Exacerbation Prevention and Management of Bronchiectasis

가톨릭의대
최준영

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Original article

Effect of exercise-based pulmonary rehabilitation in patients with bronchiectasis: A meta-analysis

Feng Yang, Lianjun Gao, Qimin Wang, Weiping Deng, Wei Gao*

Department of Respiratory and Critical Care Medicine, China Rehabilitation Research Center, Rehabilitation School of Capital Medical University, Beijing, 100068, China

Respir Med Res. 2022 Apr 19

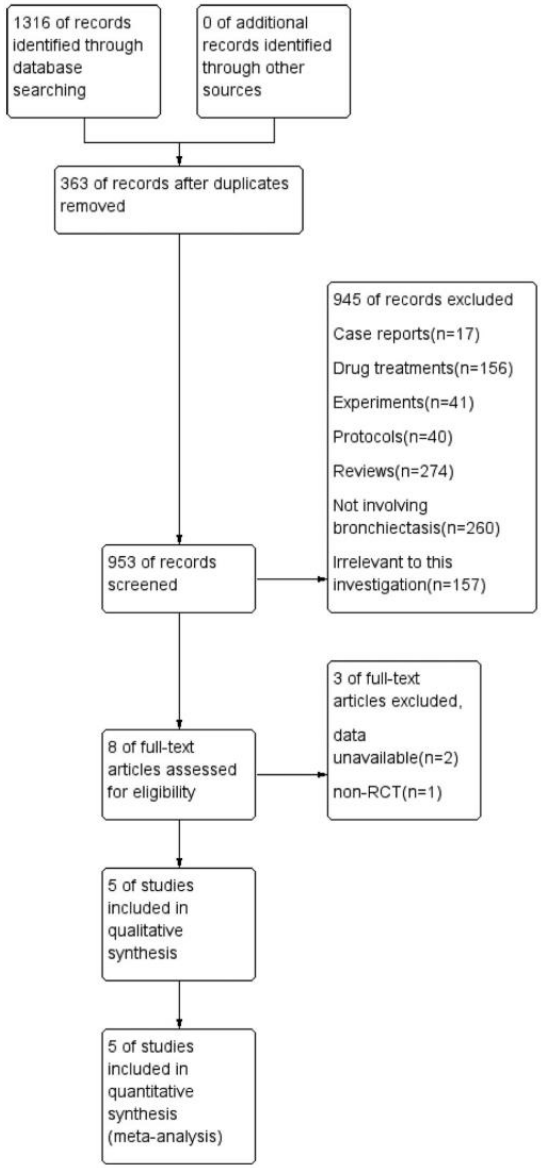

Table 1
Basic characteristics of the included studies.

Study	Pulmonary rehabilitation group				Control group				Outcome	Measurement timepoint
	Sample size	Age (years)	Female(%)	Intervention	Sample size	Age (years)	Female(%)	Intervention		
Newall, 2005	11	63.1 (3.5)	NR	Exercise training session three times per week, two sessions within the hospital and one further session at home for 8 weeks. Educational sessions.	9	62.9 (3.9)	NR	No pulmonary rehabilitation intervention. Educational sessions.	Peak oxygen uptake, PImax, PEmax, endurance exercise, lung function, ISWD, SGRQ, 24-hour sputum volume	8 weeks, 3 months
Mandal, 2012	12	64.8 (3.7)	33.33	Two supervised sessions per week and one unsupervised session at home for 8 weeks. Twice-daily chest physiotherapy for 8 weeks. Educational session.	15	64.6 (3.4)	60	Twice daily chest physiotherapy for 8 weeks. Educational session.	ISWT, EWT, LCQ, SGRQ, lung function, PImax, PEmax, white blood cell count, ESR, CRP	8 weeks, 20 weeks
Lee, 2014	42	63 (13)	71.43	Twice-weekly exercise program for 8 weeks. Review of ACT.	43	65 (12)	72.09	No exercise training. Contacted by telephone twice weekly to provide support and general advice with no discussion of exercise or physical activity.	ISWD, 6MWD, SGRQ, CRDQ, LCQ, HADS, AQOL, number of exacerbations	9 weeks, 12 months
Dal Corso, 2017	20	44 ± 18	NR	Three sessions weekly for 8 weeks with aerobic exercise (stepping training during 20 minutes) and resistance training using elastic bands.	19	47 ± 14	NR	Educational manual and a recommendation for a practice of exercises	ISWT, ESWT, SGRQ, quadriceps muscle strength	8 weeks
Chalmers, 2019	9	68 (63–71)	55.56	Exercise program: Two supervised sessions per week and two homework sessions for a total of 6 weeks. Educational activities.	18	68 (63–73)	83.33	Standard care: guideline concordant ongoing management, including daily chest physiotherapy.	6-MWD, time to the next exacerbation, LCQ, CAT, SGRQ, FEV1	8 weeks, 12 weeks

Data are presented as mean (SD), mean (SE), or median [IQR], unless otherwise stated. FEV1 – forced expiratory volume in 1 second; ISWT – incremental shuttle walk test; SGRQ – St. George's Respiratory Questionnaire; PImax – maximal inspiratory mouth pressure; PEmax – maximal expiratory mouth pressure; ACT – airway clearance techniques; EWT – endurance walk test; CAT-COPD assessment test; LCQ – Leicester Cough Questionnaire; 6-MWD – 6-minute walk distance; CRDQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; ISWD – incremental shuttle walk distance; NR – not reported

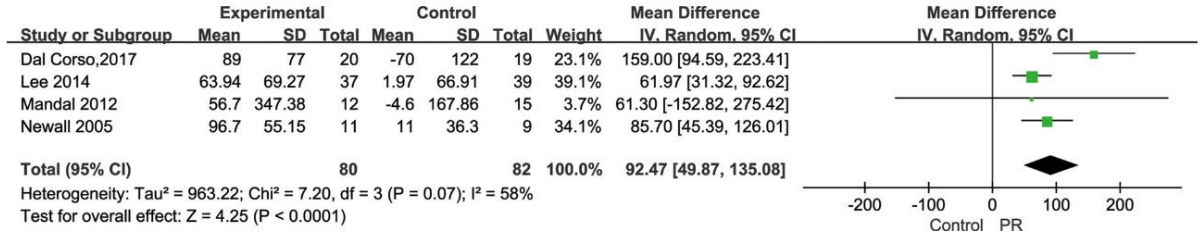

Fig. 3. META analysis of the comparison of incremental shuttle walking distance between the pulmonary rehabilitation group and the control group for bronchiectasis.

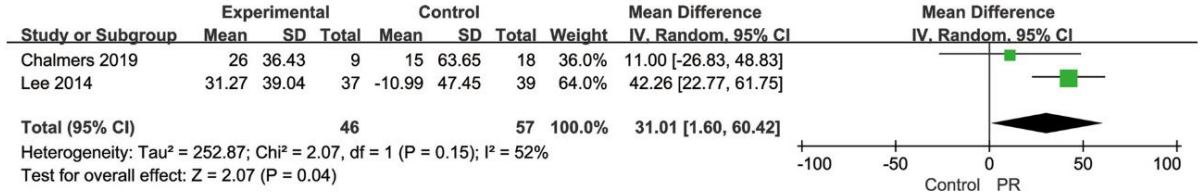

Fig. 4. META analysis of the comparison of 6-minute walk distance between the pulmonary rehabilitation group and the control group for bronchiectasis.

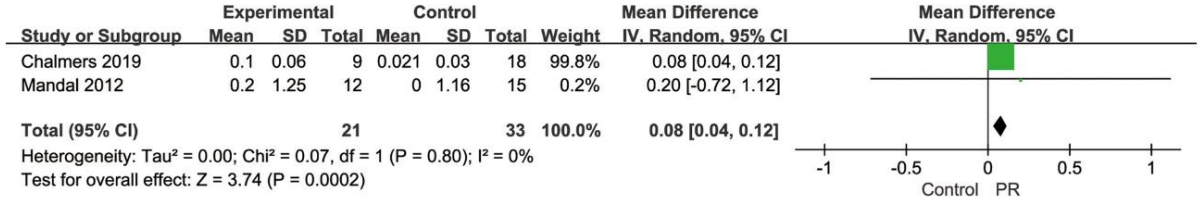

Fig. 5. Meta-analysis results of the comparison of forced expiratory volume in 1 second between the pulmonary rehabilitation group and the control group.

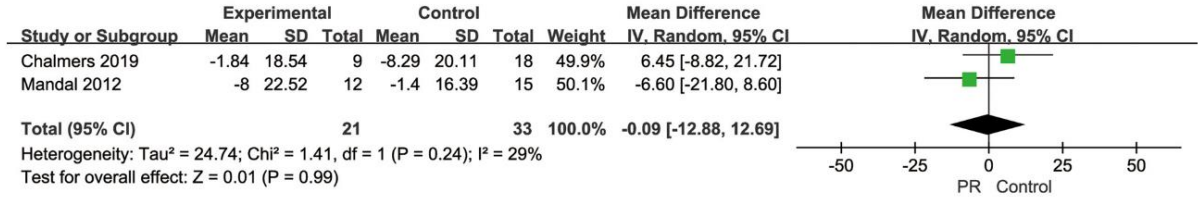

Fig. 6. Meta-analysis results of the comparison of St. George's Respiratory Questionnaire score between the pulmonary rehabilitation group and the control group.

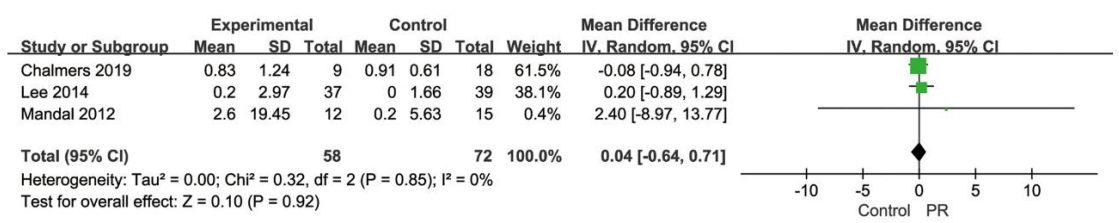

Fig. 7. Meta-analysis results of the comparison of the Leicester Cough Questionnaire score between the pulmonary rehabilitation group and the control group.

VIA MEDICA

ORIGINAL RESEARCH

İpek Candemir, Pınar Ergun, Seher Satar, Harun Karamanlı, Dicle Kaymaz, Nese Demir

Atatürk Chest Disease and Surgery Research and Education Hospital, Kecioren, Ankara, Turkey

Efficacy of pulmonary rehabilitation for bronchiectasis and related factors: which patients should receive the most treatment?

Adv Respir Med. 2021;89(1):15-22.

- A retrospective observational cohort study
- PR program between 2013.3-2019.3.
  - Comprehensive, multidisciplinary, hospital-based, and supervised outpatient program
  - Twice per week
- 130 patients with BRE who completed PR program

Table 2. Relation between some baseline values and improvements

	p/r*					
Baseline values	ΔMRC	ΔISWT	ΔESWT	ΔSGRQ	ΔCRQ	ΔAnxiety	ΔDepression
Age [years]**	0.077	0.521	0.085	**0.024** **-0.203**	0.875	0.221	0.093
Sex[#]	0.689	0.882	0.957	0.585	0.648	0.079	0.192
Hospitalization[£]	0.095	0.486	0.756	0.518	0.555	0.332	0.110
Disease[$]	0.220	0.890	0.651	0.335	0.135	0.438	0.997
Smoking status[$]	0.110	0.491	0.188	0.312	0.325	0.250	0.174
Baseline FEV_1[+]	0.148	0.699	0.682	0.798	**0.015** **0.213**	**0.014** **-0.215**	0.318
Baseline MRC**	**< 0.001** **-0.563**	0.822	0.488	**< 0.001** **-0.308**	0.106	0.289	0.358
Baseline ISWT[+]	0.129	**0.043** **-0.176**	0.284	0.932	0.062	**0.007** **-0.237**	0.374
Baseline SGRQ**	**0.003** **-0.267**	0.958	0.207	**< 0.001** **-0.648**	0.478	0.349	0.158

*Correlation coefficients were given when p values were statistically significant; **spearmans' correlation; [#]Binary logistic regression; [£]Linear regression; [$]Kruskal-Wallis test; [+]Adjusted for age, sex, and BMI using linear regression analysis

FEV_1 — forced expiratory volume in 1 sec; MRC — Medical Research Council; ISWT — incremental shuttle walking test; SGRQ — St. George's Respiratory Questionnaire

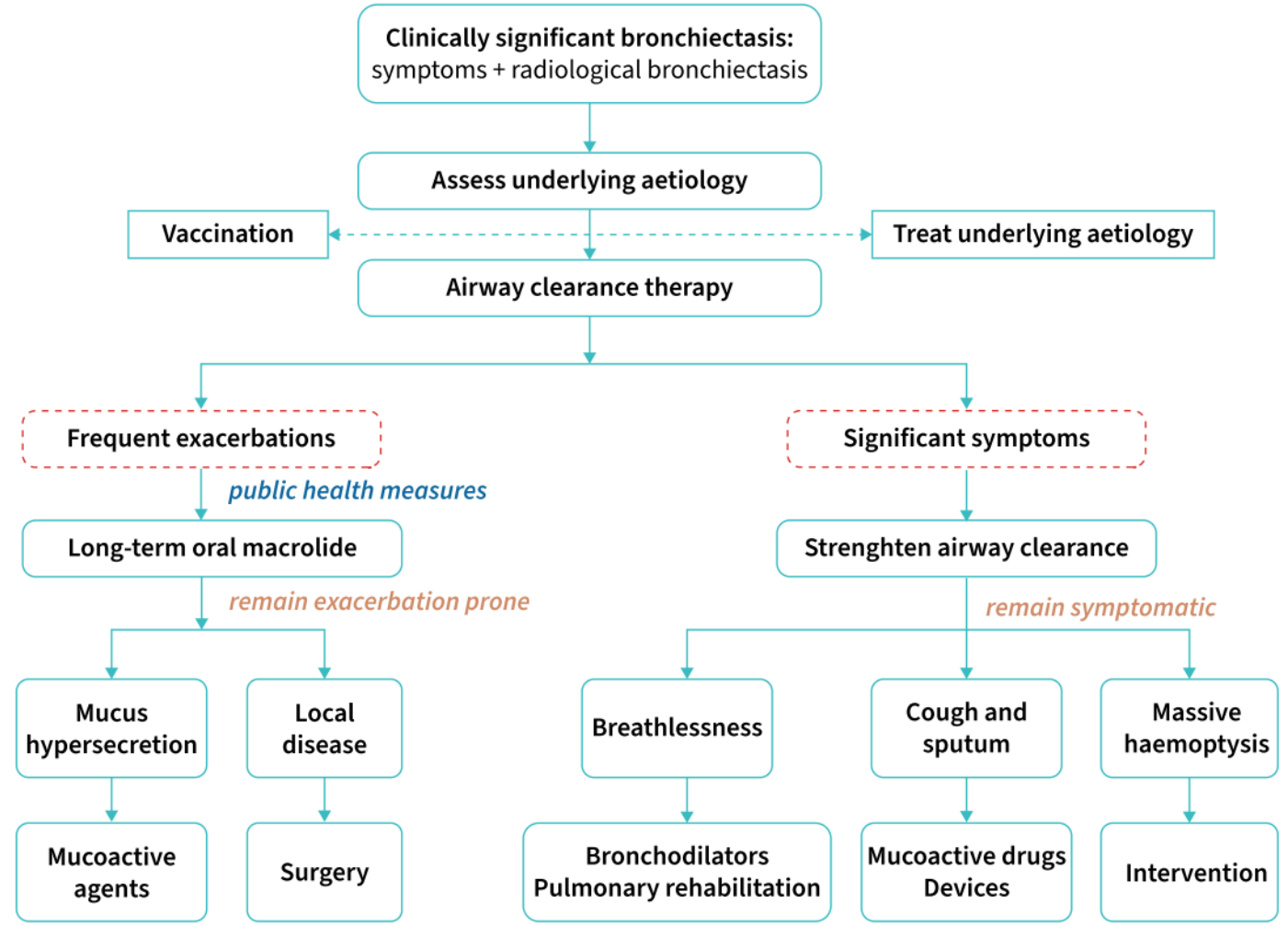

FIGURE 3 Recommended therapeutic flow chart for the management of patients with bronchiectasis.

ERJ Open Res. 2022 Apr 11;8(2):00017-2022.

EBioMedicine 72 (2021) 103587

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EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

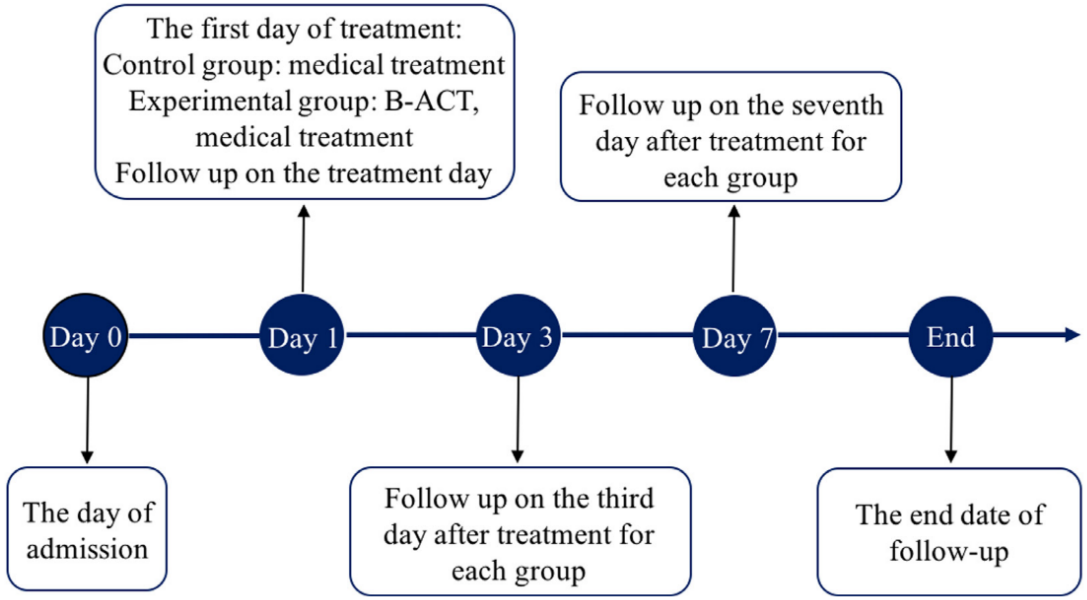
Research paper

Bronchoscopic airway clearance therapy for acute exacerbations of bronchiectasis

Yang Liu[a,1], Hai-Wen Lu[a,1], Shu-Yi Gu[a,1], Wen-Wen Wang[a,1], Juan Ge[b], Zhi-Jun Jie[c], Jin-Guang Jia[d], Zhi-Ting Gao[e], Jun Li[f], Jing-Yun Shi[g], Shuo Liang[a], Ke-Bing Cheng[a], Jiu-Wu Bai[a], Jie-Ming Qu[h,*], Jin-Fu Xu[a,*]

[a] *Department of Respiratory and Critical Care Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507 Zhengmin Road, Shanghai 200092, China*
[b] *Department of Respiratory Medicine, The Sixth People's Hospital of Nantong, Shanghai University, Jiangsu 226001, China*
[c] *Department of Respiratory and Critical Care Medicine, Shanghai Fifth People's Hospital, Fudan University, Shanghai 200240, China*
[d] *Department of Respiratory and Critical Care Medicine, People's Hospital of Zhengzhou, Henan University of Chinese Medicine, Henan 450014, China*
[e] *Department of Respiratory and Critical Care Medicine, People's Hospital of Putuo District, School of Medicine, Tongji University, Shanghai 200092, China*
[f] *Center of Clinical Research, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200092, China*
[g] *Department of Radiology Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200092, China*
[h] *Department of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

- RCT conducted in China, 2018.2-2019.2
- Inclusion criteria
  - moderate-to-severe BRE with AE
  - history of AE (+)
  - eligible for bronchoscopy
- B-ACT vs control



a)

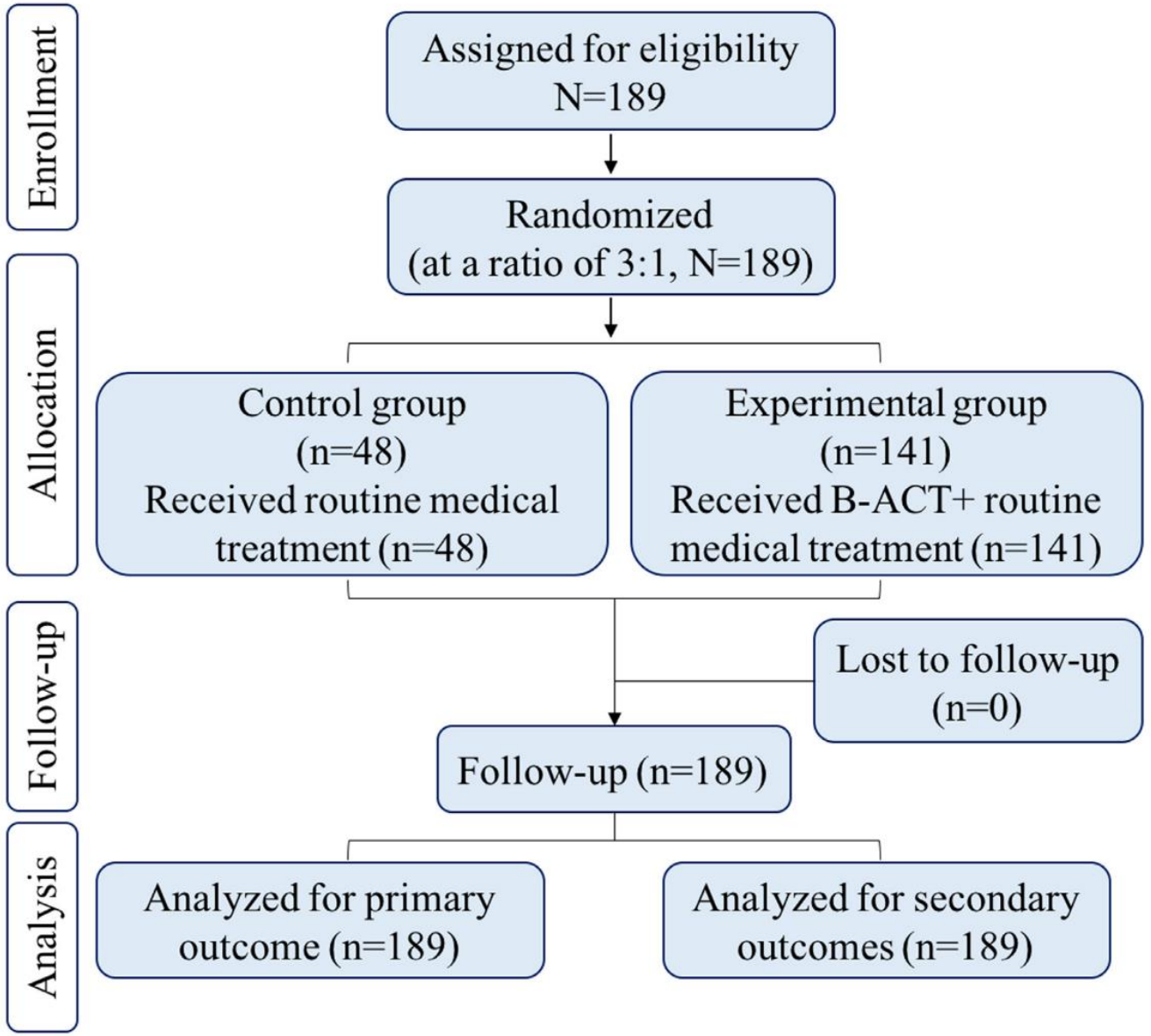
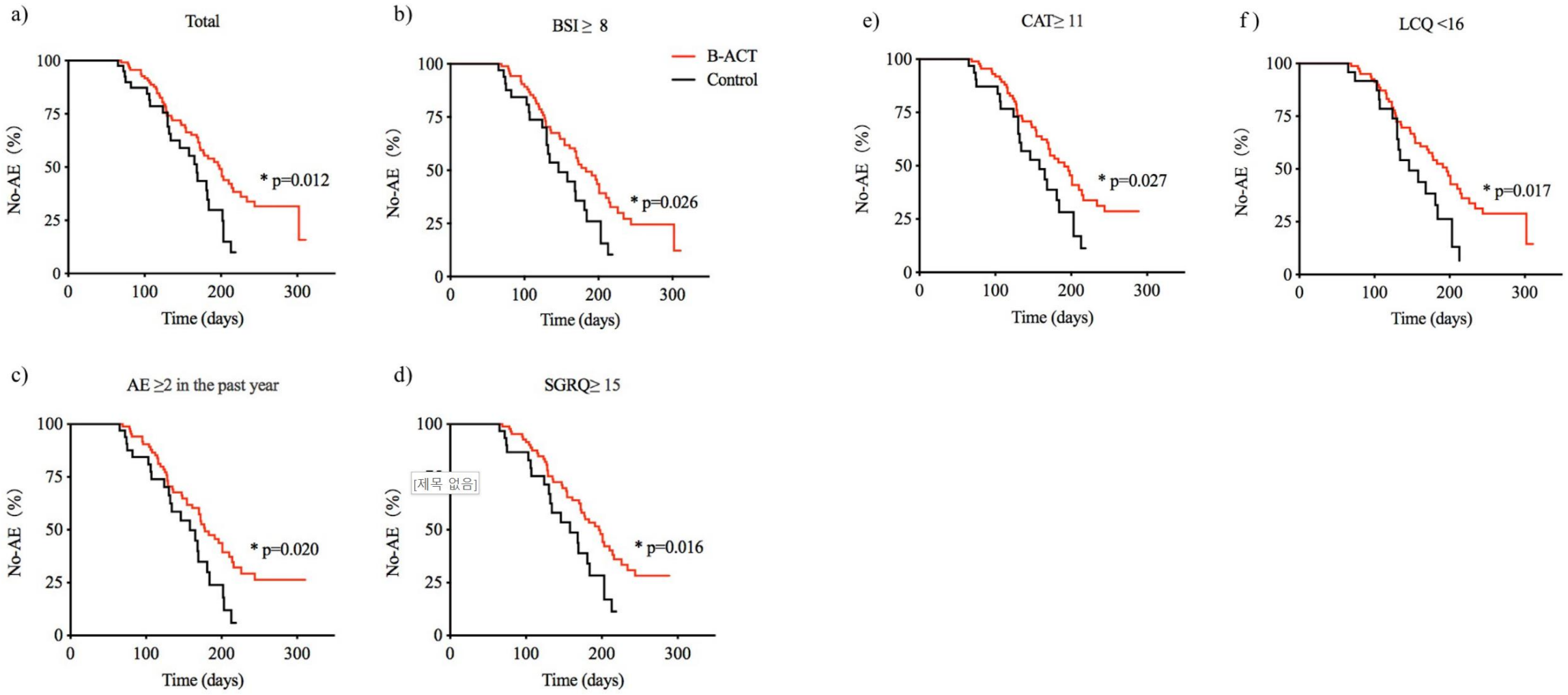

Enrollment
Assigned for eligibility
N=189
Randomized
(at a ratio of 3:1, N=189)
Allocation
Control group
(n=48)
Received routine medical
treatment (n=48)
Experimental group
(n=141)
Received B-ACT+ routine
medical treatment (n=141)
Follow-up
Lost to follow-up
(n=0)
Follow-up (n=189)
Analysis
Analyzed for primary
outcome (n=189)
Analyzed for secondary
outcomes (n=189)

Table 2

Multivariate analysis of the independent risk factors associated with the time to fist acute exacerbation after discharge.

