The Bright and Dark Sides of Macrolide Therapy in Bronchiectasis

2025.8.30
양산부산대학교병원
손은정

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Pusan National University Yangsan Hospital

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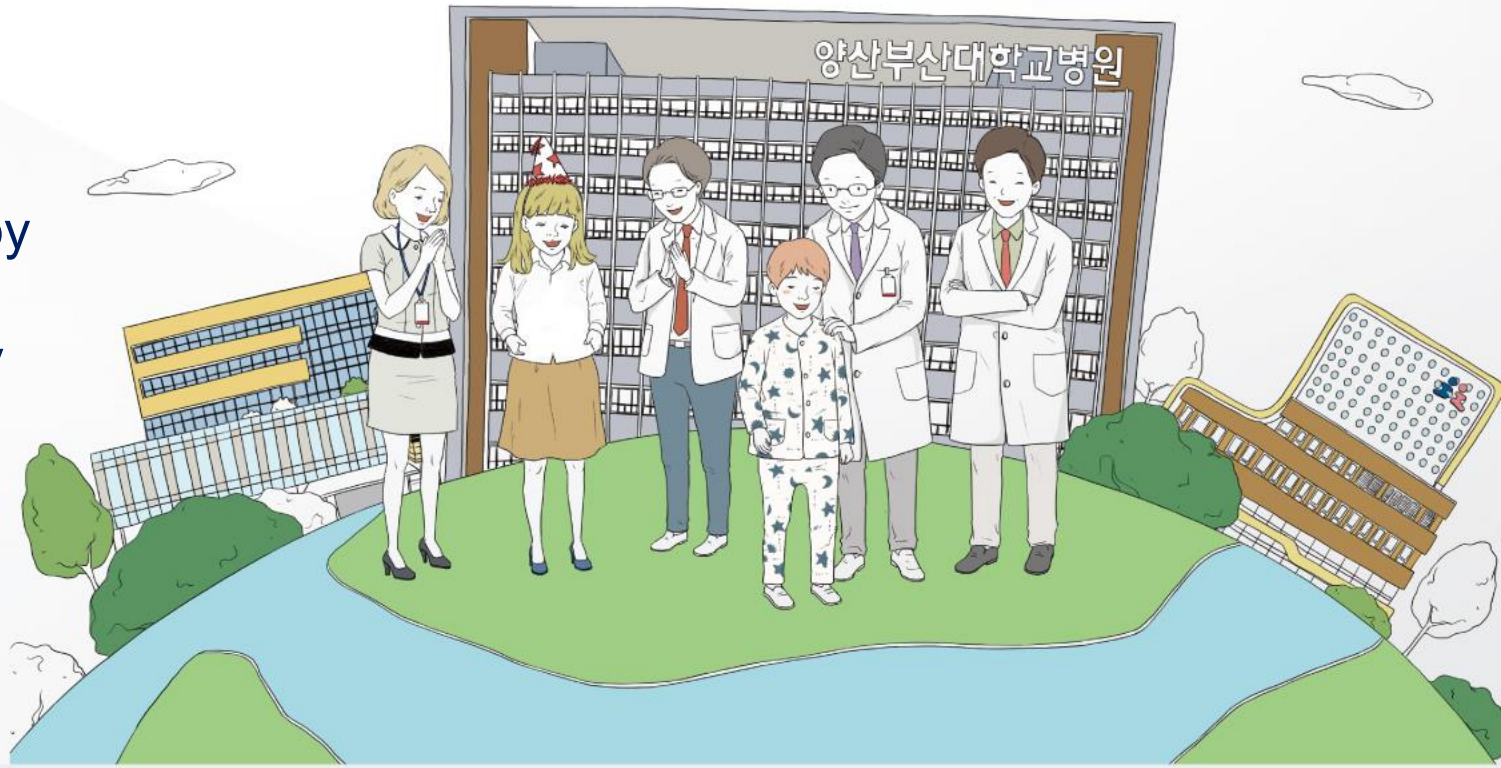

