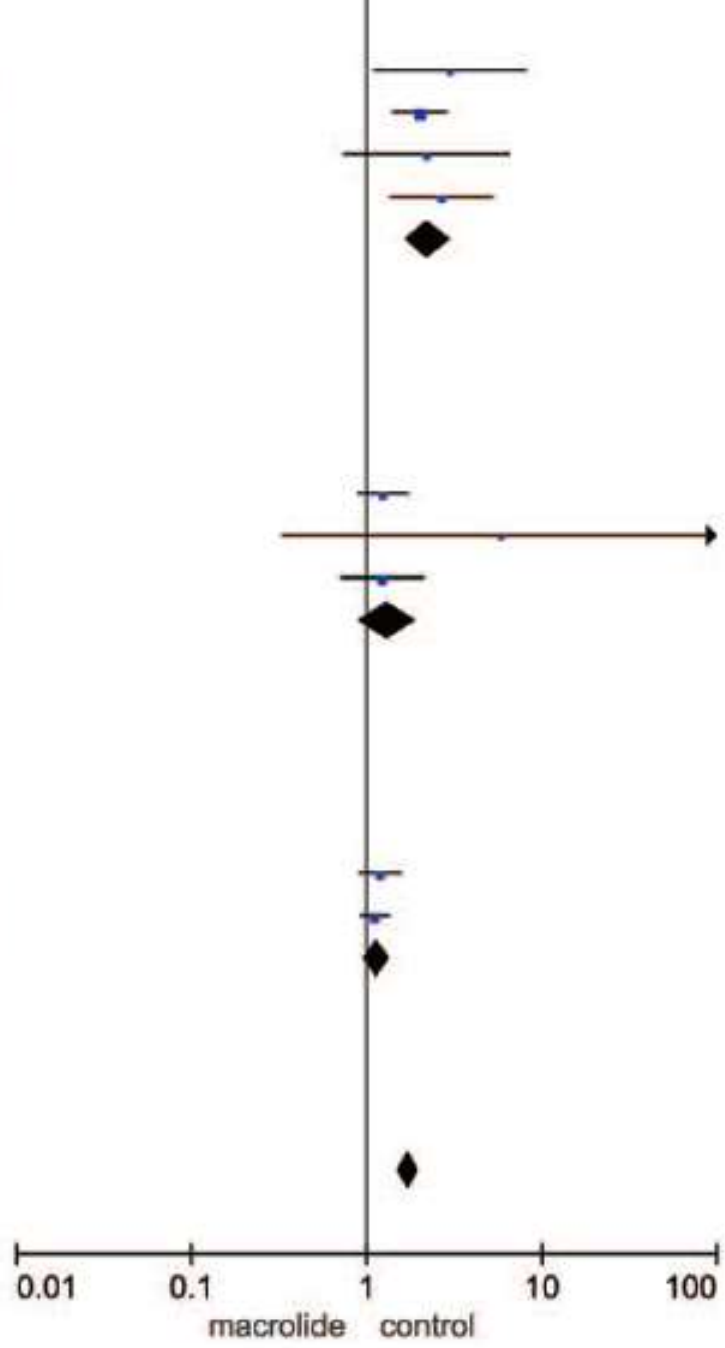


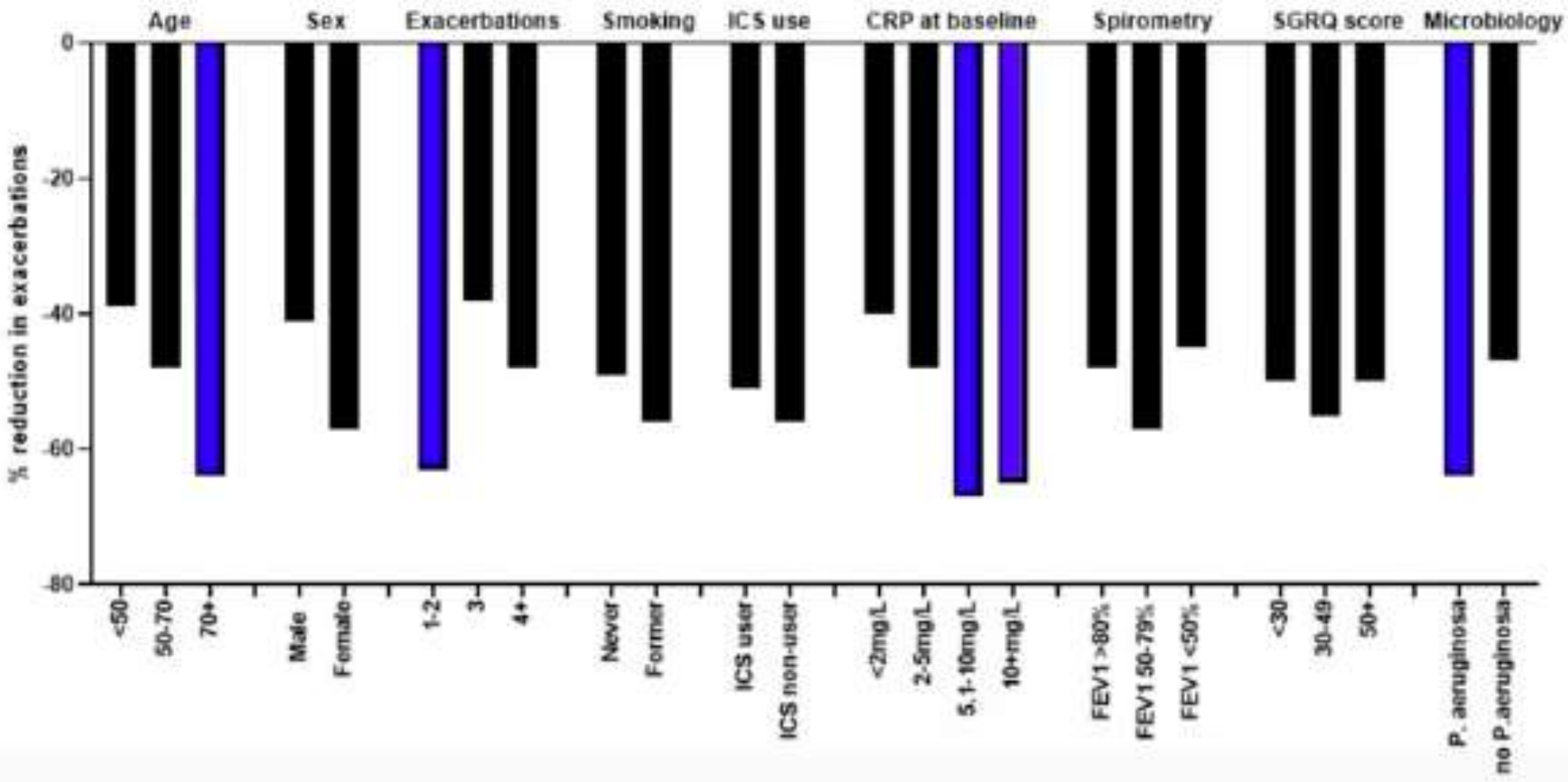
Figure 2. Subgroup analysis of effects of macrolide therapy on the number of patients with non-CF bronchiectasis free from exacerbations.

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

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

exacerbations. Studies in patients with cystic fibrosis bronchiectasis were excluded. The primary outcome of the meta-analysis was frequency of exacerbations requiring treatment with antibiotics. Secondary endpoints were time to first exacerbation, change in quality of life according to the St George's Respiratory Questionnaire (SGRQ), and change in FEV_1. IPD meta-analysis was done using fixed effects models adjusting for age, sex, FEV_1, and trial. We did prespecified subgroup analyses for each of the primary and secondary endpoints using one-step meta-analysis only. Subgroups were defined by age, sex, previous exacerbation frequency, smoking status, inhaled corticosteroid use at baseline, body-mass index at baseline, cause, C-reactive protein at baseline, baseline FEV_1 percentage of predicted, SGRQ total score, and *Pseudomonas aeruginosa* in sputum culture at baseline. The meta-analysis is registered with the PROSPERO international register of systematic reviews, number CRD42018102908.

Findings Of 234 identified studies, we included three randomised controlled trials, and IPD was obtained for 341 participants. Macrolide antibiotics reduced the frequency of exacerbations (adjusted incidence rate ratio [IRR] 0·49, 95% CI 0·36 to 0·66; p<0·0001). We also found that macrolide treatment improved the time to first exacerbation (adjusted hazard ratio 0·46, 0·34 to 0·61; p<0·0001) and was associated with improved quality of life measured by the SGRQ (mean improvement 2·93 points, 0·03 to 5·83; p=0·048). Macrolides were not associated with a significant improvement in FEV_1 (67 mL at 1 year, –22 to 112; p=0·14). Effect estimates in prespecified subgroup analyses revealed a reduced frequency of exacerbations in all prespecified subgroups, including a high level of benefit in patients with *P aeruginosa* infection (IRR 0·36, 0·18–0·72; p=0·0044) and in patients with one to two exacerbations per year (0·37, 0·16–0·88; p=0·025). Studies were rated as low risk of bias across all domains.



All groups responded

Perhaps more in

- Older
- Pseudomonas
- High CRP

Long term antibiotics therapy(>=3 months)

- Inhalational antibiotics

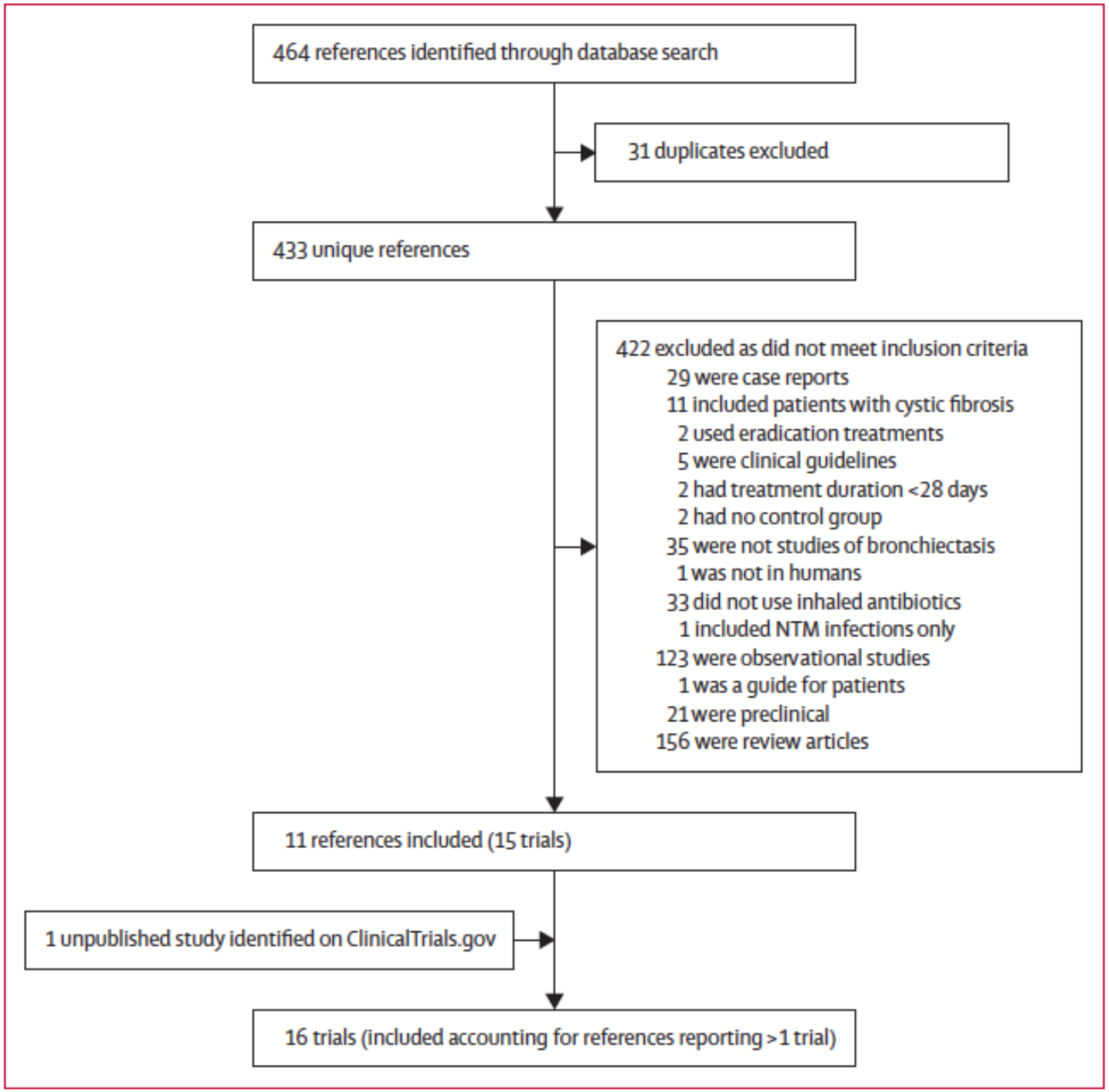
The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis

Irena F Laska, Megan L Crichton, Amelia Shoemark, James D Chalmers

Summary

Background Although use of inhaled antibiotics is the standard of care in cystic fibrosis, there is insufficient evidence to support use of inhaled antibiotics in patients with bronchiectasis not due to cystic fibrosis. We aimed to assess the efficacy and safety of inhaled antibiotics for the long-term treatment of adults with bronchiectasis and chronic respiratory tract infections.

Methods We did a systematic review and meta-analysis of all randomised controlled trials of inhaled-antibiotic use in adult patients with bronchiectasis and chronic respiratory tract infections. Eligible publications were identified by searching MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov. Randomised controlled trials of inhaled antibiotics were included if the patients were adults with stable bronchiectasis diagnosed by CT or bronchography, the trials had treatment a duration of at least 4 weeks, and their outcomes met at least one of the endpoints of interest. Studies in cystic fibrosis were excluded. Efficacy endpoints assessed were bacterial load, bacterial eradication from sputum, frequency of exacerbations, time to first exacerbation, proportion of patients with at least one exacerbation, frequency of severe exacerbations, quality of life, change in FEV_1, 6-min walk distance, mortality, adherence to treatment, and sputum volume; safety endpoints were adverse events and bacterial resistance in sputum. Each study was independently reviewed for methodological quality using the Cochrane risk of bias tool. Random-effects meta-analysis was used to pool individual studies. Heterogeneity was assessed using I^2. The review is registered on PROSPERO, number CRD42019122892.



- 16 trials in total (n=2592)
- One manuscript described two trials of inhaled aztreonam (AIR-BX1 and AIR-BX2).
- Two manuscripts described four trials of dry powder ciprofloxacin separated into 14 day on-off and 28 day on-off cycles (RESPIRE 1 and RESPIRE 2), which were treated as independent studies
- One manuscript described two studies of inhaled liposomal ciprofloxacin (ORBIT-3 and ORBIT-4)

	Drug	Duration	Number of participants, intervention *vs* control	Age, years (SD), intervention *vs* control	FEV_1 % predicted (SD), intervention *vs* control	*Pseudomonas aeruginosa* present, intervention *vs* placebo	Other pathogens present, intervention *vs* placebo	Primary outcome	Secondary outcomes
Barker et al (2000)[30]	Nebulised tobramycin (300 mg) *vs* placebo (1·25 mg quinine in saline) twice per day	6 weeks	37 (23 female, 14 male) *vs* 37 (22 female, 15 male)	66·6 (13·0) *vs* 63·2 (13·5)	56·2 (21·2) *vs* 53·3 (22·1)	37 (100%) *vs* 37 (100%)	No data	Change in *P aeruginosa* density (CFU per g) from baseline to week 4	Change in *P aeruginosa* density from baseline to week 2 and to week 6, investigator's subjective assessment of change in patients' general medical condition, percentage change in FEV_1 and FVC % predicted, and safety measurements
Drobnic et al (2005)[29]	Nebulised tobramycin (300 mg) *vs* placebo (0·9% saline) twice per day; crossover trial	13 months	10 *vs* 10 in the PP population of 30 participants included in the ITT population (sex breakdown not reported)	64·5 (range 38–75)	51·78 (16·5)	10 (100%) *vs* 10 (100%)	No data	Not specifically stated but presumed to be number of exacerbations	Number of hospital admissions, number of hospital admission days, antibiotic use, pulmonary function, SGRQ, tobramycin toxicity, density of *P aeruginosa* in sputum, emergence of bacterial resistance, and emergence of other opportunistic bacteria
Wilson et al (2013)[26]	Ciprofloxacin DPI (32·5 mg) *vs* placebo twice per day	84 days	60 (39 female and 21 male) *vs* 64 (43 female and 21 male)	64·7 (11·8) *vs* 61·4 (11·9)	57·2 (13·7) *vs* 54·6 (14·8)	32 (53%) *vs* 35 (55%)	*Haemophilus influenzae*: 14 (23%) *vs* 16 (25%); *Staphylococcus aureus*: 8 (13%) *vs* 17 (27%); *Streptococcus pneumoniae*: 7 (12%) *vs* 2 (3%); *Moraxella catarrhalis* 5 (8%) *vs* 3 (5%)	Effect of ciprofloxacin DPI on total bacterial density of predefined potential respiratory pathogens in sputum (CFU per g) after the 28-day treatment period	Time to exacerbation; emergence of new potential respiratory pathogens; emergence of resistance among baseline pathogens; changes in inflammatory biomarkers; change in 24-hour sputum volume and colour; changes in FEV_1, FVC, and SGRQ score at days 29, 56, and 84; adverse events; results of physical examinations; vital signs; and laboratory analyses
Serisier et al (2013; ORBIT-2)[27]	Liposomal ciprofloxacin (liposome encased ciprofloxacin [135 mg] and free ciprofloxacin [54 mg]) *vs* placebo (empty liposomes in	24 weeks	20 (10 female, 10 male) *vs* 22 (13 female, 9 male)	70 (5·6) *vs* 59·5 (13·2)	60·7 (24·1) *vs* 53·1 (22·7)	20 (100%) *vs* 22 (100%)	*Klebsiella*: 2 (10%) *vs* 2 (9%), *Ochrobactrum anthropic*: 0 *vs* 2 (9%)	Mean change in sputum *P aeruginosa* bacterial density (CFU per g) from baseline to end of first treatment cycle	Time to first pulmonary exacerbation, FEV_1, 6MWT, SGRQ, safety, and tolerability

	Drug	Duration	Number of participants, intervention vs control	Age, years (SD), intervention vs control	FEV_1 % predicted (SD), intervention vs control	*Pseudomonas aeruginosa* present, intervention vs placebo	Other pathogens present, intervention vs placebo	Primary outcome	Secondary outcomes
Barker et al (2014; AIR-BX 1)[28]	Nebulised aztreonam (75 mg) vs placebo three times per day	28 weeks	134 (84 female, 50 male) vs 132 (97 female, 35 male)	64·2 (12·9) vs 64·9 (12·1)	60·4 (22·6) vs 64·5 (18·7)	112 (84%) vs 105 (80%)	History of *Mycobacterium*: 16 (12%) vs 14 (10%); no data for other organisms	Change in QOL-B-RSS from baseline to week 4	Change in QOL-B-RSS from baseline to week 12, time to first exacerbation by week 16, change in CFU per g, presence or absence of respiratory pathogens, changes in MIC of aztreonam
Barker et al (2014; AIR-BX2)[28]	Nebulised aztreonam (75 mg) vs placebo three times per day	..	136 (89 female, 47 male) vs 138 (101 female, 37 male)	63·3 (14·2) vs 62·7 (13·3)	63·8 (19·5) vs 63·4 (21·6)	116 (85%) vs 103 (75%)	History of *Mycobacterium*: 8 (6%) vs 12 (9%); no data for other organisms	Change in QOL-B-RSS from baseline to week 4	Change in QOL-B-RSS from baseline to week 12, time to first exacerbation by week 16, change in CFU per g, presence or absence of respiratory pathogens, changes in MIC of aztreonam
Haworth et al (2019; ORBIT-3)[17]	Liposomal ciprofloxacin (liposome encased ciprofloxacin [135 mg] and free ciprofloxacin [54 mg]) vs placebo (empty liposomes in 0·9% saline) once per day	48 weeks	183 (127 female, 56 male) vs 95 (67 female, 28 male)	64·3 (13·6) vs 66·7 (10·7)	57·3 (21·9) vs 57·4 (20·2)	183 (100%) vs 95 (100%)	*S aureus*: 31 (17%) vs 22 (23%); *Escherichia coli* and coliforms: 11 (6%) vs 5 (5%); *S pneumoniae*: 5 (3%) vs 3 (3%); *H influenzae*: 5 (3%) vs 1 (1%); *M catarrhalis*: 2 (1%) vs 0	Time to first pulmonary exacerbation	Number and frequency of pulmonary exacerbations, number of patients requiring intravenous antibiotics, QOL-B-RSS, change in *P aeruginosa* bacterial density (CFU per g)
Haworth et al (2019; ORBIT-4)[17]	Liposomal ciprofloxacin (liposome encased ciprofloxacin [135 mg] and free ciprofloxacin [54 mg]) vs placebo (empty liposomes in 0·9% saline) once per day	..	206 (134 female, 72 male) vs 98 (63 female, 35 male)	63·3 (13·5) vs 64·2 (12·6)	62·6 (22·2) vs 59·8 (20·8)	206 (100%) vs 98 (100%)	*S aureus*: 50 (24%) vs 23 (24%); *E coli* and coliforms: 9 (4%) vs 3 (3%); *S pneumoniae*: 10 (5%) vs 3 (3%); *H influenzae*: 7 (3%) vs 4 (4%)	Time to first pulmonary exacerbation	Number and frequency of pulmonary exacerbations, number of patients requiring intravenous antibiotics, QOL-B-RSS, change in *P aeruginosa* bacterial density (CFU per g)