Variables	Odds ratio (95%CI)	p value
B-ACT	0·57 (0·35-0·93)	0·024
Numbers of AE in the past year	1·76 (1·35-2·31)	<0·0001
Hemoglobin (g/L)	0·99 (0·97-1·00)	0·042

ACT, Airway Clearance Therapy; AE, Acute Exacerbation; B, Bronchoscopic; CI, confidence interval.


a)
Total
No-AE (%)
100
75
50
25
0
0
100
200
300
Time (days)
* p=0.012
b)
BSI ≥ 8
B-ACT
Control
No-AE (%)
Time (days)
* p=0.026
e)
CAT≥ 11
No-AE (%)
Time (days)
* p=0.027
f)
LCQ <16
No-AE (%)
Time (days)
* p=0.017
c)
AE ≥2 in the past year
No-AE (%)
Time (days)
* p=0.020
d)
SGRQ≥ 15
[제목 없음]
No-AE (%)
Time (days)
* p=0.016

Pharmacologic treatments

Muco-active drugs

Qi *et al. Respiratory Research* (2019) 20:73
https://doi.org/10.1186/s12931-019-1042-x

Respiratory Research

RESEARCH Open Access

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 Yu Li[1*]

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

- Prospective RCT
- 2014.3-2016.12, in five general hospital in China
- Inclusion
  - Adult BRE patients
  - ≥2 exacerbation in prior year
- N-acetylcysteine 600mg bid vs on-demand treatments
- The primary end-point
  - incidence of exacerbations/year

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
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

Data are n (%) or mean ± SD or median (IQR). Abbreviations: *mMRC* modified Medical Research Council, *CAT* chronic obstructive pulmonary disease assessment test, *HRCT* high resolution computed tomography, *FVC* forced vital capacity, FEV_1 forced expiratory volume in 1 s, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

- Incidence of exacerbations (during 12 month of follow-up)
  - N-acetylcysteine group (1.31) vs control (1.98)
  - P=0.0011, RR=0.41

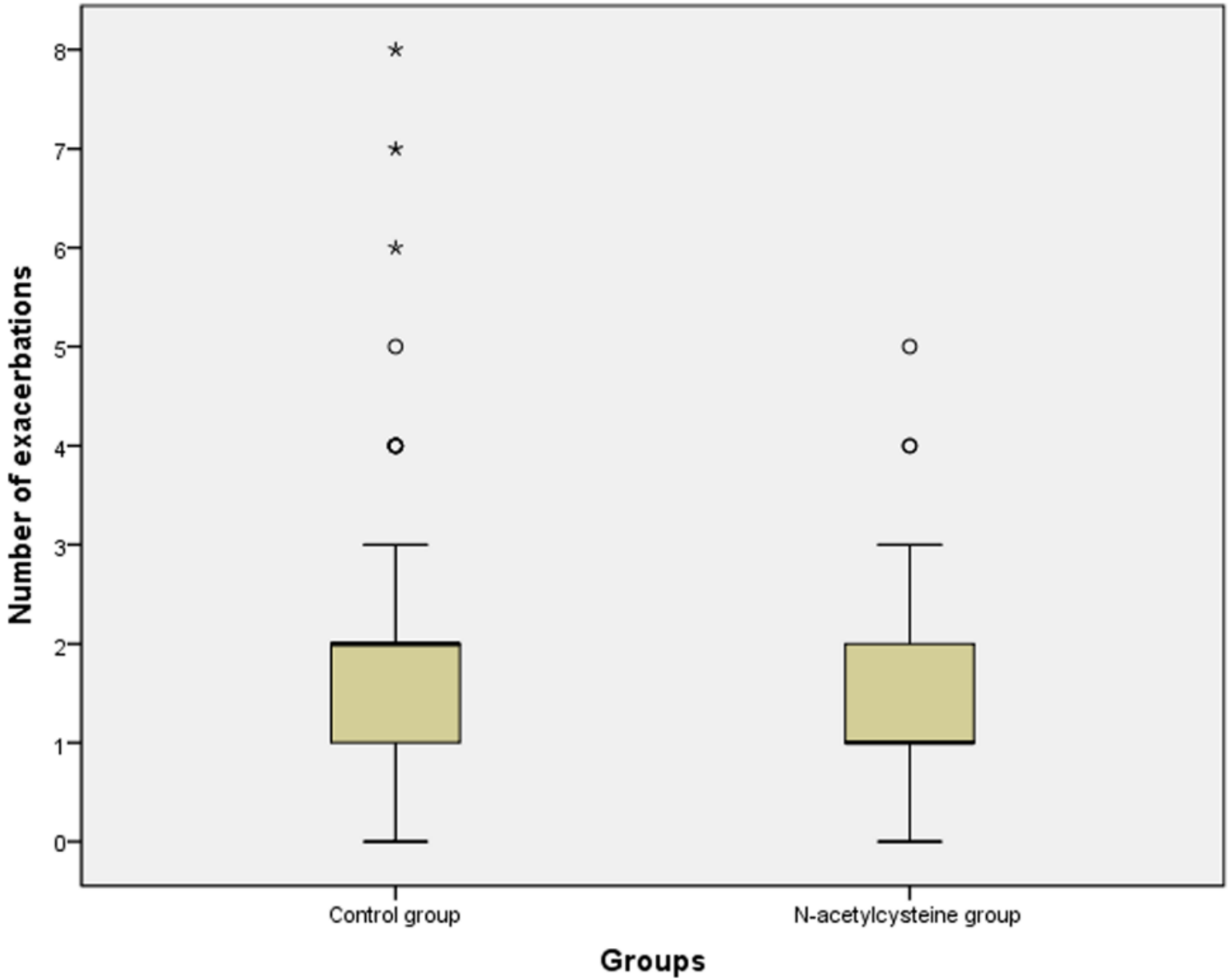


Fig. 2 Number of exacerbations for the control and N-acetylcysteine groups

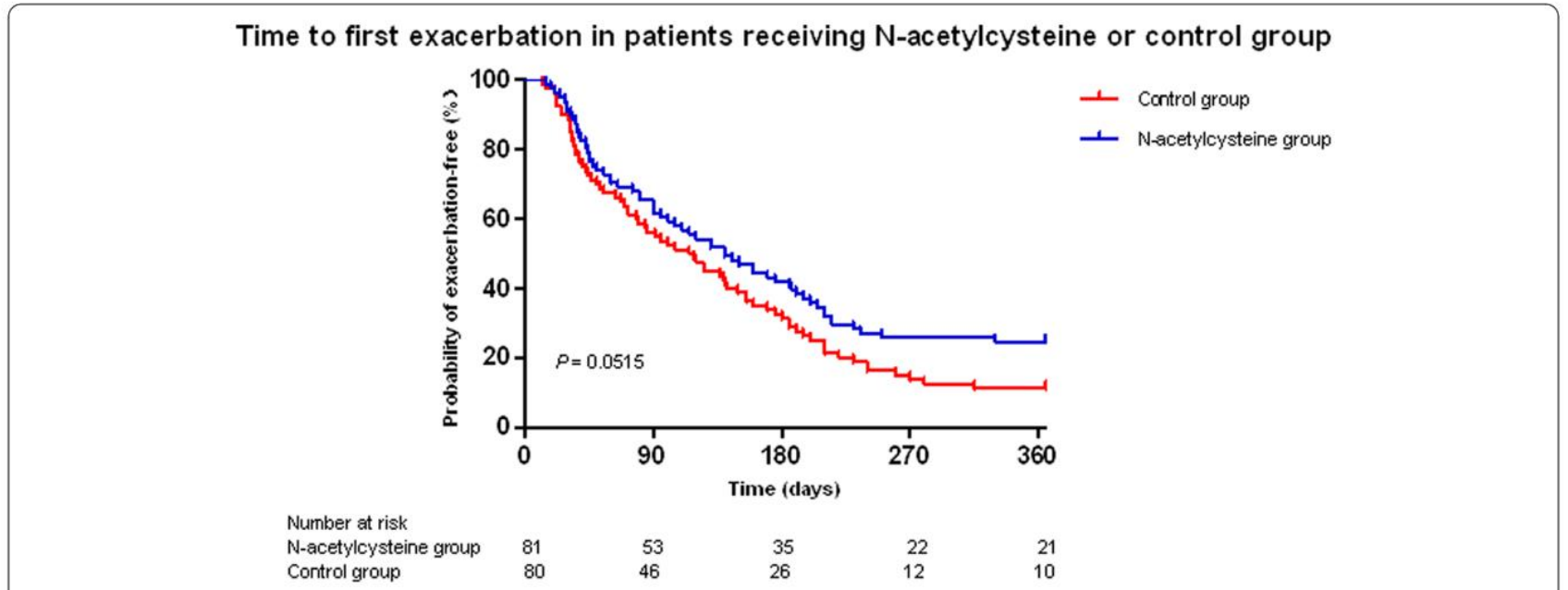


Fig. 3 Time to first exacerbation in patients receiving N-acetylcysteine or control group

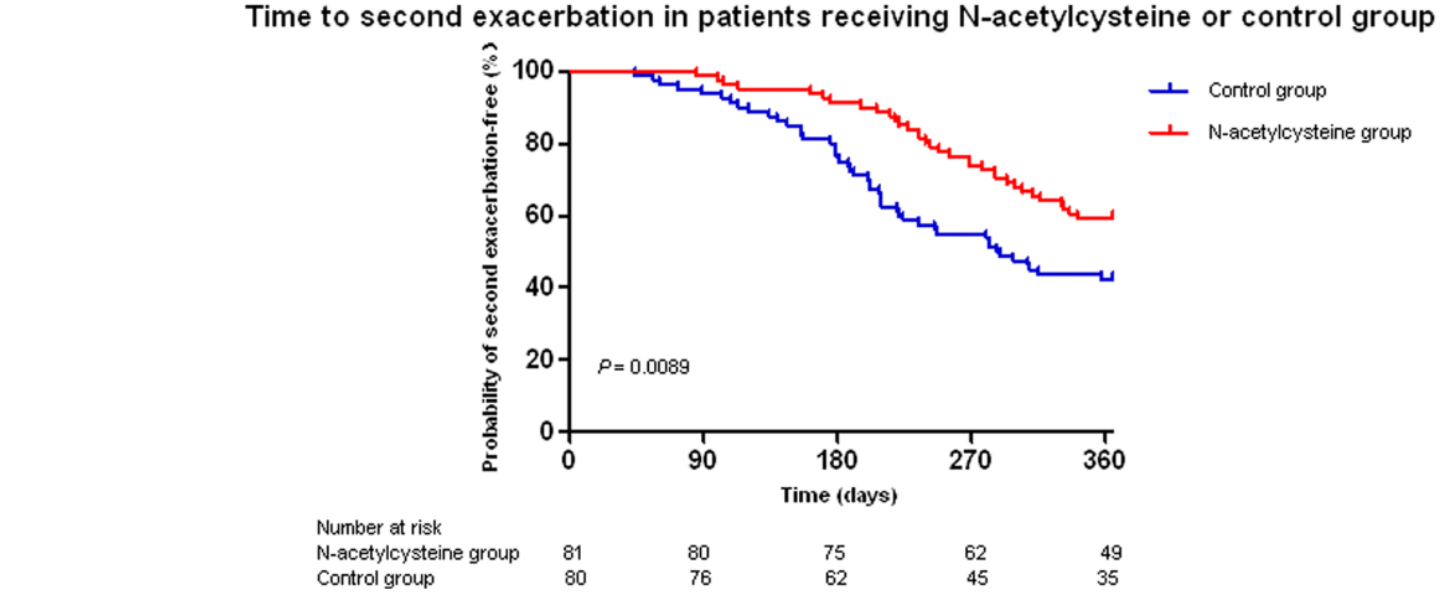


Fig. 4 Time to second exacerbation in patients receiving N-acetylcysteine or control group

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

Anti-inflammatory drugs

What is the evidence for long term anti-inflammatory therapies in bronchiectasis?

Recommendations

- Do not routinely offer inhaled corticosteroids to patients with bronchiectasis without other indications (such as ABPA, chronic asthma, COPD and inflammatory bowel disease). (B)
- Do not offer long-term oral corticosteroids for patients with bronchiectasis without other indications (such as ABPA, chronic asthma, COPD, inflammatory bowel disease). (D)
- Do not routinely offer phosphodiesterase type 4 (PDE4) inhibitors, methylxanthines or leukotriene receptor antagonists for bronchiectasis treatment. (D)
- Do not routinely offer CXCR2 antagonists, neutrophil elastase inhibitors or statins for bronchiectasis treatment. (B)

2019 BTS guideline

International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Inhaled Corticosteroid Therapy in Bronchiectasis is Associated with All-Cause Mortality: A Prospective Cohort Study

Int J Chron Obstruct Pulmon Dis. 2021 Jul 16;16:2119-2127.

- Prospective cohort follow-up study
- BE patients at two university hospitals in Capital Region of Demark 2014-2015.
- Followed until April 2020

Table 2 Pharmacological and Non-Pharmacological Treatment Strategies in 264 Respiratory Outpatients with Bronchiectasis Followed for 5 Years at Two University Hospitals, Stratified by Treatment with Inhaled Corticosteroids

Treatment Strategies	No ICS, N = 139[a]	ICS-Treated, N = 122[a]	p-value[b]
ICS Treatment		122 (100%)	N/A
Without Asthma or COPD		23 (21%)	N/A
High-Dose ICS Treatment		29 (24%)	N/A
Without Asthma or COPD		8 (35%)	N/A
With Asthma		14 (11%)	N/A
With COPD		11 (9.0%)	N/A
LAMA Treatment	11 (7.9%)	44 (36%)	<0.001
Without Asthma or COPD	3 (27%)	5 (11%)	0.5
With Asthma	2 (1.4%)	16 (13%)	<0.001
With COPD	6 (4.3%)	30 (25%)	0.015
LABA Treatment	10 (7.2%)	97 (80%)	<0.001
Without Asthma or COPD	5 (50%)	15 (15%)	0.009
With Asthma	1 (0.7%)	50 (41%)	<0.001
With COPD	4 (2.9%)	45 (37%)	<0.001
Prophylactic Antibiotics	7 (5.0%)	19 (16%)	0.005
PEP-Device	106 (99%, N=107)	96 (98%, N=98)	0.6
Pulmonary Physiotherapy	56 (72%, N=78)	55 (67%, N=82)	0.5

Table 3 Burden of Disease in 264 Respiratory Outpatients with Bronchiectasis Followed for 5 Years at Two University Hospitals, Stratified by Treatment with Inhaled Corticosteroids

Colonization and Exacerbations	**No ICS, N = 139[a]**	**ICS-Treated, N = 122[a]**	**p-value[b]**
Sputum Culture Performed	72 (52%)	87 (71%)	0.001
Positive Sputum Culture	29 (21%)	39 (32%)	0.041
P. aeruginosa-Positive Sputum Culture	9 (6.5%)	24 (20%)	0.001
History of Any Exacerbations 12 Months Prior to Baseline Of which History Moderate Exacerbations Of Which History of Severe Exacerbations	73 (54%, N=134) 73 (54%, N=134) 29 (21%)	82 (70%, N=117) 81 (70%, N=116) 50 (41%)	0.011 0.013 <0.001
Annual Exacerbation Rate per Patient during Follow-Up Of Which Moderate Exacerbations Of Which Severe Exacerbations	0.87 (1.33) 0.74 (1.05) 0.13 (0.50)	1.36 (1.76) 1.00 (1.32) 0.36 (0.86)	0.012 0.089 0.008
Deceased at End of Follow-Up	14 (10%)	25 (20%)	0.023

Table 4 HR of All-Cause Mortality in 264 Respiratory Outpatients with Bronchiectasis Followed for 5 Years at Two University Hospitals, Calculated Using Cox Regression

Mortality Regression Analyses	Bivariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	p-value	HR	95% CI	p-value
ICS Treatment						
No ICS Treatment	1			1		
Low-to-Moderate Dose	1.54	0.73, 3.23	0.3	0.86	0.30, 2.46	0.8
High Dose	4.66	2.12, 10.3	<0.001	4.93	1.73, 14.0	0.003
Age				1.10	1.05, 1.14	<0.001
Female				0.62	0.27, 1.44	0.3
Smoking Status						
Never-smoker				1		
Ex-Smoker				0.81	0.34, 1.91	0.6
Current Smoker				1.64	0.40, 6.79	0.5
FEV_1						
>70%				1		
50% to 70%				1.15	0.45, 2.90	0.8
<50%				3.72	1.30, 10.7	0.015
Asthma or COPD Diagnosis				1.40	0.53, 3.71	0.5

ORIGINAL ARTICLE

https://doi.org/10.4046/trd.2021.0051
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2022;85:67-73

trd
Tuberculosis & Respiratory Diseases

Efficacy of Roflumilast in Bronchiectasis Patients with Frequent Exacerbations: A Double-Blinded, Randomized, Placebo-Controlled Pilot Clinical Trial

Siwasak Juthong, M.D. and Pattaraporn Panyarath, M.D.
Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

Tuberc Respir Dis (Seoul). 2022 Jan;85(1):67-73.

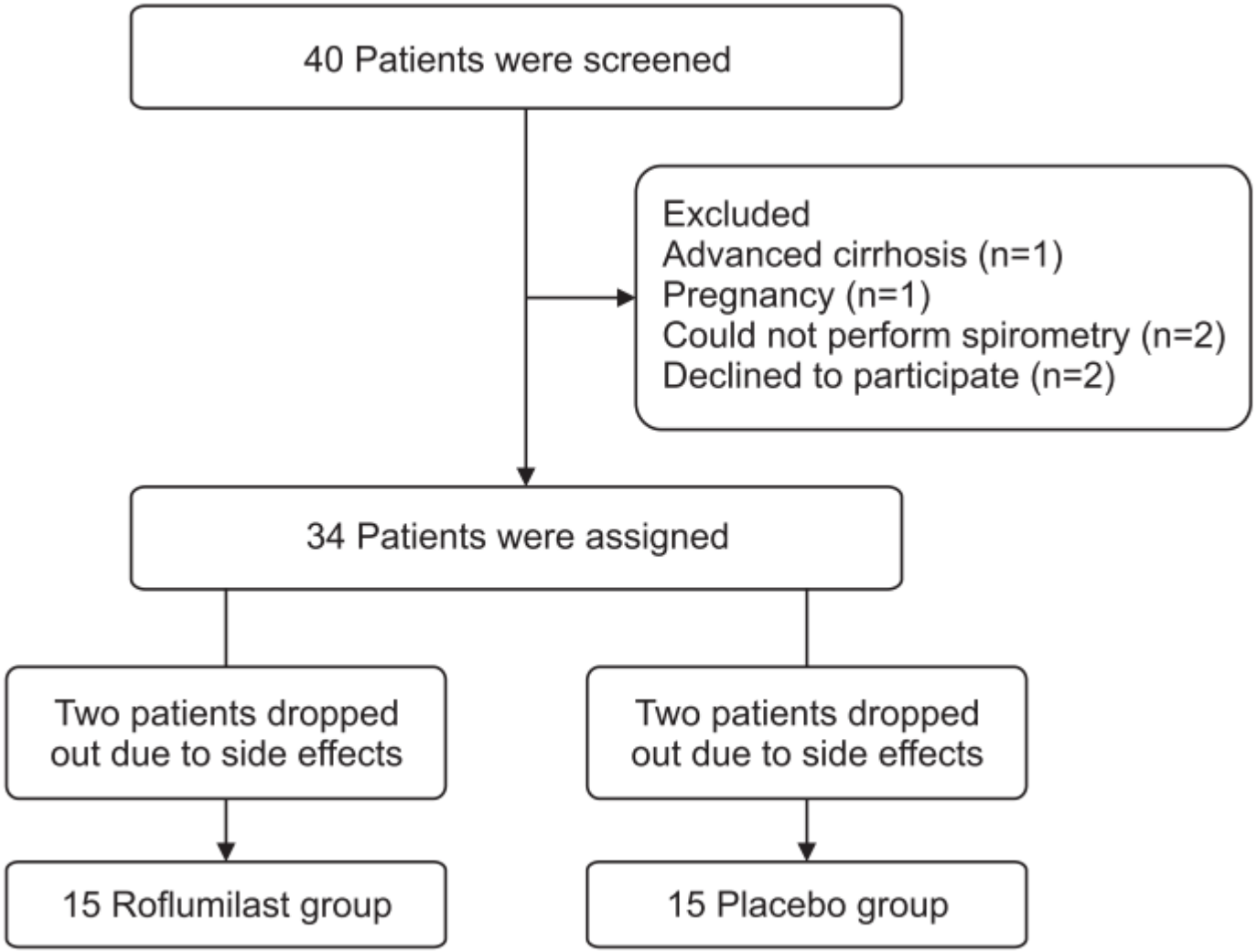


Figure 1. Patient flow diagram.

Tuberc Respir Dis (Seoul). 2022 Jan;85(1):67-73.

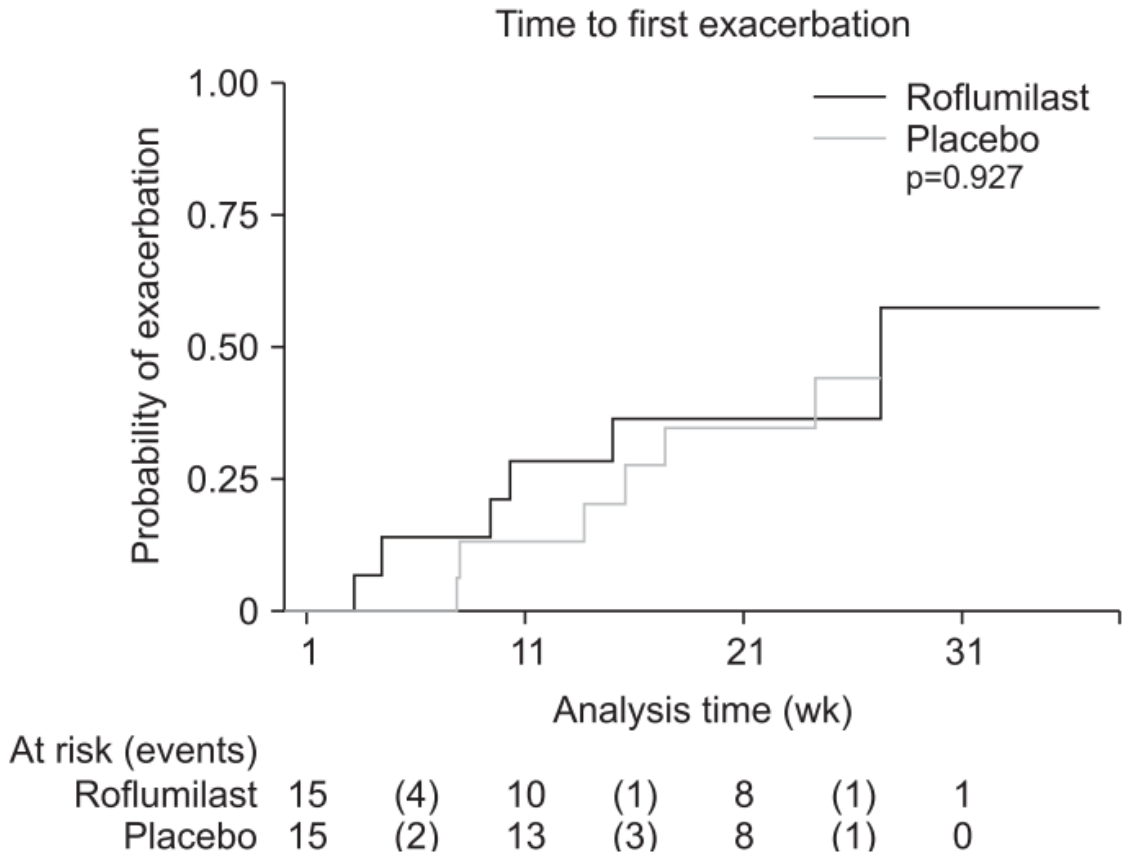


Figure 2. Kaplan-Meier curve for the time of first exacerbation in bronchiectasis patients who received roflumilast or placebo.

Tuberc Respir Dis (Seoul). 2022 Jan;85(1):67-73.

Table 2. Patient-reported outcomes and changes from baseline at 6 months after initiation of treatment

	Change from baseline		Difference (95% CI)	p-value
	Roflumilast group (n=15)	Placebo group (n=15)		
Prebronchodilator FEV_1, L	0.07	−0.01	−0.08 to 0.25	0.280
Prebronchodilator FVC, L	−0.01	−0.01	−0.19 to 0.16	0.880
Prebronchodilator FEV_1/FVC, %	1.40	−1.14	−0.12 to 5.20	0.060
Total score on St George's Respiratory Questionnaire	−13.46	−5.54	−20.27 to 4.41	0.190
Symptoms	−19.66	−8.23	−27.47 to 4.60	0.150
Activity	−8.19	−6.05	−20.25 to 15.96	0.800
Impacts	−16.52	−3.85	−27.65 to 2.32	0.090
6-Minute walk test distance, m	21.00	22.80	−66.93 to 63.22	0.950

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Tuberc Respir Dis (Seoul). 2022 Jan;85(1):67-73.

Bronchodilators

2019 BTS guideline on bronchodilators

- Use in co-existing COPD or asthma patients
- Offer a trial of long-acting bronchodilators in patients with significant breathlessness

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
L. JAYARAM ET AL.

Tiotropium treatment for bronchiectasis: a randomised, placebo-controlled, crossover trial

Lata Jayaram[1,2], Alain C. Vandal[3,4], Catherina L. Chang [5], Chris Lewis [6], Cecilia Tong[4], Christine Tuffery[5], Jill Bell[4], Wendy Fergusson[6], Gene Jeon[4], David Milne[6,7], Stuart Jones[4], Noel Karalus[5], Sandra Hotu[6] and Conroy Wong[4,7,8]

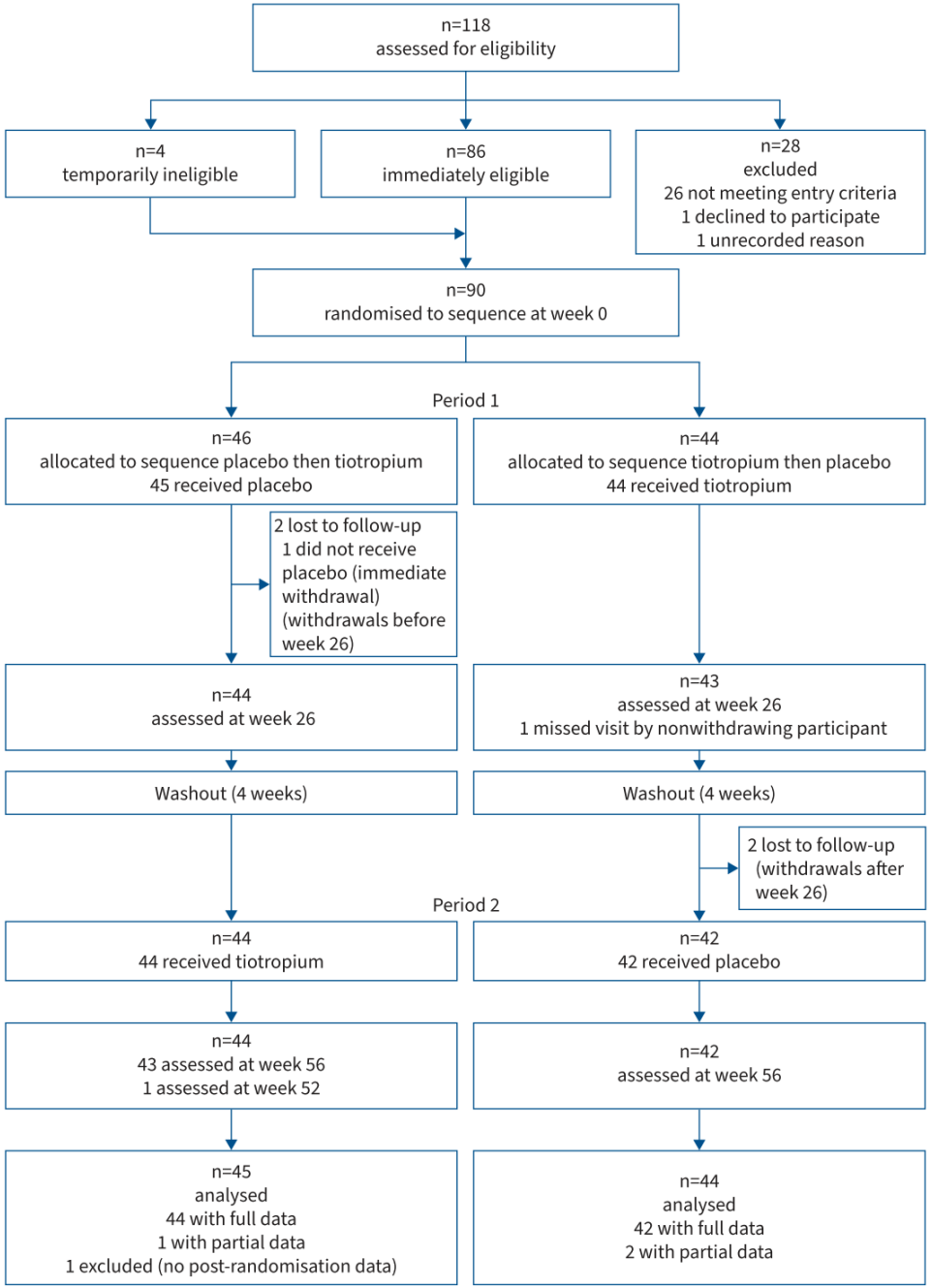
[1]Western Health, Footscray, Australia. [2]Dept of Medicine-Western Health, University of Melbourne, Melbourne, Australia. [3]Dept of Statistics, University of Auckland, Auckland, New Zealand. [4]Counties Manukau District Health Board, Auckland, New Zealand. [5]Waikato District Health Board, Hamilton, New Zealand. [6]Auckland District Health Board, Auckland, New Zealand. [7]Dept of Medicine, University of Auckland, Auckland, New Zealand. [8]Conroy Wong is the senior author.