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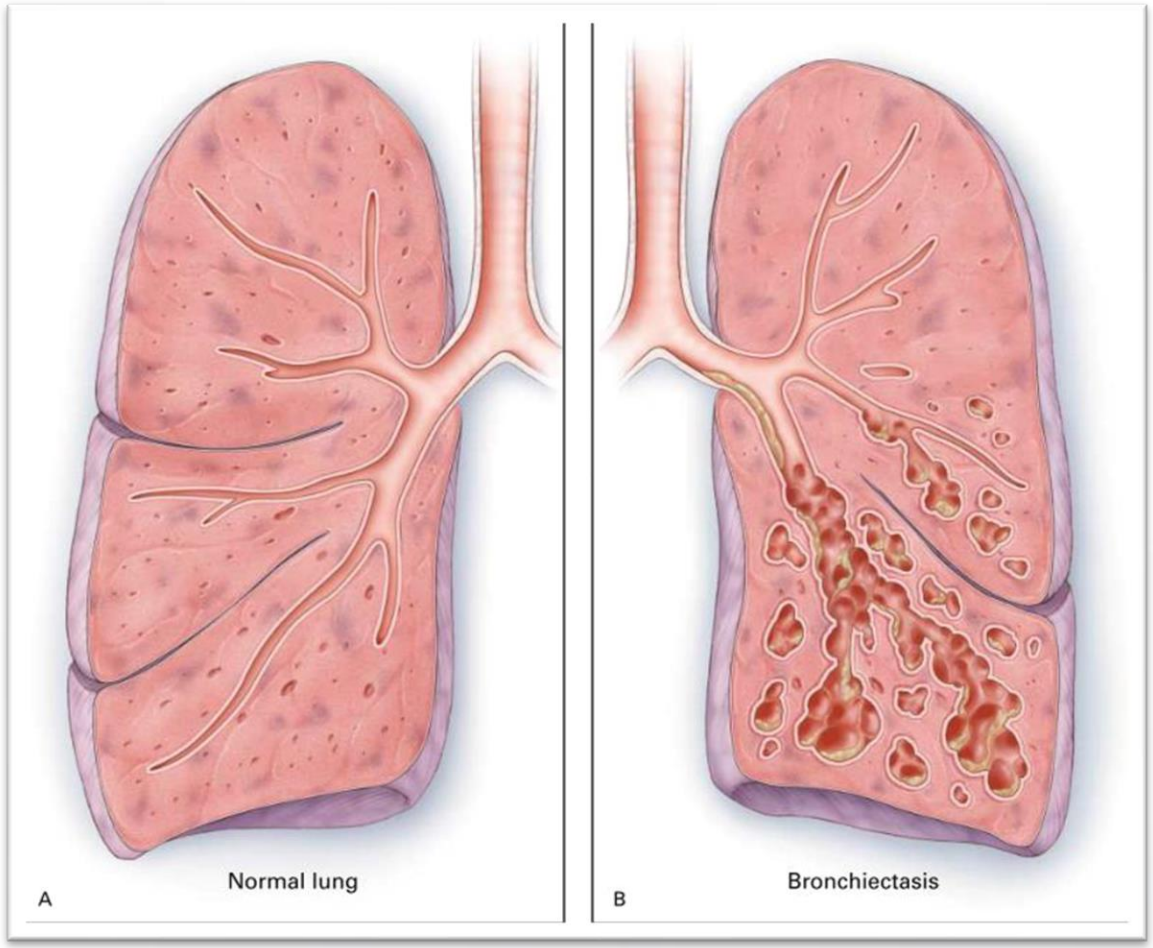
Bronchiectasis