	Drug	Duration	Number of participants, intervention *vs* control	Age, years (SD), intervention *vs* control	FEV_1 % predicted (SD), intervention *vs* control	*Pseudomonas aeruginosa* present, intervention *vs* placebo	Other pathogens present, intervention *vs* placebo	Primary outcome	Secondary outcomes
De Soyza et al (2018; RESPIRE 1, 14 days)[15]	Ciprofloxacin DPI (32·5 mg) *vs* placebo twice per day	12 months	137 (88 female and 49 male) *vs* 68 (44 female and 24 male)	65·2 (13·5) *vs* 65·5 (12·9)	59·42 (16·7) *vs* 57·37 (15·5)	83 (61%) *vs* 41 (60%)	≥1 prespecified microorganism for recruitment: *H influenzae*, *M catarrhalis*, *S aureus*, *S pneumoniae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*	Time to first exacerbation, frequency of exacerbations	Less stringent definition of an exacerbation microbiological outcomes, QOL assessments (SGRQ and QOL-B), lung function
De Soyza et al (2018; RESPIRE 1, 28 days)[15]	Ciprofloxacin DPI (32·5 mg) *vs* placebo twice per day	..	141 (101 female and 40 male) *vs* 70 (52 female and 18 male)	64·2 (12·1) *vs* 64·0 (13·5)	59·48 (15·1) *vs* 61·7 (16·7)	83 (59%) *vs* 45 (64%)	≥1 prespecified microorganism for recruitment: *H influenzae*, *M catarrhalis*, *S aureus*, *S pneumoniae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*	Time to first exacerbation, frequency of exacerbations	Less stringent definition of an exacerbation, microbiological outcomes, QOL assessments (SGRQ and QOL-B), lung function
Aksamit et al (2018; RESPIRE 2, 14 days)[16]	Ciprofloxacin DPI (32·5 mg) *vs* placebo twice per day	..	176 (96 female, 80 male) *vs* 88 (62 female, 26male)	60·4 (13·7) *vs* 60·4 (15·0)	54·3 (17·3) *vs* 55·8 (18·6)	107 (61%) *vs* 55 (63%)	≥1 prespecified microorganism for recruitment: *H influenzae*, *M catarrhalis*, *S aureus*, *S pneumoniae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*	Time to first exacerbation, frequency of exacerbations	Less stringent definition of an exacerbation, microbiological outcomes, QOL assessments (SGRQ and QOL-B), lung function
Aksamit et al (2018; RESPIRE 2, 28 days)[16]	Ciprofloxacin DPI (32·5 mg) *vs* placebo twice per day	..	171 (92 female, 79 male) *vs* 86 (52 female, 34 male)	59·3 (14·2) *vs* 60·6 (13·7)	56·4 (18·8) *vs* 56·2 (18·2)	99 (58%) *vs* 54 (63%)	≥1 prespecified microorganism for recruitment: *H influenzae*, *M catarrhalis*, *S aureus*, *S pneumoniae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*	Time to first exacerbation, frequency of exacerbations	Less stringent definition of an exacerbation, microbiological outcomes, QOL assessments (SGRQ and QOL-B), lung function

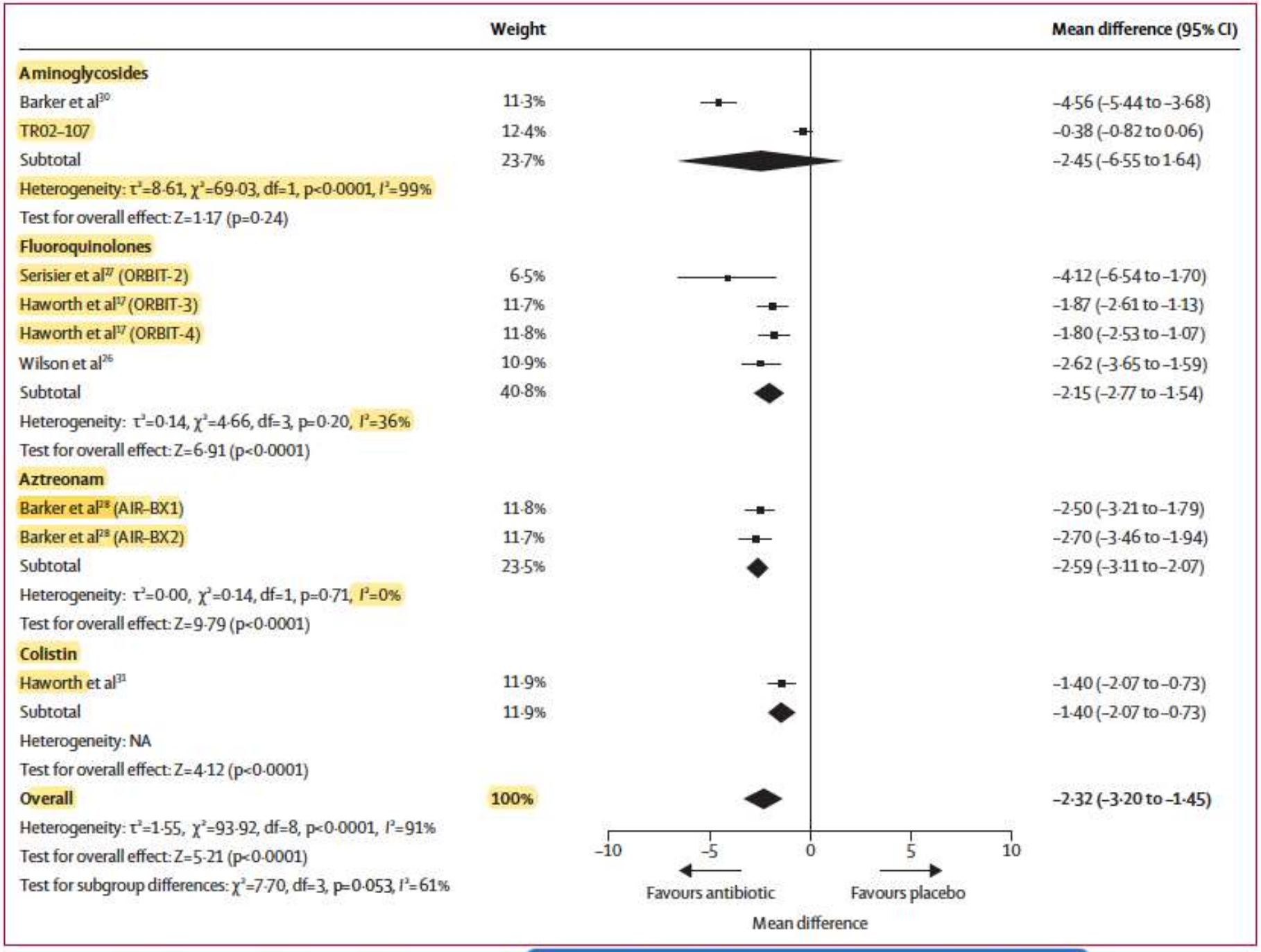
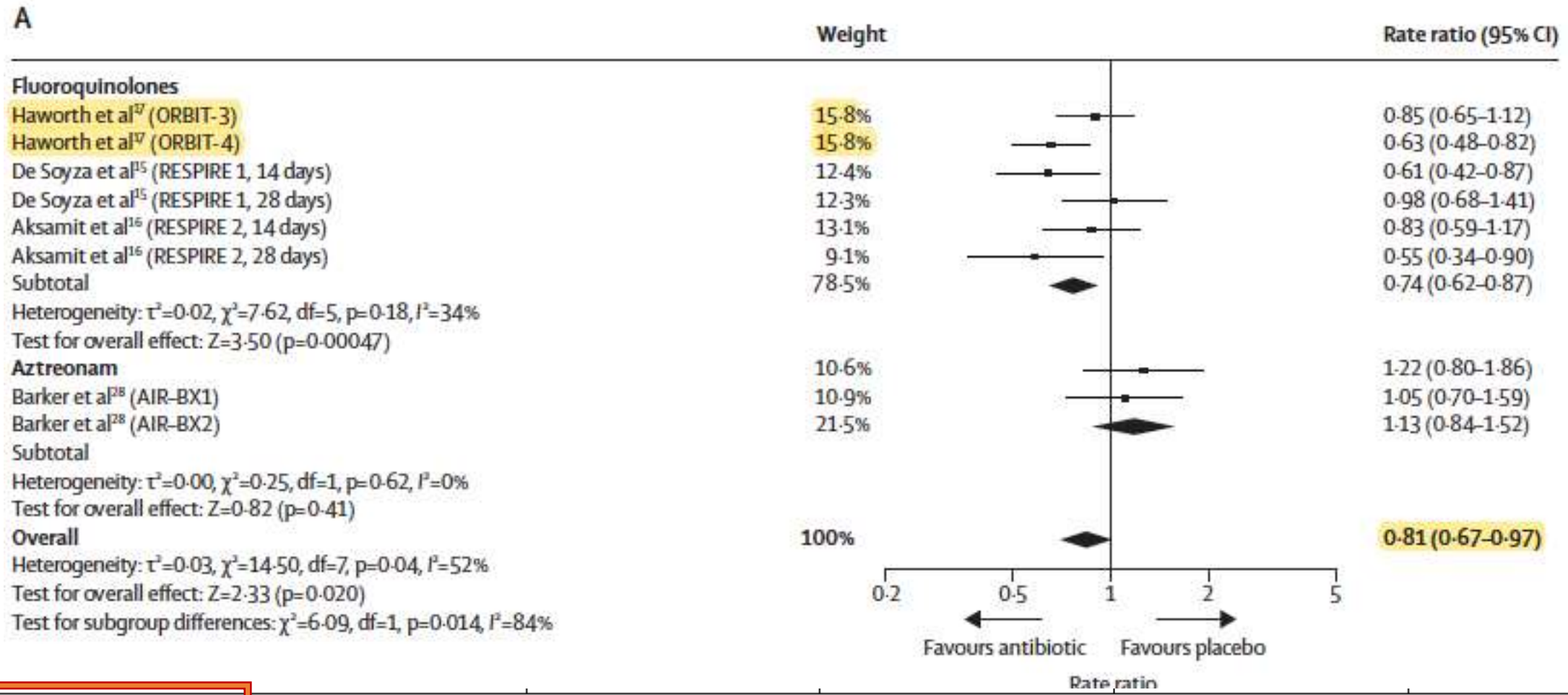


Figure 2: **Forest plot of the effect of inhaled antibiotic treatment on quantitative bacterial load in colony forming units per g of sputum**

Nine studies provided data on bacterial load, demonstrating a consistent reduction in CFU per g of sputum with inhaled antibiotic treatment

Endpoint	N trials	N patients	Effect estimate (95% CI)	I^2 heterogeneity
Bacterial load (mean difference)				
All studies	9	1568	-2·32 (-3·20, -1·45)	91%
Aminoglycosides	2	136	-2·45 (-6·55, 1·64)	99%
Fluoroquinolones	4	748	-2·15 (-2·77, -1·54)	36%
Aztreonam	2	540	-2·59 (-3·11, -2·07)	0%
Colistin	1	144	-1·40 (-2·07, -0·73)	N/A
Low risk of bias	6	1288	-2·18 (-2·64, -1·72)	52%
6 month studies	3	726	-1·67 (-2·08, -1·26)	0%
P. aeruginosa only	6	904	-2·20 (-3·41, -0·99)	94%
Bacterial eradication from sputum (odds ratio)				
All studies	11	1379	3·36 (1·63, 6·91)	77%
Aminoglycosides	4	184	10·92 (0·60, 198·13)	82%
Fluoroquinolones	6	1066	2·50 (1·14, 5·45)	78%
Aztreonam	0	0	Not estimable	Not estimable
Colistin	1	129	2·51 (1·04, 6·04)	N/A
Low risk of bias	6	1066	2·50 (1·14, 5·45)	78%
6 month studies	8	1176	2·02 (1·01, 4·05)	73%
P. aeruginosa only	5	298	3·99 (1·17, 13·59)	61%

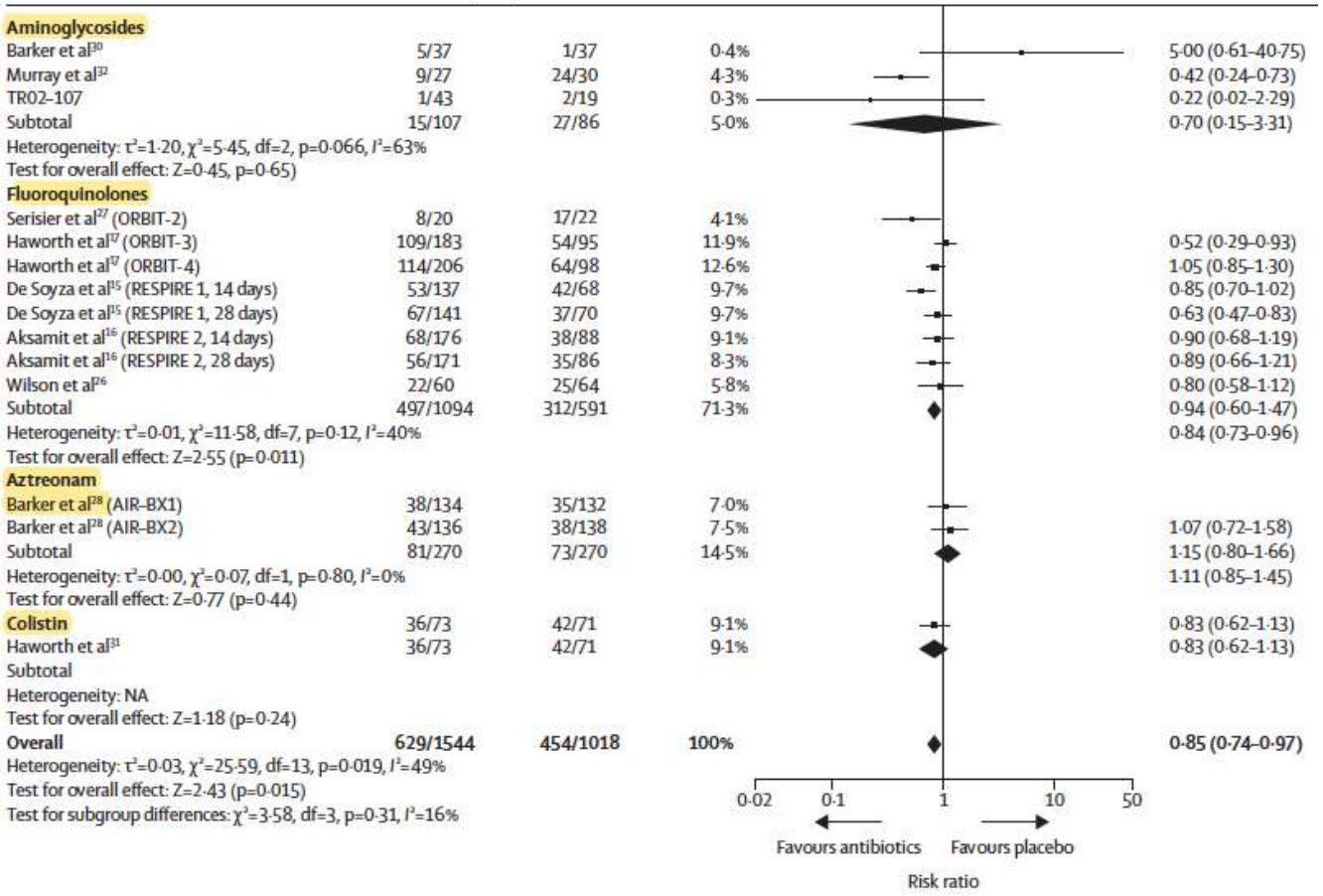
Frequency of exacerbations Rate ratio 0.81



Frequency of exacerbations (rate ratio)				
All studies	8	2059	0·81 (0·67, 0·97)	52%
Aminoglycosides	0	0	Not estimable	Not estimable
Fluoroquinolones	6	1519	0·74 (0·62, 0·87)	34%
Aztreonam	2	540	1·13 (0·84, 1·52)	0%
Low risk of bias	8	2059	0·81 (0·67, 0·97)	52%
6 month studies	6	1519	0·74 (0·62, 0·87)	34%
P. aeruginosa only	2	582	0·73 (0·54, 0·99)	59%

Number of participants experiencing at least one exacerbation

Number of patients with at least one exacerbation (risk ratio)				
All studies	14	2562	0·85 (0·74, 0·97)	49%
Aminoglycosides	3	193	0·70 (0·15, 3·31)	63%
Fluoroquinolones	8	1685	0·84 (0·73, 0·96)	40%
Aztreonam	2	540	1·11 (0·85, 1·45)	0%
Colistin	1	144	0·83 (0·62-1·13)	N/A
Low risk of bias	10	2225	0·88 (0·77, 0·99)	40%
6 month studies	8	1720	0·82 (0·72, 0·93)	41%
P. aeruginosa only	6	904	0·86 (0·69, 1·08)	50%



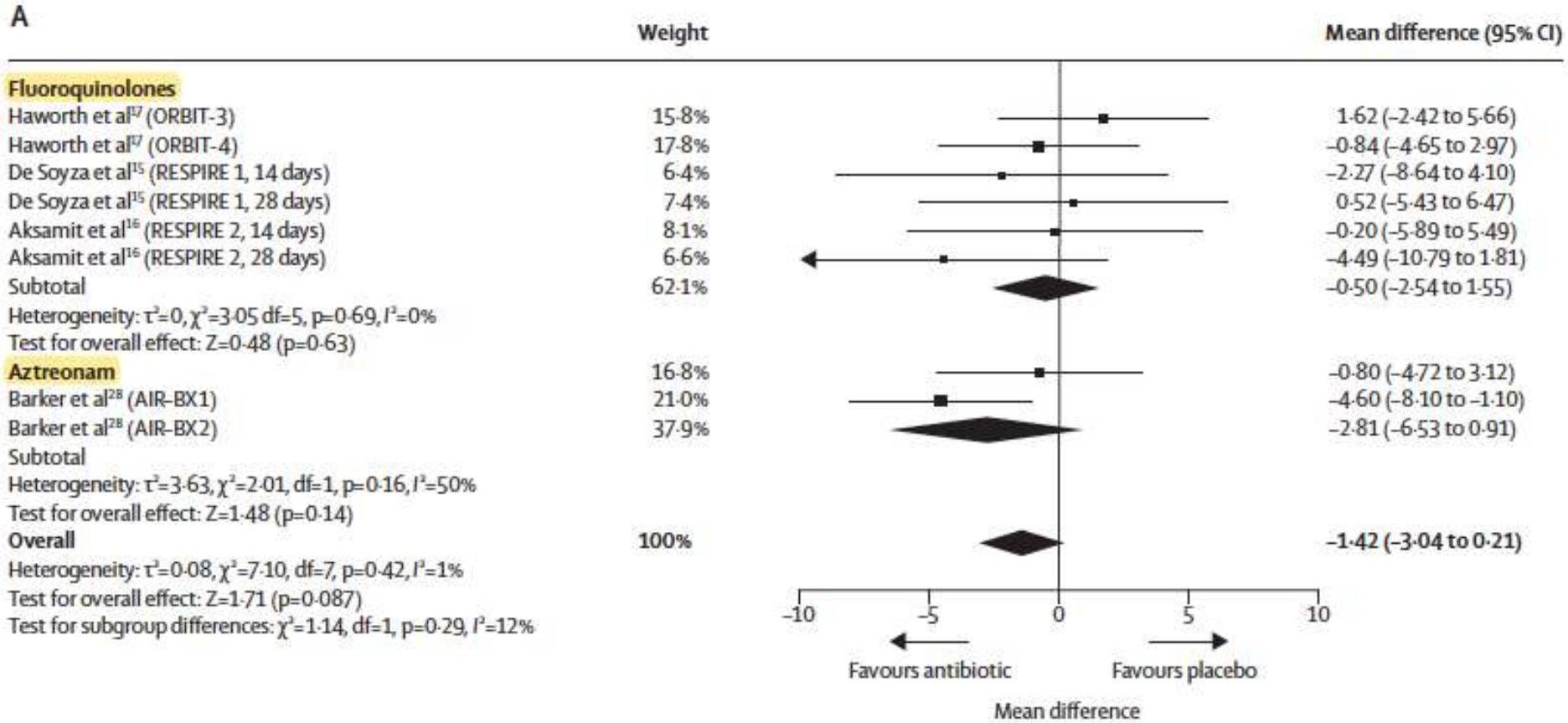
Reduce exacerbations with a rate ratio of 0.85