Eur Respir J. 2022 Jun 9;59(6):2102184.

Inclusion criteria

- Aged > 18
- At least on exacerbation in past year
- BRE by HRCT
- FEV1/FVC < 0.7

Eur Respir J. 2022 Jun 9;59(6):2102184.



Eur Respir J. 2022 Jun 9;59(6):2102184.

Primary outcome

The annual rate of exacerbations was 2.17 per patient under tiotropium treatment and 2.27 per patient under placebo (rate ratio 0.96, 95% CI 0.72–1.27; p=0.77).

Eur Respir J. 2022 Jun 9;59(6):2102184.

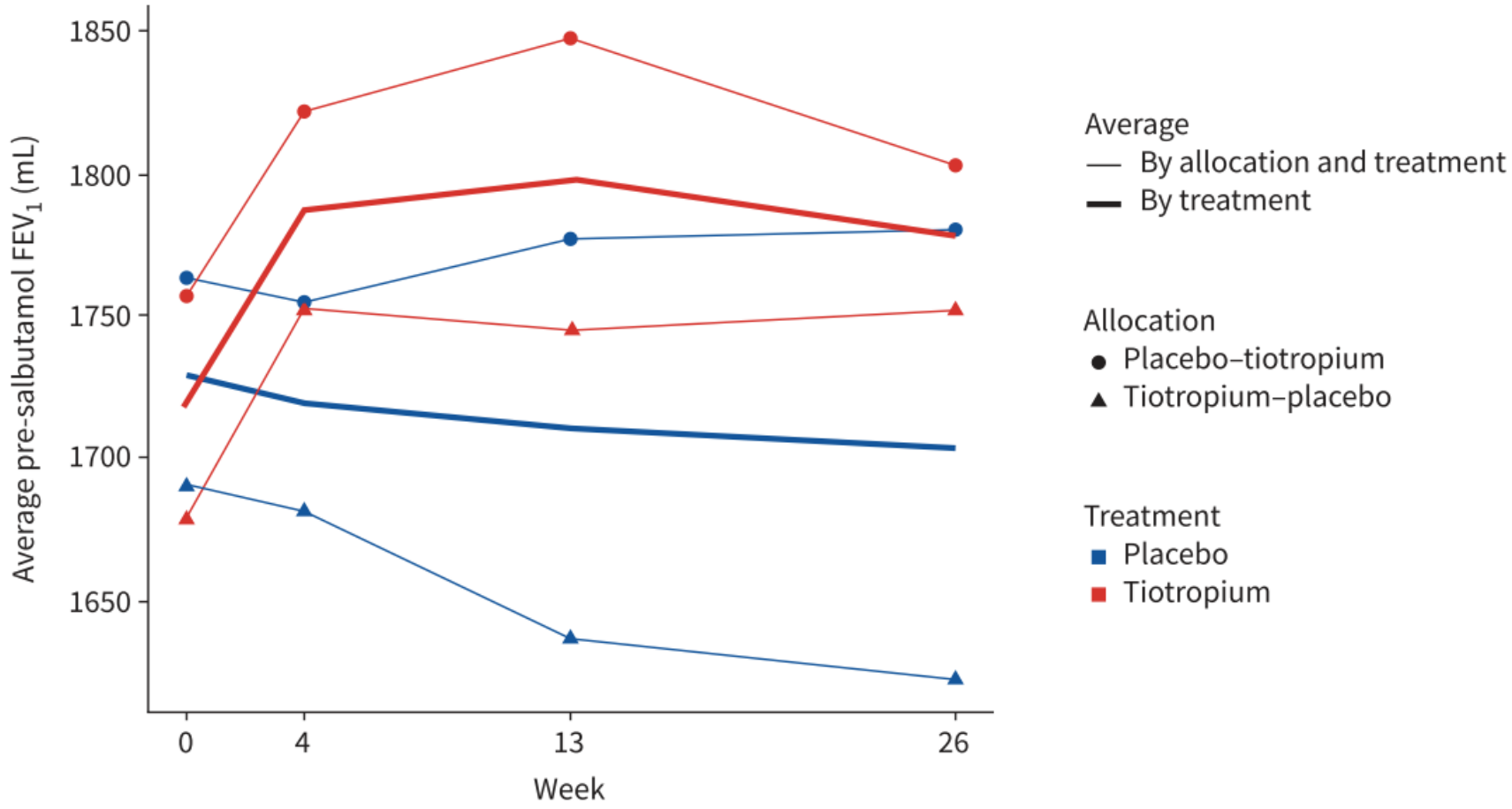
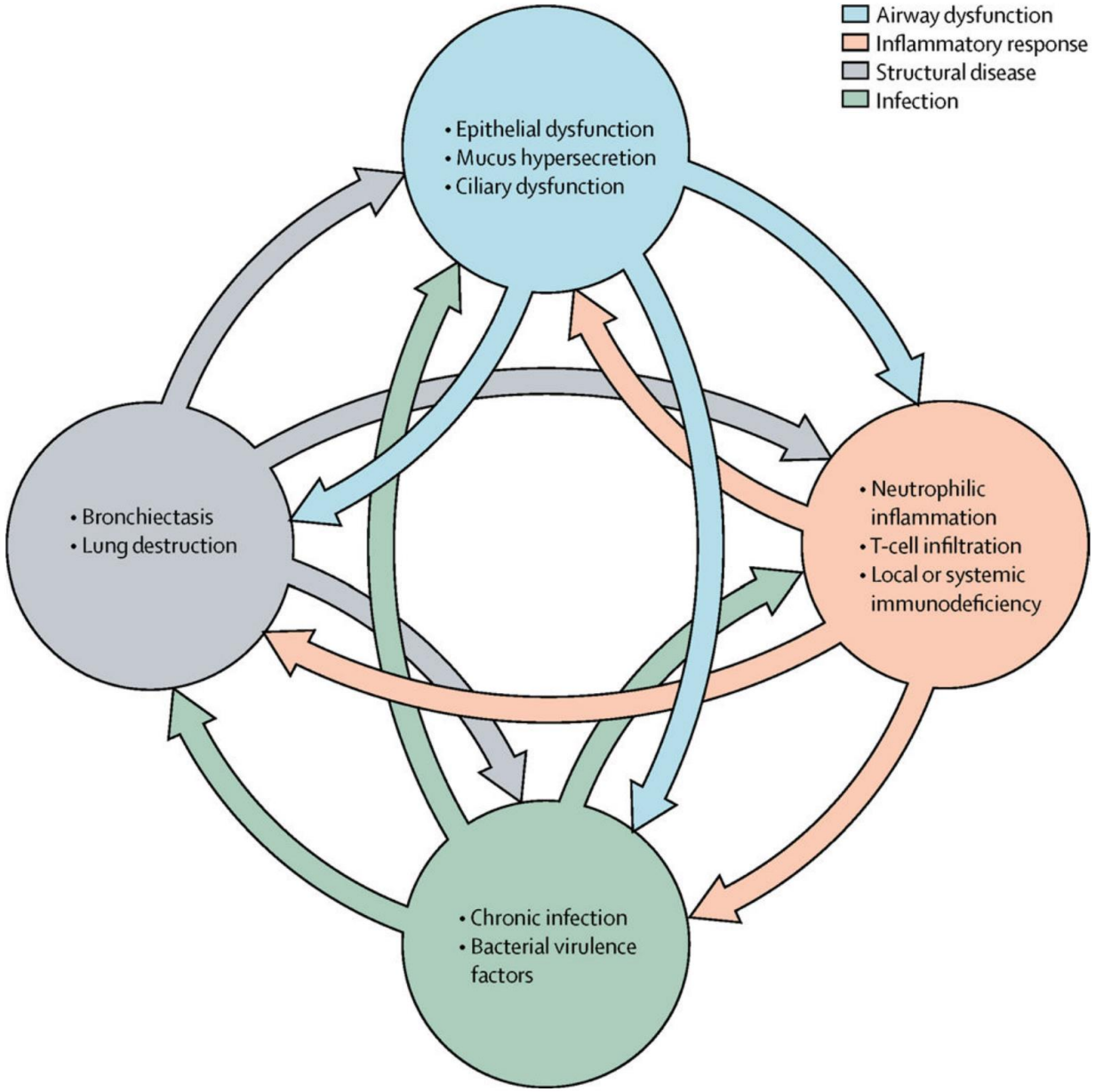


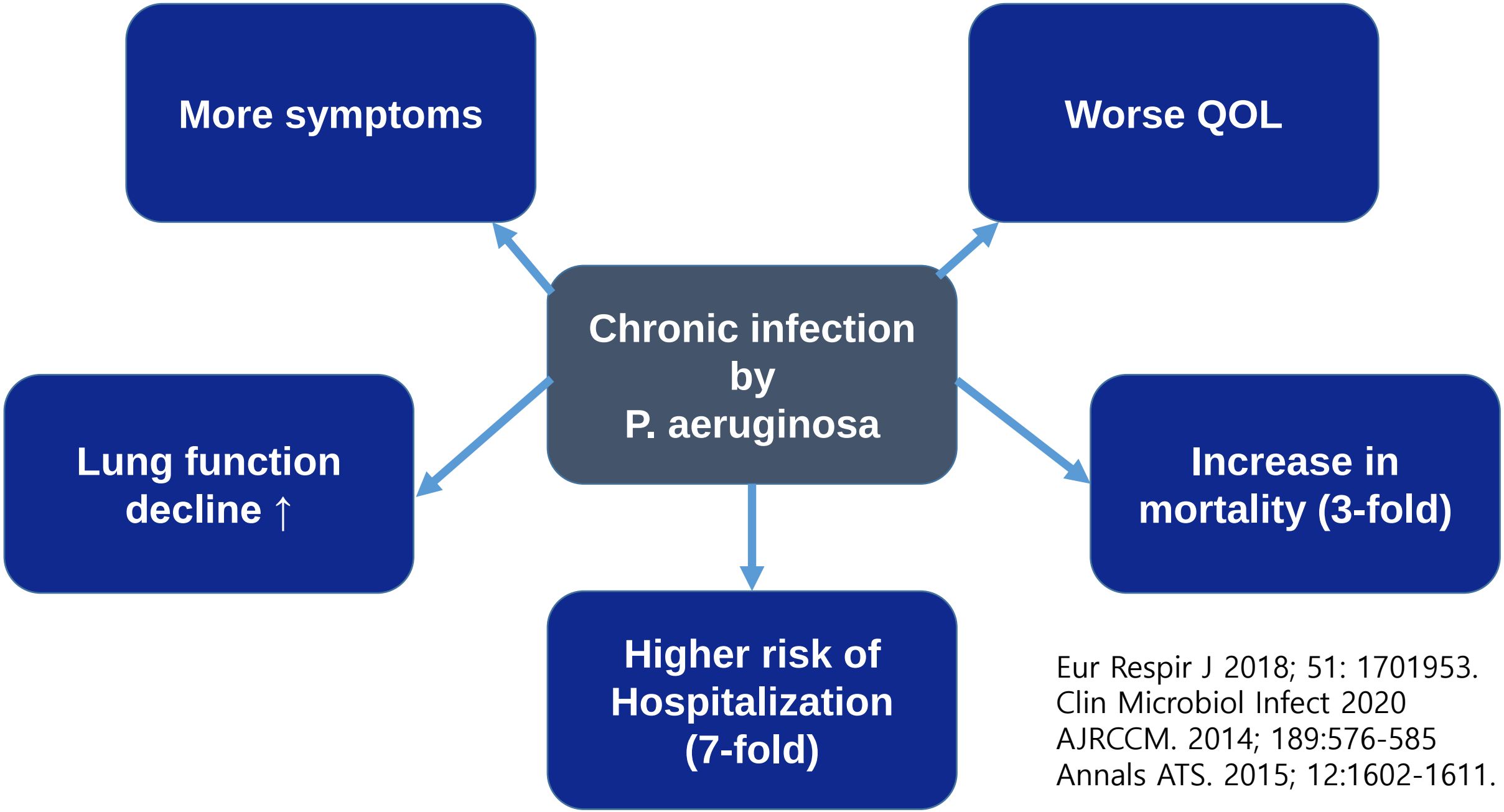
FIGURE 2 Pre-bronchodilator (salbutamol) forced expiratory volume in 1 s (FEV_1) by treatment and allocation. For graphing purposes, weeks 30, 34, 43 and 56 are represented by weeks 0, 4, 13 and 26, respectively

Eur Respir J. 2022 Jun 9;59(6):2102184.

Long-term antibiotics



Lancet. 2018 Sep 8;392(10150):880-890.



Eur Respir J 2018; 51: 1701953.
Clin Microbiol Infect 2020
AJRCCM. 2014; 189:576-585
Annals ATS. 2015; 12:1602-1611.

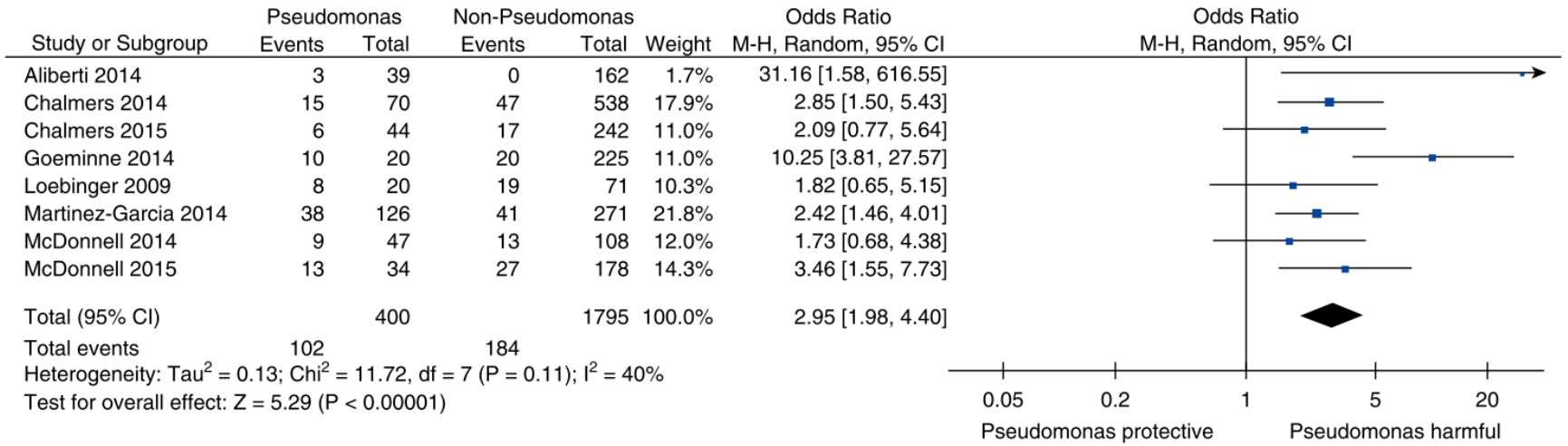


Figure 2. Association between *Pseudomonas aeruginosa* colonization and mortality in bronchiectasis. CI = confidence interval; M-H = Mantel-Haenszel.

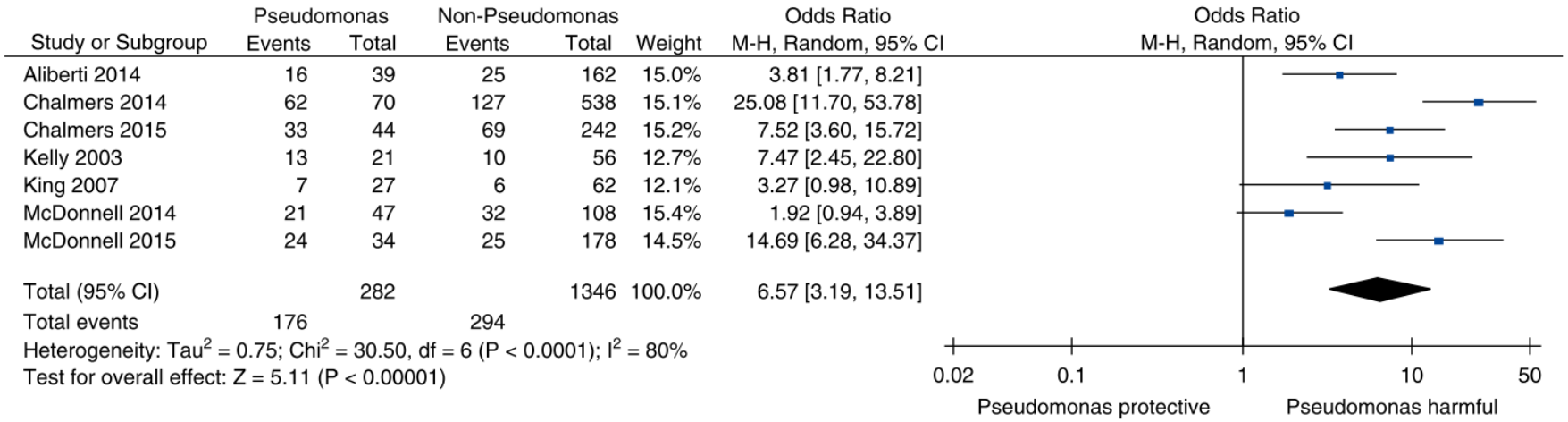


Figure 3. Association between *Pseudomonas aeruginosa* colonization and hospital admissions in bronchiectasis. CI = confidence interval; M-H = Mantel-Haenszel.

Ann Am Thorac Soc. 2015 Nov;12(11):1602-11.

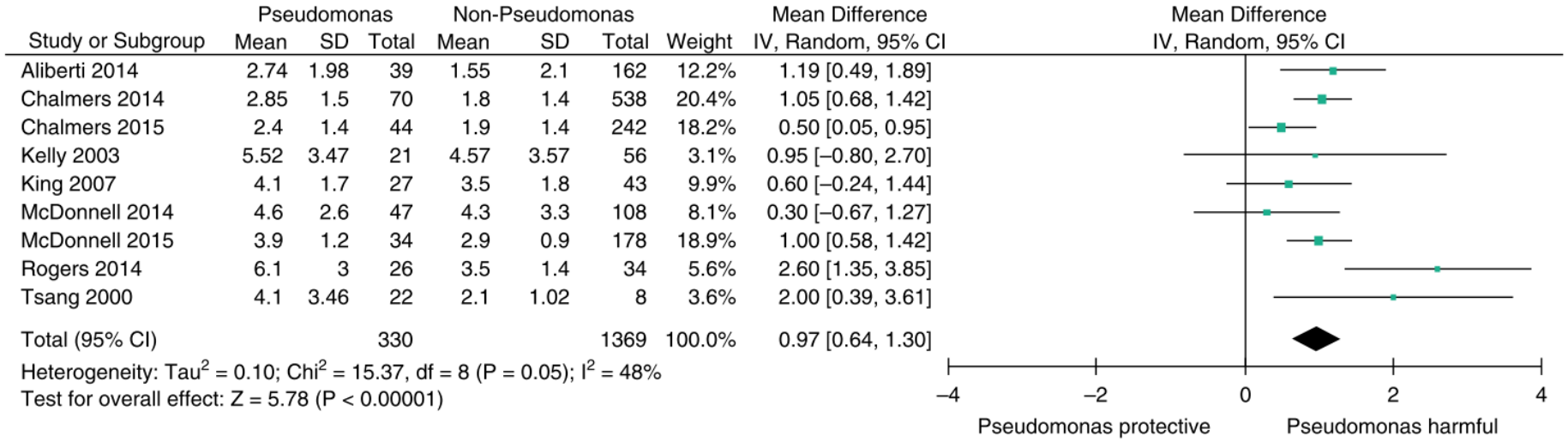


Figure 4. Exacerbation frequency compared between patients with *Pseudomonas aeruginosa* colonization and patients without *P. aeruginosa* colonization. CI = confidence interval; IV = inverse variance.

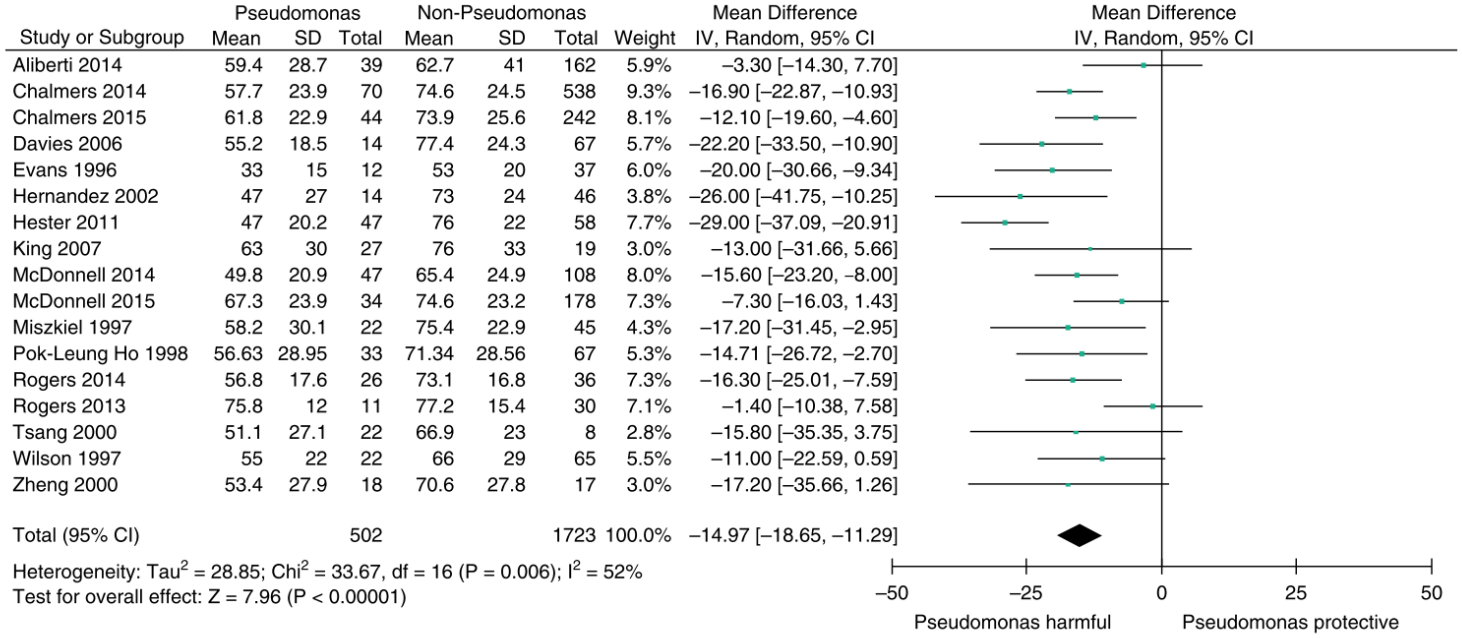
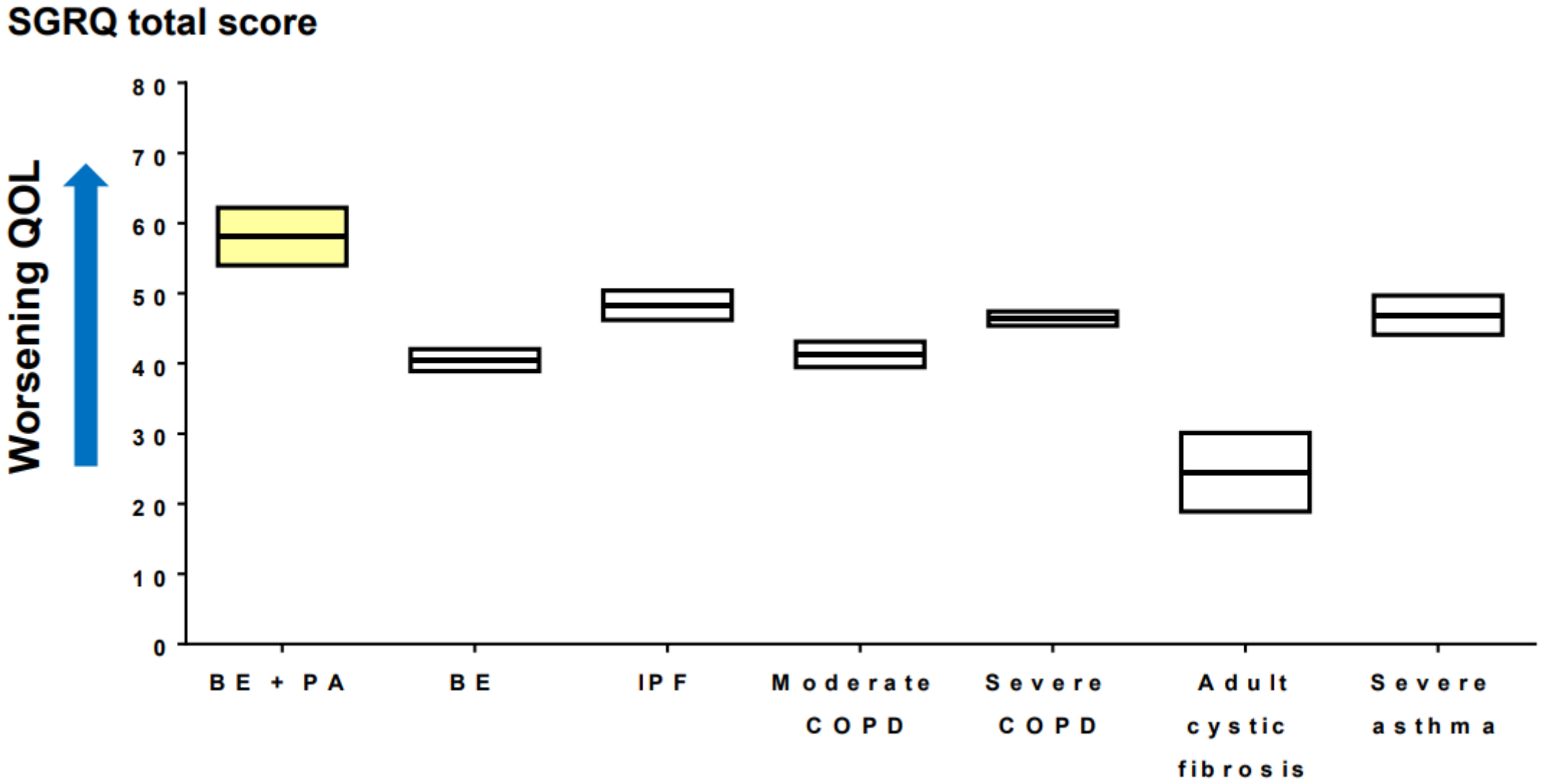


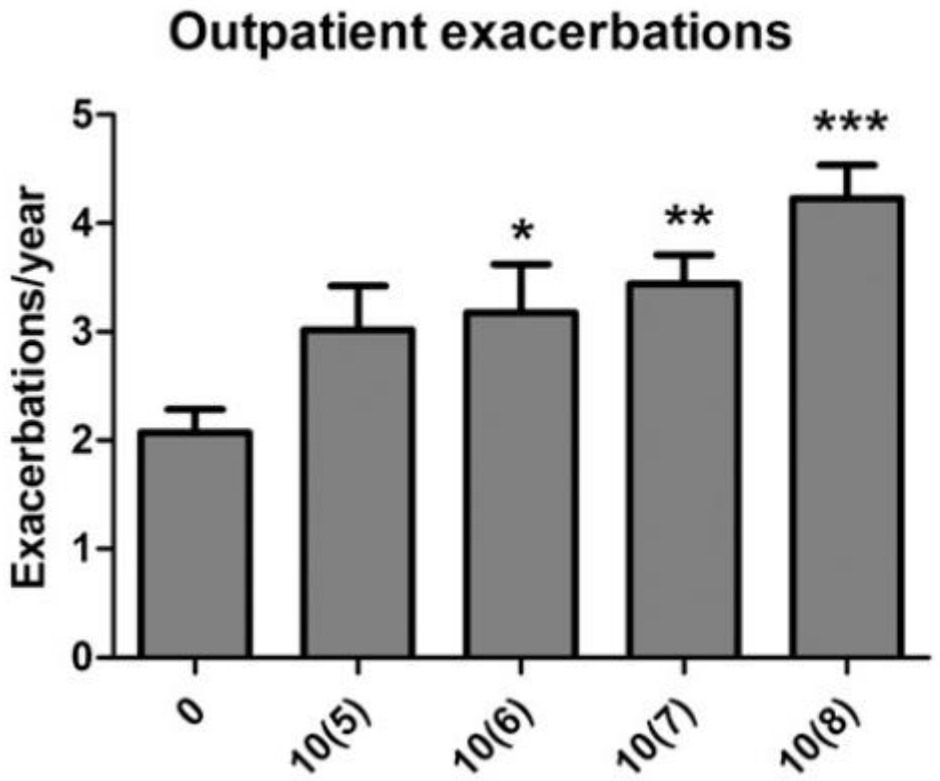
Figure 5. FEV_1% predicted compared between patients with *Pseudomonas aeruginosa* colonization and patients without *P. aeruginosa* colonization. CI = confidence interval; IV = inverse variance.