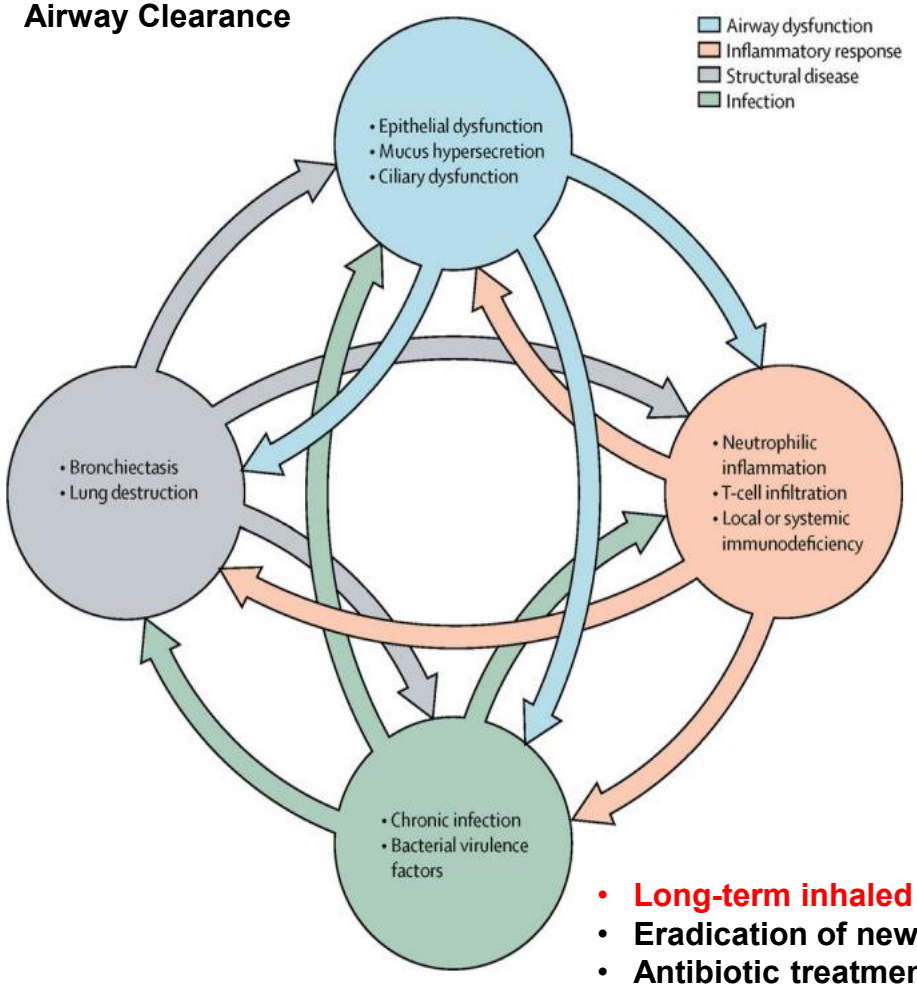
- Bronchiectasis is a chronic airway disorder characterized by permanent dilation of the bronchi.
- Clinical presentations vary widely, from asymptomatic cases to patients with chronic cough, sputum, recurrent infection and exacerbations.
- Prevalence is 464 cases per 100 000 population in South Korea.
- Bronchiectasis is associated with increased economic burden, hospital admission, and mortality rate.

N Engl J Med. 2002;346(18):1383-93, Eur Respir J . 2019 Aug 29;54(2):1900194., Eur Respir J. 2017;50(3)

Pathogenesis of Bronchiectasis

Vicious vortex

- Long-term mucoactive treatments
- Airway Clearance



- Long-term bronchodilator therapy
- Surgery
- Pulmonary rehabilitation

- Long-tern anti-inflammatory therapies

- Long-term inhaled or oral antibiotic therapy
- Eradication of new pathogenic microorganisms
- Antibiotic treatment of exacerbations