Time to first exacerbation (Hazard ratio)				
All studies	9	2203	0·83 (0·69, 0·99)	44%
Aminoglycosides	0	0	Not estimable	Not estimable
Fluoroquinolones	6	1519	0·76 (0·64, 0·90)	20%
Aztreonam	2	540	1·25 (0·91, 1·71)	0%
Colistin	1	144	0·70 (0·45-1·08)	N/A
Low risk of bias	9	2203	0·83 (0·69, 0·99)	44%
6 month studies	7	1663	0·76 (0·65, 0·88)	7%
P. aeruginosa only	3	726	0·80 (0·64, 1·00)	18%
Frequency of severe exacerbations (rate ratio)				
All studies	4	617	0·43 (0·24, 0·78)	44%
Aminoglycosides	2	35	0·22 (0·08, 0·58)	0%
Fluoroquinolones	2	582	0·56 (0·28, 1·11)	58%
Aztreonam	0	0	Not estimable	Not estimable
Colistin	0	0	Not estimable	Not estimable
Low risk of bias	2	582	0·56 (0·28, 1·11)	58%
6 month studies	4	617	0·43 (0·24, 0·78)	44%
P. aeruginosa only	4	617	0·43 (0·24, 0·78)	44%

FEV_1% predicted (mean difference)				
All studies	8	1386	-0·87 (-2·00, 0·26)	0%
Aminoglycosides	3	140	-1·28 (-3·16, 0·60)	0%
Fluoroquinolones	3	706	0·88 (-1·09, 2·86)	0%
Aztreonam	2	540	-2·25 (-4·28, -0·21)	0%
Colistin	0	0	Not estimable	Not estimable
Low risk of bias	5	1246	-0·63 (-2·05, 0·78)	21%
6 month studies	4	659	-0·30 (-1·83, 1·23)	0%
P. aeruginosa only	4	665	-0·20 (-1·93, 1·54)	0%
FEV_1 absolute change (mean difference)				
All studies	9	1735	0·00 (-0·03, -0·03)	32%
Aminoglycosides	2	72	-0·11 (-0·45, 0·22)	0%
Fluoroquinolones	6	1519	-0·03 (-0·07, 0·01)	0%
Aztreonam	0	0	Not estimable	Not estimable
Colistin	1	144	-0·10 (-0·22, 0·02)	N/A
Low risk of bias	6	1519	-0·03 (-0·07, 0·01)	0%
6 month studies	7	1693	0·00 (-0·03, -0·03)	41%
P. aeruginosa only	5	783	0·00 (-0·03, 0·04)	29%
Six-minute walk distance (mean difference)				
All studies	3	509	-1.37 (-12.68, 9.95)	0%
Aminoglycosides	0	0	Not estimable	Not estimable
Fluoroquinolones	1	42	8·20 (-41·52, 57·92)	N/A
Aztreonam	2	540	-1·72 (-15·20, 11·77)	25%
Colistin	0	0	Not estimable	Not estimable
Low risk of bias	3	509	-1.37 (-12.68, 9.95)	0%
6 month studies	0	0	Not estimable	Not estimable
P. aeruginosa only	1	42	8·20 (-41·52, 57·92)	N/A

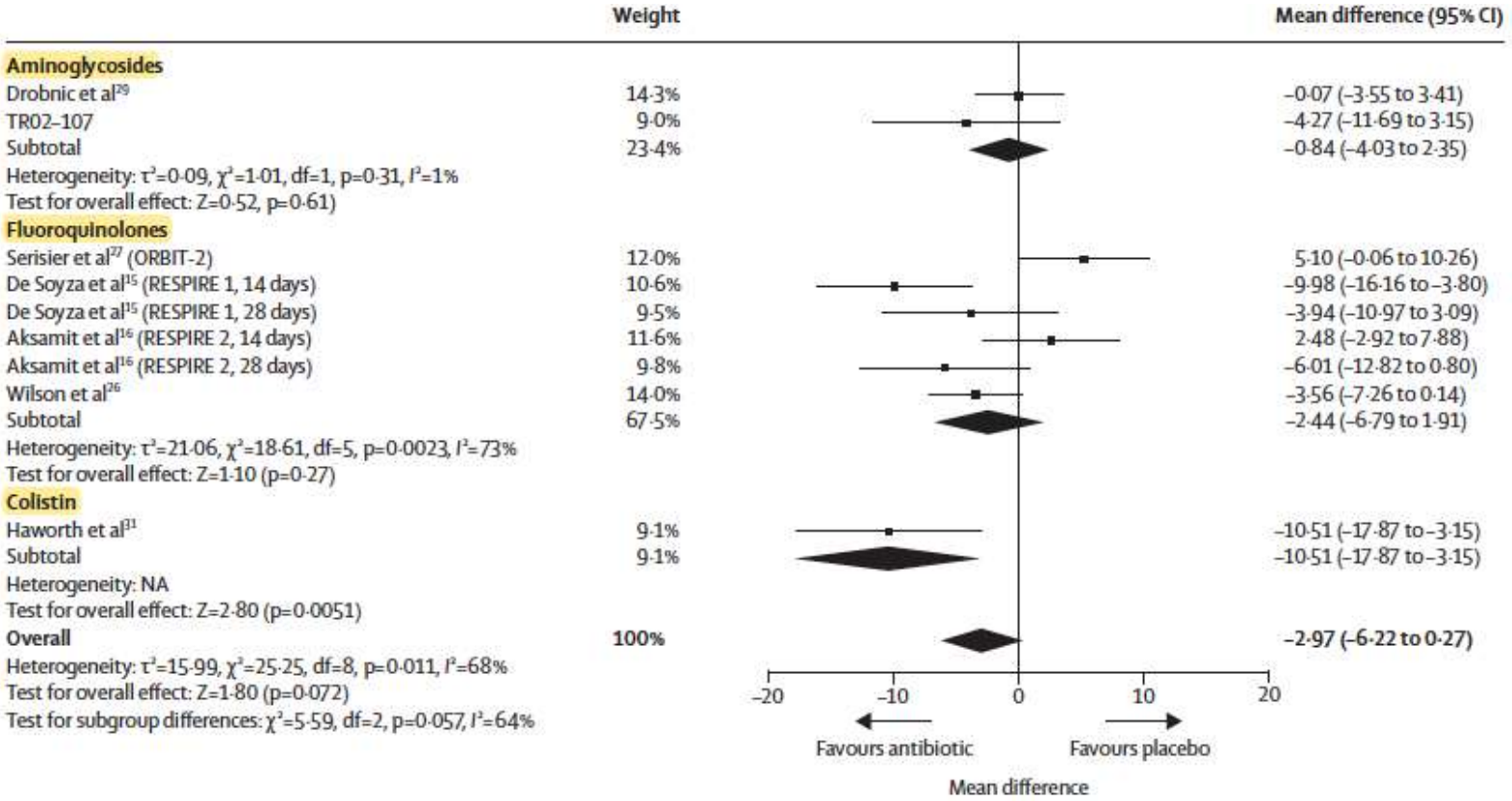
Quality of life and symptom scales-QOL-B questionnaire

Quality of Life Bronchiectasis questionnaire (mean difference)				
All studies	8	2059	-1·42 (-3·04, 0·21)	1%
Aminoglycosides	0	0	Not estimable	Not estimable
Fluoroquinolones	6	1519	-0·50 (-2·54, 1·55)	0%
Aztreonam	2	540	-2·81 (-6·53, 0·91)	50%
Colistin	0	0	Not estimable	Not estimable
Low risk of bias	8	2059	-1·42 (-3·04, 0·21)	1%
6 month studies	6	1519	-0·50 (-2·54, 0·79)	0%
P. aeruginosa only	2	582	0·32 (-2·46, 3·09)	0%



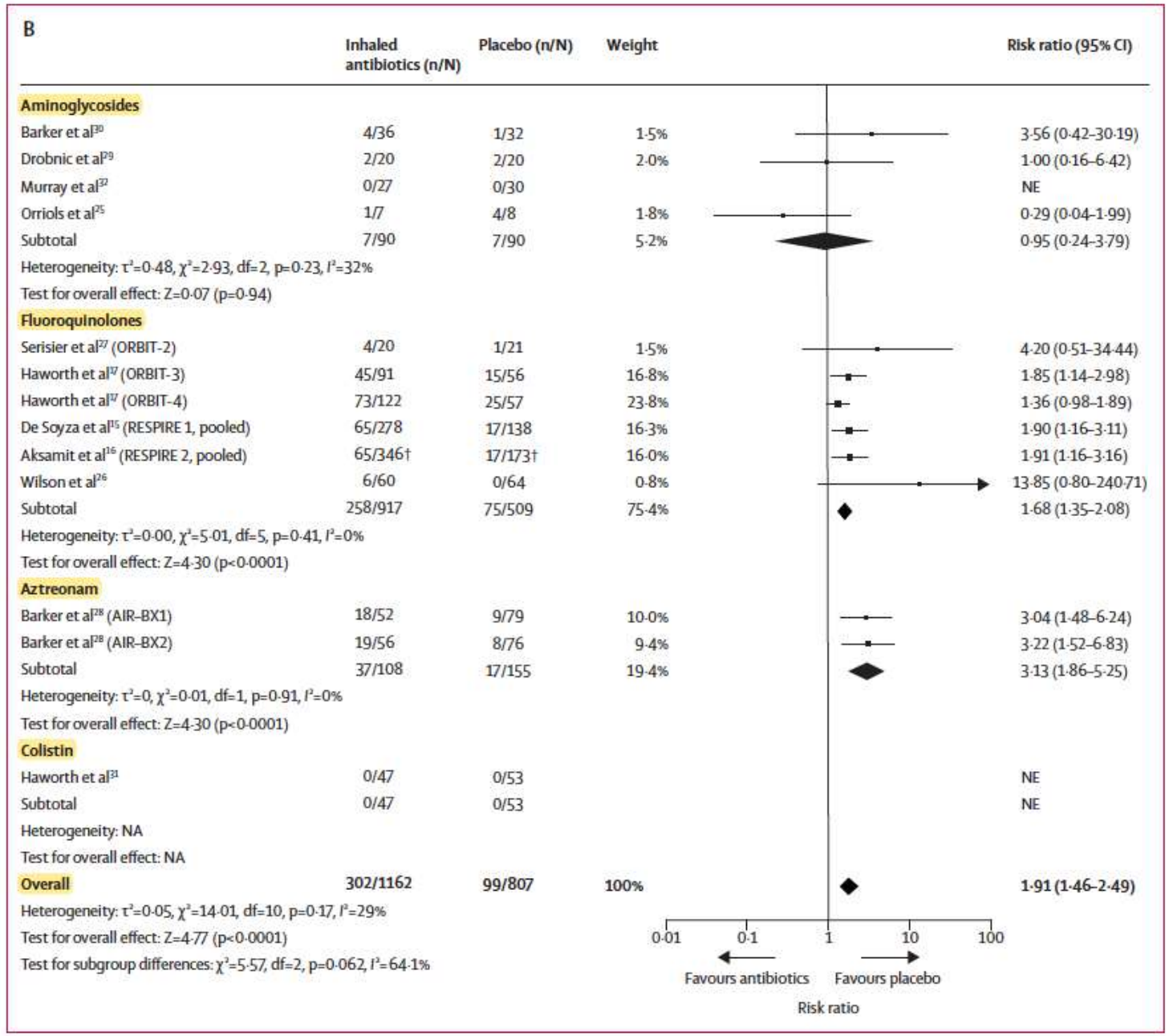
Quality of life and symptom scales-SGRQ (B)

St Georges Respiratory Questionnaire (mean difference)				
All studies	9	1329	-2·97 (-6·22, 0·27)	68%
Aminoglycosides	2	82	-0·84 (-4·03, 2·35)	1%
Fluoroquinolones	6	1103	-2·44 (-6·79, 1·91)	73%
Aztreonam	0	0	Not estimable	Not estimable
Colistin	1	144	-10·51 (-17·87, -3·15)	N/A
Low risk of bias	6	1103	-2·44 (-6·79, 1·91)	73%
6 month studies	6	1101	-4·22 (-8·50, 0·06)	70%
P. aeruginosa only	4	268	-1·88 (-7·60, 3·84)	76%
Excluding studies reporting symptom domain only	5	392	-2·13 (-6·39, 2·13)	72%



Below the MCID of 4 points

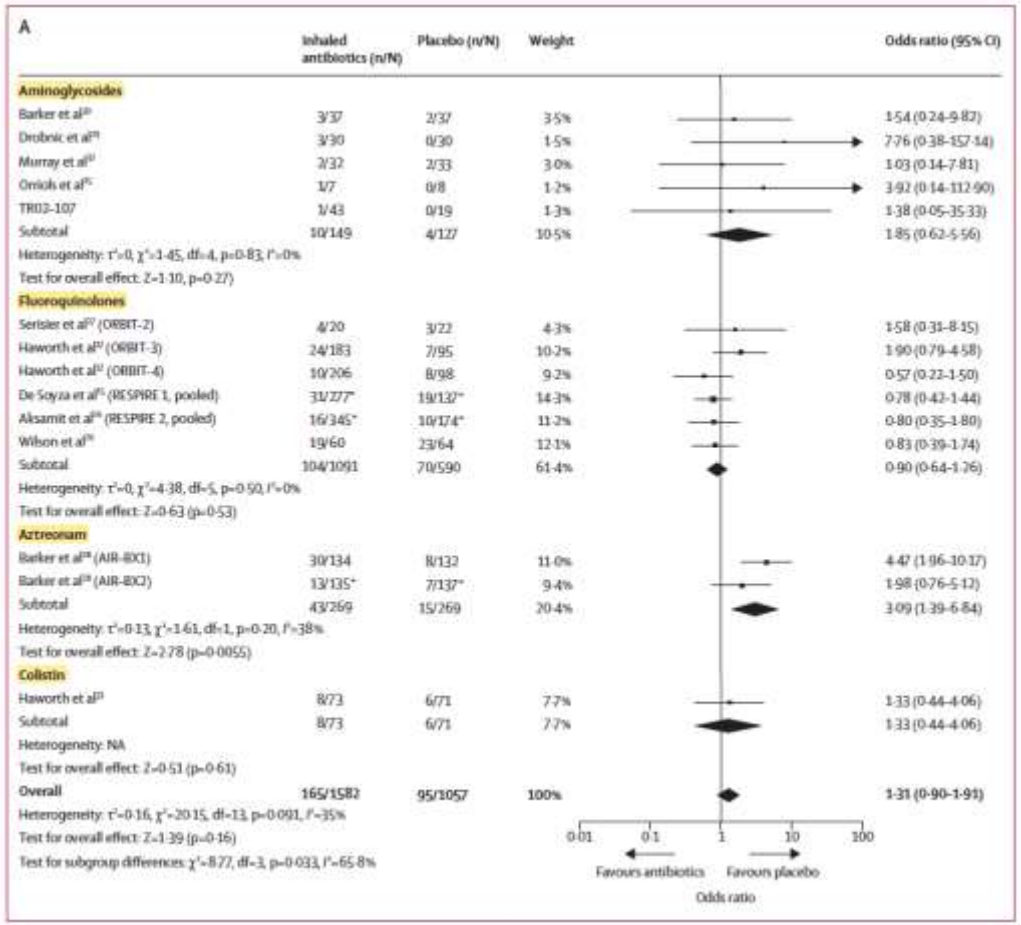
Isolated bacteria with a minimum inhibitory concentration above the resistant breakpoint at the end of treatment



Adherence (risk ratio)				
All studies	12	2436	1·01 (0·98, 1·03)	0%
Aminoglycosides	2	131	0·96 (0·88, 1·05)	0%
Fluoroquinolones	7	1643	1·02 (0·98, 1·05)	0%
Aztreonam	2	540	1·00 (0·93, 1·08)	57%
Colistin	1	122	1·04 (0·86, 1·25)	N/A
Low risk of bias	9	2183	1·01 (0·99, 1·04)	0%
6 month studies	8	1698	1·01 (0·98, 1·04)	0%
P. aeruginosa only	4	778	0·99 (0·93, 1·05)	0%
Mortality (risk ratio)*				
All studies	13	2360	1·03 (0·53, 1·98)	0%
Aminoglycosides	4	200	2·39 (0·53, 10·83)	0%
Fluoroquinolones	6	1515	0·86 (0·37, 1·98)	0%
Aztreonam	2	501	1·05 (0·15, 7·08)	0%
Colistin	1	144	0·49 (0·05, 5·24)	N/A
Low risk of bias	8	2016	0·90 (0·42, 1·92)	0%
6 month studies	10	1799	1·02 (0·51, 2·05)	0%
P. aeruginosa only	6	861	0·92 (0·36, 2·34)	0%
Antibiotic resistance (defined as described in table E4, risk ratio)				
All studies	15	1969	1·91 (1·46, 2·49)	29%
Aminoglycosides	4	180	0·95 (0·24, 3·79)	32%
Fluoroquinolones	8	1426	1·68 (1·35, 2·08)	0%
Aztreonam	2	263	3·13 (1·86, 5·25)	0%
Colistin	1	100	Not estimable	N/A
Low risk of bias	10	1689	1·96 (1·52, 2·53)	28%
6 month studies	10	1473	1·60 (1·28, 2·02)	8%
P. aeruginosa only	7	590	1·50 (1·09, 2·07)	10%

Adverse events leading to study drug discontinuation

Adverse events leading to discontinuation (odds ratio)				
All studies	16	2639	1·31 (0·90, 1·91)	35%
Aminoglycosides	5	274	1·85 (0·62, 5·56)	0%
Fluoroquinolones	8	1681	0·90 (0·64, 1·26)	0%
Aztreonam	2	540	3·09 (1·39, 6·84)	38%
Colistin	1	144	1·33 (0·44, 4·06)	N/A
Low risk of bias	10	2219	1·26 (0·77, 2·06)	61%
6 month studies	10	1799	0·98 (0·68, 1·40)	0%
P. aeruginosa only	8	979	1·32 (0·80, 2·15)	0%



Treatment emergent adverse events (odds ratio)				
All studies	13	2477	0·97 (0·67, 1·40)	51%
Aminoglycosides	2	114	1·16 (0·38, 3·51)	0%
Fluoroquinolones	8	1681	0·69 (0·46, 1·03)	41%
Aztreonam	2	540	2·13 (1·16, 3·93)	0%
Colistin	1	144	1·57 (0·80, 3·06)	N/A
Low risk of bias	10	2219	1·03 (0·49, 2·14)	84%
6 month studies	8	1699	1·14 (0·48, 2·70)	86%
Serious adverse events (odds ratio)				
All studies	11	2298	0·91 (0·65, 1·28)	10%
Aminoglycosides	1	60	0·84 (0·28, 2·53)	N/A
Fluoroquinolones	7	1556	0·84 (0·61, 1·15)	0%
Aztreonam	2	540	10·29 (1·12, 94·99)	8%
Colistin	1	144	0·97 (0·36, 2·60)	N/A
Low risk of bias	9	2094	1·01 (0·59, 1·70)	33%
6 month studies	7	1660	0·84 (0·62, 1·14)	0%
P. aeruginosa only	5	826	0·99 (0·53, 1·86)	0%
Bronchospasm (risk ratio)				
All studies	15	2563	0·99 (0·66, 1·48)	13%
Aminoglycosides	3	140	4·01 (1·18, 13·57)	0%
Fluoroquinolones	8	1681	0·66 (0·44, 1·01)	0%
24-hour sputum volume (mean difference)				
All studies	2	201	-2·57 (-7·79, 2·64)	0%

Eight-weekly intravenous antibiotics is beneficial in severe bronchiectasis

P. MANDAL[1], M.K. SIDHU[2], L.S. DONALDSON[2], J.D. CHALMERS[1], M.P. SMITH[2],

Aim: The aim of our study was to assess the impact of 8-weekly intravenous (IV) antibiotics on exacerbation frequency and health-related quality of life in bronchiectasis.