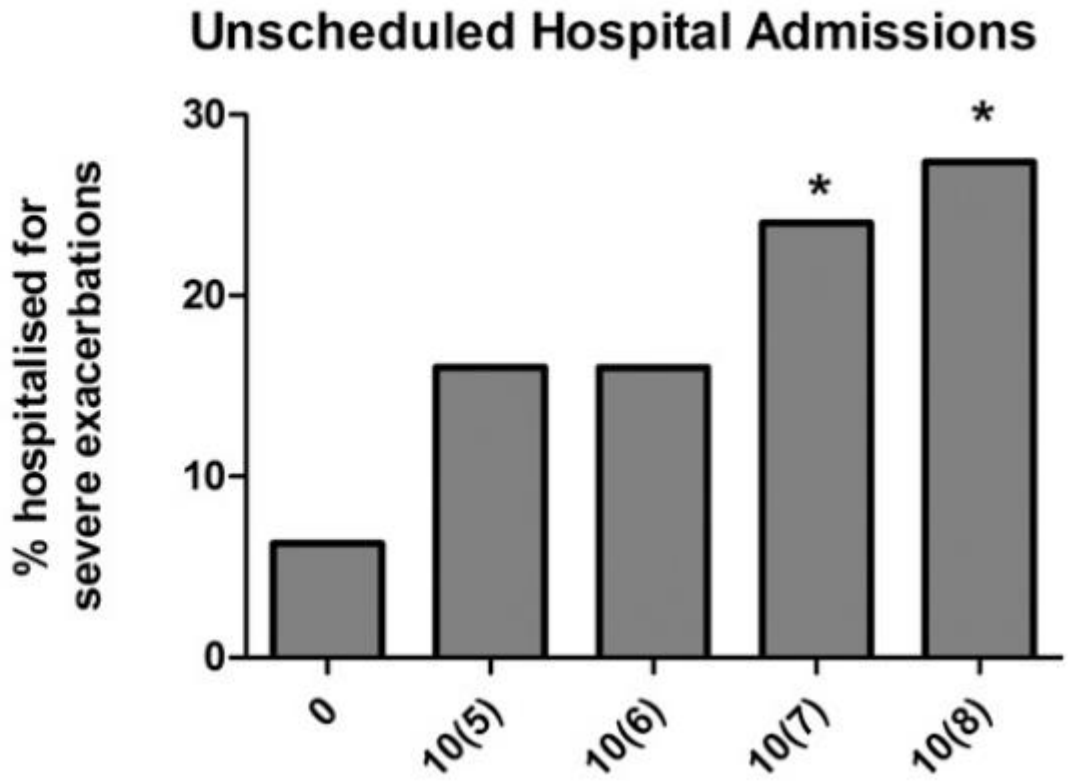
Ann Am Thorac Soc. 2015 Nov;12(11):1602-11.



Antimicrobial Drugs Advisory Committee Meeting, January 11, 2018 https://www.fda.gov/media/110669/download

1. Kreuter, et al. Respir Res. 2017. 2. Kerwin, et al. Intl J COPD. 2017. 3. Magnussen, et al. NEJM. (Oct) 2014. 4. Padilla, et al. Arch Bronconeumol. 2007. 5. Ortega, et al. NEJM. (Sept) 2014.





Am J Respir Crit Care Med. 2012 Oct 1;186(7):657-65.

Table 2 Factors associated with *Pseudomonas aeruginosa* colonization (in the multivariate model)

Parameters	Multivariable analysis	
	OR (95% C.I.)	*p* value
Age > 55 years	0.150 (0.042–0.540)	*0.004*
HRCT (> 3 lobes affected)	0.516 (0.188–1.418)	0.199
PCD	0.040 (0.007–0.288)	< *0.001*
Post-infectious cause	0.048 (0.013–0.186)	< *0.001*
Macrolide maintenance	0.950 (0.321–2.901)	0.950
Hypertonic saline inhalation	0.309 (0.100–0.959)	*0.042*
Inhalation antibiotics	0.059 (0.016–0.220)	< *0.001*

Eur J Clin Microbiol Infect Dis. 2019 Dec;38(12):2299-2304

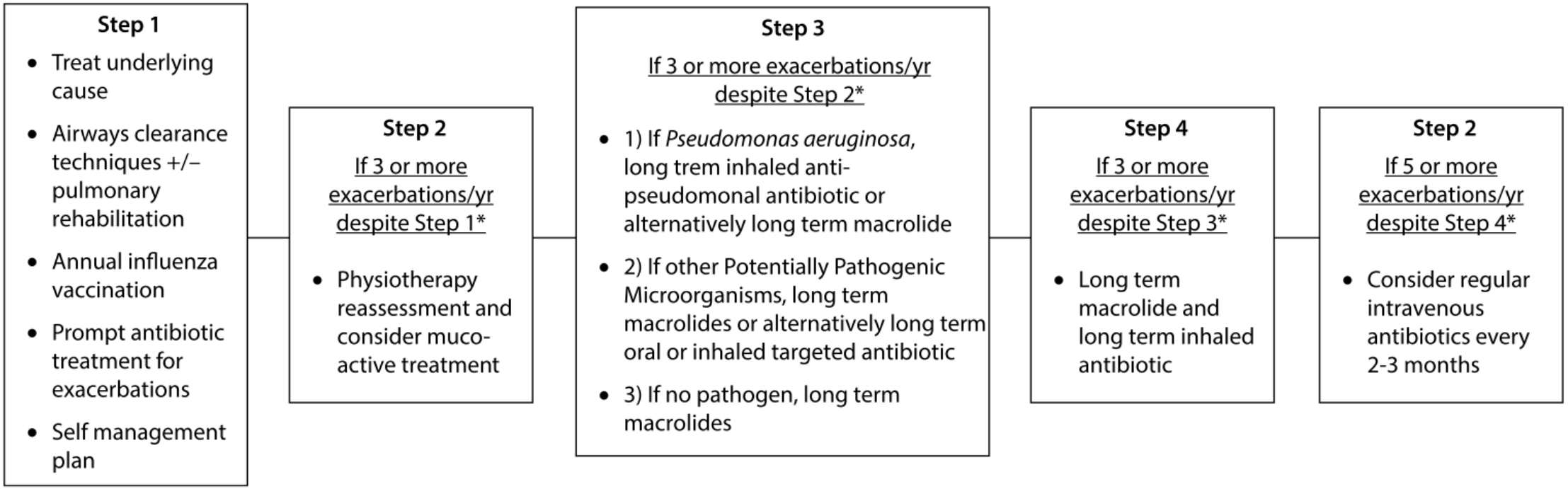
Long-term use antibiotics

- Consider in patients who experience ≥ 3 exacerbation/yr

P.aeruginosa colonised pts	Non-P.aeruginosa colonised pts

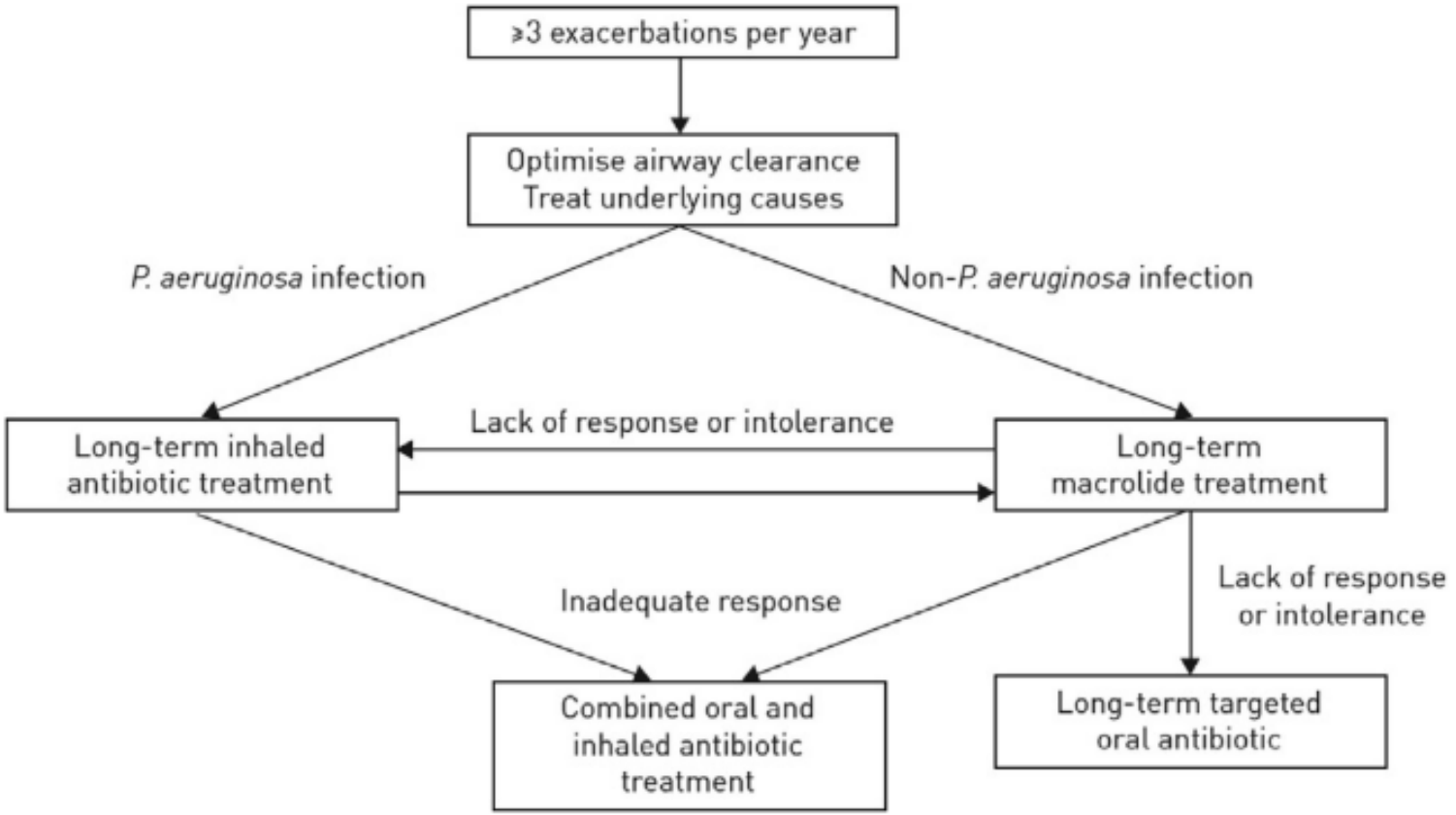
• Inhaled colistin
• Inhaled gentamicin (2nd line)
• Azithro/erythromycin
  • Alternative
  • Additive to inhaled antibiotics
	• Azithromycin/Erythromycin
	• Inhaled gentamicin (2nd line)
	• Doxycycline (alternative)

2019 BTS guideline



Antibiotics are used to treat exacerbations that present with an acute deterioration (usually over several days) with worsening local symtoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset. The flow diagram refers to three or more annual exacerbations.

2019 BTS guideline



2017 ERS guideline

Articles

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*

Lancet Respir Med. 2019 Oct;7(10):845-854.

- Meta-analysis on double blind RCTs (2000-2018)
- Primary outcome
  - Frequency of exacerbation requiring antibiotics
- Secondary endpoint
  - Time to first exacerbation
  - Change in SGRQ
  - Change in FEV1

	Setting	Key inclusion criteria	Age per group (intervention *vs* placebo), years	Number of participants	Macrolide treatment	Number of participants per group (intervention *vs* placebo)	Study duration
Altenburg et al (2013)[14]	14 hospitals in the Netherlands (2008–2010)	≥3 exacerbations; positive sputum culture in the year before baseline	59·9 (12·3) *vs* 64·6 (9·1)	83 (30 men, 53 women)	Azithromycin (250 mg daily)	43 *vs* 40*	12 months with a 3-month run-out period
Serisier et al (2013)[15]	Single centre in Australia (2008–2011)	≥2 exacerbations; daily sputum production	61·1 (10·5) *vs* 63·5 (9·5)	117 (46 men, 71 women)	Erythromycin ethylsuccinate (400 mg twice daily)	59 *vs* 58	48 weeks with a 4-week washout period
Wong et al (2012)[16]	Three centres in New Zealand (2008–2009)	≥1 exacerbation in the previous year	60·9 (13·6) *vs* 59·0 (13·3)	141 (43 men, 98 women)	Azithromycin (500mg three times per week)	71 *vs* 70	6 months of treatment followed by 6 months of observation without treatment

Data are mean (SD), unless otherwise specified. *Two patients in the azithromycin group and four patients in the placebo group were excluded after randomisation before receiving the first dose of drug; these patients were not included in our individual-patient data analysis.

Table 1: **Randomised controlled trials of macrolide use in patients with bronchiectasis**

AE frequency

	Number of participants (intervention vs placebo)	Incident rate ratio (95% CI)	p value	$p_{interaction}$ value
Age groups	..	..	..	0·18
<50 years	53 (27 vs 26)	0·61 (0·27–1·37)	0·23	..
50–69 years	211 (110 vs 101)	0·52 (0·36–0·76)	0·0011	..
≥70 years	77 (36 vs 41)	0·36 (0·18–0·71)	0·0032	..
Sex	..	..	..	0·31
Male	119 (59 vs 60)	0·59 (0·35–0·99)	0·047	..
Female	222 (114 vs 108)	0·43 (0·29–0·62)	<0·0001	..
Previous exacerbations (per year)	..	..	..	0·86
1–2	73 (37 vs 36)	0·37 (0·16–0·88)	0·025	..
3	85 (48 vs 37)	0·62 (0·32–1·20)	0·072	..
≥4	183 (88 vs 95)	0·52 (0·36–0·77)	0·0019	..
Smoking status	..	..	..	0·64
Never	222 (115 vs 107)	0·51 (0·35–0·74)	<0·0001	..
Former	112 (56 vs 56)	0·44 (0·27–0·73)	0·0024	..
Current	7 (2 vs 5)	NE	NA	..
Inhaled corticosteroid use	..	..	..	0·46
Yes	223 (112 vs 111)	0·49 (0·34–0·71)	<0·0001	..
No	118 (61 vs 57)	0·44 (0·26–0·75)	0·0036	..
BMI at baseline (kg/m²)	..	..	..	0·50
<21	38 (20 vs 18)	0·36 (0·13–1·02)	0·054	..
21–24·9	179 (92 vs 87)	0·56 (0·37–0·84)	0·0050	..
25–29·9	65 (36 vs 29)	0·55 (0·27–1·10)	0·093	..
30 or more	59 (25 vs 34)	0·27 (0·12–0·61)	0·0018	..
Cause	..	..	..	0·034
Idiopathic and post-infective	267 (149 vs 118)	0·56 (0·39–0·80)	0·0029	..
Other	74 (24 vs 50)	0·23 (0·11–0·52)	<0·0001	..
Baseline concentration of C-reactive protein (mg/L)	..	..	..	0·27
<2	98 (49 vs 49)	0·60 (0·34–1·03)	0·065	..
2–5	95 (51 vs 44)	0·52 (0·30–0·92)	0·023	..
5·1–10	71 (36 vs 35)	0·33 (0·15–0·73)	0·0061	..
>10	60 (30 vs 30)	0·35 (0·17–0·76)	0·0086	..
Baseline FEV_1 (% predicted)	..	..	..	0·51
≥80	137 (64 vs 73)	0·52 (0·32–0·84)	0·0088	..
50–79	144 (82 vs 62)	0·43 (0·27–0·70)	0·0015	..
<50	60 (27 vs 33)	0·55 (0·27–1·12)	0·10	..
SGRQ total score	..	..	..	0·90
<30	139 (72 vs 67)	0·50 (0·29–0·84)	0·0082	..
30–49	123 (64 vs 59)	0·45 (0·27–0·74)	0·0024	..
≥50	79 (37 vs 42)	0·50 (0·28–0·90)	0·022	..
Pseudomonas aeruginosa infection	..	..	..	0·45
Yes	61 (31 vs 30)	0·36 (0·18–0·72)	0·0044	..
No	280 (142 vs 138)	0·53 (0·38–0·74)	<0·0001	..

IRR=incident rate ratio. NE=not estimable. NA=not applicable. BMI=body-mass index. SGRQ=St George's Respiratory Questionnaire.

Table 2: **Subgroup analysis of bronchiectasis exacerbation frequency**

Time to first exacerbation

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

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

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

SGRQ score

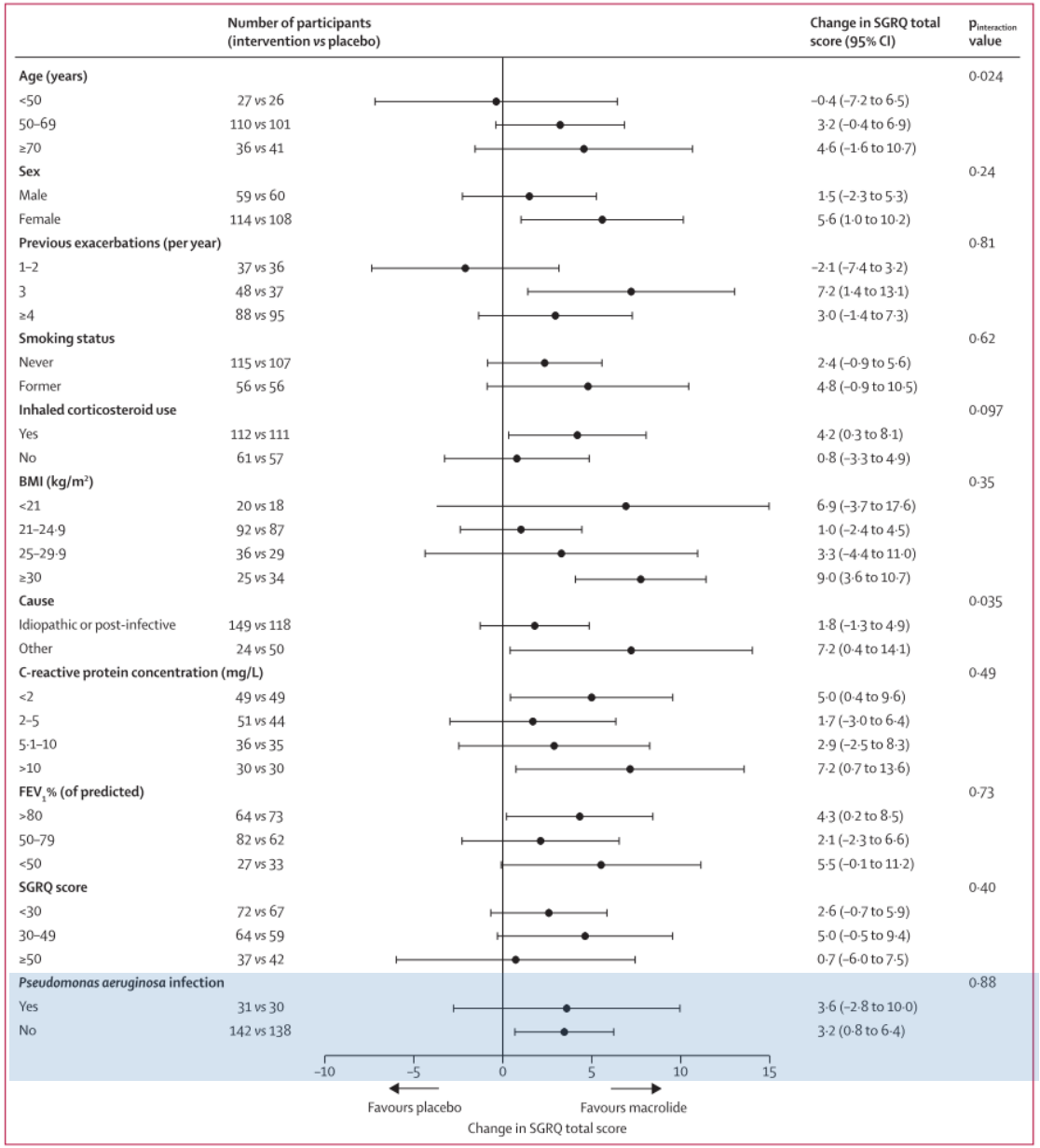


***Figure 2*: Forest plot of the effect of macrolide treatment on the change in quality of life**
The change in quality of life was assessed using the SGRQ total score in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). Values for change in SGRQ score and the associated 95% CIs and p values are also summarised in the appendix (p 3). BMI=body-mass index. NE=not estimable. SGRQ=St George's Respiratory Questionnaire.

Change in FEV_1

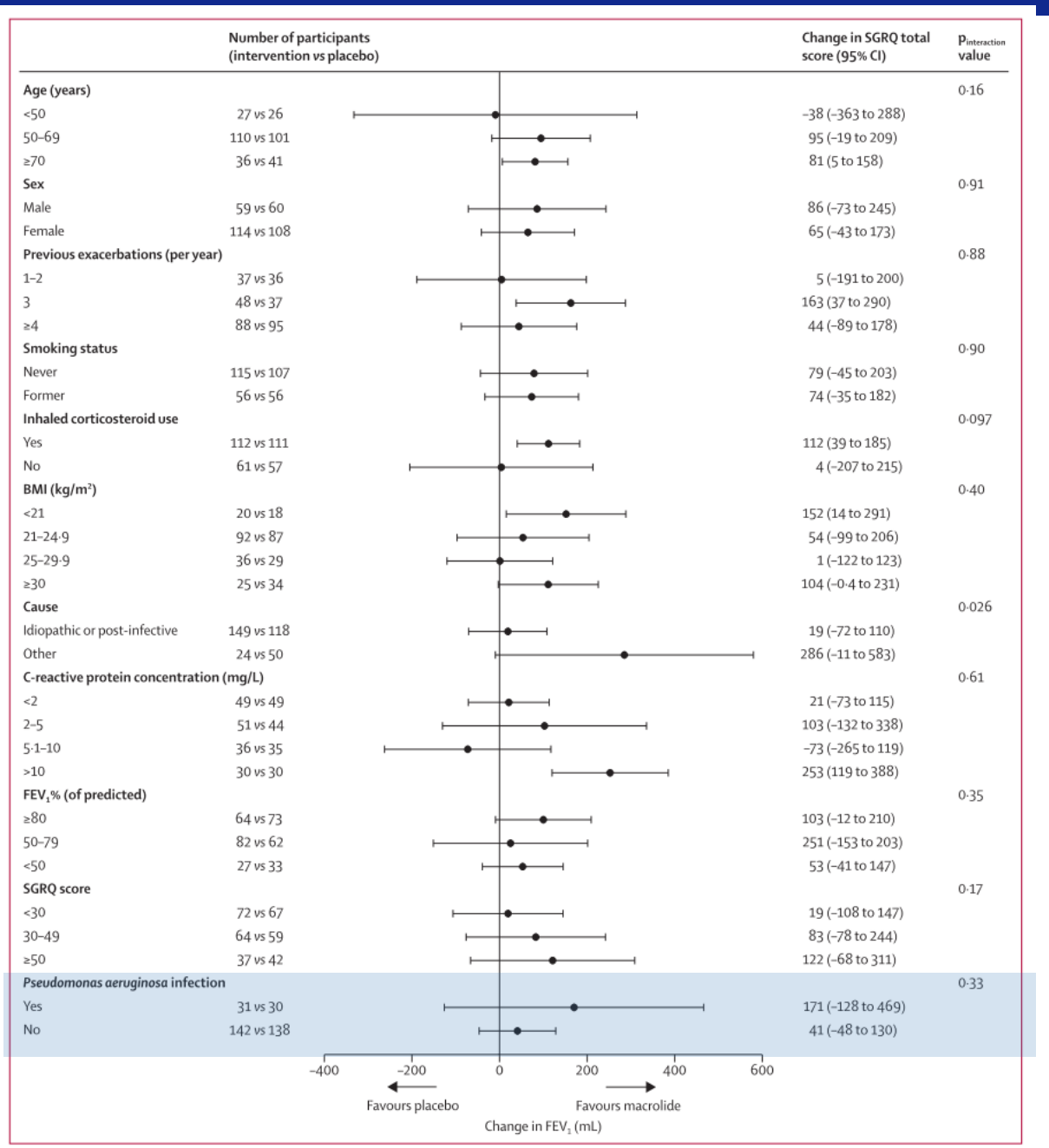


***Figure 3*: Forest plot of the effect of macrolide treatment on the change in FEV_1**
The change in FEV_1 was assessed in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). BMI=body-mass index. Values for change in FEV_1 and the associated 95% CIs and p values are listed in the appendix (p 3). BMI=body-mass index. NE=not estimable.