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

Causes of Exacerbations

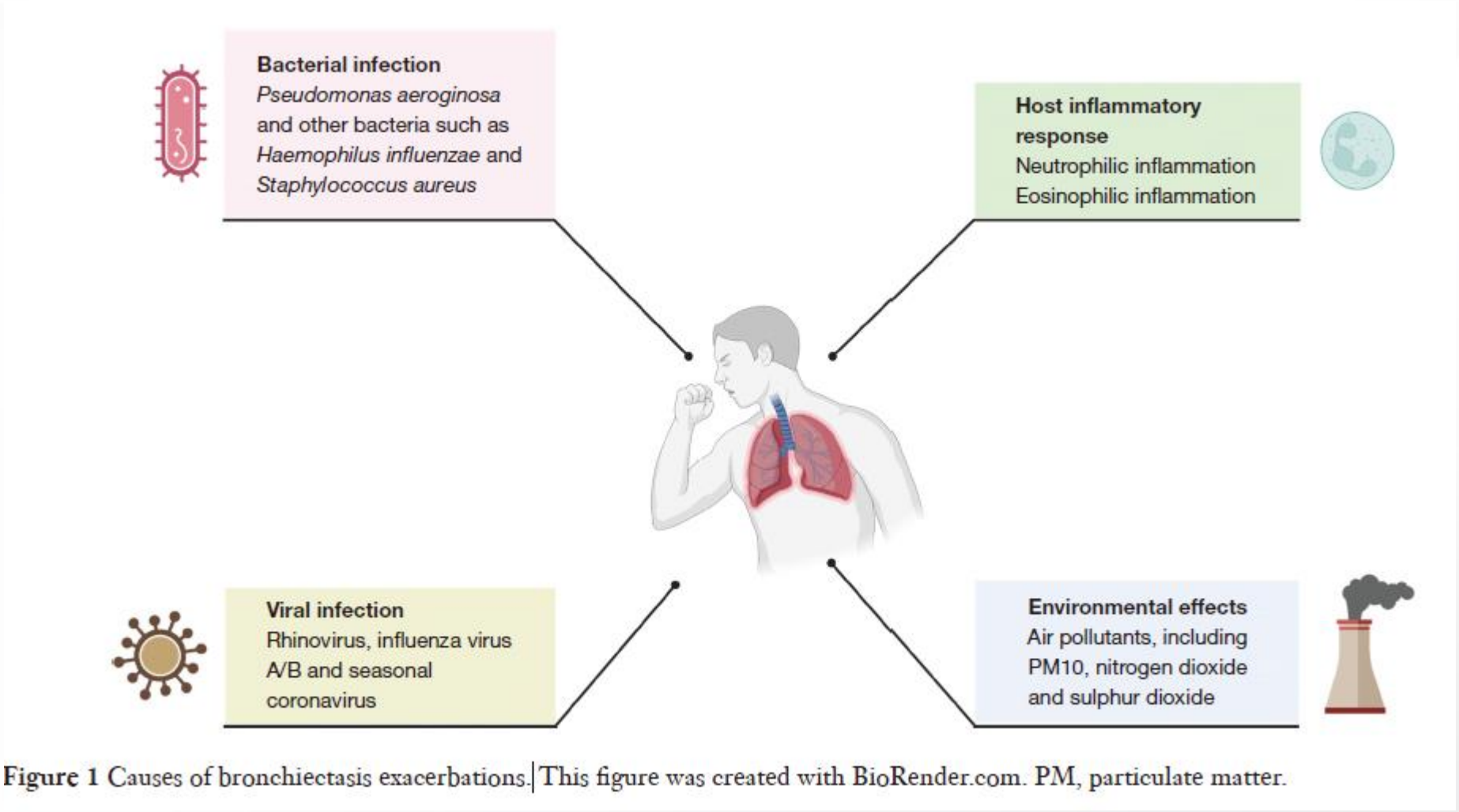


Figure 1 Causes of bronchiectasis exacerbations. This figure was created with BioRender.com. PM, particulate matter.

Am J Respir Crit Care Med. 2014 Mar 1;189(5):576-85.

Definition of Exacerbation in BE

1. Person with bronchiectasis with a deterioration ≥ 3 symptoms for at least 48 hours
    - Cough
    - Sputum volume and/or consistency
    - Sputum purulence
    - Breathlessness and/or exercise intolerance
    - Fatigue and/or malaise
    - Hemoptysis

2. Clinician's decision that a change in bronchiectasis treatment is required.

Am J Respir Crit Care Med. 2014 Mar 1;189(5):576-85.

Clinical Impact of Exacerbation

ORIGINAL ARTICLE

Characterization of the "Frequent Exacerbator Phenotype" in Bronchiectasis

James D. Chalmers[1], Stefano Aliberti[2,3], Anna Filonenko[4], Michal Shteinberg[5], Pieter C. Goeminne[6,7], Adam T. Hill[8,9], Thomas C. Fardon[1], Dusanka Obradovic[10], Christoph Gerlinger[4,11] Giovanni Sotgiu[12], Elisabeth Operschall[4], Robert M. Rutherford[13], Katerina Dimakou[14], Eva Polverino[15], Anthony De Soyza[16,17], and Melissa J. McDonnell[13,17]

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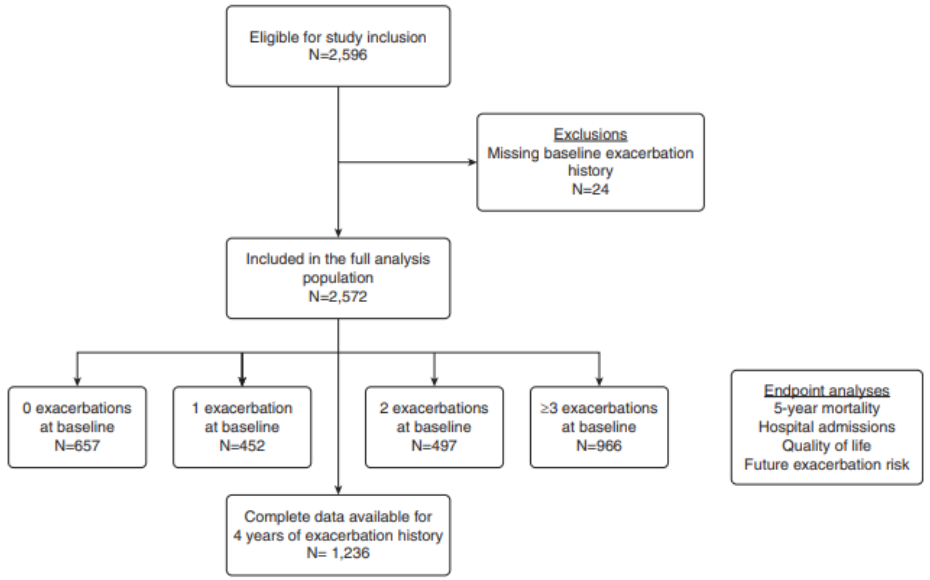


Figure 1. Patient groups and endpoints used in the analysis.