Methods: Patients were recruited prospectively from June 2008 to December 2010. Patients with recurrent exacerbations (five or more exacerbations per year) and subjectively reporting ill health between antibiotic courses were recruited. Eight-weekly IV antibiotics (for 14 days) were initiated. Patients were followed up for 1 year. Main outcome was reduction in exacerbation frequency and improvement in health-related quality of life (HRQoL) at 1 year after starting intravenous antibiotic therapy. Other outcomes recorded were forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), incremental shuttle walk test (ISWT), 24-h sputum volume, sputum microbiology, body mass index (BMI), markers of inflammation—white cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Results: In total, 19 patients were recruited. Mean age was 64.1 years and 52.6% were female. With 8-weekly antibiotics, there was a significant reduction in the number of exacerbations [mean (SE): 9.3 (0.5) in the year before vs. 8.0 (0.4) in the year after; $P=0.02$]. In 63.2%, Leicester Cough Questionnaire (LCQ) improved by $\geqslant 1.3$ U ($P=0.006$)] and in 42.1% St. George's Respiratory Questionnaire (SGRQ) improved by $\geqslant 4$ U ($P=0.03$). Exercise capacity increased by 58.7 m ($P=0.004$). There was no improvement in the other end points.

Conclusion: Treatment with 8-weekly intravenous antibiotics in severe bronchiectasis reduced exacerbation frequency and improved exercise tolerance and health-related quality of life.

Table 3 Microorganisms isolated during stable state at time points indicated above

Microorganisms isolated	Pre 8-weekly intravenous antibiotic therapy	1 year post 8-weekly intravenous antibiotic therapy
Pseudomonas aeruginosa	73.7	63.2
Coliforms	15.8	15.8
Haemophilus influenzae	10.5	5.2
Moraxella catarrhalis	10.5	5.2
Streptococcus pneumoniae	0	10.5
Staphylococcus aureus	0	5.2
Mixed normal flora	5.2	21.1*

Table 4 Intravenous and oral antibiotics used

Antibiotic	%
Ceftazidime + oral ciprofloxacin	31.6
Tazobactam/piperacillin + oral ciprofloxacin	26.3
Ceftazidime	26.3
Ceftazidime + gentamicin	10.6
Aztreonam	5.2

Values are expressed in percent, unless specified.

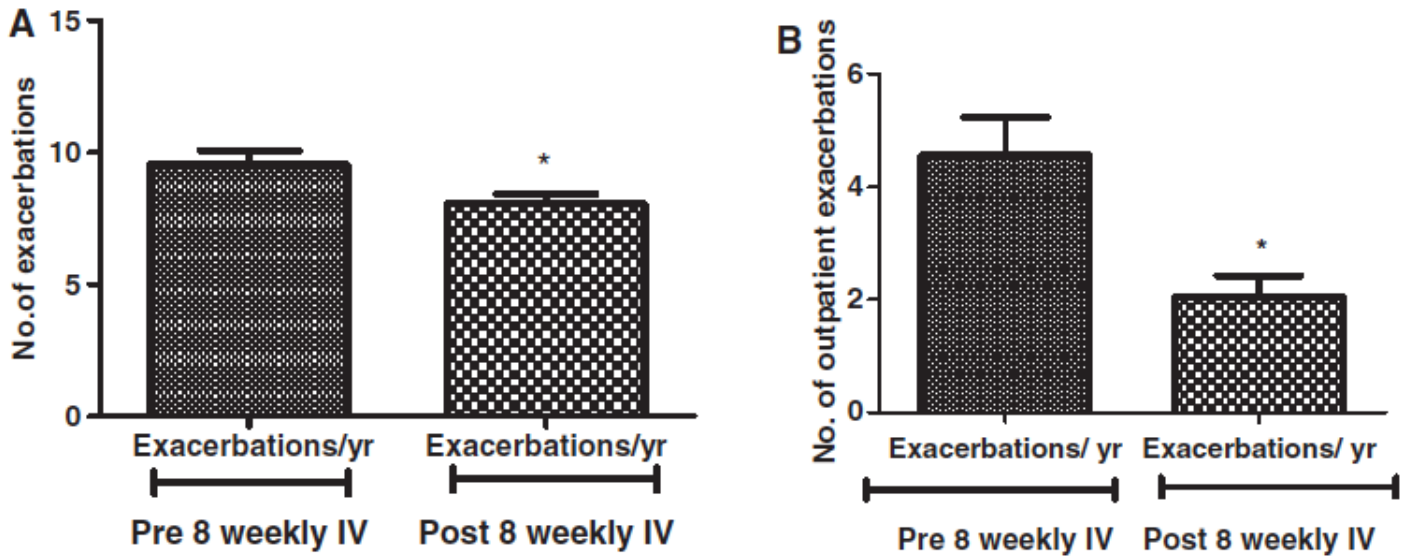


Figure 1. (**A**) Total number of exacerbations recorded; *$P = 0.02$. (**B**) Only outpatient exacerbations recorded; *$P = 0.01$.

LCQ	After 1 year on 8-weekly IV antibiotics	LCQ score at baseline	LCQ score after 1 year
Percent improvement in LCQ $\geq$ 1.3 U	63.2	12.2 (1.2)	16* (1)
Percent improvement in LCQ 0-1.3 U	21.1	11.5 (2.5)	12.2 (2.7)
Percent LCQ deteriorated	15.7	11.6 (1.9)	10.5 (1.7)

SGRQ	After 1 year on 8-weekly IV antibiotics	SGRQ score at baseline	SGRQ score after 1 year
Percent improvement in SGRQ $\geqslant$ 4 U	42.1	70.5 (4.8)	54* (7.4)
Percent improvement in SGRQ 0–3.9 U	10.5	45.7 (7.1)	44.7 (7.8)
Percent SGRQ deteriorated	47.4	51 (9.1)	57.5 (9.6)

Clinical parameter	Pre 8-weekly IV antibiotic therapy	1 year post 8-weekly IV antibiotic therapy	*P*-value
ISWT (m)	238 (34.3)	296.7 (46.5)	0.004
FEV_1 (l)	1.40 (0.1)	1.43 (0.1)	0.2
FVC (l)	2.5 (0.2)	2.3 (0.2)	0.5
24-h sputum volume (ml)	31.6 (6)	28.1 (5.3)	0.8
BMI (kg/m^2)	24.7 (1.1)	24.3 (0.9)	0.6
WCC ($*10^9/l$)	8.6 (0.7)	8.5 (0.7)	0.8
CRP (mg/l)	14.1 (5.8)	13.6 (5.2)	0.8
ESR (mm/h)	40.9 (6.3)	29.8 (5.1)	0.02

Cochrane Library

Cochrane Database of Systematic Reviews

Currently no evidence indicating whether orally administered antibiotics are more beneficial compared to inhaled antibiotics

Oral versus inhaled antibiotics for bronchiectasis (Review)

Spencer S, Felix LM, Milan SJ, Normansell R, Goeminne PC, Chalmers JD, Donovan T

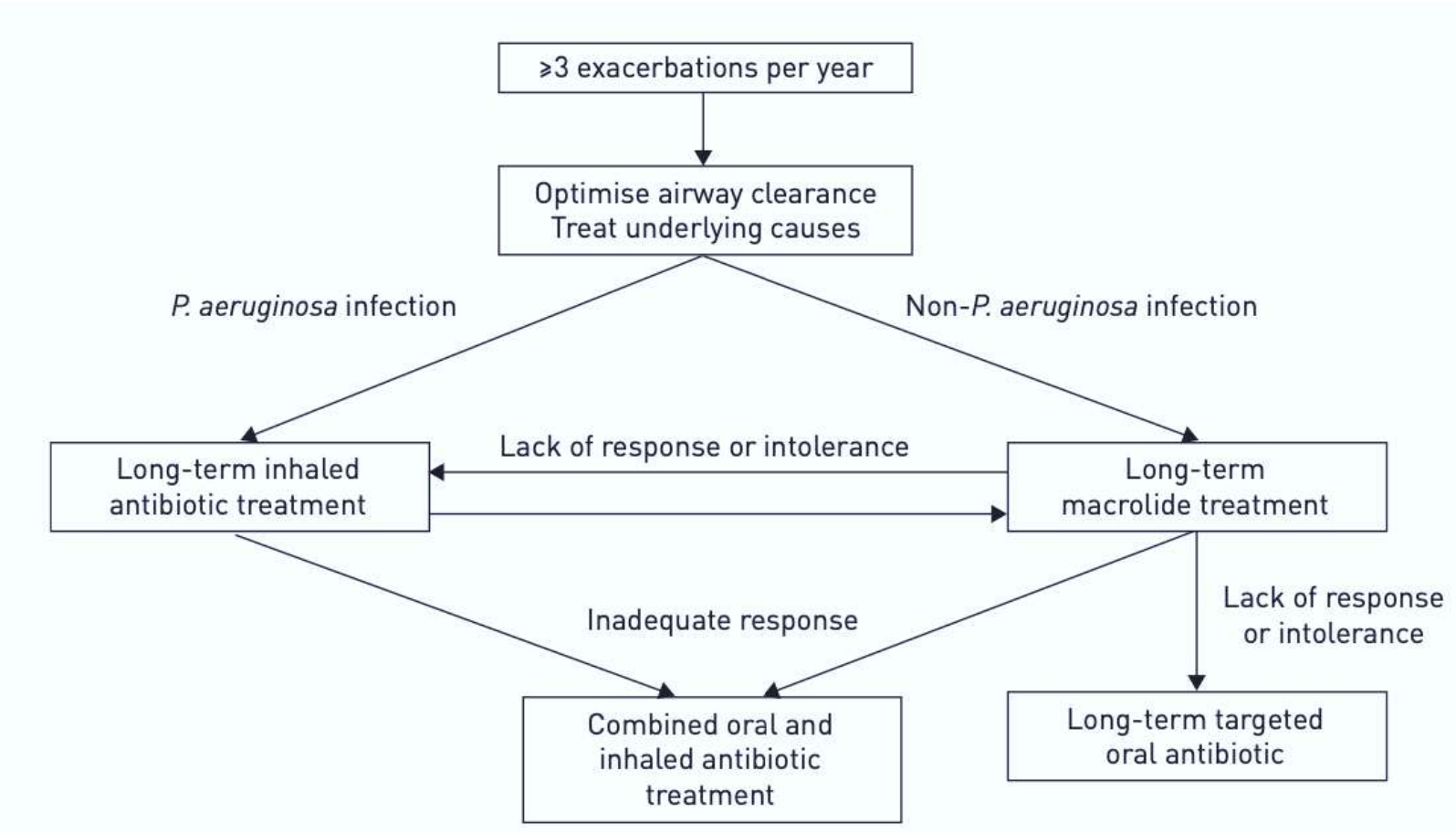
Continuous versus intermittent antibiotics for bronchiectasis (Review)

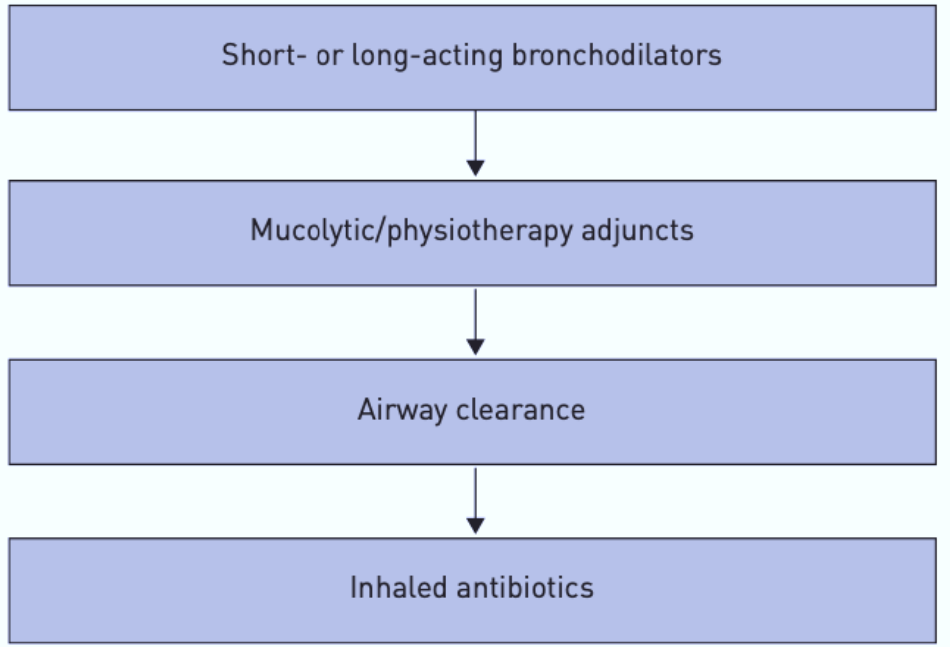
Donovan T, Felix LM, Chalmers JD, Milan SJ, Mathioudakis AG, Spencer S

Authors' conclusions

No randomised controlled trials have compared the effectiveness and risks of continuous antibiotic therapy versus intermittent antibiotic therapy for bronchiectasis. High-quality clinical trials are needed to establish which of these interventions is more effective for reducing the frequency and duration of exacerbations, antibiotic resistance and the occurrence of serious adverse events.

ERS guidelines-2017





Air way clearance-Pharmacological-Mucoactive agents

Type of agent	Mechanism	Examples
Mucolytics	Thin mucus	• Dnase • Bromhexine • Ambroxol • Carbocystiene • NAC • Erdosteine
Mucokinetics	Facilitate cough transportability	• Humidification • Normal/isotonic saline Hypertonic saline (3% saline and above) • mannitol
Expectorants	Aid and/or induce cough	
Mucoregulators	Suppress mechanisms underlying chronic mucus hyper secretion	• Glucocorticosteroids

Humidification

Study	Type	Subjects	Intervention	Comaparison	Outcome
Conway et al,1992 N=9 (7 completed)	Randomised crossover single blind study	Bronchiectasis and chronic sputum production. No reversible airflow limitation	30 mins of cold water jet nebulising humidification as an adjunct to chest PT	Chest PT alone (PD plus FET)	26% increase in median sputum yield ($p<0.05$). Increase in total clarance of radioaerosol -8.7% with humidification ($p<0.05$).
Hasani, A.;Chapman, T. H.;McCool, D.;Smith, R. E.;Dilworth, J. P.;Agnew, J. E (N=10 (14 recruited 4 dropped out)	Before-After	Bronchiectasis diagnosed by HRCT	warm air humidification 3 hours per day for 7 days		Sig increased in tracheobronchial clearance, also sign improvement in TBC. Reduction in coughs, no sig diff in spirometry

Role of Bromhexine in Exacerbations of Bronchiectasis

Double-Blind Randomized Multicenter Study versus Placebo

D. Olivieri[a], *A. Ciaccia*[b], *E. Marangio*[a], *S. Marsico*[c], *T. Todisco*[d], *M. Del Vita*[e]

[a] Department of Respiratory Diseases, University of Parma, Italy; [b] Department of Phthisiology and Respiratory Diseases, University of Ferrara, Italy; [c] Department of Phthisiology and Respiratory Diseases, University of Catanzaro, Italy; [d] Department of Respiratory Pathophysiology, University of Perugia, Italy, and [e] Medical Department, Boehringer Ingelheim Italia, Florence, Italy

- RCT ,multi centre with n=88 addition of bromhexine hydrochloride to an antibiotic during an acute infective exacerbation compared with a placebo
- Change in sputum production was greater in the bromhexine group at 7, 10 and 16 days (mean difference (MD) −21.5 mL, 95% CI −38.9 to −4.1 at day 16). Moreover the difficulty in expectoration was also improved in the bromhexine group at day 10 (MD −0.53, 95% CI −0.81 to −0.25) however it
- No impact on FEV1.

Short-term Recombinant Human DNase in Bronchiectasis

Effect on Clinical State and *In Vitro* Sputum Transportability

PETER J. WILLS, THERESA WODEHOUSE, KEVIN CORKERY, KEN MALLON, ROBERT WILSON, and PETER J. COLE

Host Defence Unit, Royal Brompton National Heart and Lung Institute, Imperial College of Science, Technology and Medicine, London, United Kingdom; and Genentech Inc., South San Francisco, California

We report a double blind placebo-controlled phase II study of the efficacy and safety of nebulized recombinant human DNase (rhDNase) administered for 14 d to adults with bronchiectasis not caused by cystic fibrosis. All were in a stable clinical state at the commencement of the study, and they received (*1*) rhDNase 2.5 mg twice daily, (*2*) rhDNase once daily, or (*3*) placebo (excipient only) inhalation. The outcome measures were spirometry, subjective quality of life/dyspnea, and safety. We also measured the ciliary transportability of the sputum expectorated before and after the treatment period, using the mucus-depleted bovine trachea. The drug was well tolerated, but it produced no significant change in any of the outcome variables or in sputum transportability. When the drug was incubated with bronchiectatic sputum *in vitro*, a fall in transportability was observed. We discuss possible explanations for the lack of a measurable benefit from rhDNase in this study population, which appears to contrast with the improvements shown in cystic fibrosis using studies of similar design. **Wills PJ, Wodehouse T, Corkery K, Mallon K, Wilson R, Cole PJ. Short-term recombinant human DNase in bronchiectasis: effect on clinical state and *in vitro* sputum transportability.**

AM J RESPIR CRIT CARE MED 1996;154:413–7.

Treatment of Idiopathic Bronchiectasis With Aerosolized Recombinant Human DNase I*

2.5 mg twice daily (n=349)

Anne E. O'Donnell, MD, FCCP; Alan F. Barker, MD, FCCP;

Study objective: To study the safety and efficacy of aerosolized recombinant human DNase I in the treatment of idiopathic bronchiectasis.
Design: Double-blind, randomized, placebo-controlled, multicenter study.
Populations: Three hundred forty-nine adult outpatients in stable condition with idiopathic bronchiectasis from 23 centers in North America, Great Britain, and Ireland.
Interventions and measurements: Study patients received aerosolized rhDNase or placebo twice daily for 24 weeks. Primary end points were incidence of pulmonary exacerbations and mean percent change in FEV_1 from baseline over the treatment period.
Results: Pulmonary exacerbations were more frequent and FEV_1 decline was greater in patients who received rhDNase compared with placebo during this 24-week trial.
Conclusions: rhDNase was ineffective and potentially harmful in this group of adult outpatients in stable condition with idiopathic bronchiectasis. This contrasts with previously published results that demonstrated efficacy of rhDNase in patients with cystic fibrosis bronchiectasis.

(CHEST 1998; 113:1329-34)

Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis

F. Kellett*, J. Redfern, R. McL Niven

Summary Sputum clearance is of prime importance in the management of patients with bronchiectasis. While nebulised normal isotonic saline (0.9%) (IS) has been anecdotally used to treat patients with tenacious sputum, the use of hypertonic saline (7%) (HS) could have potential muco-protective and clearance properties.

24 patients with bronchiectasis were randomised to receive four single treatment schedules in random order: (1) active cycle breathing technique (ACBT) alone, (2) nebulised terbutaline then ACBT, (3) nebulised terbutaline, nebulised IS then ACBT and (4) nebulised terbutaline, nebulised HS then ACBT.

Sputum weights were significantly higher after HS than IS ($P = 0.002$). Ease of expectoration also differed overall ($P = <0.0001$) and was significantly lower with HS than with IS ($P = 0.0005$). Sputum viscosity differed between treatment phases, with a significant linear trend to reduced sputum viscosity with HS ($P = 0.0002$). These changes were associated with small but statistically significant differences in FEV_1 ($P = 0.043$) and FVC ($P = 0.011$) between treatment phases.