International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Favorable Response to Long-Term Azithromycin Therapy in Bronchiectasis Patients with Chronic Airflow Obstruction Compared to Chronic Obstructive Pulmonary Disease Patients without Bronchiectasis

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

Int J Chron Obstruct Pulmon Dis. 2021 Mar 30;16:855-863.

Table 3 Outcomes of Long-Term Azithromycin Treatment at 12 Months Follow-Up

	Total (N = 59)	Bronchiectasis with CAO (n = 43)	COPD without Bronchiectasis (n = 16)	*P*-value
Exacerbation				
Moderate	27 (45.8)	15 (34.9)	12 (75.0)	0.006
Severe	17 (28.8)	12 (27.9)	5 (31.3)	1.000
≥2 moderate or ≥1 severe	34 (57.6)	20 (46.5)	14 (87.5)	0.005
Adverse event	3 (5.1)	1 (2.3)[a]	2 (12.5)[b]	0.176

Notes: Data are presented as number (%). [a]A patient reported lip swelling. [b]A patient reported abdominal discomfort, and the other presented general weakness.
Abbreviations: CAO, chronic airflow obstruction; COPD, chronic obstructive pulmonary disease.

Table 4 Risk Factors for Acute Exacerbations[a] During 12 Months of Follow-Up

	Univariable		Multivariable	
	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.03 (0.99–1.08)	0.137	1.01 (0.96–1.06)	0.693
Sex, male	3.14 (1.07–9.19)	0.037	2.52 (0.37–17.03)	0.343
Smoking, ever	3.04 (1.03–8.97)	0.044	0.74 (0.11–4.96)	0.760
FEV_1 < 50% pred	1.85 (0.61–5.59)	0.274	1.04 (0.26–4.14)	0.959
Bronchiectasis with CAO (vs COPD without bronchiectasis)	0.12 (0.03–0.61)	0.011	0.15 (0.03–0.87)	0.035
ICS use	1.85 (0.61–5.59)	0.274	0.92 (0.25–3.40)	0.904

Notes: [a]Defined as ≥2 moderate (hospital visit) or ≥1 severe (emergency department or hospitalization) acute exacerbations.
Abbreviations: CAO, chronic airflow obstruction; CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; OR, odds ratio.

Responder
: ≥2 decrement of CAT

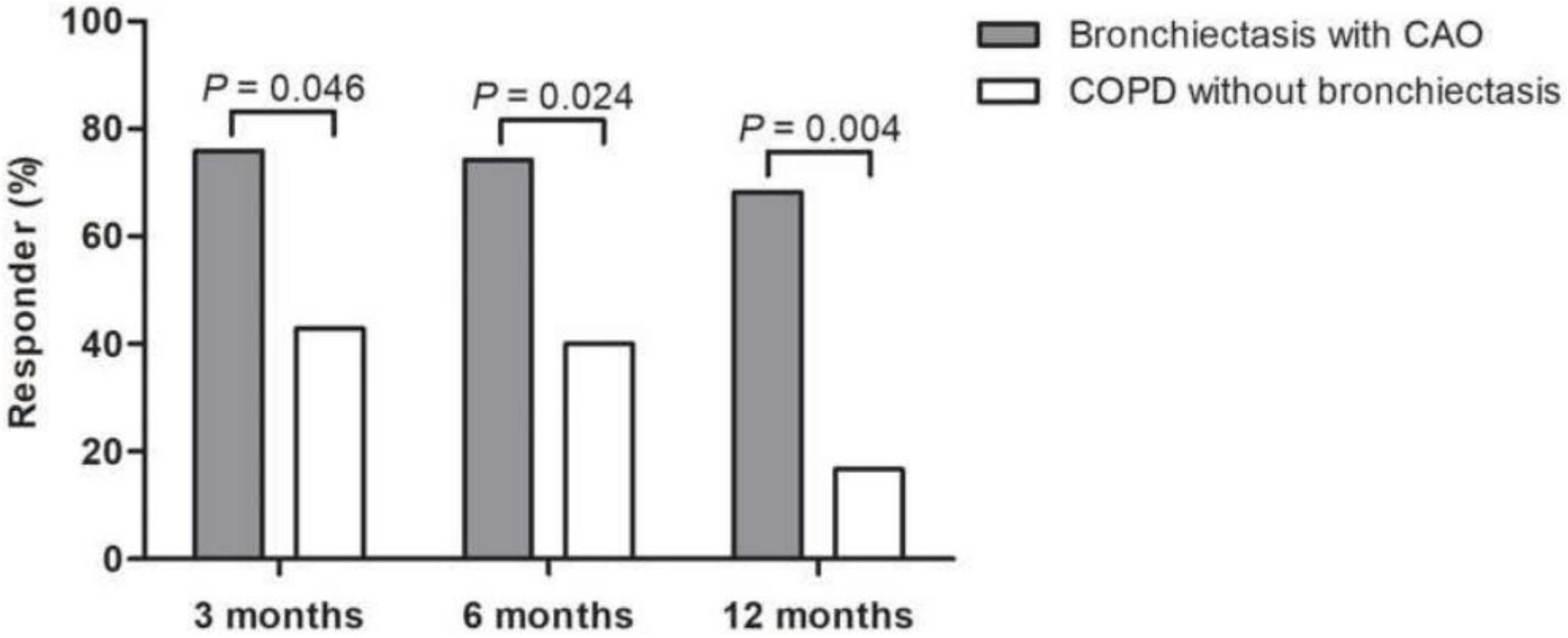


Figure 1 The proportion of symptomatic responders* after long-term azithromycin treatment. *Defined as patients with ≥2 points decrement from the initial COPD Assessment Test (CAT) score. CAT was measured in 43, 47, and 35 patients at 3, 6, and 12 months after initiation of azithromycin treatment.
Abbreviations: CAO, chronic airflow obstruction; COPD, chronic obstructive pulmonary disease.

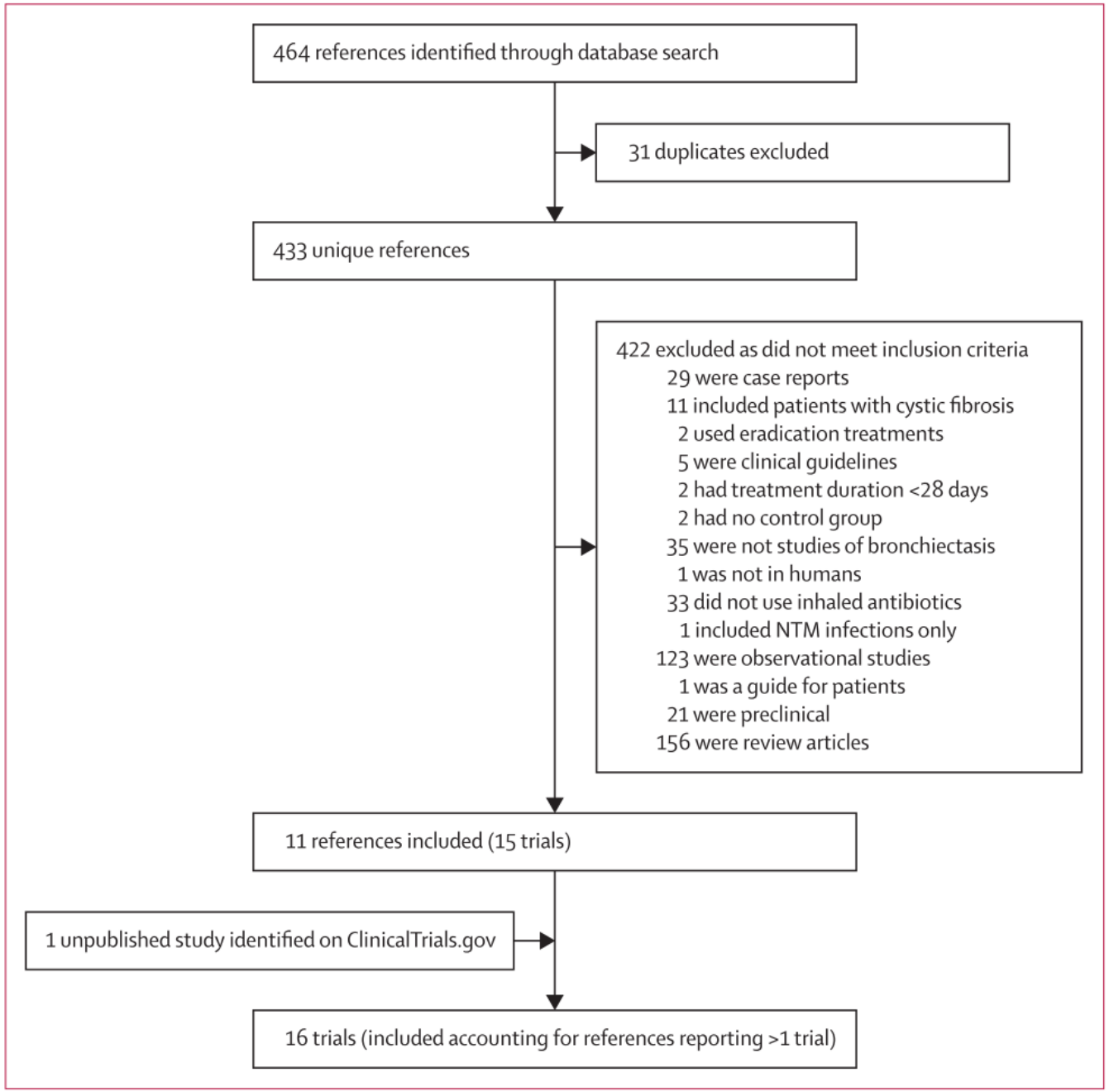
The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis

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

- Meta-analysis

- Efficacy endpoints
  - Bacterial load/bacterial eradication from sputum
  - Frequency of exacerbation, time to first exacerbation
  - QOL
  - Change in FEV1, 6MWT
  - Mortality
  - Adherence
  - Sputum volume

- Safety endpoint
  - Adverse events
  - Bacterial resistance in sputum


464 references identified through database search
31 duplicates excluded
433 unique references
422 excluded as did not meet inclusion criteria
29 were case reports
11 included patients with cystic fibrosis
2 used eradication treatments
5 were clinical guidelines
2 had treatment duration <28 days
2 had no control group
35 were not studies of bronchiectasis
1 was not in humans
33 did not use inhaled antibiotics
1 included NTM infections only
123 were observational studies
1 was a guide for patients
21 were preclinical
156 were review articles
11 references included (15 trials)
1 unpublished study identified on ClinicalTrials.gov
16 trials (included accounting for references reporting >1 trial)

Quantitative bacterial load (CFU per g of sputum)

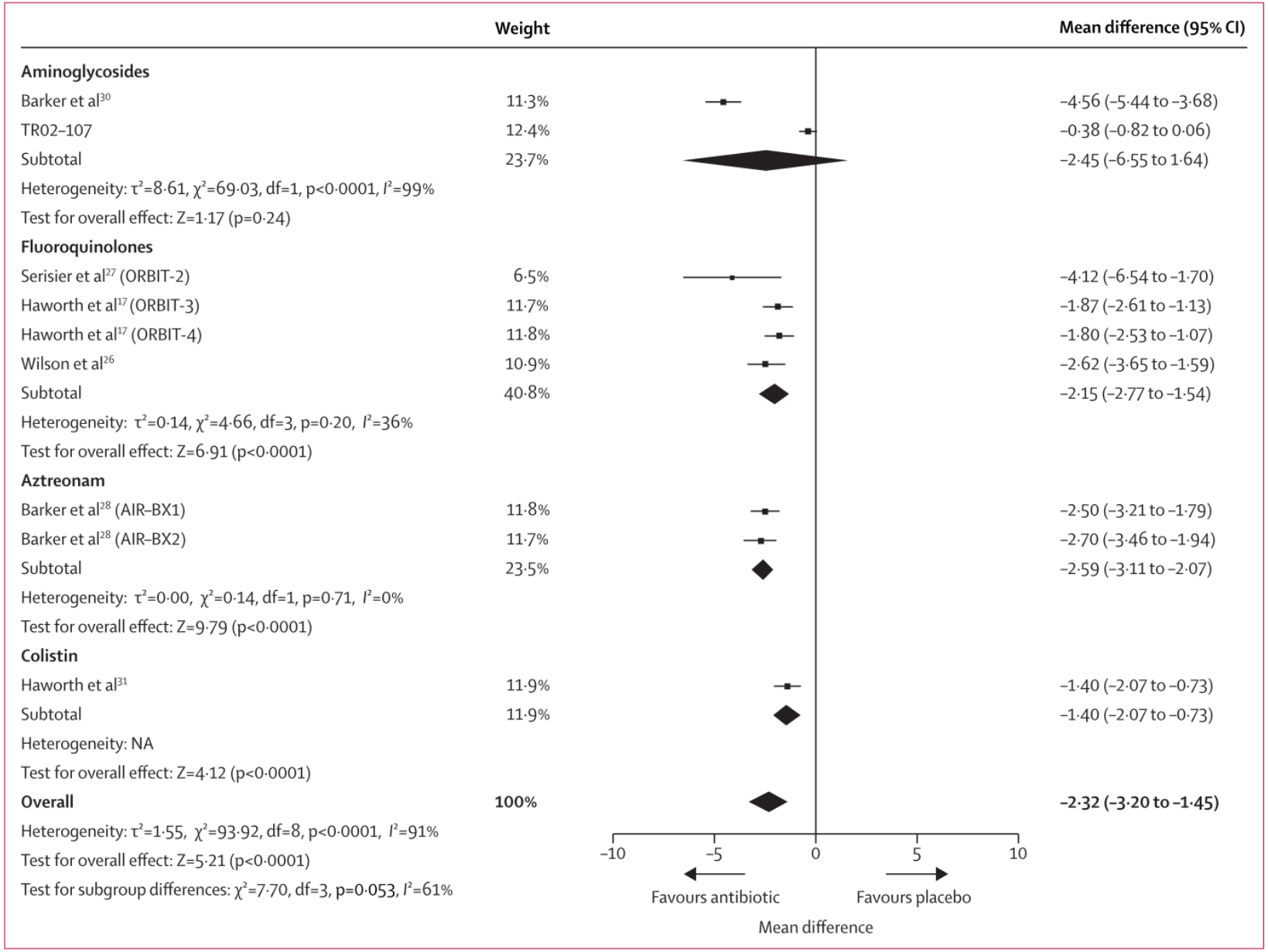


Figure 2: **Forest plot of the effect of inhaled antibiotic treatment on quantitative bacterial load in colony forming units per g of sputum**
The weight represents the percentage contribution of each study to the summary effect estimate. Weights of individual studies might not add up to the subtotal or overall weights because of rounding. df=degrees of freedom.

A

Fluoroquinolones
Haworth et al[17] (ORBIT-3)
Haworth et al[17] (ORBIT-4)
De Soyza et al[15] (RESPIRE 1, 14 days)
De Soyza et al[15] (RESPIRE 1, 28 days)
Aksamit et al[16] (RESPIRE 2, 14 days)
Aksamit et al[16] (RESPIRE 2, 28 days)
Subtotal
Heterogeneity: τ^2=0·02, χ^2=7·62, df=5, p=0·18, I^2=
Test for overall effect: Z=3·50 (p=0·00047)
Aztreonam
Barker et al[28] (AIR–BX1)
Barker et al[28] (AIR–BX2)
Subtotal
Heterogeneity: τ^2=0·00, χ^2=0·25, df=1, p=0·62, I^2=0%
Test for overall effect: Z=0·82 (p=0·41)
Overall
Heterogeneity: τ^2=0·03, χ^2=14·50, df=7, p=0·04, I^2=52%
Test for overall effect: Z=2·33 (p=0·020)
Test for subgroup differences: χ^2=6·09, df=1, p=0·014, I^2=84%

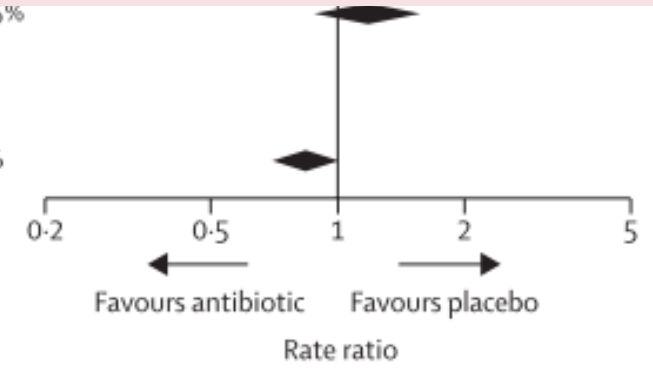
Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

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*

Pseudomonas aeruginosa infection	..	..	..	0·45
Yes	61 (31 vs 30)	0·36 (0·18–0·72)	0·0044	..
No	280 (142 vs 138)	0·53 (0·38–0·74)	<0·0001	..

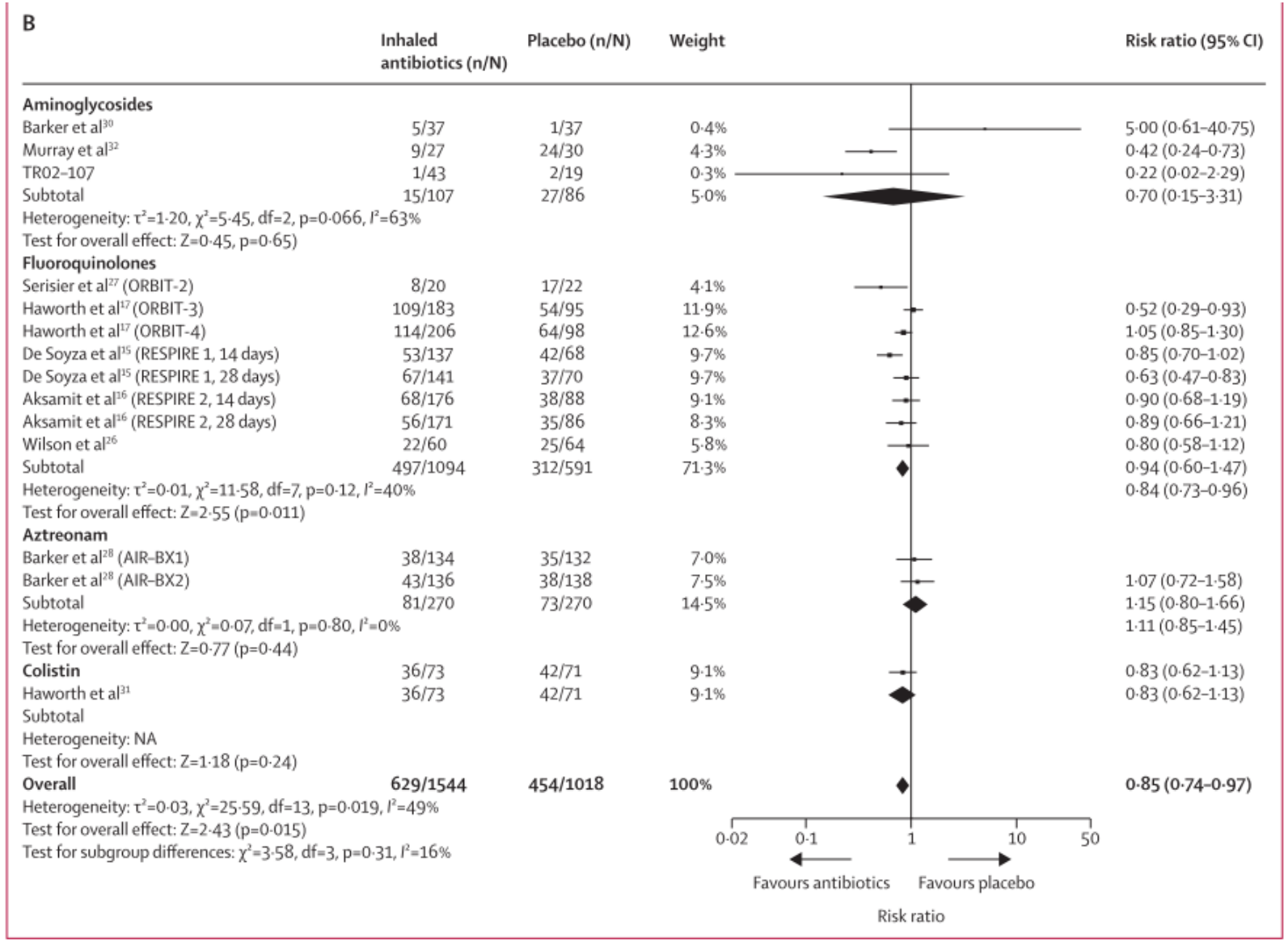
21·5% 1·13 (0·84–1·52)

100% 0·81 (0·67–0·97)



Frequency of exacerbation

B



	Inhaled antibiotics (n/N)	Placebo (n/N)	Weight	Risk ratio (95% CI)
Aminoglycosides				
Barker et al[30]	5/37	1/37	0·4%	5·00 (0·61–40·75)
Murray et al[32]	9/27	24/30	4·3%	0·42 (0·24–0·73)
TR02–107	1/43	2/19	0·3%	0·22 (0·02–2·29)
Subtotal	15/107	27/86	5·0%	0·70 (0·15–3·31)
Heterogeneity: τ^2=1·20, χ^2=5·45, df=2, p=0·066, I^2=63%				
Test for overall effect: Z=0·45, p=0·65)				
Fluoroquinolones				
Serisier et al[27] (ORBIT-2)	8/20	17/22	4·1%	
Haworth et al[17] (ORBIT-3)	109/183	54/95	11·9%	0·52 (0·29–0·93)
Haworth et al[17] (ORBIT-4)	114/206	64/98	12·6%	1·05 (0·85–1·30)
De Soyza et al[15] (RESPIRE 1, 14 days)	53/137	42/68	9·7%	0·85 (0·70–1·02)
De Soyza et al[15] (RESPIRE 1, 28 days)	67/141	37/70	9·7%	0·63 (0·47–0·83)
Aksamit et al[16] (RESPIRE 2, 14 days)	68/176	38/88	9·1%	0·90 (0·68–1·19)
Aksamit et al[16] (RESPIRE 2, 28 days)	56/171	35/86	8·3%	0·89 (0·66–1·21)
Wilson et al[26]	22/60	25/64	5·8%	0·80 (0·58–1·12)
Subtotal	497/1094	312/591	71·3%	0·94 (0·60–1·47)
Heterogeneity: τ^2=0·01, χ^2=11·58, df=7, p=0·12, I^2=40%				0·84 (0·73–0·96)
Test for overall effect: Z=2·55 (p=0·011)				
Aztreonam				
Barker et al[28] (AIR–BX1)	38/134	35/132	7·0%	
Barker et al[28] (AIR–BX2)	43/136	38/138	7·5%	1·07 (0·72–1·58)
Subtotal	81/270	73/270	14·5%	1·15 (0·80–1·66)
Heterogeneity: τ^2=0·00, χ^2=0·07, df=1, p=0·80, I^2=0%				1·11 (0·85–1·45)
Test for overall effect: Z=0·77 (p=0·44)				
Colistin	36/73	42/71	9·1%	0·83 (0·62–1·13)
Haworth et al[31]	36/73	42/71	9·1%	0·83 (0·62–1·13)
Subtotal				
Heterogeneity: NA				
Test for overall effect: Z=1·18 (p=0·24)				
Overall	**629/1544**	**454/1018**	**100%**	**0·85 (0·74–0·97)**
Heterogeneity: τ^2=0·03, χ^2=25·59, df=13, p=0·019, I^2=49%				
Test for overall effect: Z=2·43 (p=0·015)				
Test for subgroup differences: χ^2=3·58, df=3, p=0·31, I^2=16%				

Number of pts experiencing at least one exacerbation

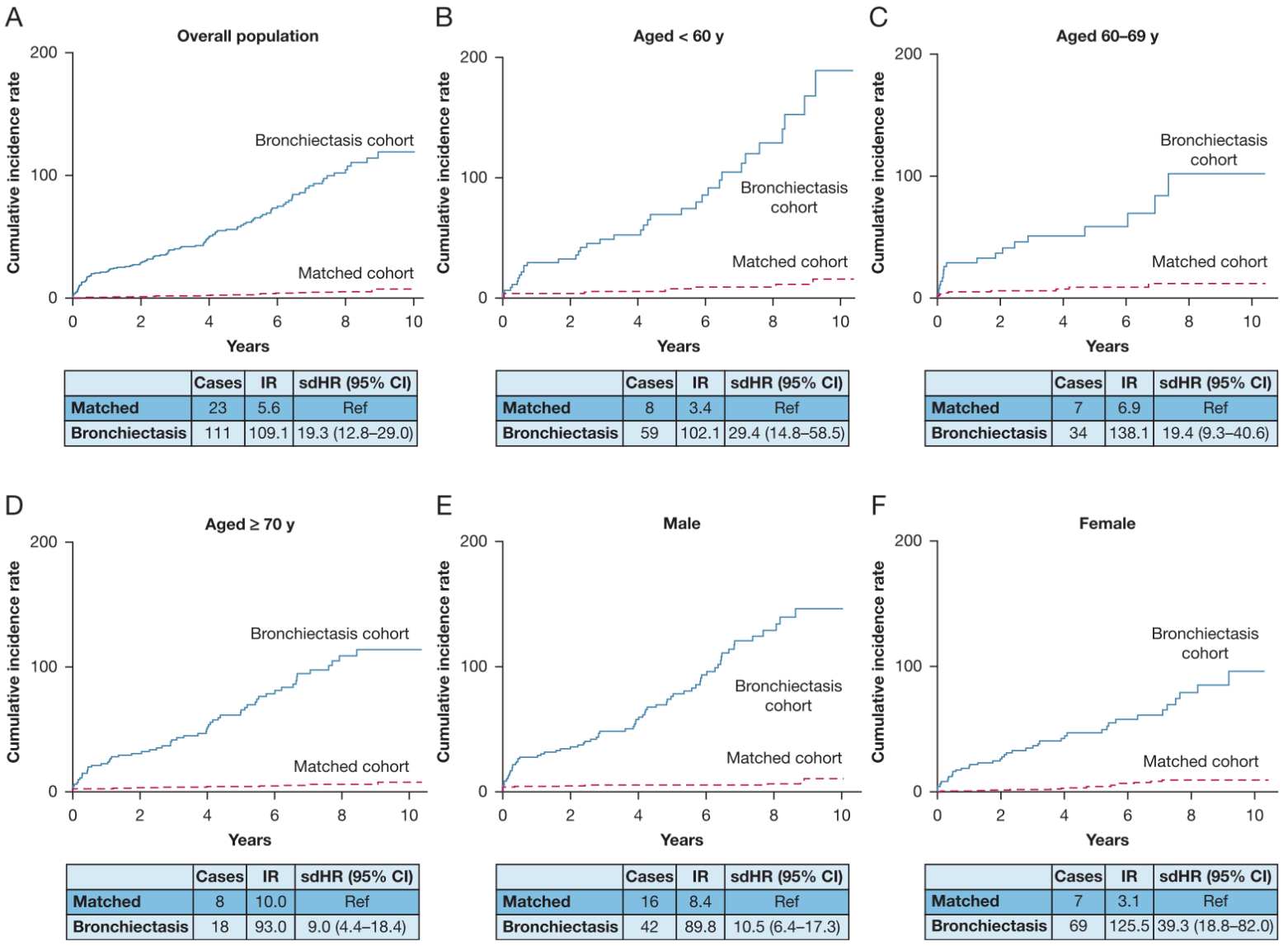
- Consider macrolide as first line long-term antibiotics in pseudomonas colonized pts.

- In use of macrolides, take caution for
  - Hearling loss
  - GI sx.
  - QT prolongation
  - NTM infection

CHEST

Impact of Bronchiectasis on Incident Nontuberculous Mycobacterial Pulmonary Disease

A 10-Year National Cohort Study



	Cases	IR	sdHR (95% CI)
Matched	23	5.6	Ref
Bronchiectasis	111	109.1	19.3 (12.8–29.0)

	Cases	IR	sdHR (95% CI)
Matched	8	3.4	Ref
Bronchiectasis	59	102.1	29.4 (14.8–58.5)

	Cases	IR	sdHR (95% CI)
Matched	7	6.9	Ref
Bronchiectasis	34	138.1	19.4 (9.3–40.6)

	Cases	IR	sdHR (95% CI)
Matched	8	10.0	Ref
Bronchiectasis	18	93.0	9.0 (4.4–18.4)

	Cases	IR	sdHR (95% CI)
Matched	16	8.4	Ref
Bronchiectasis	42	89.8	10.5 (6.4–17.3)

	Cases	IR	sdHR (95% CI)
Matched	7	3.1	Ref
Bronchiectasis	69	125.5	39.3 (18.8–82.0)

Figure 1 – *Cumulative incidence rates and subdistribution hazard ratios for nontuberculous mycobacterial pulmonary disease (/100,000 person-years) in the bronchiectasis cohort and matched cohort. A, Overall population, B, aged < 60 y, C, aged 60-69 y, D, aged ≥ 70 y, E, male, and F, female. The start of the X-axis indicates the first year of follow-up after a 1-y washout period. IR = incidence rate; Ref = reference; sdHR = subdistribution hazard ratio.*

TABLE 1] Risk Factors for Nontuberculous Mycobacterial Pulmonary Disease in Patients With Bronchiectasis

	Univariable Analysis			Multivariable Analysis[a]		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Age group						
≤39 y	Ref	Ref		Ref	Ref	
40-49 y	5.35	1.86-15.42	.002	5.50	1.90-15.88	.002
50-59 y	5.69	2.01-16.13	.001	5.22	1.83-14.86	.002
60-69 y	5.80	2.06-16.34	.001	4.98	1.75-14.18	.003
≥70 y	3.99	1.35-11.81	.012	3.58	1.20-10.71	.023
Sex						
Male	Ref	Ref		Ref	Ref	
Female	1.39	0.95-2.04	.091	1.64	1.11-2.41	.014
Type of insurance						
Self-employed health insurance	Ref	Ref		Ref	Ref	
Employee health insurance	1.21	0.82-1.79	.339	1.25	0.84-1.85	.271
Medical aid	1.40	0.34-5.82	.646	1.39	0.33-5.81	.652
Comorbidities						
COPD	1.36	0.92-2.02	.125	0.90	0.58-1.38	.620
Asthma	1.31	0.90-1.92	.160	0.99	0.64-1.51	.945
Previous pulmonary TB	4.71	3.20-6.93	<.001	4.26	2.84-6.39	<.001
Rheumatoid arthritis	0.74	0.30-1.82	.516	0.58	0.23-1.44	.239
Lung cancer	0.99	0.37-2.69	.984	0.61	0.22-1.69	.344
Medication						
Use of inhaled corticosteroids						
0	Ref	Ref		Ref	Ref	
Less than 1 y	0.93	0.54-1.62	.800	0.70	0.39-1.25	.229
1 or more years	2.04	1.21-3.45	.008	1.18	0.64-2.17	.592
Oral corticosteroid use						
<10 mg/d	Ref	Ref		Ref	Ref	
10 mg/d or more	1.46	0.64-3.32	.371	1.17	0.50-2.77	.720
Macrolide use	9.26	5.97-14.37	<.001	6.82	4.26-10.90	<.001

Tobramycin inhalation powder (TOBI podhaler)

approved for the management of chronic P. aeruginosa pulmonary infection in patients with cystic fibrosis

Efficacy and safety of TOBI Podhaler in *Pseudomonas aeruginosa*-infected bronchiectasis patients: iBEST study

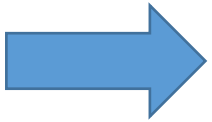
Michael R. Loebinger[1,2], Eva Polverino[3], James D. Chalmers[4], Harm A.W.M. Tiddens[5,6], Herman Goossens[7], Michael Tunney[8], Felix C. Ringshausen[9], Adam T. Hill[10], Rashidkhan Pathan[11], Gerhild Angyalosi[12], Francesco Blasi[13,14], Stuart J. Elborn[2,15,16] and Charles S. Haworth[17,18] on behalf of the iBEST-1 Trial Team

Eur Respir J. 2021 Jan 5;57(1):2001451.

- Aim : to determine the efficacy of TIP (tobramycin inhalation poweder) on P. aeruginosa sputum density

- Phase II, double-blind RCT in BRE

- Cohort A: 3 capsules bid
- Cohort B: 5 capsules qd
- Cohort C: 4 capsules bid



- TIP continously
- TIP cyclically (altering 28 days of TIP and placebo)
- Placebo

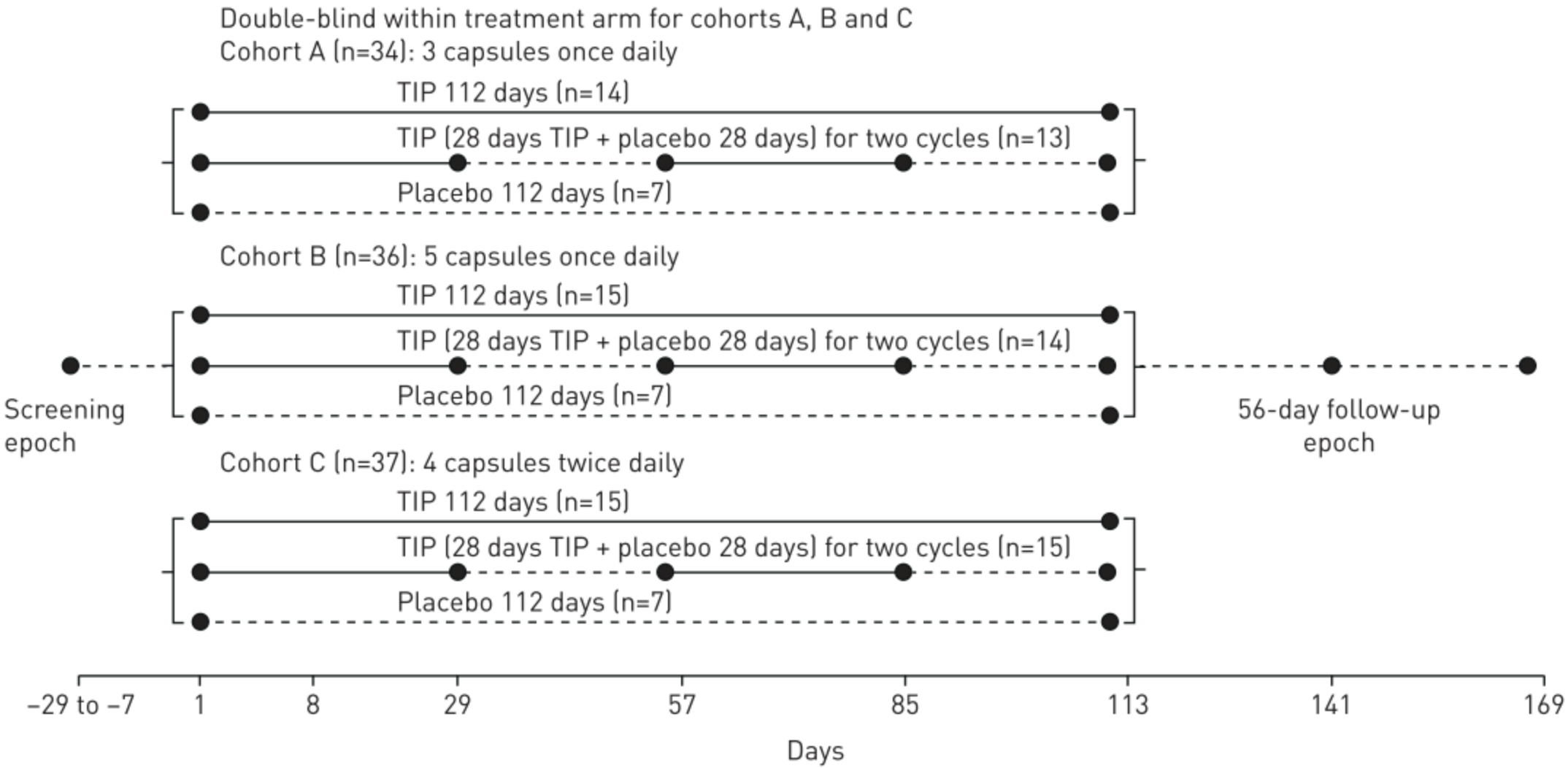


FIGURE 1 Study design (adapted from [20]). n: number of patients; TIP: tobramycin inhalation powder.

Change in P. aeruginosa sputum density

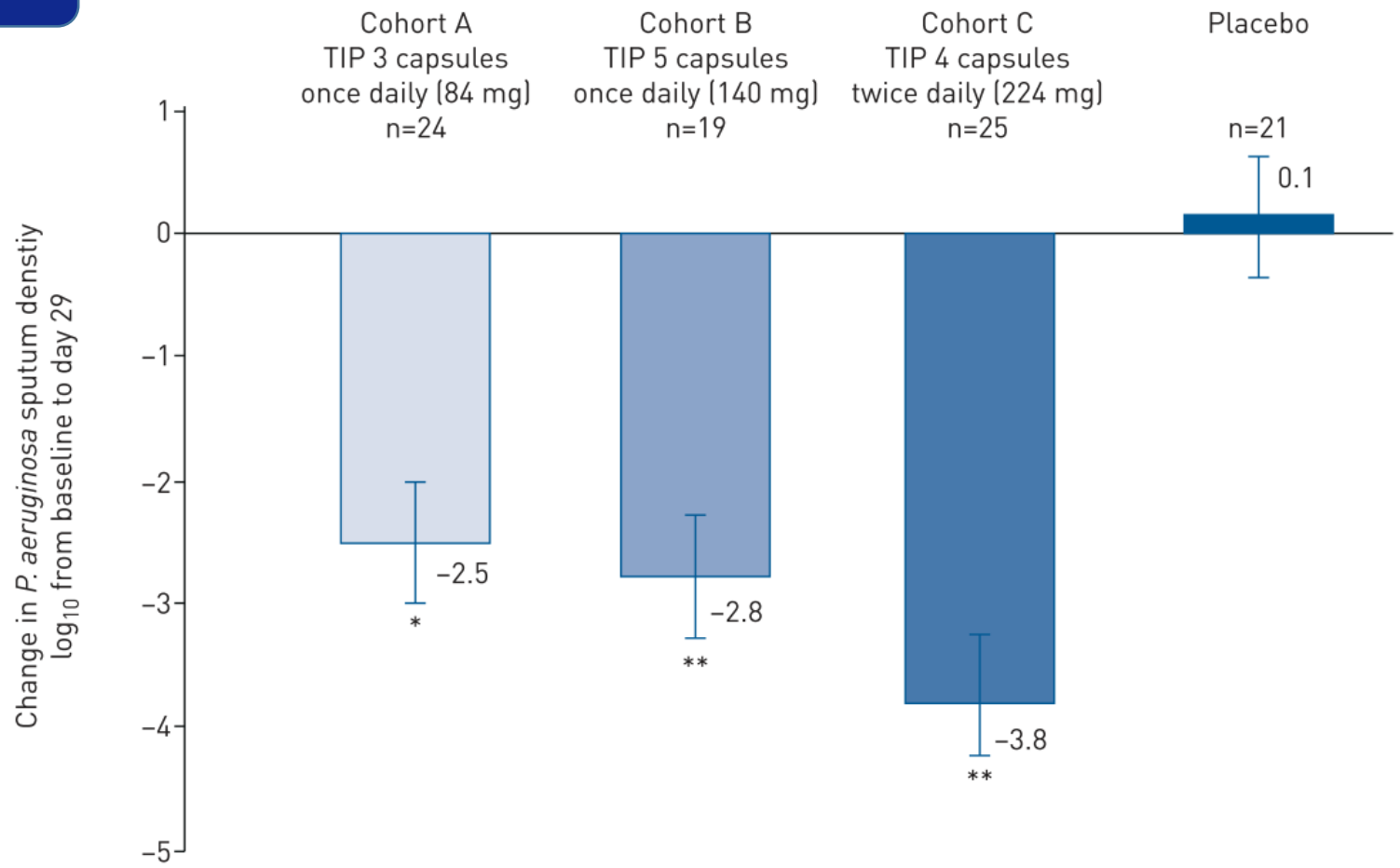


FIGURE 2 Change in *Pseudomonas aeruginosa* sputum density from baseline to day 29 for the treatment and placebo groups. CFU: colony-forming unit; n: number of patients; TIP: tobramycin inhalation powder. *: p=0.0001, **: p<0.0001, *versus* placebo. p-values for each treatment cohort are in comparison to the pooled placebo group.

AE frequency

Use of antibiotics

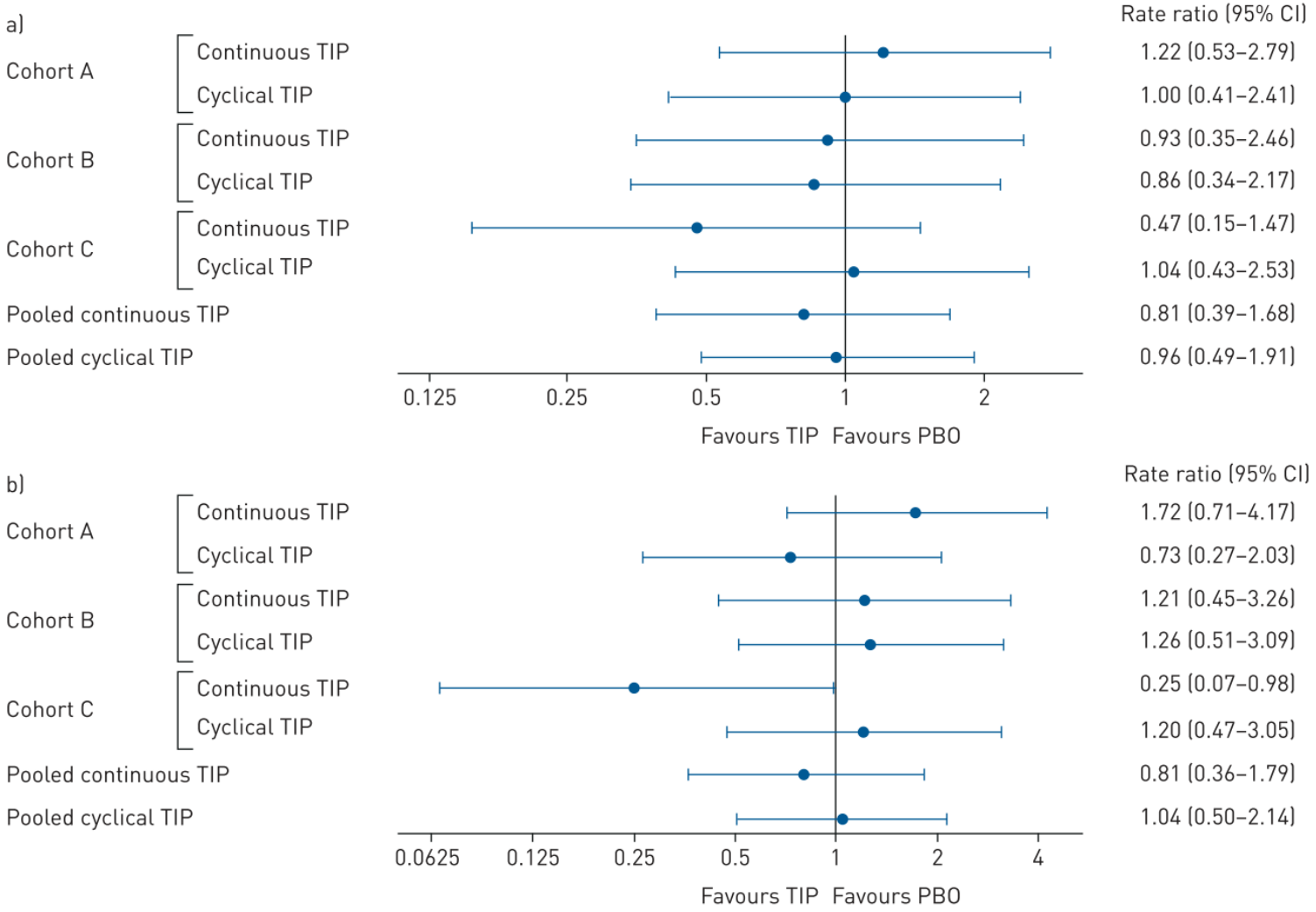


FIGURE 3 a) Forest plots showing the effect of different doses of TIP as compared to pooled PBO and different regimens on frequency of pulmonary exacerbation. b) Usage pattern of anti-pseudomonal antibiotics with different TIP doses as compared to pooled PBO and different treatment regimens. CI: confidence interval; PBO: placebo; TIP: tobramycin inhalation powder. Cohort A: TIP 3 capsules once daily (84 mg); Cohort B: TIP 5 capsules once daily (140 mg); Cohort C: TIP 4 capsules twice daily (224 mg).

TABLE 4 TEAEs leading to study drug discontinuation by preferred term

	Patients n	Infective exacerbation of bronchiectasis	Glomerular filtration rate decreased	Blood creatinine increased	Dyspnoea	Percentage of patients with at least one TEAE
Cohort A: three capsules once daily (84 mg)						
Continuous TIP	14	2 (14.3)	0	0	0	3 (21.4)
Cyclical TIP	13	0	0	0	0	1 (7.7)
Placebo	7	0	0	0	0	1 (14.3)
Cohort B: five capsules once daily (140 mg)						
Continuous TIP	15	1 (6.7)	1 (6.7)	0	0	3 (20)
Cyclical TIP	14	0	1 (7.1)	1 (7.1)	1 (7.1)	3 (21.4)
Placebo	7	0	0	0	0	0
Cohort C: four capsules twice daily (224 mg)						
Continuous TIP	15	0	2 (13.3)	2 (13.3)	2 (13.3)	6 (40)
Cyclical TIP	15	2 (13.3)	0	0	0	7 (46.7)
Placebo	7	0	0	0	0	1 (14.3)
Total (n=107)	107	5 (4.7)	4 (3.7)	3 (2.8)	3 (2.8)	25 (23.4)

Data are presented as n (%), unless otherwise stated. TEAE: treatment-emergent adverse event; TIP: tobramycin inhalation powder.

Respiratory Medicine 176 (2021) 106283

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Inhaled tobramycin for chronic infection with pseudomonas aeruginosa in non-cystic fibrosis bronchiectasis: A systematic review and meta-analysis

Saveria Sangiovanni [a], Eliana I. Morales [b,c], Liliana Fernández-Trujillo [d,c,*]

[a] *Clinical Research Center, Fundación Valle del Lili, Cali, Colombia*
[b] *Department of Internal Medicine, Pulmonology Service, Fundación Valle del Lili, Cali, Colombia*
[c] *Faculty of Health Sciences, Universidad Icesi, Cali, Colombia*
[d] *Department of Internal Medicine, Pulmonology Service, Interventional Pulmonology, Fundación Valle del Lili, Cali, Colombia*

Respir Med. 2021 Jan;176:106283.

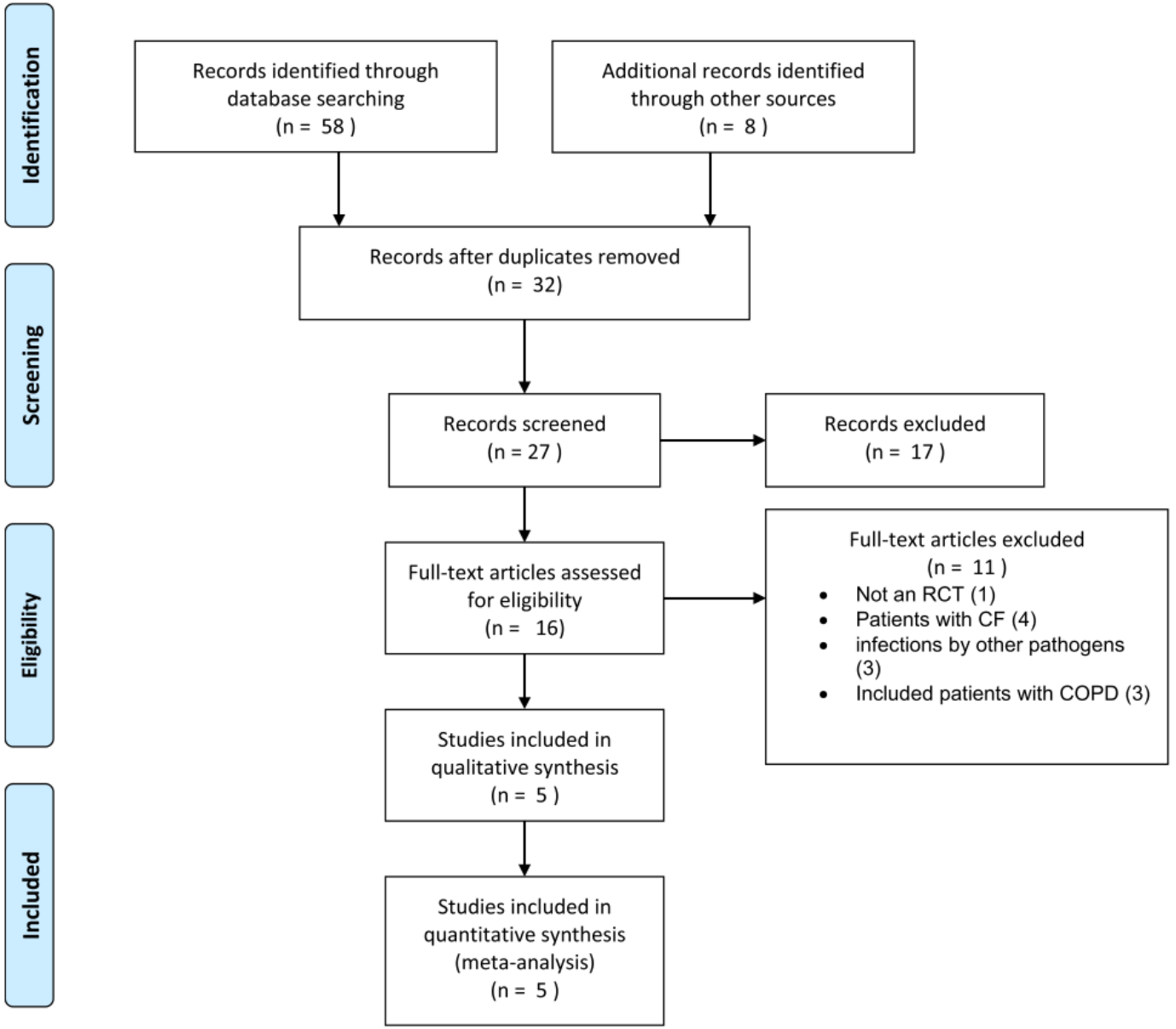

Fig. 1. Prisma 2009 flow diagram.

Primary outcomes

1. P. aeruginosa sputum density
2. Eradication of P. aeruginosa in sputum.
3. Emergence of antibiotic resistance to Tobramycin
4. Exacerbations requiring hospitalization.
5. FEV1

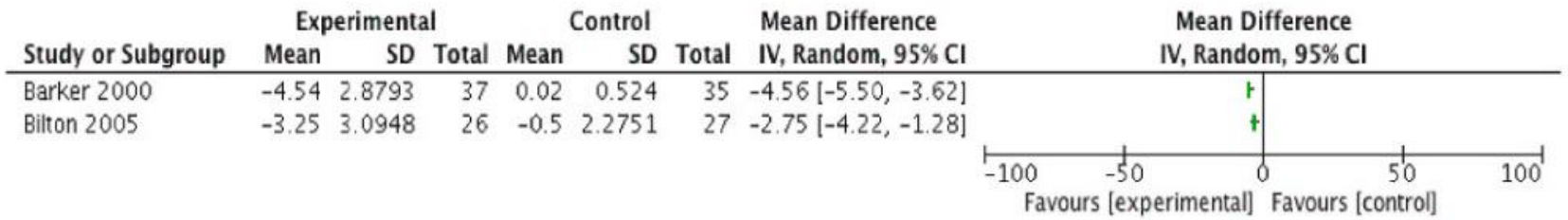

Fig. 3. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.I Change in *P. aeruginosa* density in sputum ($\log_{10}$ cfu/g sputum).

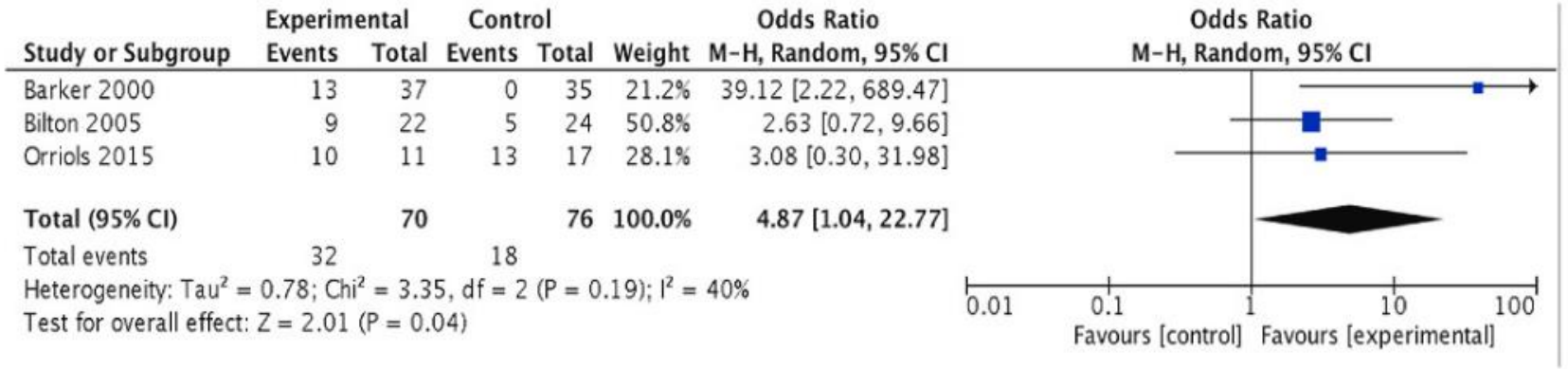

Fig. 4. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.2 Eradication of *P. aeruginosa* in sputum.

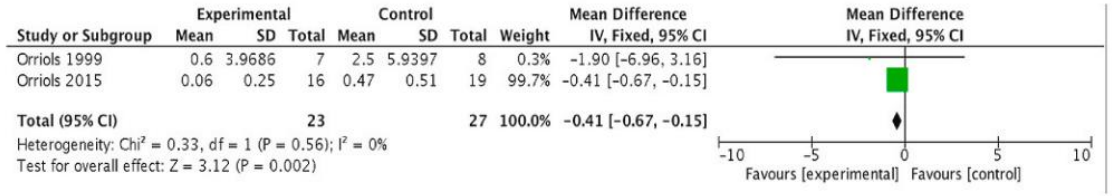

Fig. 7. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.4 Acute exacerbations requiring hospitalization.

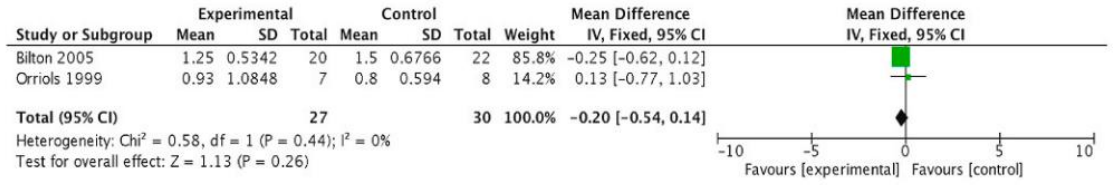

Fig. 8. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.5 Forced expiratory volume in 1 s (FEV_1).