Nebulised hypertonic saline can be used safely and effectively as an adjunct to physiotherapy in selected patients. A long-term prospective trial is now indicated to determine its effectiveness on long-term infection rate, quality of life and lung function.

Mucolytics for bronchiectasis (Review)

Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I

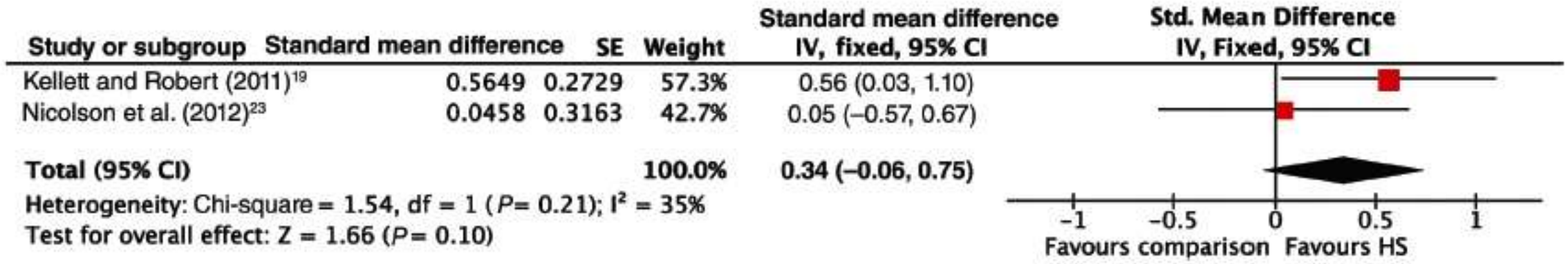


Figure 3 HS in bronchiectasis. Meta-analysis of FEV_1 at 3 months. CI, confidence interval; FEV_1, forced expiratory volume in 1 s; HS, hypertonic saline; IV, inverse variance; SE, standard error.

4 mL 7% once daily vs IS
n=28

5 mL 6% twice daily vs IS
n=40

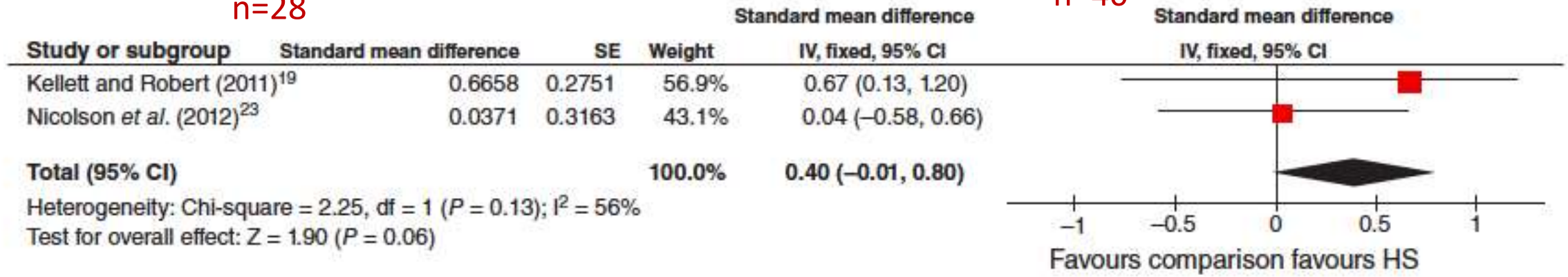


Figure 4 HS in bronchiectasis. Meta-analysis of FVC at 3 months. CI, confidence interval; FVC, forced vital capacity; HS, hypertonic saline; IV, inverse variance; SE, standard error.

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;

Background: Inhaled dry powder mannitol enhanced mucus clearance and improved quality of life over 2 weeks in non-cystic fibrosis bronchiectasis. This study's objective was to investigate the efficacy and safety of dry powder mannitol over 12 weeks.

Methods: Patients with bronchiectasis confirmed by high-resolution CT (HRCT) scan, aged 15 to 80 years, with $FEV_1 \geq 50\%$ predicted and ≥ 1 L participated in a randomized, placebo-controlled, double-blind study. Patients with a negative mannitol provocation test were randomized to inhale 320 mg mannitol (n = 231) or placebo (n = 112) bid for 12 weeks. To further assess safety, the same mannitol dose/frequency was administered to a patient subset in an open-label extension over 52 weeks. Primary end points were changes from baseline at 12 weeks in 24-h sputum weight and St. George's Respiratory Questionnaire (SGRQ) score.

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;

Results: **There was a significant difference of 4.3 g in terms of change in sputum weight over 12 weeks (95% CI, 1.64-7.00; $P = .002$) between mannitol and placebo; however, this was largely driven by a decrease in sputum weight in the placebo group. This was associated, in turn, with more antibiotic use in the placebo group (50 of 112 [45%]) than in the inhaled mannitol group (85 of 231 [37%]). There was no statistical difference between the groups ($P = .304$) in total SGRQ score (mannitol, −3.4 points [95% CI, −4.81 to −1.94] vs placebo, −2.1 points [95% CI, −4.12 to −0.09]). In a subgroup study (n = 82), patients receiving mannitol showed less small airway mucus plugging on HRCT scan at 12 weeks compared with patients receiving placebo ($P = .048$). Compliance rates were high, and mannitol was well tolerated with adverse events similar to those of placebo.**

Conclusion: **Because the difference in sputum weights appears to be associated with increased antibiotic use in the placebo group, a larger controlled study is now required to investigate the long-term mannitol effect on pulmonary exacerbations and antibiotic use.**

Trial registry: **ClinicalTrials.gov; No.: NCT0027753; URL: www.clinicaltrials.gov**

CHEST 2013; 144(1):215–225

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]

- 18–85 years of age
- Patients with non-CF bronchiectasis
- History of chronic excess production of sputum
- ≥2 pulmonary exacerbations in the previous 12 months
- Baseline FEV1 ≥40% and ≤85% predicted
- Baseline SGRQ score ≥30

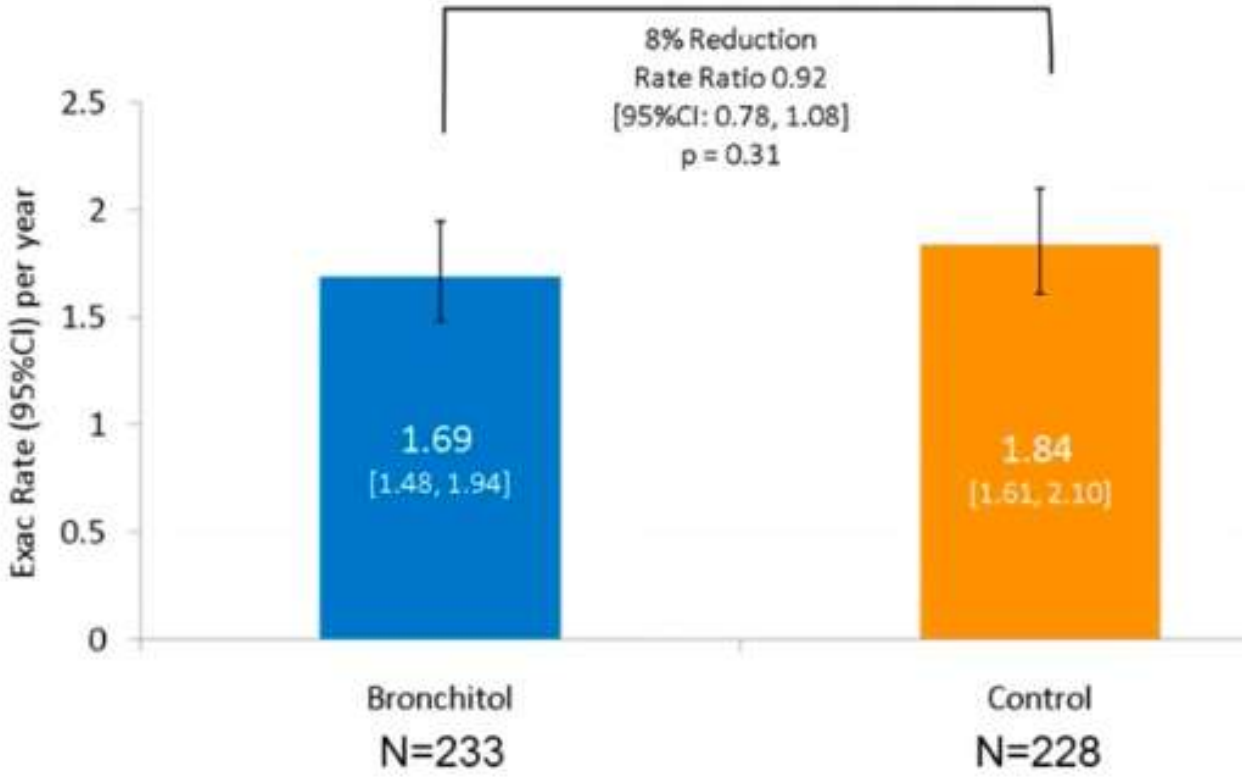
Randomised (1:1) to 52 weeks treatment with inhaled mannitol 400 mg vs 50 mg twice a day

Primary objective

- Exacerbation rates

Secondary objective

- Time to first exacerbation,
- Duration of exacerbations,
- Antibiotic use for exacerbations
- Quality of life (QOL)
- SGRQ



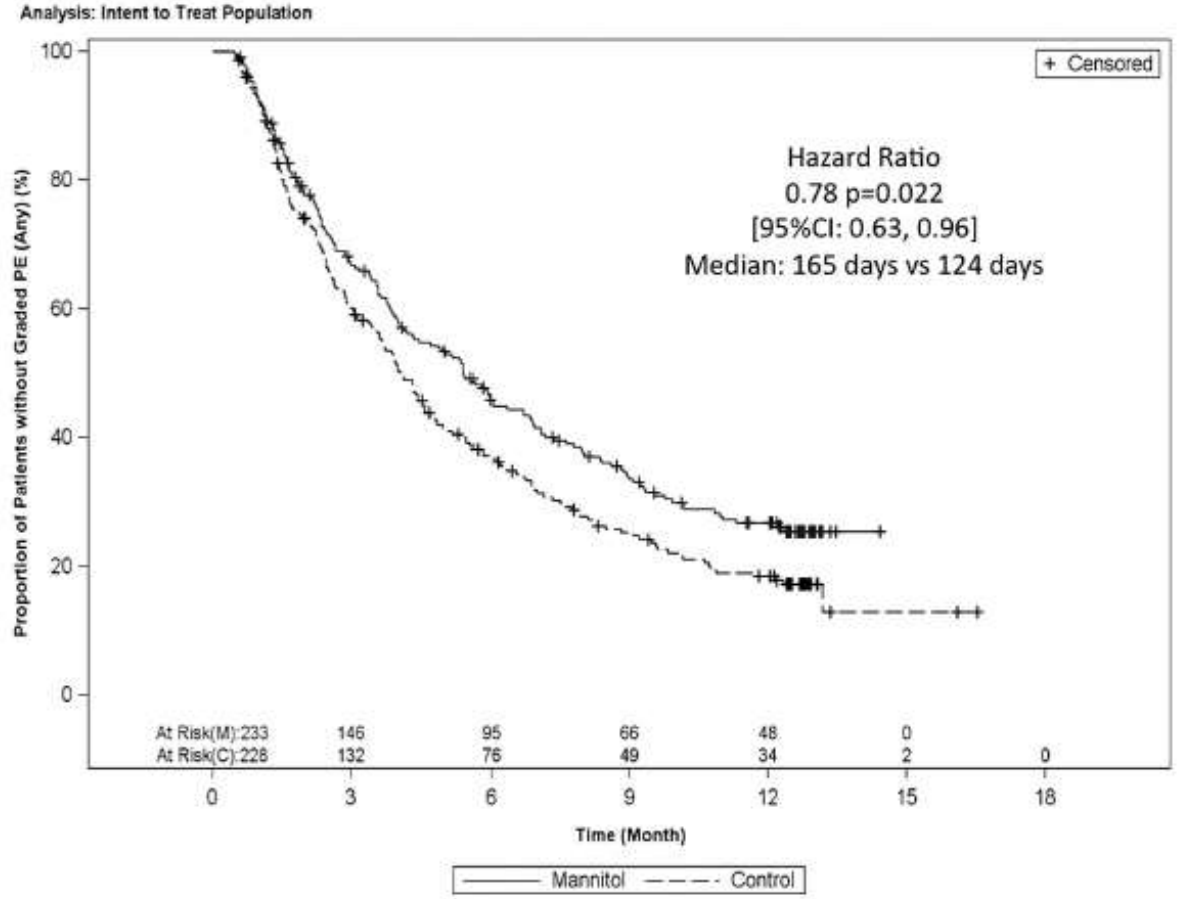


Figure 3 Kaplan–Meier plot of the time to first graded pulmonary exacerbation.

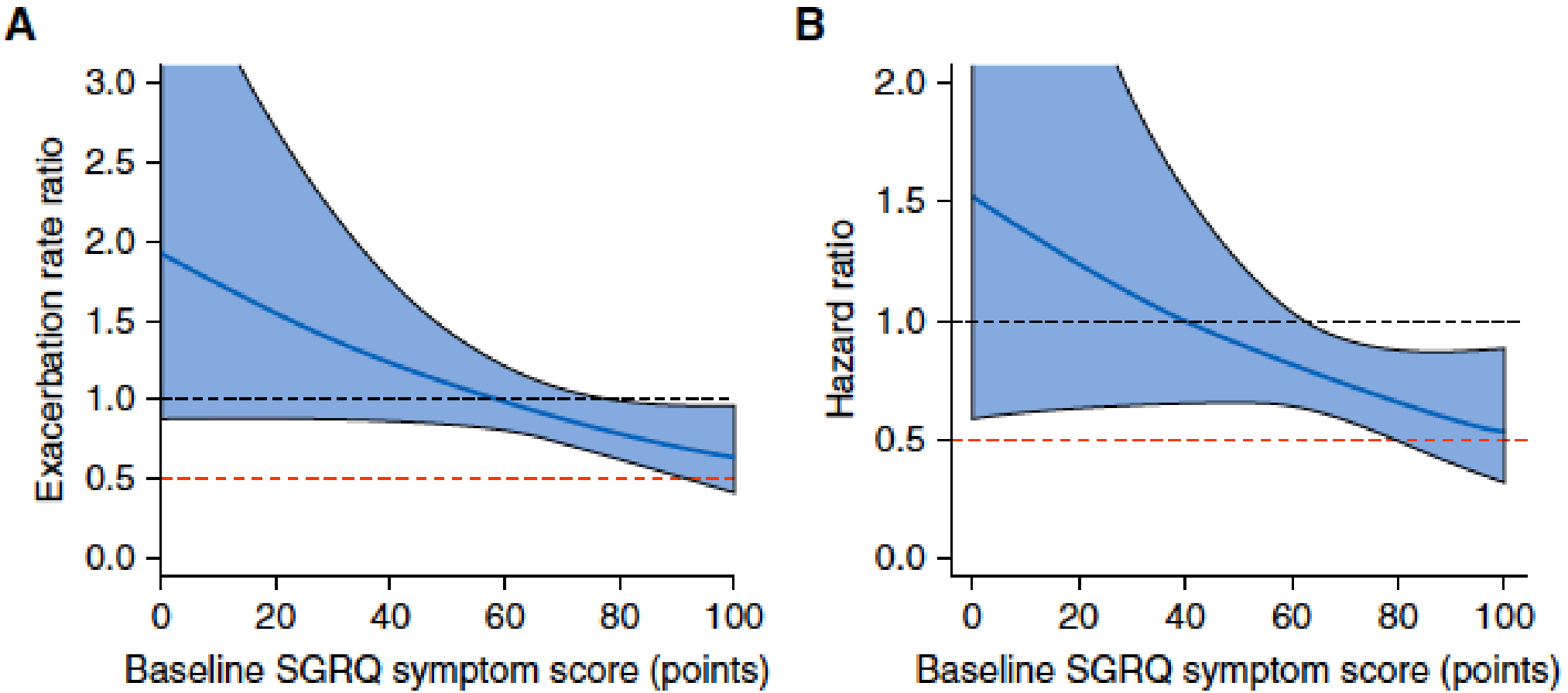
Table 2 Summary of results for key secondary efficacy endpoints

	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	

Rate ratio is calculated using the negative binomial regression model for mannitol versus control. Model includes treatment, region and baseline pulmonary exacerbation rate as predictors.
HR, estimated from Cox regression, is for mannitol versus control.
Log-rank test and Cox regression are stratified by region and baseline PE rate (≤2/year, >2/year).
LS Mean: Least Squares Mean Difference, estimated from mixed model, is for mannitol versus control. Model includes treatment, visit, treatment×visit, region and baseline SGRQ Total score.
*Negative binomial regression.
†Mixed model analysis.
GPE, graded pulmonary exacerbation (any type); SGRQ, St George's Respiratory Questionnaire.

Relationship between Symptoms, Exacerbations, and Treatment Response in Bronchiectasis

Yong-hua Gao[1,2], Hani Abo Leyah[2], Simon Finch[2], Mike Lonergan[2], Stefano Aliberti[3], Anthony De Soyza[4], Thomas C. Fardon[2], Gregory Tino[5], and James D. Chalmers[2]



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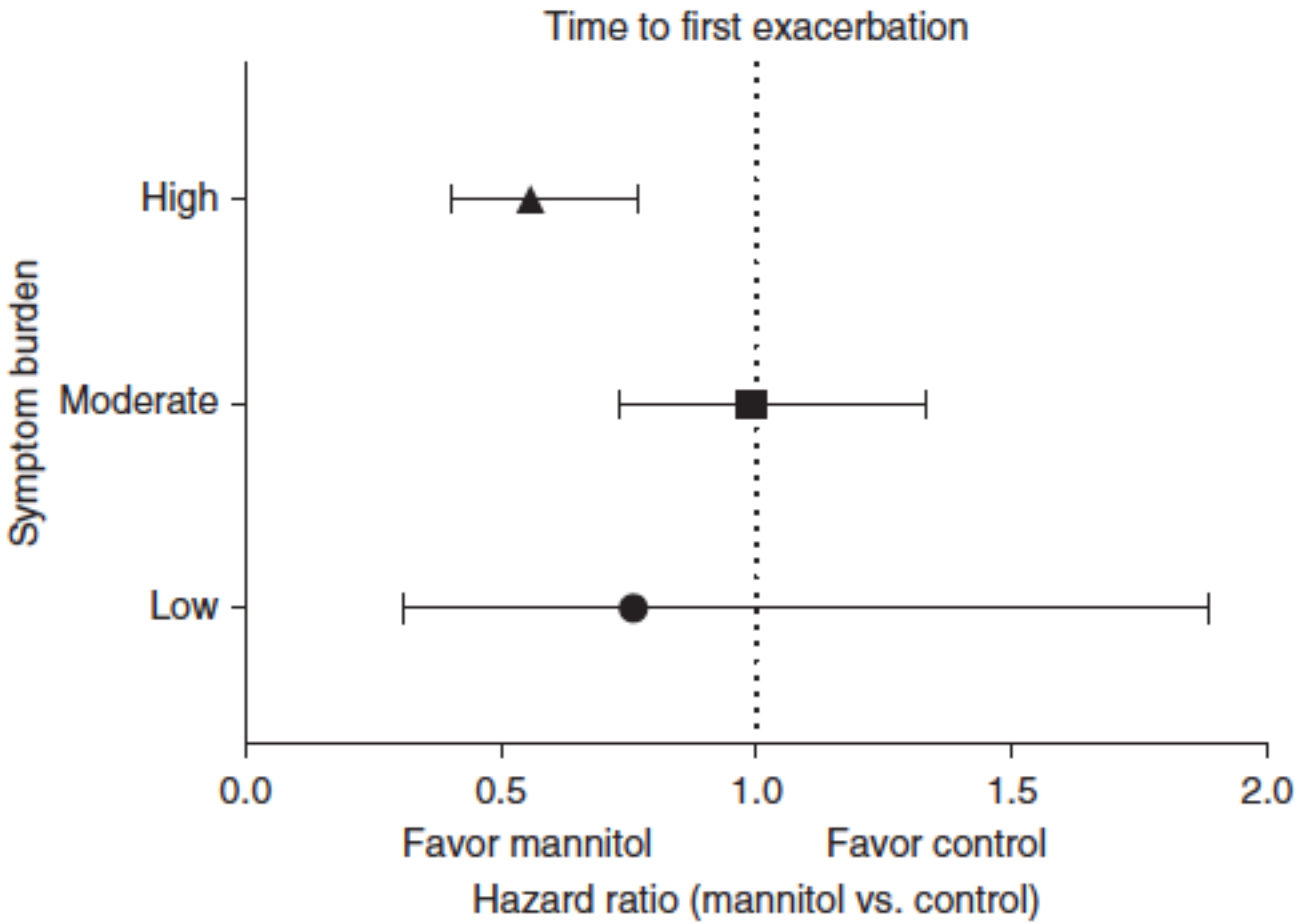


Effect of N-acetylcysteine on exacerbations of bronchiectasis (BENE): a randomized controlled trial

Qian Qi[1,2], Yirepanjaing Ailiyaer[3], Ruijuan Liu[4], Yan Zhang[5], Caiyu Li[6], Mingtao Liu[7], Xiuxiu Wang[1], Lijun Jing[1] and

Background: N-acetylcysteine is a classic mucolytic agent. This study aimed to investigate the efficacy of N-acetylcysteine on reducing the risk of exacerbations in bronchiectasis patients.

Methods: A prospective, randomized, controlled trial was conducted between April 1, 2014 and December 31, 2016 in five general hospitals in Shandong Province, China. Adult bronchiectasis patients with at least two exacerbations in the past year were potentially eligible. Patients were randomly assigned to receive oral N-acetylcysteine (600 mg, twice daily, 12 months) or on-demand treatment.

Results: A total of 161 patients were eligible for randomization (81 to the N-acetylcysteine group and 80 to the control group). During the 12-month follow-up, the incidence of exacerbations in the N-acetylcysteine group was significantly lower than that in the control group (1.31 vs. 1.98 exacerbations per patient-year; risk ratio, 0.41; 95% CI, 0.17–0.66; $P = 0.0011$). The median number of exacerbations in the N-acetylcysteine group was 1 (0.5–2), compared with 2 (1–2) in the control group ($U = -2.95$, $P = 0.003$). A total of 24.7% of the N-acetylcysteine group patients and 11.3% of the control group patients remained exacerbation-free throughout the 12-month follow-up ($\chi^2 = 4.924$, $P = 0.026$). Compared with the control group, the volume of 24-h sputum in the N-acetylcysteine group was significantly reduced ($t = -3.091$, $P = 0.002$). Additionally, the N-acetylcysteine group showed a significant improvement in the quality of life. No severe adverse events were reported in the intervention group.

Table 1 Baseline characteristics of the study patients

Characteristic	Group		*P*-value
	Control group ($N = 80$)	N-acetylcysteine group ($N = 81$)	
Gender			
Female, n (%)	52 (65.0)	45 (55.6)	0.144
Age, years	56.56 ± 12.41	53.28 ± 11.90	0.089
Body mass index, kg/m^2	22.16 ± 4.22	22.72 ± 3.57	0.362
Ex-smoker, n (%)	8 (10.0)	6 (7.4)	0.381
mMRC score(≥2)	48 (60.0)	45 (55.6)	0.341
CAT score	19.55 ± 7.26	19.15 ± 7.12	0.723
24-h sputum volume, mL	28.84 ± 40.94	29.74 ± 41.35	0.890
Etiology of bronchiectasis			0.179
Postinfectious	38 (47.5)	30 (37.0)	
Idiopathic	42 (52.5)	51 (63.0)	
HRCT grade, n (%)			0.194
1	28 (35.0)	27 (33.3)	
2	41 (51.2)	34 (42.0)	
3	11 (13.8)	20 (24.7)	
Number of lesion lobes, n (%)			0.822
1 lobe	15 (18.8)	18 (22.2)	
2–3 lobes	47 (58.8)	44 (54.3)	
4–6 lobes	18 (22.5)	19 (23.5)	
Cystiform bronchiectasis, n (%)	33 (41.2)	44 (54.3)	0.097

Table 1 Baseline characteristics of the study patients

Characteristic	Group		*P*-value
	Control group (*N* = 80)	N-acetylcysteine group (*N* = 81)	
Pseudomonas aeruginosa positive, n (%)	20 (25.0)	27 (33.3)	0.245
Medications, n (%)			
Inhaled corticosteroids and long-acting β-agonist	45 (56.2)	56 (69.1)	0.091
Inhaled short-acting β-agonist	20 (25.0)	15 (18.5)	0.391
Inhaled anticholinergics	22 (27.5)	24 (29.6)	0.765
Inhaled corticosteroids	17 (21.2)	11 (13.6)	0.199
Prednisone	2 (2.5)	3 (3.8)	1.000
Theophylline	6 (7.5)	4 (5.0)	0.746
Pulmonary function			
FVC, L	2.42 ± 0.94	2.32 ± 0.74	0.483
FEV_1, L	1.56 ± 0.81	1.62 ± 0.73	0.629
Predicted FEV_1, %	63.63 ± 26.28	60.23 ± 27.32	0.451
FEV_1/FVC, %	64.39 ± 14.63	67.44 ± 16.49	0.226
Inspiratory capacity, L	1.77 ± 0.70	1.88 ± 0.81	0.368
ESR, mm/h	25.39 ± 19.86	27.53 ± 24.07	0.540
CRP, mg/dL	16.99 ± 21.26	13.37 ± 17.12	0.246
Number of exacerbations in the last year	2 (2–3)	2 (2–3)	0.713
Bronchiectasis Severity Index	8.00 ± 4.27	8.43 ± 4.68	0.548

Table 2 Change from baseline parameters after the 12-month follow-up for the N-acetylcysteine and control groups

	Control group	N-acetylcysteine group	*P* value
CAT score	−1.44 ± 6.19	−3.79 ± 5.40	0.011
24-h sputum volume, mL	−6.46 ± 22.73	−18.28 ± 25.69	0.002
ESR	−0.36 ± 8.74	−4.21 ± 10.57	0.115
CRP	−1.68 ± 9.62	−2.83 ± 6.68	0.089
Pseudomonas aeruginosa positive, n (%)	−5 (25.0)	−8 (29.6)	0.726
Pulmonary function			
FVC, L	0.03 ± 0.22	0.01 ± 0.46	0.991
FEV_1, L	0.03 ± 0.16	−0.10 ± 0.37	0.210
Predicted FEV_1, %	0.13 ± 7.78	1.16 ± 16.50	0.445
FEV_1/FVC, %	−0.29 ± 4.29	0.53 ± 7.45	0.394
Inspiratory capacity, L	0.01 ± 0.22	0.06 ± 0.24	0.098

Data are n (%) or mean ± SD. Abbreviations: *CAT* chronic obstructive pulmonary disease assessment test, *FVC* forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

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

Jordan Minov[1*], Sasho Stoleski[1], Tatjana Petrova[2], Kristina Vasilevska[3], Dragan Mijakoski[1], Jovanka Karadzinska-Bislimovska[1]

METHODS: We performed an observational, non-randomized, open study (a real-life study) including 64 patients with bronchiectasis divided into two groups, examined group (EG) and control group (CG). All participants were treated with appropriate treatment for the stable disease, but in the study, subjects of EG two capsules 375 mg carbocysteine three times a day was added over three months. Daily diary cards realised collection of data regarding the occurrence and duration of exacerbation in all study subjects.

RESULTS: Over the study period 43 exacerbations were documented, 17 in the EG and 26 in the CG, 10 (23.4%) of which required hospital treatment (four in the EG [23.5%] and six in the CG [23.1%]). A mean number of exacerbations over the study period was significantly lower in the EG (0.5 ± 0.1) as compared to their mean number in the CG (0.8 ± 0.2) (P = 0.0000). Mean duration of exacerbations expressed in days needed for complete resolution of symptoms or return of the symptoms to their baseline severity in the EG was significantly shorter than the mean duration of exacerbations in the CG (10.1 ± 2.6 vs 12.8 ± 2.1; P = 0.0000). The frequency of adverse effects, i.e. mild gastrointestinal manifestations and headache which did not require discontinuation of the treatment, in the EG during the study period was 15.6%.

Randomised Open Label Trial of Hypertonic Saline and Carbocisteine in Bronchiectasis (CLEAR) (CLEAR)

Condition or disease	Intervention/treatment	Phase
Bronchiectasis	Drug: Hypertonic saline Drug: Carbocysteine 750 MG	Phase 3

In conclusion(non-CF bronchiectasis)

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

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 of evidence*).

We recommend not offering recombinant human DNase to adult patients with bronchiectasis (*strong recommendation, moderate quality of evidence*).

European Respiratory Society guidelines

British Thoracic Society Guideline

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

Effects of ICS in non-CF bronchiectasis

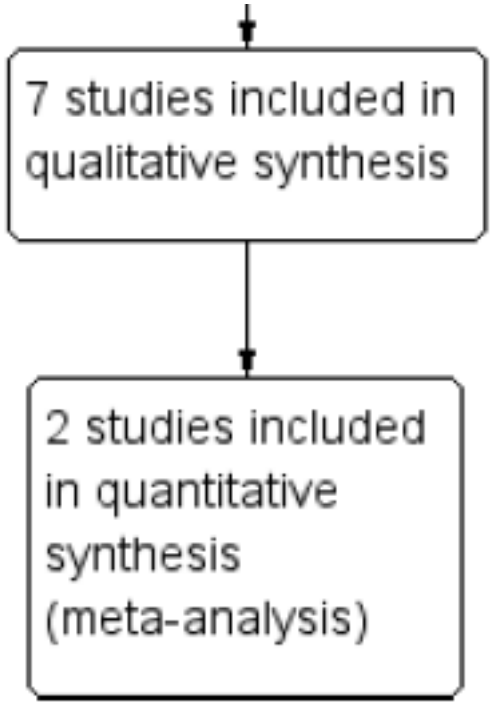
Cochrane Library

Cochrane Database of Systematic Reviews

Inhaled corticosteroids for bronchiectasis (Review)

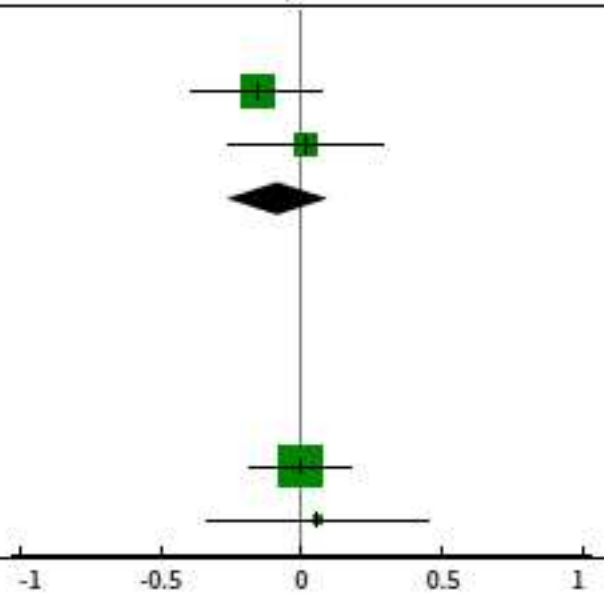
Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB

Seven studies
380 adults



Analysis 1.1. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 1 Lung function (spirometry indices).

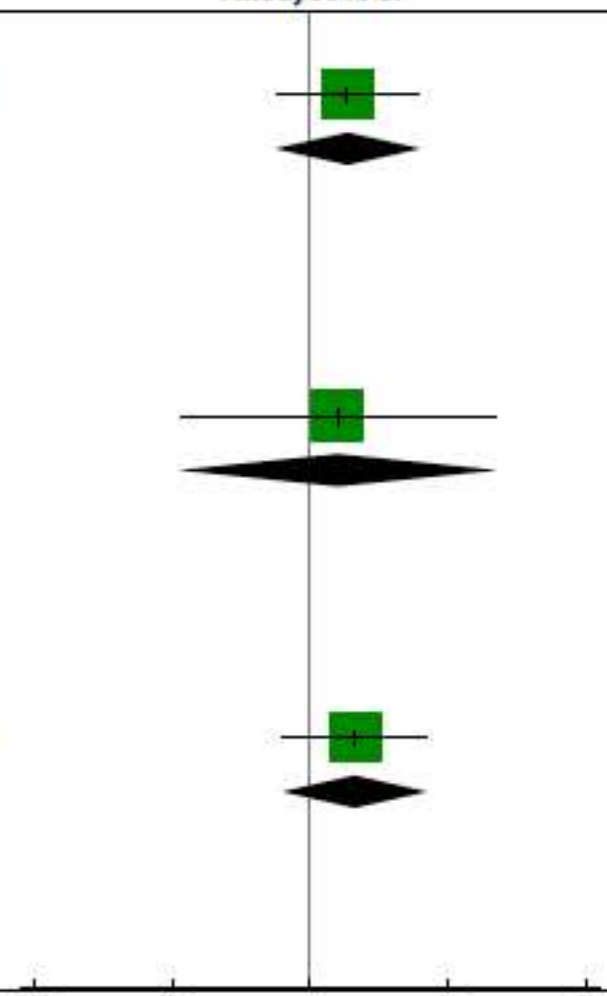
Study or subgroup	Inhaled Corticosteroids N	Inhaled Corticosteroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 FEV1 (in L, end study minus baseline values)							
Hernando 2012	37	0.6 (0.5)	33	0.8 (0.5)		58.68%	-0.16[-0.39,0.07]
Martinez-Garcia 2006	58	-0 (0.7)	28	-0 (0.6)		41.32%	0.02[-0.26,0.29]
Subtotal ***	**95**		**61**			**100%**	**-0.09[-0.26,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.91, df=1(P=0.34); I^2=0%							
Test for overall effect: Z=0.97(P=0.33)							
1.1.2 FVC (in L, end study minus baseline values)							
Hernando 2012	37	0 (0.4)	33	0 (0.4)		82.87%	-0[-0.18,0.17]
Martinez-Garcia 2006	58	-0 (0.7)	28	-0.1 (1)		17.13%	0.06[-0.34,0.45]



Small improvement in FEV1 and FVC (0.09L) at 6 months – not sustained later

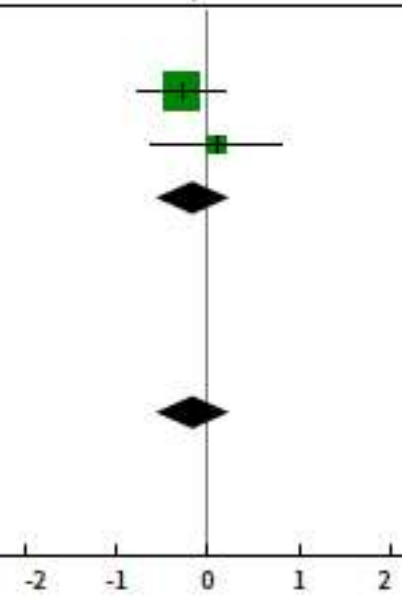
Analysis 1.2. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 2 Lung function (other indices).

Study or subgroup	Favours ICS N	Favours ICS Mean(SD)	Favours placebo N	Favours placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 Diffusion capacity % predicted (end of study)							
Martinez-Garcia 2006	29	86.9 (10)	28	84.2 (10)		100%	2.7[-2.49,7.89]
Subtotal ***	**29**		**28**			**100%**	**2.7[-2.49,7.89]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.02(P=0.31)							
1.2.2 RV % predicted (end of study values)							
Martinez-Garcia 2006	29	108 (10)	28	106 (29.2)		100%	2[-9.41,13.41]
Subtotal ***	**29**		**28**			**100%**	**2[-9.41,13.41]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.34(P=0.73)							
1.2.3 TLC % predicted (end of study values)							
Martinez-Garcia 2006	29	89.6 (10)	28	86.4 (10)		100%	3.2[-1.99,8.39]
Subtotal ***	**29**		**28**			**100%**	**3.2[-1.99,8.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.21(P=0.23)							
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.98), I^2=0%							



Analysis 1.4. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 4 Exacerbations.

Study or subgroup	Inhaled Corticosteroids N	Inhaled Corticosteroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 Average number of exacerbations per participant							
Hernando 2012	37	0.7 (0.8)	33	1 (1.2)		68.68%	-0.29[-0.76,0.18]
Martinez-Garcia 2006	29	1.4 (1.3)	28	1.3 (1.4)		31.32%	0.09[-0.61,0.79]
Subtotal ***	**66**		**61**			**100%**	**-0.17[-0.56,0.22]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.77$, df=1(P=0.38); $I^2=0\%$							
Test for overall effect: Z=0.85(P=0.39)							
Total ***	**66**		**61**			**100%**	**-0.17[-0.56,0.22]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.77$, df=1(P=0.38); $I^2=0\%$							
Test for overall effect: Z=0.85(P=0.39)							



Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis (Review)

Goyal V, Chang AB

We found no RCTs comparing ICS and LABA combination with either placebo or usual care. We included one RCT that compared combined ICS and LABA with high-dose ICS in 40 adults with non-CF bronchiectasis without co-existent asthma. All participants received three months of high-dose budesonide dipropionate treatment (1600 micrograms). After three months, participants were randomly assigned to receive either high-dose budesonide dipropionate (1600 micrograms per day) or a combination of budesonide with formoterol (640 micrograms of budesonide and 18 micrograms of formoterol) for three months. The study was not blinded. We assessed it to be an RCT with overall high risk of bias. Data analysed in this review showed that those who received combined ICS-LABA (in stable state) had a significantly better transition dyspnoea index (mean difference (MD) 1.29, 95% confidence interval (CI) 0.40 to 2.18) and cough-free days (MD 12.30, 95% CI 2.38 to 22.2) compared with those receiving ICS after three months of treatment. No significant difference was noted between groups in quality of life (MD -4.57, 95% CI -12.38 to 3.24), number of hospitalisations (odds ratio (OR) 0.26, 95% CI 0.02 to 2.79) or lung function (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)). Investigators reported 37 adverse events in the ICS group versus 12 events in the ICS-LABA group but did not mention the number of individuals experiencing adverse events. Hence differences between groups were not included in the analyses. We assessed the overall evidence to be low quality.

Authors' conclusions

In adults with bronchiectasis without co-existent asthma, during stable state, a small single trial with a high risk of bias suggests that combined ICS-LABA may improve dyspnoea and increase cough-free days in comparison with high-dose ICS. No data are provided for or against, the use of combined ICS-LABA in adults with bronchiectasis during an acute exacerbation, or in children with bronchiectasis in a stable or acute state. The absence of high quality evidence means that decisions to use or discontinue combined ICS-LABA in people

No randomized trails in

- Oral corticosteroids
- Phosphodiesterase four inhibitors (PDE4 inhibitors)
- Methylxanthines
- Leukotriene receptor antagonists
- Indomethacin
- Neutrophil elastase inhibitors
- CXCR2 inhibitors

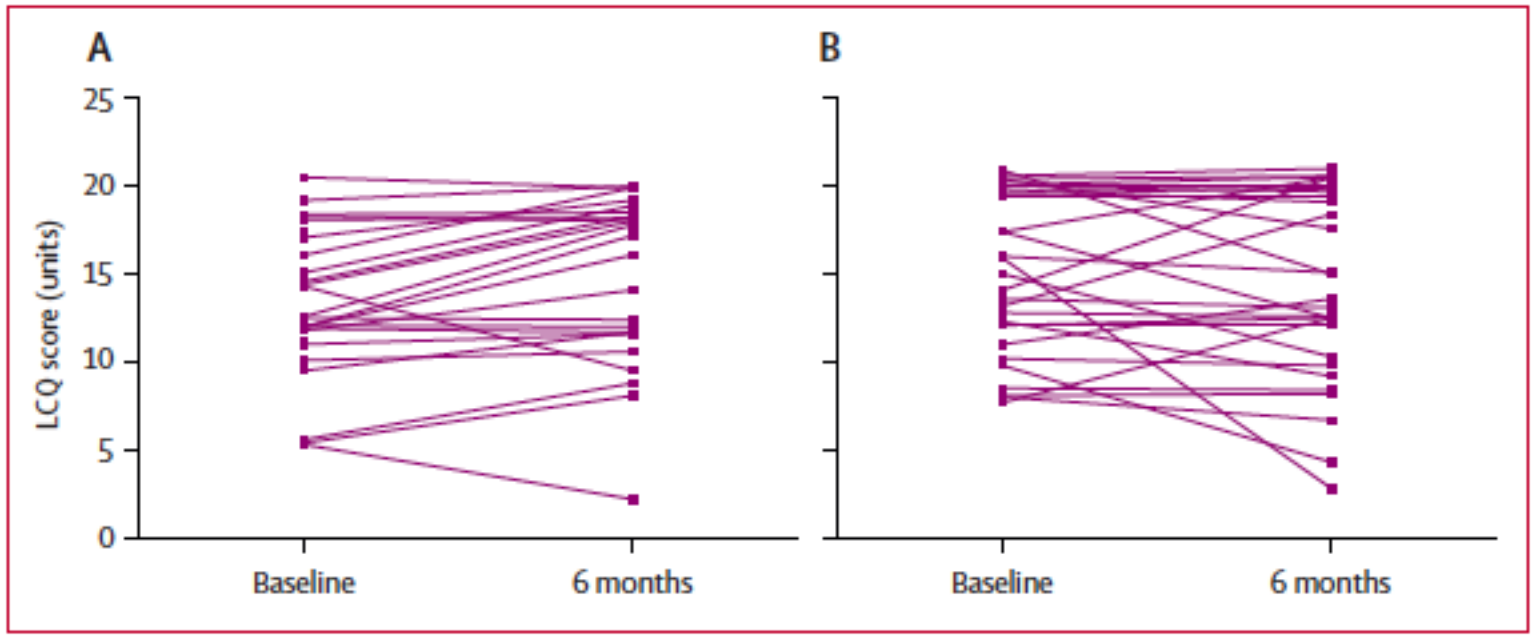
Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial

Pallavi Mandal, James D Chalmers, Catriona Graham, Catherine Harley, Manjit K Sidhu, Catherine Doherty, John W Govan, Tariq Sethi, Donald J Davidson, Adriano G Rossi, Adam T Hill

for patients with bronchiectasis. We did a proof-of-concept randomised controlled trial to establish if atorvastatin could reduce cough in patients with bronchiectasis.