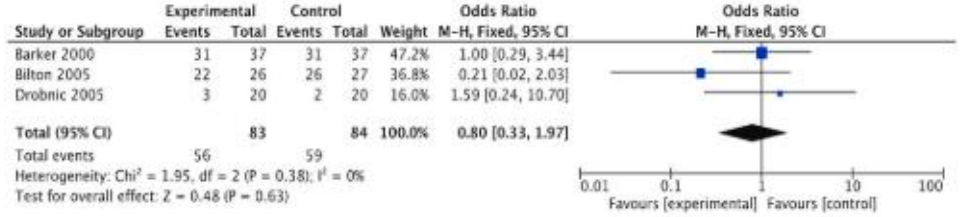

Fig. 9. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.6 Non-fatal adverse events.

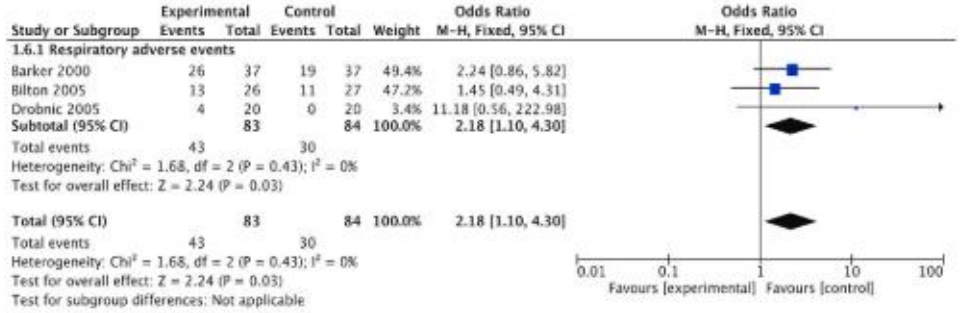

Fig. 10. Forest plot of comparison: Inhaled Tobramycin vs placebo, outcome: I.6. I Subgroup analysis, Respiratory adverse events.

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Original Research

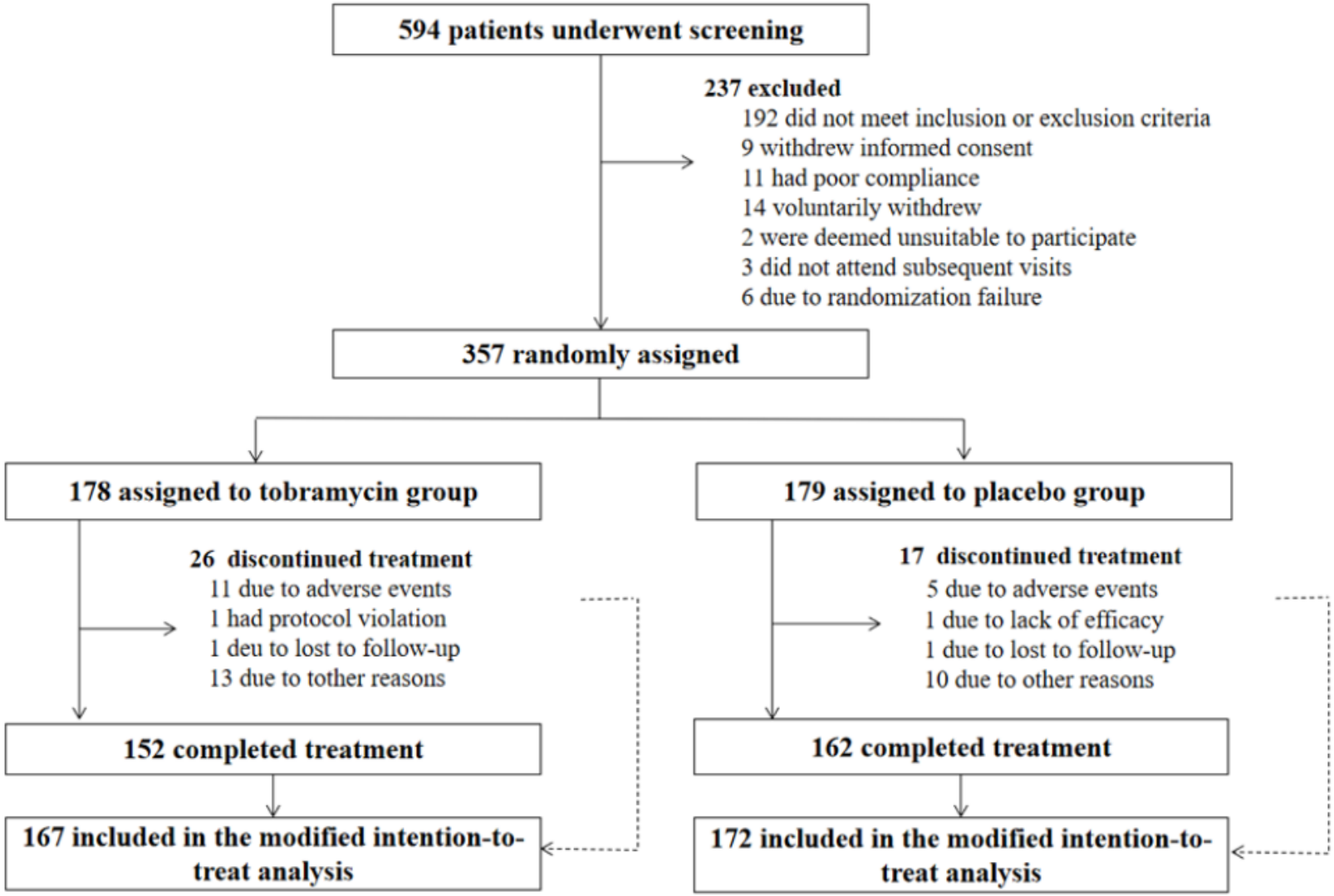
A Double-blind Randomized Placebo-controlled Phase-3 Trial of Tobramycin Inhalation Solution in Adults with Bronchiectasis with *Pseudomonas aeruginosa* Infection

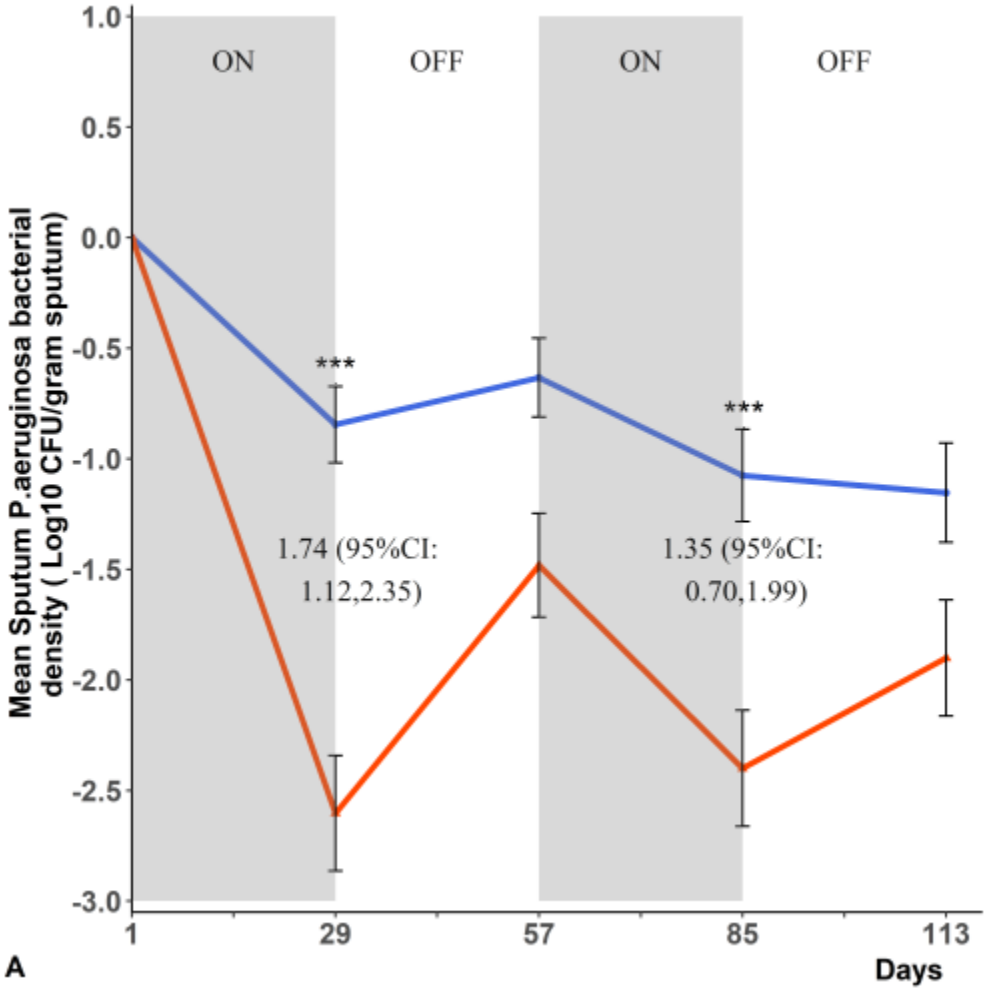
Wei-jie Guan Ph.D. [1, 2] [#] ✉, Jin-fu Xu M.D. [3, #], Hong Luo M.D. [4, #], Xing-xiang Xu [5, #], Yuan-lin Song M.D. [6, #], Wan-li Ma M.D. [7, #], Zong-an Liang M.D. [8], Xue-dong Liu M.D. [9], Guo-jun Zhang M.D., Ph.D. [10], Xiao-ju Zhang M.D. [11], Rong-kai Li M.D. [12], Shu-yang Zhu M.D. [13], Yi-jie Zhang M.D. [14], Xing-jun Cai M.D. [15], Li-ping Wei M.D. [16], Dong-bo Tian M.D. [17], Hui Zhao M.D. [18], Ping-yan Chen M.D. [19] … Nan-shan Zhong M.D. [1] [a] ✉

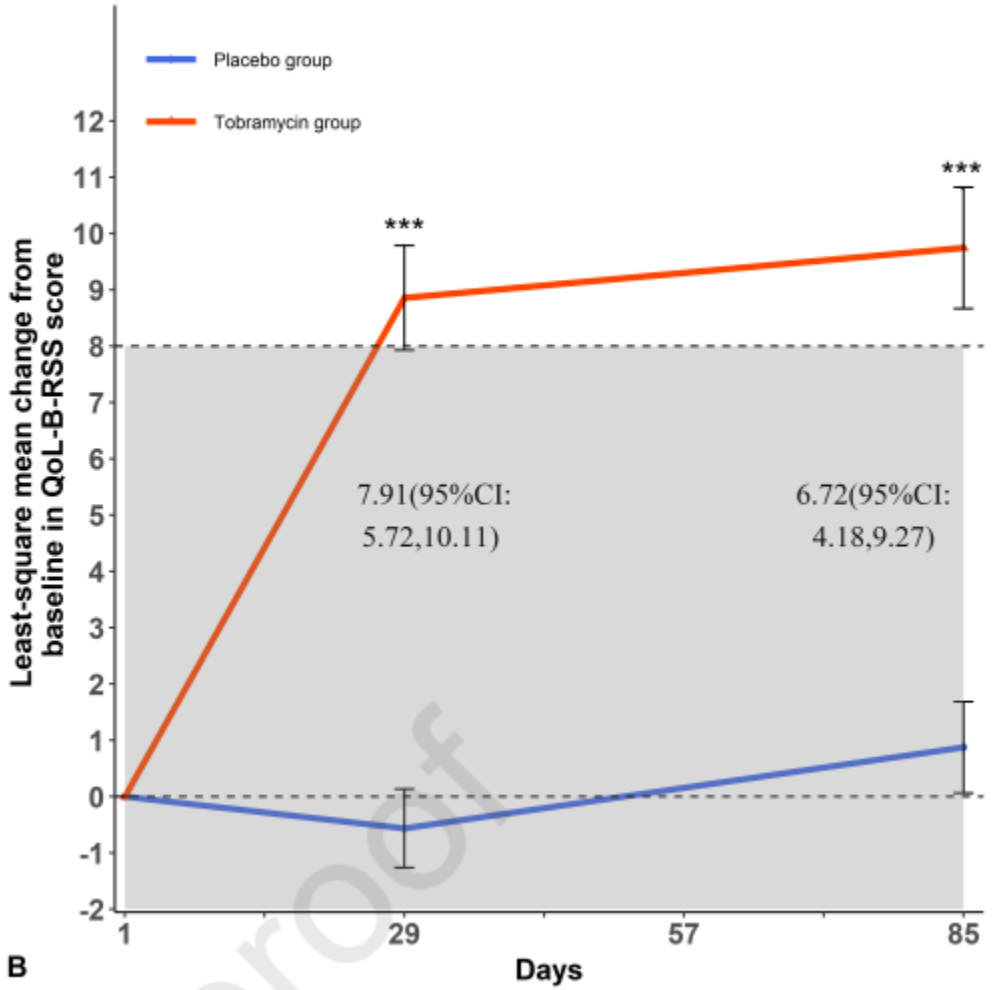
Chest. 2022 Jul 18:S0012-3692(22)01247-8.

- Phase III, 16-week, multi-center RCT
- October 2018 to July 2021
- Nebulized tobramycin inhalation solution (TIS) vs normal saline
- Two cycles of 28 days on- and off-treatment alternating period

- Primary endpoint
  - Change from baseline in P.aeruginosa density
  - Quality-of-life-Bronchiectasis Respiratory Symptom score (QOL-B RSS)


594 patients underwent screening
237 excluded
192 did not meet inclusion or exclusion criteria
9 withdrew informed consent
11 had poor compliance
14 voluntarily withdrew
2 were deemed unsuitable to participate
3 did not attend subsequent visits
6 due to randomization failure
357 randomly assigned
178 assigned to tobramycin group
179 assigned to placebo group
26 discontinued treatment
11 due to adverse events
1 had protocol violation
1 deu to lost to follow-up
13 due to tother reasons
17 discontinued treatment
5 due to adverse events
1 due to lack of efficacy
1 due to lost to follow-up
10 due to other reasons
152 completed treatment
162 completed treatment
167 included in the modified intention-to-treat analysis
172 included in the modified intention-to-treat analysis


ON
OFF
ON
OFF
Mean Sputum P.aeruginosa bacterial density (Log10 CFU/gram sputum)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
***
***
1.74 (95%CI: 1.12,2.35)
1.35 (95%CI: 0.70,1.99)
1
29
57
85
113
Days
A


Placebo group
Tobramycin group
Least-square mean change from baseline in QoL-B-RSS score
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
***
***
7.91(95%CI: 5.72,10.11)
6.72(95%CI: 4.18,9.27)
1
29
57
85
Days
B

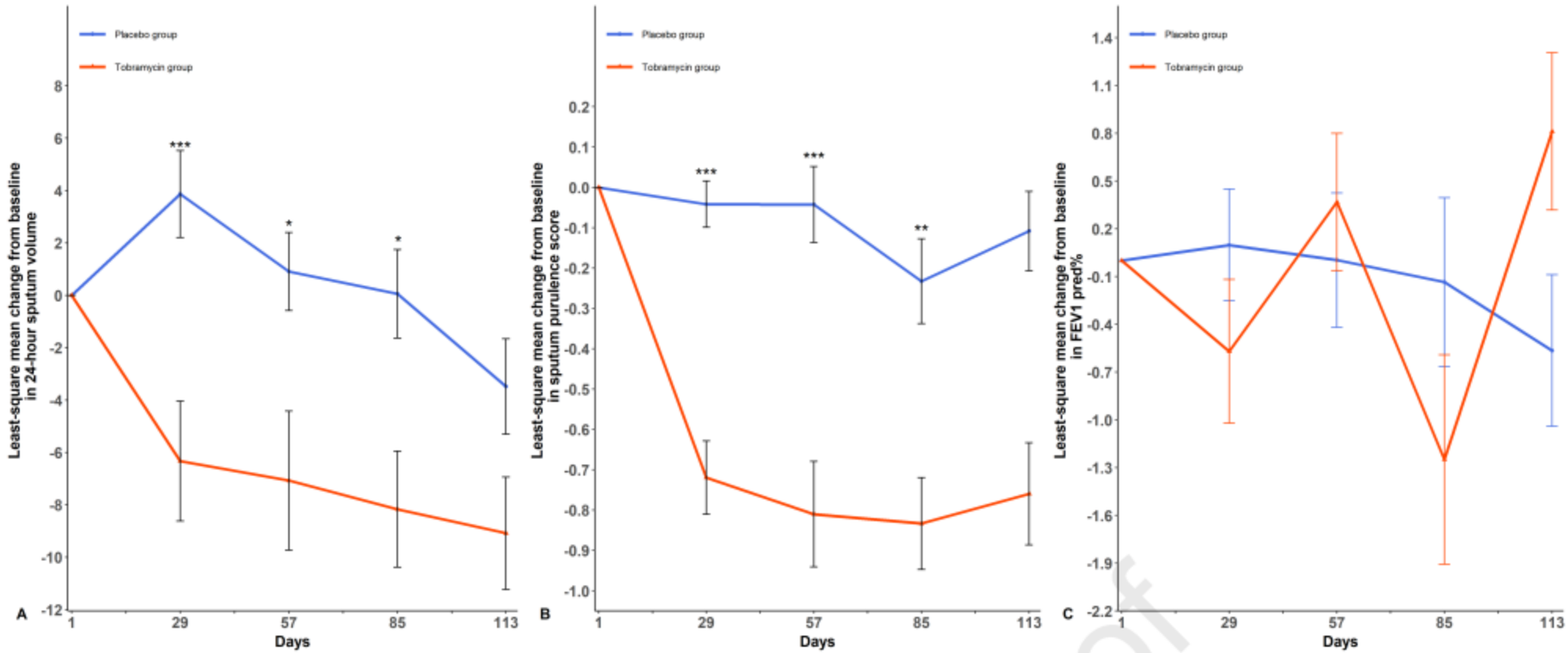

Placebo group
Tobramycin group
Least-square mean change from baseline in 24-hour sputum volume
8
6
4
2
0
-2
-4
-6
-8
-10
-12
***
*
*
A
1
29
57
85
113
Days
Placebo group
Tobramycin group
Least-square mean change from baseline in sputum purulence score
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1.0
***
***
**
B
1
29
57
85
113
Days
Placebo group
Tobramycin group
Least-square mean change from baseline in FEV1 pred%
1.4
1.1
0.8
0.5
0.2
-0.1
-0.4
-0.7
-1.0
-1.3
-1.6
-1.9
-2.2
C
1
29
57
85
113
Days

Table 3. Summary of adverse events in the safety set

Event	Tobramycin (N=167)	Placebo (N=172)	Total (N=357)
Any adverse event - No., %	145 (81.5%)	146 (81.6%)	291 (81.5%)
At least one treatment-associated adverse events - No., %	140 (78.7%)	139 (77.7%)	279 (78.2%)
Most common treatment-associated adverse events - No., %			
Hemoptysis [a]	37 (20.8%)	46 (25.7%)	83 (23.2%)
Chest discomfort	17 (9.6%)	16 (8.9%)	33 (9.2%)
Acute upper respiratory tract infection	15 (8.4%)	17 (9.5%)	32 (9.0%)
Increased cough	21 (11.8%)	12 (6.7%)	33 (9.2%)
Fever	11 (6.2%)	17 (9.5%)	28 (7.8%)
Chest pain	13 (7.3%)	10 (5.6%)	23 (6.4%)
Rhinitis	6 (3.4%)	12 (6.7%)	18 (5.0%)
Treatment-associated adverse events of special interest - No., %			
Hearing impairment	0 (0%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (1.1%)	2 (0.6%)
Renal impairment	1 (0.6%)	0 (0%)	1 (0.3%)
Blurred vision	1 (0.6%)	0 (0%)	1 (0.3%)
Any abnormal laboratory findings - No., %	23 (12.9%)	14 (7.8%)	37 (10.4%)
Severe treatment-associated adverse events - No., %	18 (10.1%)	19 (10.6%)	37 (10.4%)
Adverse events related to the study drug - No., %	37 (20.8%)	13 (7.3%)	50 (14.0%)
Severe adverse events related to the study drug - No., %	1 (0.6%)	1 (0.6%)	2 (0.6%)
Serious adverse event - No., %	20 (11.2%)	19 (10.6%)	39 (10.9%)
Treatment-associated adverse events leading to death - No., %	1 (0.6%)	0 (0%)	1 (0.3%)
Treatment-associated adverse events leading to trial discontinuation - No., %	11 (6.2%)	5 (2.8%)	16 (4.5%)

Inhaled ciprofloxacin (ARD-3150)

Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials

Charles S Haworth, Diana Bilton, James D Chalmers, Angela M Davis, Juergen Froehlich, Igor Gonda, Bruce Thompson, Adam Wanner, Anne E O'Donnell

Lancet Respir Med. 2019 Mar;7(3):213-226.

OPEN ACCESS

ORIGINAL ARTICLE

Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial

David J Serisier,[1] Diana Bilton,[2] Anthony De Soyza,[3] Philip J Thompson,[4] John Kolbe,[5] Hugh W Greville,[6] David Cipolla,[7] Paul Bruinenberg,[8] Igor Gonda,[7] the ORBIT-2 investigators

► Additional material is

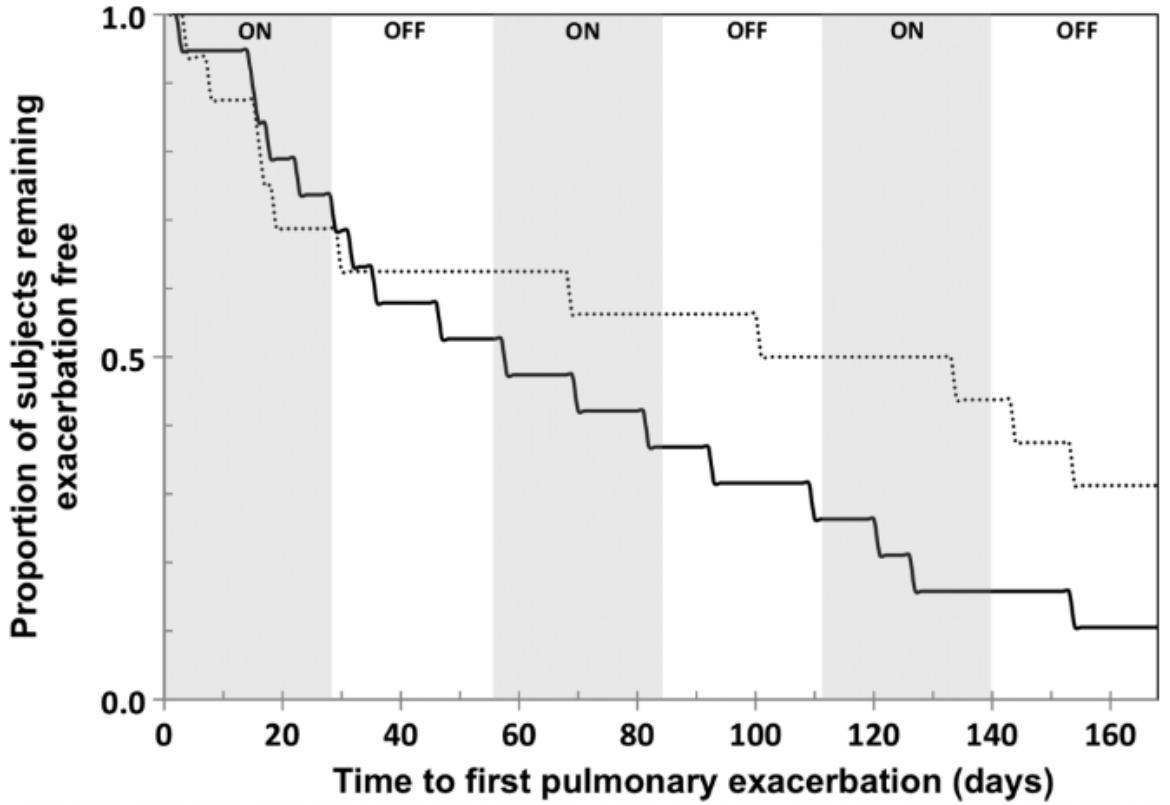
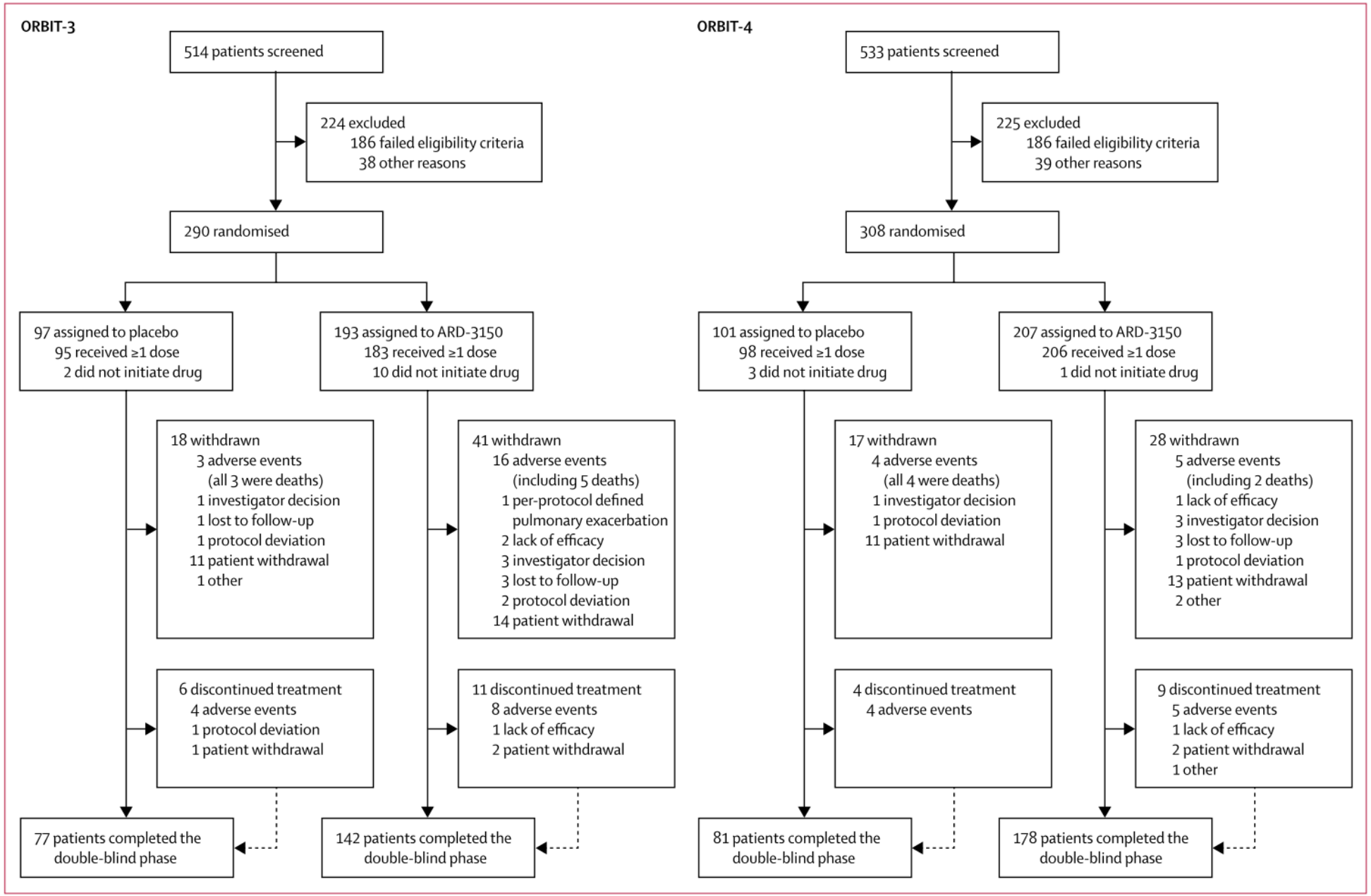
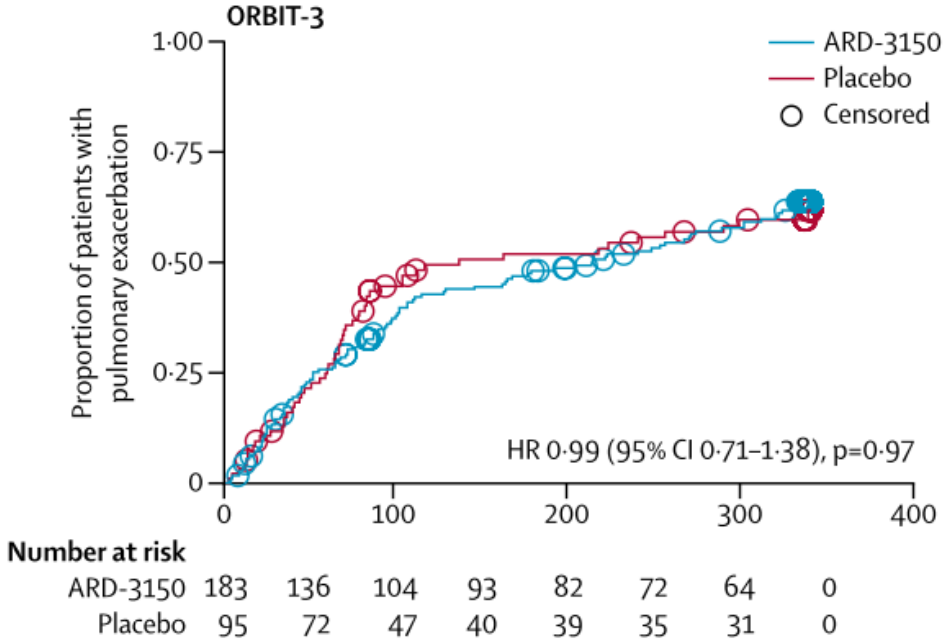