Methods Patients aged 18–79 years were recruited from a secondary-care clinic in Edinburgh, UK. Participants had clinically significant bronchiectasis (ie, cough and sputum production when clinically stable) confirmed by chest CT and two or more chest infections in the preceding year. Individuals were randomly allocated to receive either high-dose atorvastatin (80 mg) or a placebo, given orally once a day for 6 months. Sequence generation was done with a block randomisation of four. Random allocation was masked to study investigators and patients. The primary endpoint was reduction in cough from baseline to 6 months, measured by the Leicester Cough Questionnaire (LCQ) score, with a lower score indicating a more severe cough (minimum clinically important difference, 1·3 units). Analysis was done by intention-to-treat. The trial is registered with ClinicalTrials.gov, number NCT01299181.

Findings Between June 23, 2011, and Jan 30, 2011, 82 patients were screened for inclusion in the study and 22 were excluded before randomisation. 30 individuals were assigned atorvastatin and 30 were allocated placebo. The change from baseline to 6 months in LCQ score differed between groups, with a mean change of 1·5 units in patients allocated atorvastatin versus –0·7 units in those assigned placebo (mean difference 2·2, 95% CI 0·5–3·9; p=0·01). 12 (40%) of 30 patients in the atorvastatin group improved by 1·3 units or more on the LCQ compared with five (17%) of 30 in the placebo group (difference 23%, 95% CI 1–45; p=0·04). Ten (33%) patients assigned atorvastatin had an adverse event versus three (10%) allocated placebo (difference 23%, 95% CI 3–43; p=0·02). No serious adverse events were recorded.



	Atorvastatin (n=30)	Placebo (n=30)
Leg pain	2 (7%)	0
Raised creatine kinase level*	1 (3%)	2 (7%)
Headache	3 (10%)	0
Diarrhoea	3 (10%)	0
Abdominal discomfort	1 (3%)	1 (3%)
Abnormal liver-function tests	1 (3%)	0
Haematuria	1 (3%)	0

Two patients had more than one adverse event. *Greater than two times the upper limit of normal.

Table 3: **Adverse events**

A Randomized Controlled Trial of Atorvastatin in Patients With Bronchiectasis Infected With *Pseudomonas Aeruginosa*

A Proof of Concept Study

Pallavi Bedi, MD; James D. Chalmers, PhD; Catriona Graham, MSc; Andrea Clarke, MSc; Samantha Donaldson, BSc; Catherine Doherty, PhD; John R. W. Govan, DSc; Donald J. Davidson, PhD; Adriano G. Rossi, DSc; and Adam T. Hill, MD

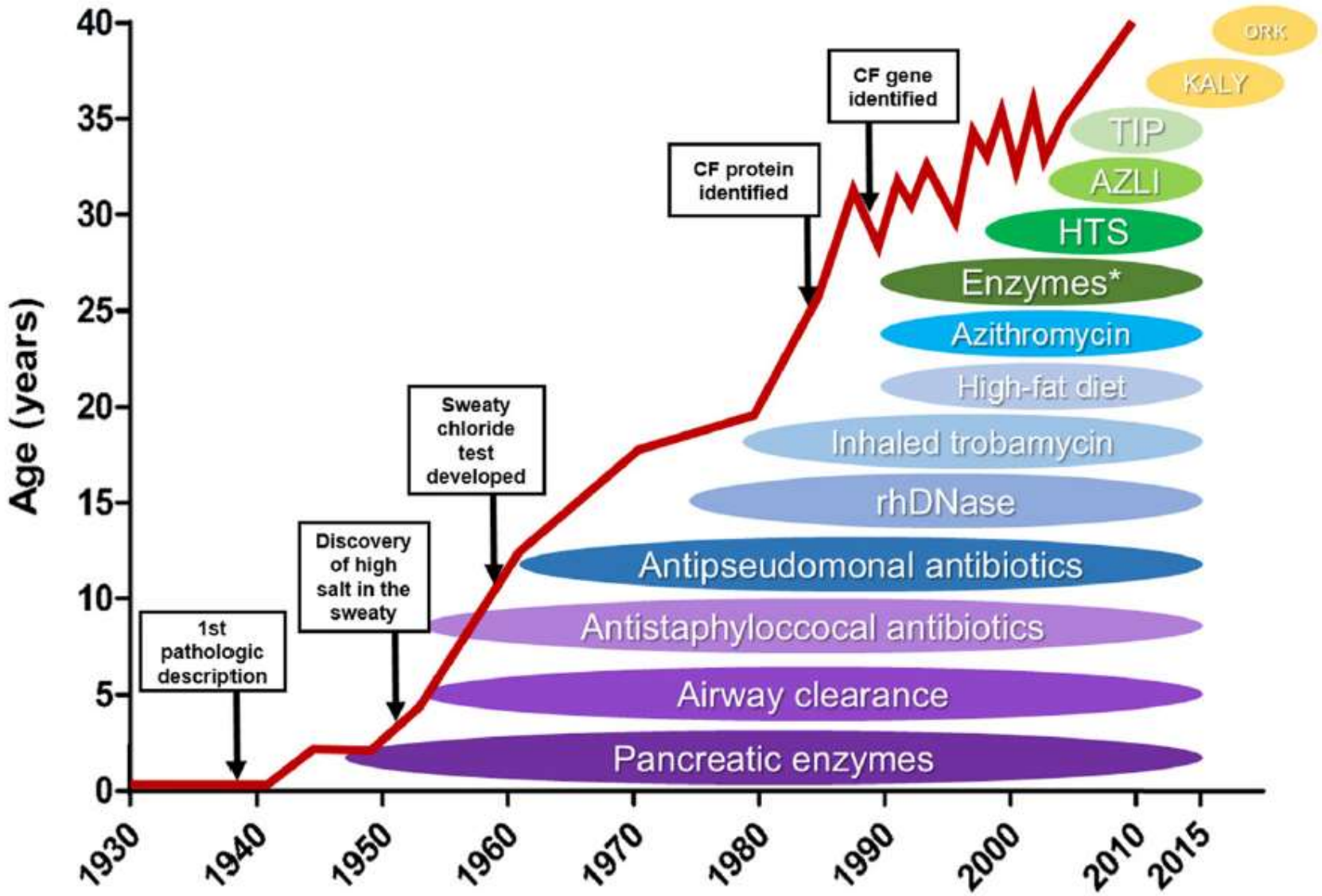
BACKGROUND: There are no randomized controlled trials of statin therapy in patients with severe bronchiectasis who are chronically infected with *Pseudomonas aeruginosa*.

METHODS: Thirty-two patients chronically infected with *P aeruginosa* were recruited in this double-blind cross-over randomized controlled trial. Sixteen patients were recruited in each arm, were given atorvastatin 80 mg or placebo for 3 months followed by a washout period for 6 weeks, and then crossed over and administered the alternative therapy for 3 months.

RESULTS: Twenty-seven patients completed the study. Atorvastatin did not significantly improve the primary end point of cough as measured by the Leicester Cough Questionnaire (mean difference, 1.92; 95% CI for difference, –0.57-4.41; $P = .12$). However, atorvastatin treatment resulted in an improved St. Georges Respiratory Questionnaire (–5.62 points; $P = .016$) and reduced serum levels of CXCL8 ($P = .04$), tumor necrosis factor ($P = .01$), and intercellular adhesion molecule 1 ($P = .04$). There was a trend toward improvement in serum C-reactive protein and serum neutrophil counts ($P = .07$ and $P = .06$, respectively). We demonstrated in vitro that atorvastatin 10 μM reduced formyl-methionyl-leucyl phenylalanine-induced upregulation of CD11b expression and changes in calcium flux, reflecting an ability to decrease neutrophil activation.

Bronchiectasis in Cystic fibrosis

Cystic fibrosis management over decades



Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Peter J. Mogayzel, Jr.[1], Edward T. Naureckas[2], Karen A. Robinson[3], Gary Mueller[4], Denis Hadjiliadis[5], Jeffrey B. Hoag[6], Lisa Lubsch[7], Leslie Hazle[8], Kathy Sabadosa[8], Bruce Marshall[8], and the Pulmonary Clinical Practice Guidelines Committee*

Treatment Question	Studies	Total (*n*)
Inhaled tobramycin—moderate to severe disease	6 RCT (40–45) 1 RCO (46)	1,110
Inhaled tobramycin—mild disease	3 RCT (47–49)	234
Dornase alfa—moderate to severe disease	8 RCT (50–57) 1 RCO (58)	1,800
Dornase alfa—mild disease	4 RCT (59–62) 3 RCO (63–65)	649
Inhaled hypertonic saline	2 RCT (66, 67) 1 RCO (68)	241
Azithromycin with *P. aeruginosa*	4 RCT (13–15, 17) 1 RCO (18)	271
Azithromycin without *P. aeruginosa*	4 RCT (13, 14, 16, 17) 1 RCO (18)	365
Oral antistaphylococcal antibiotics, prophylactic use	1 RCT (21) 1 RCO (20)	226
Oral antistaphylococcal antibiotics, chronic use	1 RCT (21) 1 RCO (20)	226

Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Peter J. Mogayzel, Jr.[1], Edward T. Naureckas[2], Karen A. Robinson[3], Gary Mueller[4], Denis Hadjiliadis[5], Jeffrey B. Hoag[6], Lisa Lubsch[7], Leslie Hazle[8], Kathy Sabadosa[8], Bruce Marshall[8], and the Pulmonary Clinical Practice Guidelines Committee*

Inhaled corticosteroids	6 RCT (69–74) 2 RCO (75, 76)	426
Chronic oral corticosteroids	3 RCT (77–79)	354
Other inhaled antibiotics (Carbenicillin, Ceftazidime, Colistin, Gentamicin)	1 RCT (80) 5 RCO (81–84)	177
Oral antipseudomonal antibiotics	1 RCT (85)	40
Leukotriene modifiers	2 RCO (86, 87)	48
Inhaled or oral *N*-acetylcysteine, or inhaled glutathione	2 RCT (88, 89) 1 RCO (90)	72
Inhaled anticholinergics	0	0
Ivacaftor	3 RCT (25–27) 1 RCO (27)	252
Inhaled aztreonam—moderate to severe disease	3 RCT (30–32)	515
Inhaled aztreonam—mild disease	1 RCT (36)	157
Chronic use of Ibuprofen (age $<$ 18 yr)	4 RCT (7–10)	287
Chronic use of Ibuprofen (age $\geq$ 18 yr)	1 RCT (7)	41
Chronic inhaled β_2-adrenergic agents	1 RCT (4) 1 RCO (5)	57

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Inhaled tobramycin—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled tobramycin—mild disease*	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B
Dornase alfa—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa—mild disease*	For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
Inhaled hypertonic saline	For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.	Moderate	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic	High	Moderate	B

Oral antistaphylococcal antibiotics, prophylactic use	For individuals with CF, the CF Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Moderate	Negative	D
Inhaled corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.	High	Zero	D
Oral corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations.	High	Negative	D
Other inhaled antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Leukotriene modifiers	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled or oral *N*-acetylcysteine, or inhaled glutathione	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral *N*-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled anticholinergics	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.	Low	—	I

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Ivacaftor*	For individuals with CF, 6 years of age and older, with at least one G551D *CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.	High	Substantial	A
Inhaled aztreonam—moderate to severe disease†	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam—mild disease†	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B
Chronic use of ibuprofen (age $<$ 18 yr)	For individuals with CF, between 6 and 17 years of age, with an $FEV_1 \geq 60\%$ predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.	Moderate	Moderate	B
Chronic use of ibuprofen (age $\geq$ 18 yr)	For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.	Low	—	I
Azithromycin without *P. aeruginosa*	For individuals with CF, 6 years of age and older, without *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	Moderate	Small	C
Chronic inhaled β_2-adrenergic receptor agonists	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antistaphylococcal antibiotics, chronic use	For individuals with CF, 6 years of age and older, with *Staphylococcus aureus* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I

Not much changes except on CFTR modulators

Journal of Cystic Fibrosis 17 (2018) 153–178

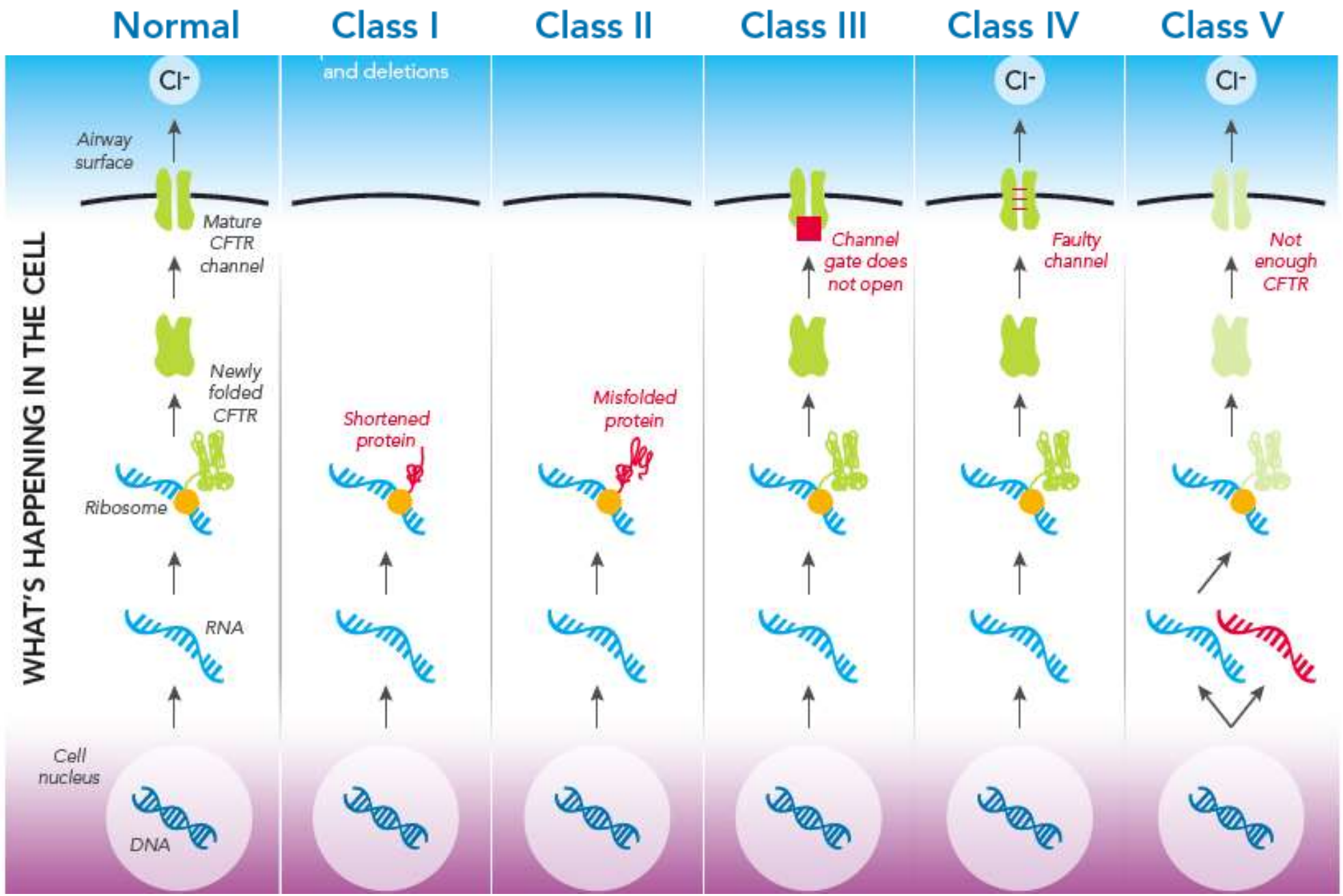
Journal of Cystic Fibrosis

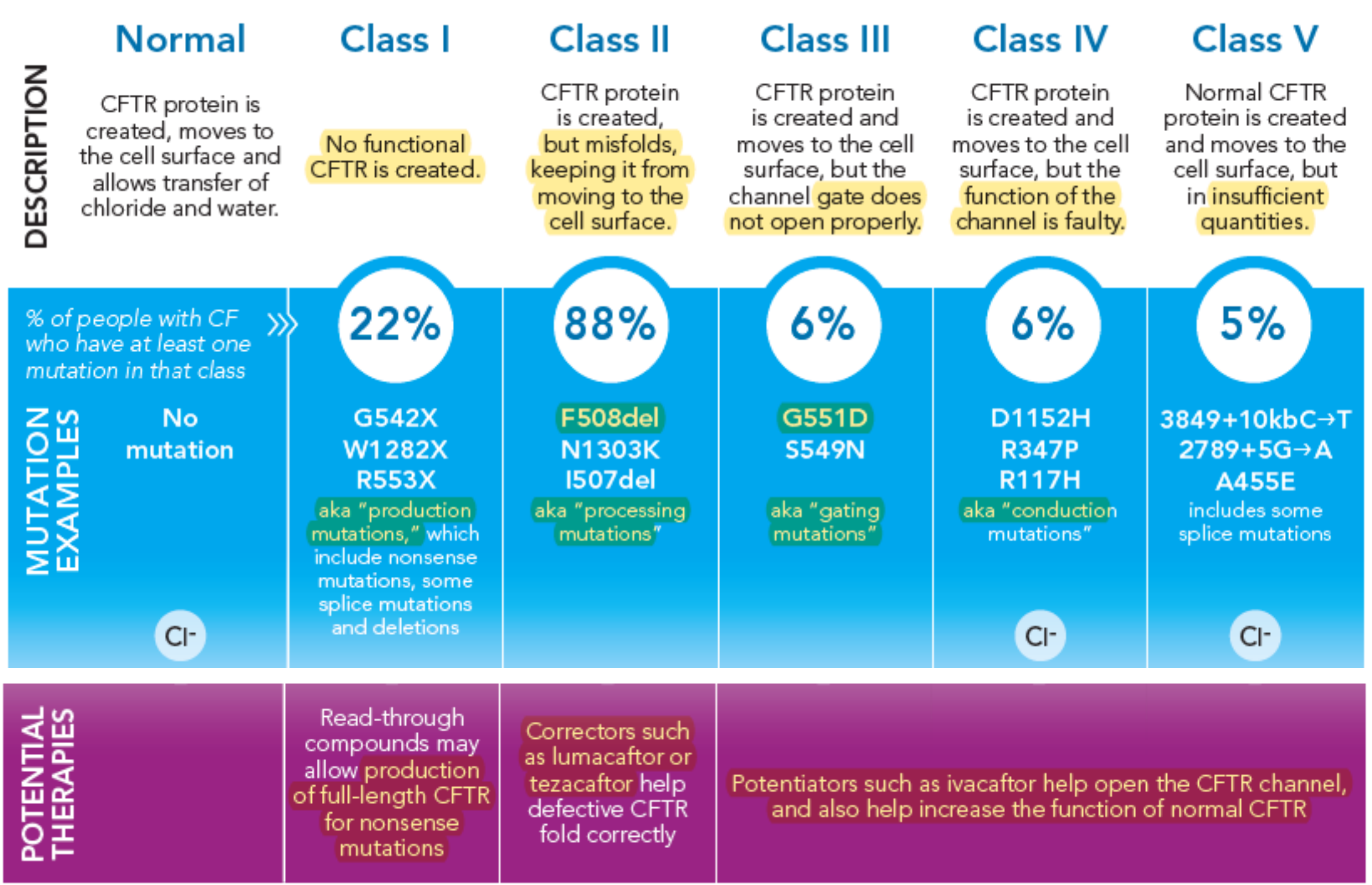
www.elsevier.com/locate/jcf

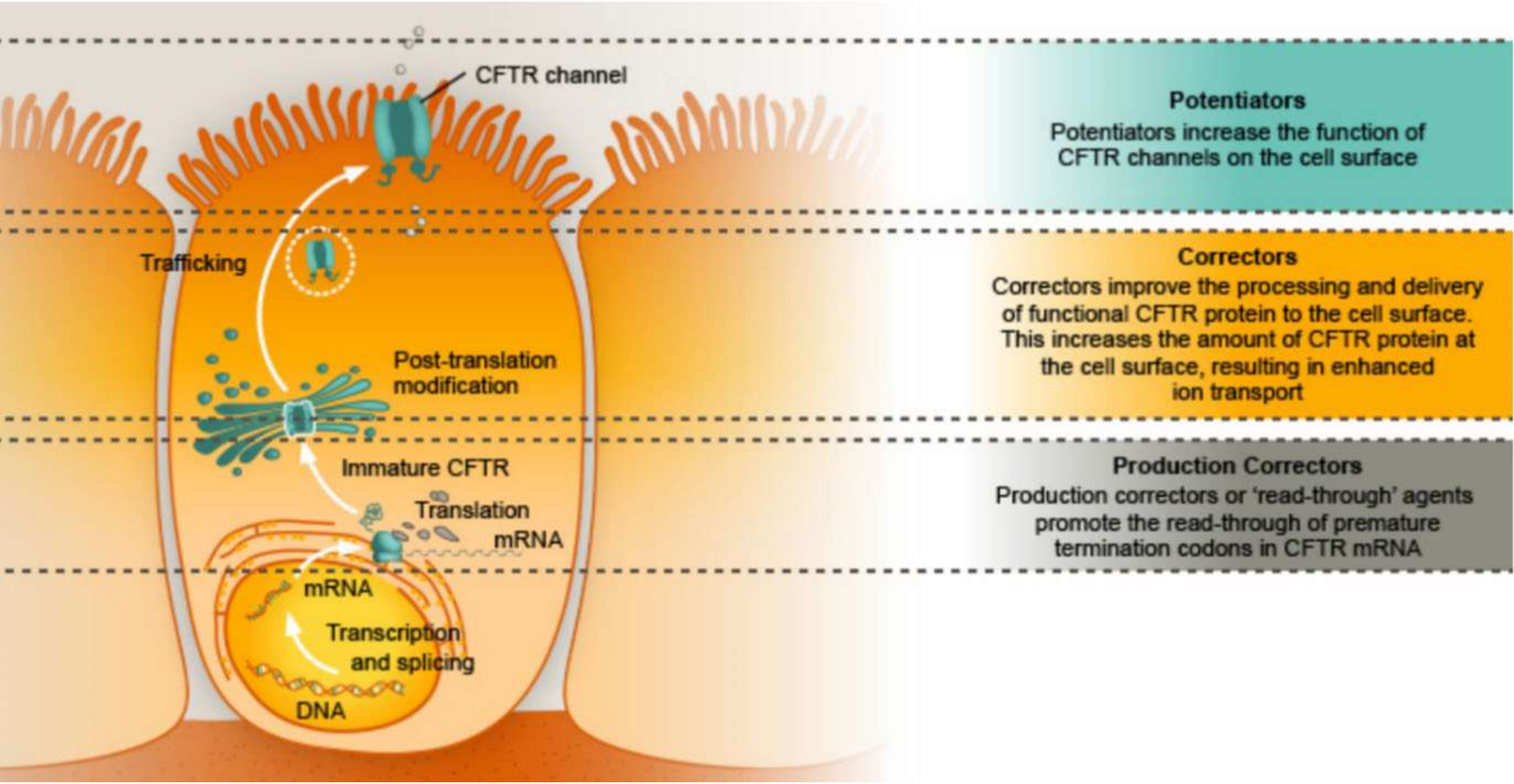
Review

ECFS best practice guidelines: the 2018 revision

Carlo Castellani [a,b], Alistair J.A. Duff [c,d,*], Scott C. Bell [e], Harry G.M. Heijerman [f], Anne Munck [g], Felix Ratjen [h], Isabelle Sermet-Gaudelus [i], Kevin W. Southern [j], Jurg Barben [k], Patrick A. Flume [l], Pavla Hodková [m], Nataliya Kashirskaya [n], Maya N. Kirszenbaum [o], Sue Madge [p], Helen Oxley [q], Barry Plant [r], Sarah Jane Schwarzenberg [s], Alan R. Smyth [t], Giovanni Taccetti [u], Thomas O.F. Wagner [v], Susan P. Wolfe [w], Pavel Drevinek [x]

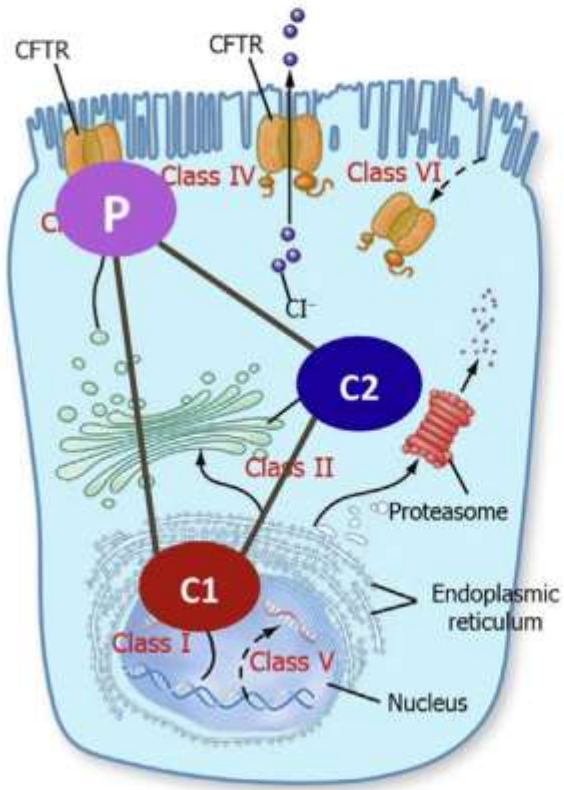

Normal
Class I
Class II
Class III
Class IV
Class V
and deletions
Cl-
Cl-
Cl-
Airway surface
Mature CFTR channel
Channel gate does not open
Faulty channel
Not enough CFTR
Newly folded CFTR
Shortened protein
Misfolded protein
Ribosome
RNA
Cell nucleus
DNA
WHAT'S HAPPENING IN THE CELL


DESCRIPTION
Normal
CFTR protein is created, moves to the cell surface and allows transfer of chloride and water.
Class I
No functional CFTR is created.
Class II
CFTR protein is created, but misfolds, keeping it from moving to the cell surface.
Class III
CFTR protein is created and moves to the cell surface, but the channel gate does not open properly.
Class IV
CFTR protein is created and moves to the cell surface, but the function of the channel is faulty.
Class V
Normal CFTR protein is created and moves to the cell surface, but in insufficient quantities.
% of people with CF who have at least one mutation in that class
22%
88%
6%
6%
5%
MUTATION EXAMPLES
No mutation
Cl-
G542X
W1282X
R553X
aka "production mutations," which include nonsense mutations, some splice mutations and deletions
F508del
N1303K
I507del
aka "processing mutations"
G551D
S549N
aka "gating mutations"
D1152H
R347P
R117H
aka "conduction mutations"
Cl-
3849+10kbC→T
2789+5G→A
A455E
includes some splice mutations
Cl-
POTENTIAL THERAPIES
Read-through compounds may allow production of full-length CFTR for nonsense mutations
Correctors such as lumacaftor or tezacaftor help defective CFTR fold correctly
Potentiators such as ivacaftor help open the CFTR channel, and also help increase the function of normal CFTR


CFTR channel
Trafficking
Post-translation
modification
Immature CFTR
Translation
mRNA
mRNA
Transcription
and splicing
DNA
Potentiators
Potentiators increase the function of
CFTR channels on the cell surface
Correctors
Correctors improve the processing and delivery
of functional CFTR protein to the cell surface.
This increases the amount of CFTR protein at
the cell surface, resulting in enhanced
ion transport
Production Correctors
Production correctors or 'read-through' agents
promote the read-through of premature
termination codons in CFTR mRNA

CFTR Modulators

Modulators targeting the F508delCFTR maturation and other mutations



Potentiators

- Kalydeco (Marketed)
- GLPG1837
- ABBV/GLPG2451
- ABBV/GLPG3067
- QBW-251
- CTP-656
- FDL-176
- PTI-808

Correctors C1

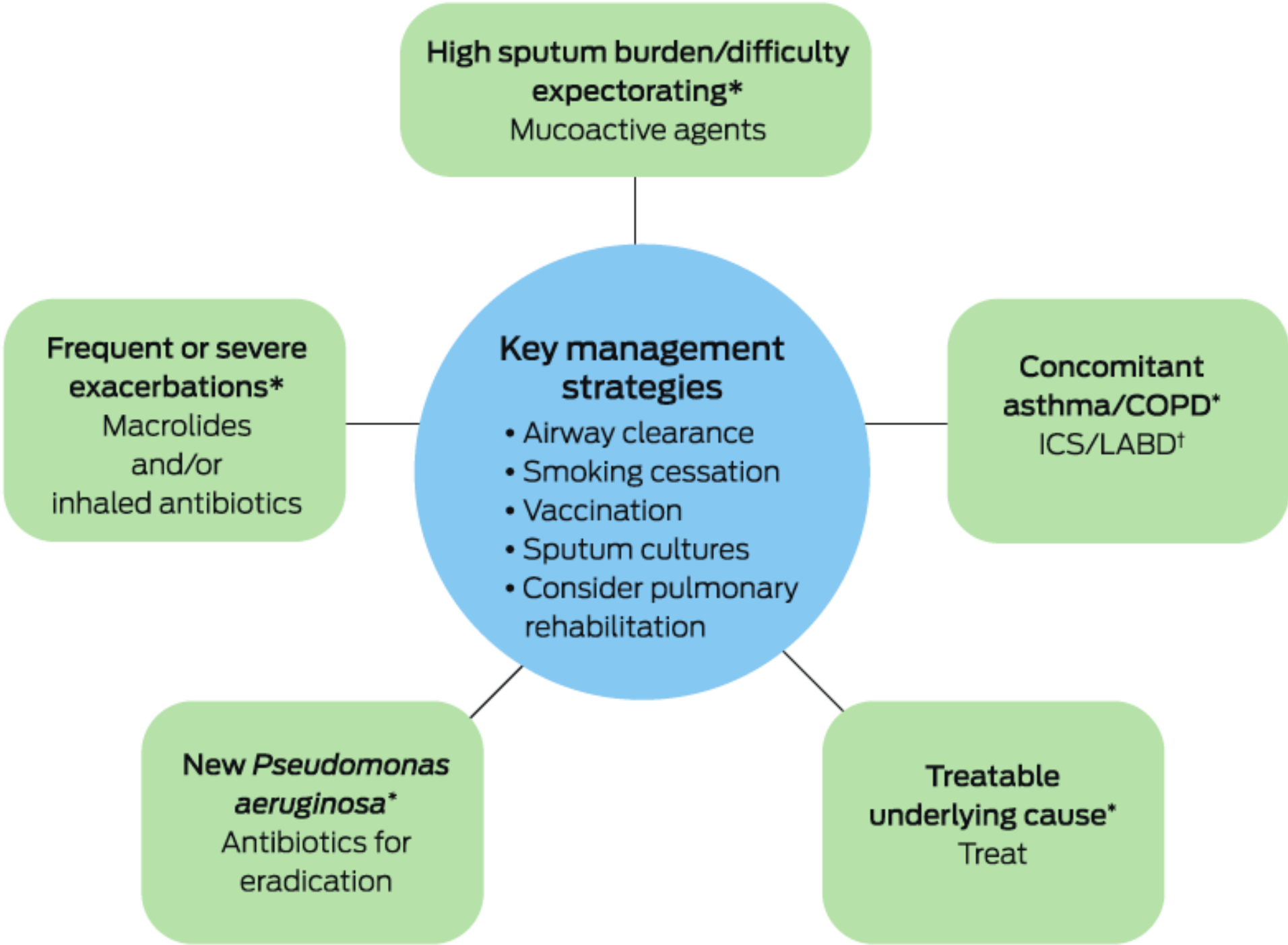
- Lumacaftor (Marketed) in combination with Kalydeco – Orkambi
- Tezacaftor
- ABBV/GLPG2222
- ABBV/GLPG2851
- FDL-169
- PTI-801

Correctors C2

- VX-152
- VX-440
- VX-659
- VX-445
- ABBV/GLPG2737
- ABBV/GLPG3221
- FD2052160

Recommendations for therapy with CFTR modulators in patients with cystic fibrosis

Genotype	Age group	Elexacaftor-tezacaftor-ivacaftor*	Tezacaftor-ivacaftor*	Lumacaftor-ivacaftor*	Ivacaftor*	No CFTR modulator therapy available
F508del homozygote	2 to 5 years			√		
	6 to 11 years		√¶			
	≥12 years	√				
F508del heterozygote WITHOUT a gating or residual function mutation	<12 years					√
	≥12 years	√				
F508del heterozygote WITH **gating mutation** at other allele[Δ]	6 months to 11 years				√	
	≥12 years	√				
F508del heterozygote WITH **residual function mutation** at other allele[Δ]	6 months to 5 years				√	
	6 to 11 years		√			
	≥12 years	√				
Gating mutation WITHOUT F508del[◈]	≥6 months				√	
Residual function mutation WITHOUT F508del[◈]	6 months to 5 years				√	
	≥6 years		√			


High sputum burden/difficulty expectorating*
Mucoactive agents
Frequent or severe exacerbations*
Macrolides and/or inhaled antibiotics
Key management strategies
• Airway clearance
• Smoking cessation
• Vaccination
• Sputum cultures
• Consider pulmonary rehabilitation
Concomitant asthma/COPD*
ICS/LABD†
New Pseudomonas aeruginosa*
Antibiotics for eradication
Treatable underlying cause*
Treat

Treatable (therapeutic) traits

Chronic airway infection
- Antibiotic therapy
  - Inhaled
  - Targeted
  - Macrolides

Pathogen acquisition
- *Pseudomonas aeruginosa* eradication therapy

Immunodeficiency
- Immunoglobin replacement
- Prophylactic antibiotics

NTM
- Antibiotic therapy

ABPA
- Corticosteroids
- +/– antifungals

Airflow obstruction and functional impairment
- Pulmonary rehabilitation
- Bronchodilators

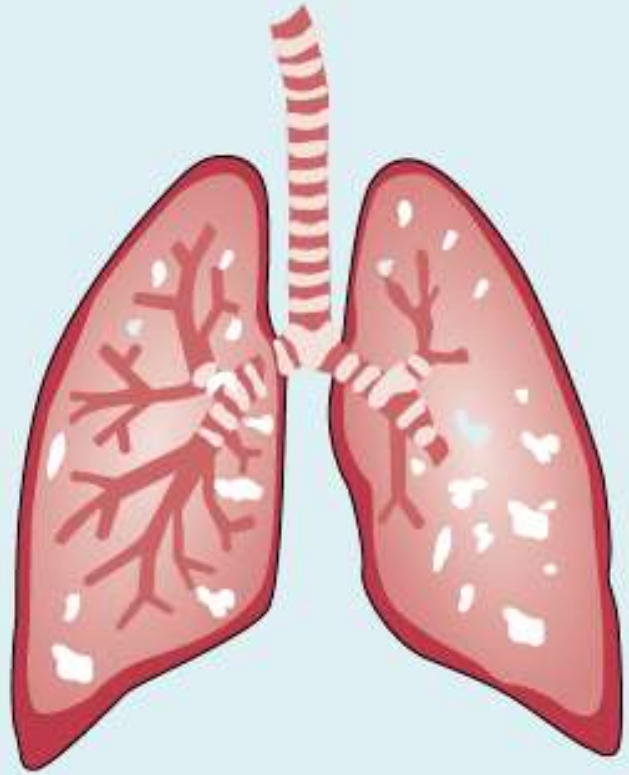
Sputum production
- Airway clearance
- Mucoactive drugs

Asthma and eosinophilia
- Inhaled corticosteroids

Low BMI
- Nutrition

GORD
- PPI
- +/– prokinetics

Other comorbidities
- Treat appropriately



Other factors
- Ethnic differences
- Environmental exposures
- Climatic variation
- Lifestyle
- Psychosocial

Targetable (endophenotypic) traits

Microbial (bacterial) dysbiosis
- Probiotics

Mycobiome (fungal) dysbiosis
- Antifungals

Neutrophil dysfunction
- Neutrophli elastase inhibitors

Protease-mediated lung damage
- Protease inhibitors

Ciliary dysfunction (primary or secondary)
- Airway clearance
- CFTR potentiator therapy

Systemic inflammation and vascular dysfunction
- Anti-inflammatory therapy

CFTR dysfunction
- CFTR potentiators
- CFTR correctors

Innate immune deficiency
- TLR-based therapeutics
- Antibiotic prophylaxis

	Phase	Trial design	Primary outcome or objective	Duration	Participants (n)	Single centre or multicentre	Location	Current status	Trial registration number
Recombinant GM-CSF (molgramostim)	1	Single-ascending dose and multiple-ascending dose in healthy people	Safety	28 days	42	Single centre	UK	Completed	NCT02468908
Human mesenchymal stem cells	1	Non-randomised safety assessment	Safety	Single infusion with up to 48 weeks' follow-up	6	Single centre	Miami, FL, USA	Recruiting	NCT02625246
Neutrophil elastase inhibitor (CHF6333)	1	Single-ascending dose and multiple-ascending dose in healthy people	Safety	15 days	72	Single centre	Belgium	Completed	NCT03056326
Cathepsin C inhibitor (GSK2793660)	1	Single-ascending dose and multiple-ascending dose in healthy people	Safety	18 days	33	Single centre	UK	Terminated because of adverse events	NCT02058407
Cathepsin C inhibitor (INS1007)	2	Double-blind, randomised, placebo-controlled	Time to first exacerbation	24 weeks	240	Multicentre	Worldwide	Not yet recruiting	NCT03218917
Roflumilast	2	Open-label	Change in CASA-Q	16 weeks	25	Single centre	South Korea	Unknown	NCT01580748
N-acetylcysteine	3	Randomised open-label	Frequency of acute exacerbations	12 months	150	Single centre	China	Recruiting	NCT02088216
ENaC inhibitor*	3	Randomised crossover	Change in FEV_1 and safety	28 days	150	Multicentre	Worldwide	Recruiting	NCT02871778
Theophylline	3	Randomised, blinded, placebo-controlled	SGRQ	24 weeks	100	Single centre	China	Completed	NCT01684683
Vitamin D	3	Randomised, blinded, placebo-controlled	Time to first exacerbation	1 year	200	Single centre	China	Unknown	NCT02507843 (registered retrospectively)
Neutrophil elastase inhibitor (BAY85-8501)	3	Randomised, double-blind, placebo-controlled	Safety	56 days	94	Multicentre	Worldwide	Completed	NCT01818544
OM-85 (extracts of multiple bacteria)	3	Randomised, placebo-controlled	Percentage of patients free from exacerbations	1 year	244	Multicentre	China	Recruiting	NCT01968421