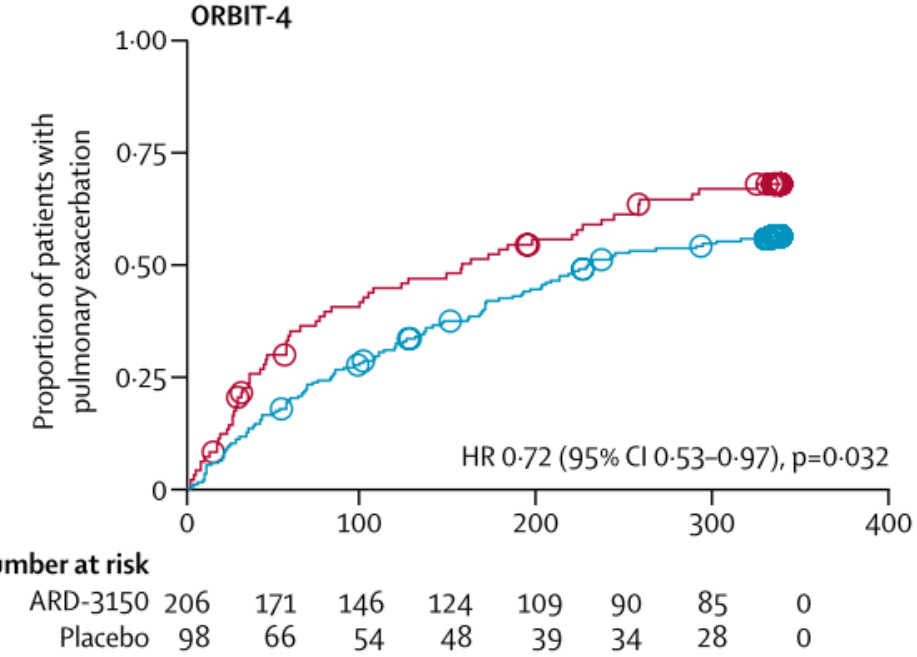
Figure 3 Kaplan–Meier curves comparing DRCFI and placebo groups for time to first pulmonary exacerbation in the modified intention to treat (mITT) population. (Dotted line represents DRCFI, solid line represents placebo; median 134 vs 58 days, p=0.057 mITT, p=0.046 per protocol, by log-rank test; DRCFI, dual release ciprofloxacin for inhalation.)

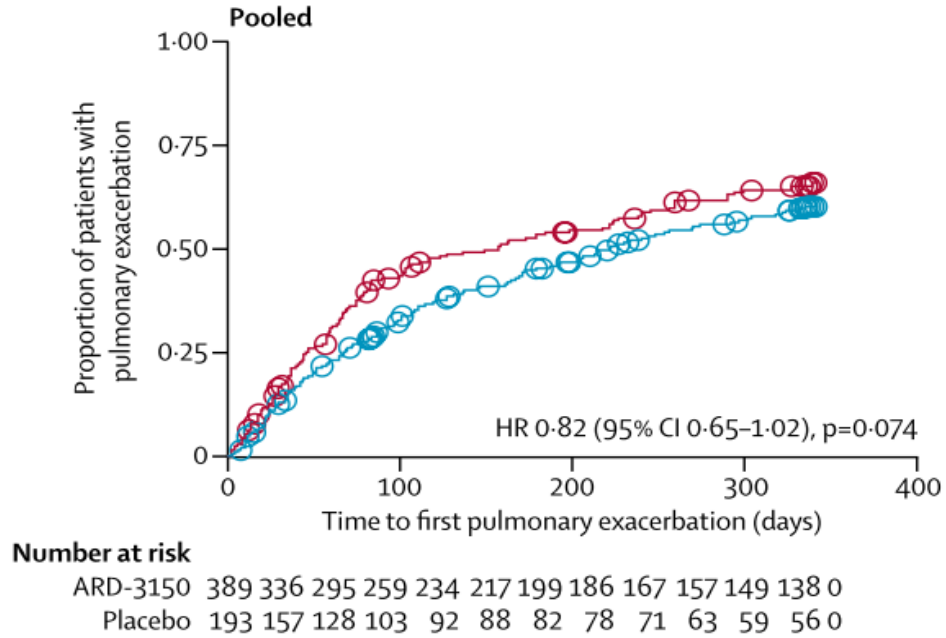
Thorax. 2013 Sep;68(9):812-7.

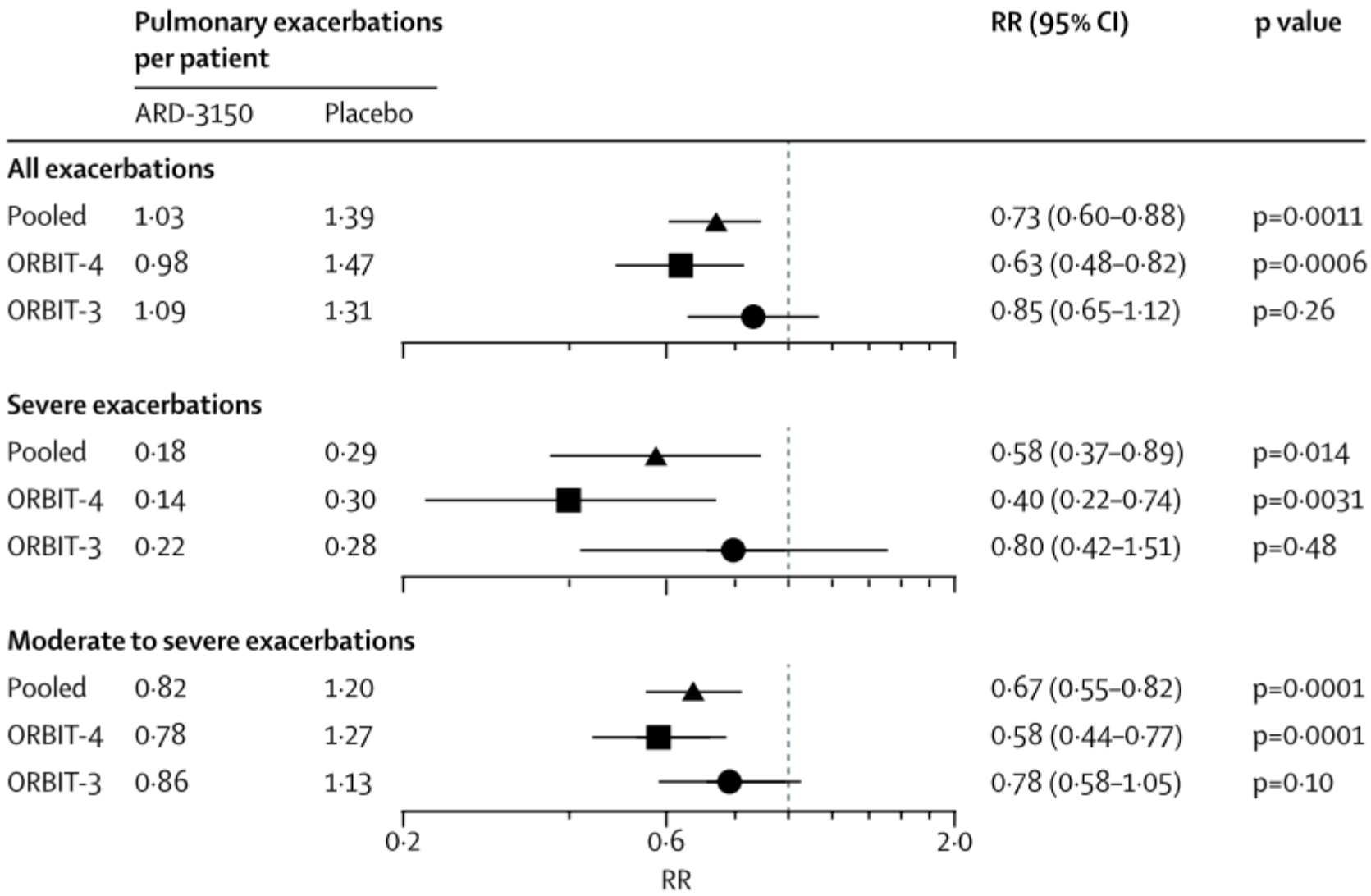
- Two identical RCT (ORBIT-3 and ORBIT-4)
- BRE + chronic PA infection + ≥ 2 exacerbation
- 28 days on and 28 days off
- 48 wks

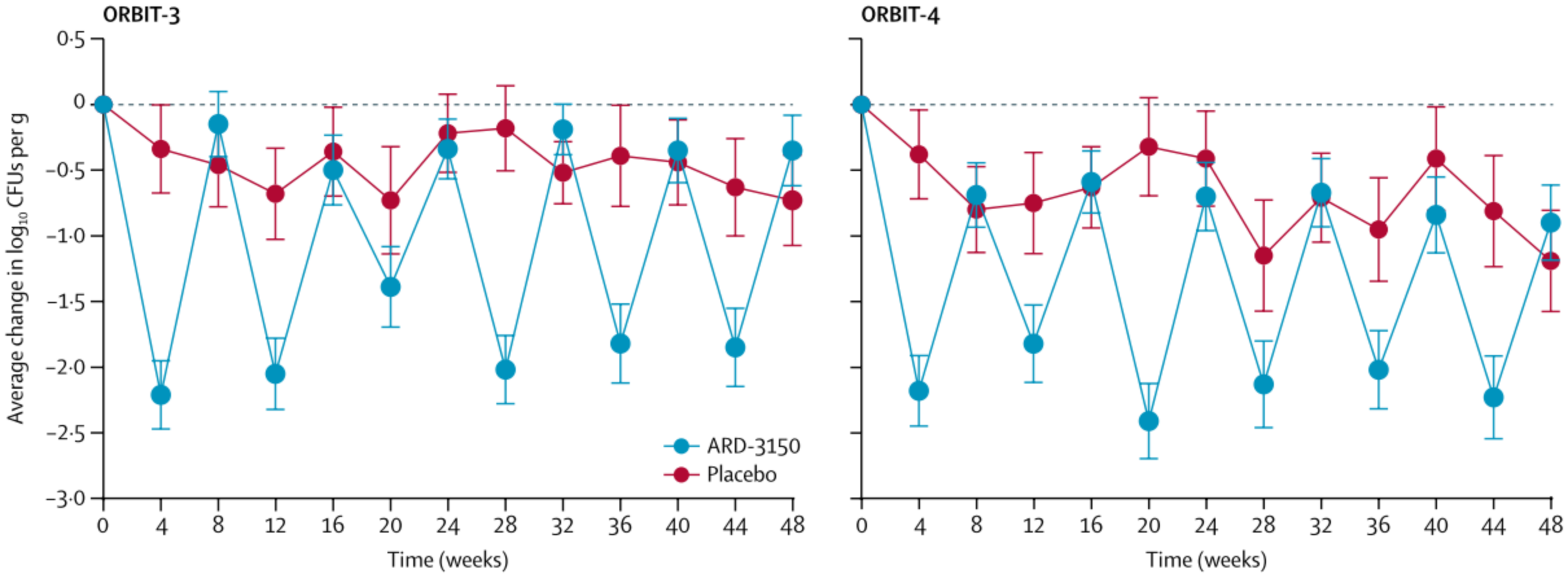

ORBIT-3
514 patients screened
224 excluded
186 failed eligibility criteria
38 other reasons
290 randomised
97 assigned to placebo
95 received ≥1 dose
2 did not initiate drug
193 assigned to ARD-3150
183 received ≥1 dose
10 did not initiate drug
18 withdrawn
3 adverse events
(all 3 were deaths)
1 investigator decision
1 lost to follow-up
1 protocol deviation
11 patient withdrawal
1 other
41 withdrawn
16 adverse events
(including 5 deaths)
1 per-protocol defined
pulmonary exacerbation
2 lack of efficacy
3 investigator decision
3 lost to follow-up
2 protocol deviation
14 patient withdrawal
6 discontinued treatment
4 adverse events
1 protocol deviation
1 patient withdrawal
11 discontinued treatment
8 adverse events
1 lack of efficacy
2 patient withdrawal
77 patients completed the
double-blind phase
142 patients completed the
double-blind phase
ORBIT-4
533 patients screened
225 excluded
186 failed eligibility criteria
39 other reasons
308 randomised
101 assigned to placebo
98 received ≥1 dose
3 did not initiate drug
207 assigned to ARD-3150
206 received ≥1 dose
1 did not initiate drug
17 withdrawn
4 adverse events
(all 4 were deaths)
1 investigator decision
1 protocol deviation
11 patient withdrawal
28 withdrawn
5 adverse events
(including 2 deaths)
1 lack of efficacy
3 investigator decision
3 lost to follow-up
1 protocol deviation
13 patient withdrawal
2 other
4 discontinued treatment
4 adverse events
9 discontinued treatment
5 adverse events
1 lack of efficacy
2 patient withdrawal
1 other
81 patients completed the
double-blind phase
178 patients completed the
double-blind phase


ORBIT-3
ARD-3150
Placebo
Censored
Proportion of patients with pulmonary exacerbation
1·00
0·75
0·50
0·25
0
HR 0·99 (95% CI 0·71–1·38), p=0·97
0
100
200
300
400
Number at risk
ARD-3150 183 136 104 93 82 72 64 0
Placebo 95 72 47 40 39 35 31 0


ORBIT-4
Proportion of patients with pulmonary exacerbation
1·00
0·75
0·50
0·25
0
HR 0·72 (95% CI 0·53–0·97), p=0·032
0
100
200
300
400
Number at risk
ARD-3150 206 171 146 124 109 90 85 0
Placebo 98 66 54 48 39 34 28 0


Pooled
Proportion of patients with pulmonary exacerbation
1·00
0·75
0·50
0·25
0
HR 0·82 (95% CI 0·65–1·02), p=0·074
0
100
200
300
400
Time to first pulmonary exacerbation (days)
Number at risk
ARD-3150 389 336 295 259 234 217 199 186 167 157 149 138 0
Placebo 193 157 128 103 92 88 82 78 71 63 59 56 0


Pulmonary exacerbations per patient
ARD-3150
Placebo
RR (95% CI)
p value
All exacerbations
Pooled 1·03 1·39 0·73 (0·60–0·88) p=0·0011
ORBIT-4 0·98 1·47 0·63 (0·48–0·82) p=0·0006
ORBIT-3 1·09 1·31 0·85 (0·65–1·12) p=0·26
Severe exacerbations
Pooled 0·18 0·29 0·58 (0·37–0·89) p=0·014
ORBIT-4 0·14 0·30 0·40 (0·22–0·74) p=0·0031
ORBIT-3 0·22 0·28 0·80 (0·42–1·51) p=0·48
Moderate to severe exacerbations
Pooled 0·82 1·20 0·67 (0·55–0·82) p=0·0001
ORBIT-4 0·78 1·27 0·58 (0·44–0·77) p=0·0001
ORBIT-3 0·86 1·13 0·78 (0·58–1·05) p=0·10
0·2
0·6
2·0
RR


ORBIT-3
ORBIT-4
Average change in log10 CFUs per g
0·5
0
−0·5
−1·0
−1·5
−2·0
−2·5
−3·0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (weeks)
ARD-3150
Placebo

	ARD-3150 (n=389)	Placebo (n=193)
Tendonitis	3 (1%)	1 (1%)
Tendon rupture	0	1 (1%)
Paraesthesia	0	2 (1%)
Muscle weakness	3 (1%)	0
Nervous system disorder	153 (39%)	72 (37%)
Psychiatric disorders	21 (5%)	16 (8%)
Drug hypersensitivity	2 (1%)	0
Hepatobiliary disorder	4 (1%)	3 (2%)
Diarrhoea (any)	21 (5%)	19 (10%)
QTc change >30 ms	21 (5%)	13 (7%)
QTc change >60 ms	8 (2%)	6 (3%)
Photosensitivity	1 (<1%)	0

Data are n (%).

Table 4: **Side-effects associated with the quinolone class of antibiotics over the 48-week double-blind study period (pooled analysis)**

Inhaled ciprofloxacin (ARD-3150)

ORIGINAL ARTICLE
BRONCHIECTASIS

CrossMark

Changes in respiratory symptoms during 48-week treatment with ARD-3150 (inhaled liposomal ciprofloxacin) in bronchiectasis: results from the ORBIT-3 and -4 studies

Eur Respir J. 2020 Oct 22;56(4):2000110.

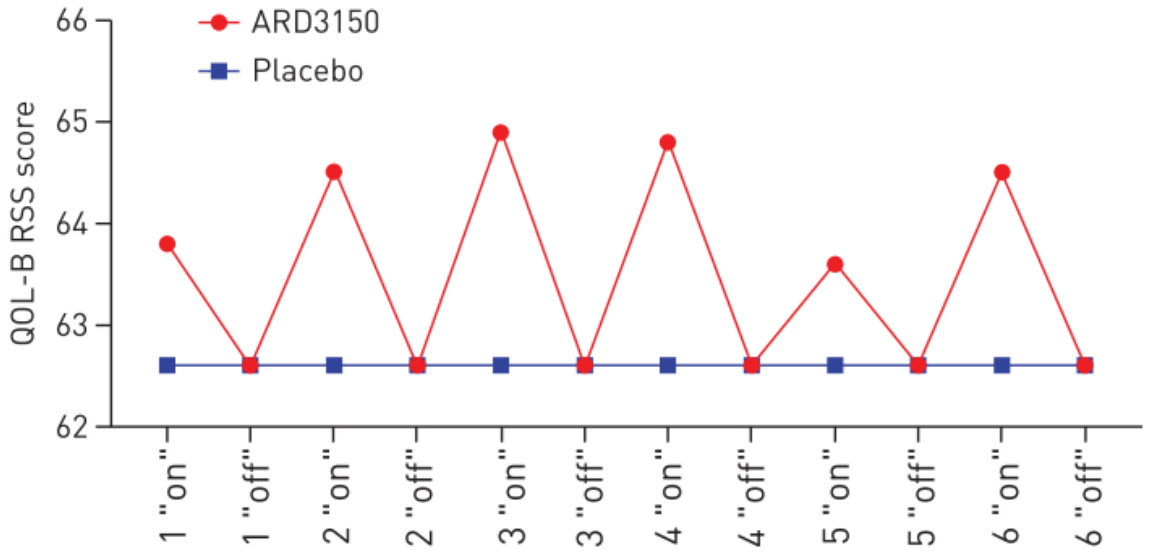


FIGURE 3 Results of the mixed model repeated measures for the pooled ORBIT-3 and -4 studies. The maximum has been allowed to vary according to the observed mean at each treatment cycle for the ARD-3150-treated group, and the placebo response rate has been set to the grand mean for the placebo-treated subjects. QOL-B RSS: quality-of-life bronchiectasis respiratory symptom scale.

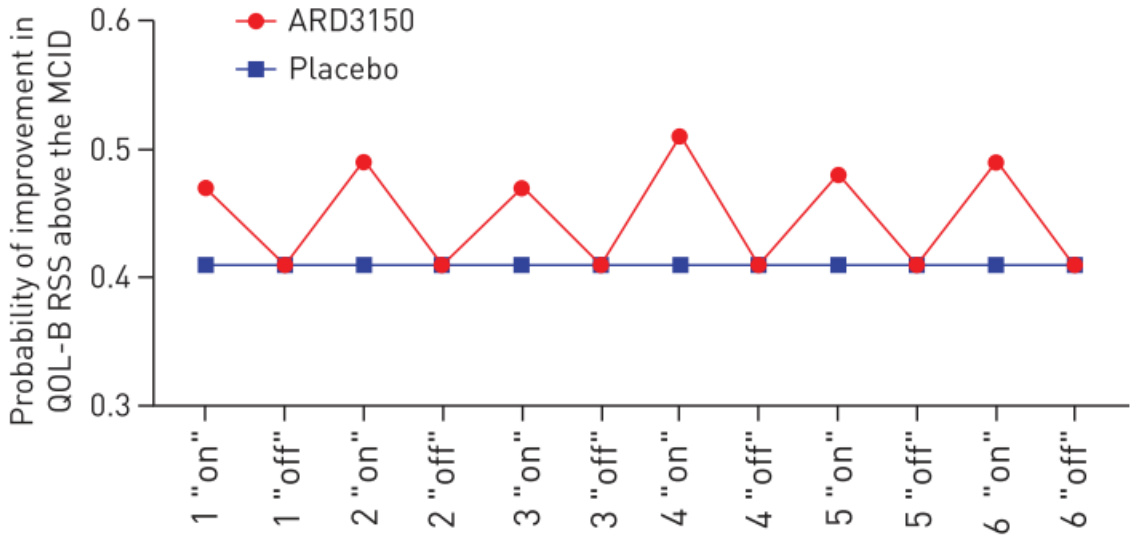


FIGURE 4 Results of the GEE model for the pooled ORBIT-3 and -4 studies. The maximum has been allowed to vary according to the observed mean at each treatment cycle for the ARD-3150-treated group, and the placebo response rate has been set to the average response rate for the placebo-treated subjects. QOL-B RSS: quality-of-life bronchiectasis respiratory symptom scale.

Inhaled aztreonam

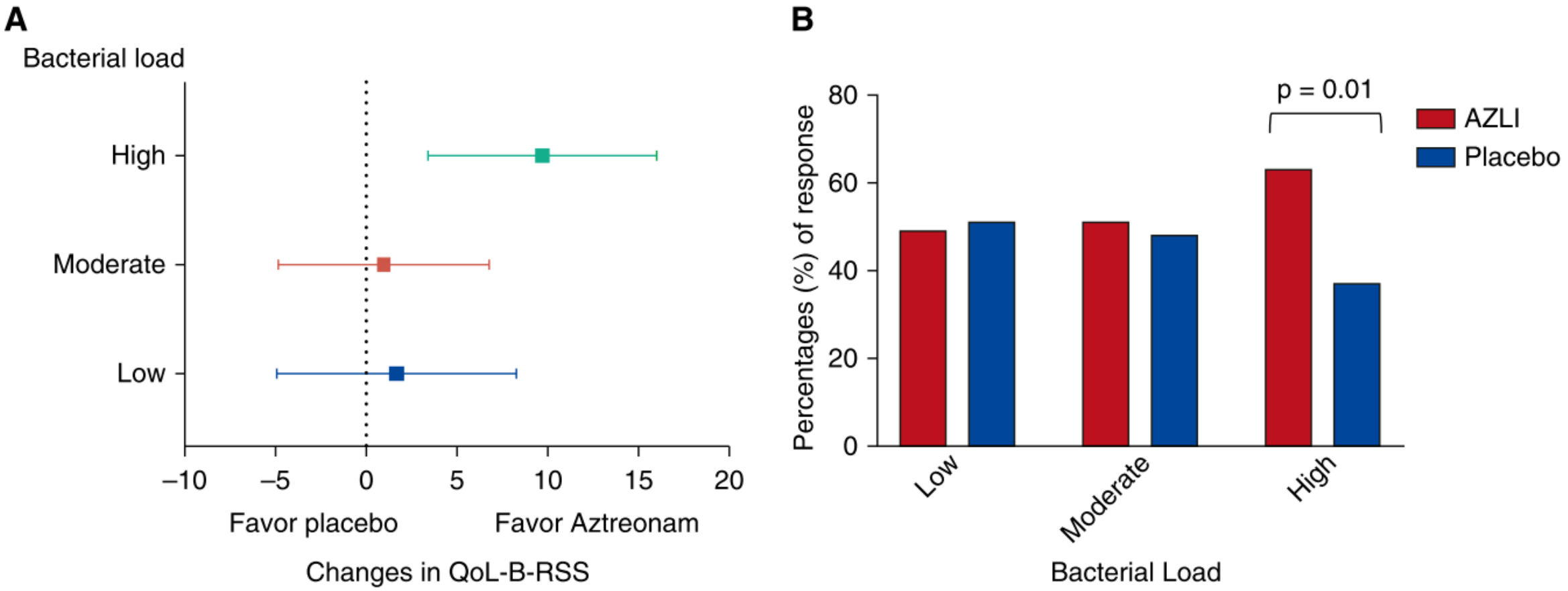
ORIGINAL ARTICLE

Airway Bacterial Load and Inhaled Antibiotic Response in Bronchiectasis

Oriol Sibila[1,2], Elena Laserna[3], Amelia Shoemark[4], Holly R. Keir[4], Simon Finch[4], Ana Rodrigo-Troyano[1,2], Lidia Perea[2], Mike Lonergan[4], Pieter C. Goeminne[5,6], and James D. Chalmers[4]

[1]Respiratory Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [2]Biomedical Research Institute Sant Pau, Barcelona, Spain; [3]Hospital Comarcal de Mollet, Mollet del Vallés, Spain; [4]Scottish Centre for Respiratory Medicine, University of Dundee, Dundee, United Kingdom; [5]Department of Respiratory Medicine, AZ Nikolaas, Sint-Niklaas, Belgium; and [6]Department of Respiratory Medicine, UZ Leuven, Leuven, Belgium

Am J Respir Crit Care Med. 2019 Jul 1;200(1):33-41.


A
Bacterial load
High
Moderate
Low
−10
−5
0
5
10
15
20
Favor placebo
Favor Aztreonam
Changes in QoL-B-RSS
B
p = 0.01
AZLI
Placebo
Percentages (%) of response
80
60
40
20
0
Low
Moderate
High
Bacterial Load

Take home messages

- Pulmonary rehabilitation
  - Functional limitation + mMRC≥1
  - Younger, better QOL, better lung function → benefit ↑
- B-ACT
  - Time to first exacerbation ↑
- High dose NAC
  - Time to second exacerbation ↑
- Anti-inflammatory drugs
  - Limited role. Maybe harmful.
- Bronchodilator
  - Trial in patients with significant breathlessness
  - FEV1 ↑ in AFO pts.
- Long-term antibiotics
  - Macrolide / inhaled antibiotics
  - TIP, inhaled ciprofloxacin, aztreonam

Thank you for your attention