Objectives

- To establish if there is a "frequent exacerbator phenotype" in bronchiectasis and the impact of exacerbations on long-term clinical outcomes.

Methods

- Multicenter cohort: 2,572 patients (Europe & Israel).
- Follow-up: up to 5 years.
- Categorization by baseline exacerbation frequency: 0 / 1 / 2 / ≥3 per year
- Outcomes: Repeatability, hospitalizations, QoL, mortality.

Am J Respir Crit Care Med . 2018 Jun 1;197(11):1410-1420

Table 2. Adjusted and Unadjusted Incident Rate Ratios for Exacerbation Frequency during Follow-up

	Unadjusted			Adjusted		
	IRR	95% CI	*P* Value	IRR	95% CI	*P* Value
0 Exacerbations	1.0 (reference)			1.0 (reference)		
1 Exacerbation	1.73	1.47–2.02	<0.0001	1.81	1.54–2.12	<0.0001
2 Exacerbations	3.14	2.70–3.66	<0.0001	3.07	2.62–3.60	<0.0001
3 Exacerbations	5.97	5.27–6.78	<0.0001	5.18	4.51–5.95	<0.0001
Age (per 10 yr)	1.00	0.96–1.03	0.8	0.96	0.95–1.03	0.6
Sex (M)	1.11	1.00–1.23	0.04	0.95	0.86–1.06	0.4
MRC dyspnea score	1.24	1.19–1.29	<0.0001	1.02	0.97–1.07	0.4
FEV_1% predicted (per 10%)	0.88	0.87–0.90	<0.0001	0.96	0.94–0.98	0.001
Reiff score	1.04	1.03–1.06	<0.0001	1.02	1.00–1.03	0.05
Smoking history	1.22	1.10–1.35	<0.0001	0.95	0.85–1.06	0.3
Haemophilus influenzae	1.07	0.96–1.20	0.2	1.13	1.01–1.28	0.04
Moraxella catarrhalis	0.94	0.78–1.14	0.5	0.94	0.77–1.15	0.5
Staphylococcus aureus	1.19	0.97–1.45	0.1	1.08	0.88–1.32	0.5
Enterobacteriaceae	1.30	1.08–1.57	0.006	0.99	0.82–1.20	0.9
Pseudomonas aeruginosa	1.94	1.69–2.23	<0.0001	1.20	1.04–1.40	0.01
Asthma	1.22	1.03–1.44	0.02	1.16	0.98–1.38	0.09
COPD	1.89	1.66–2.16	<0.0001	1.43	1.22–1.67	<0.0001
Idiopathic	0.72	0.65–0.79	<0.0001	0.92	0.83–1.02	0.1

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IRR = incident rate ratio; MRC = Medical Research Council.

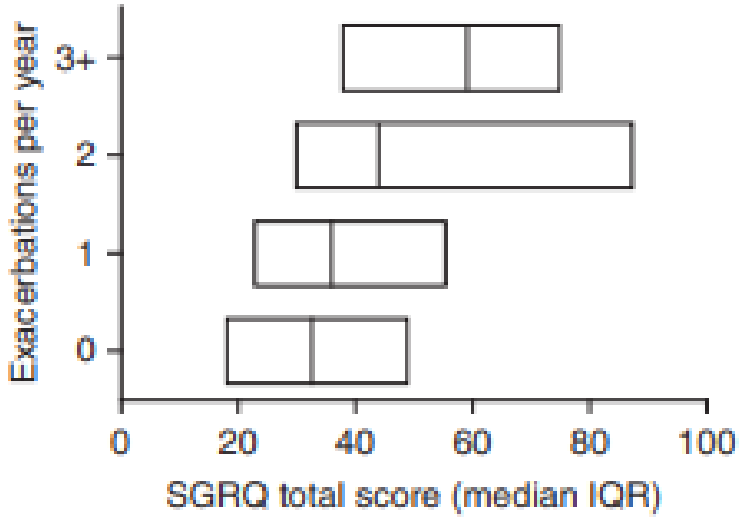
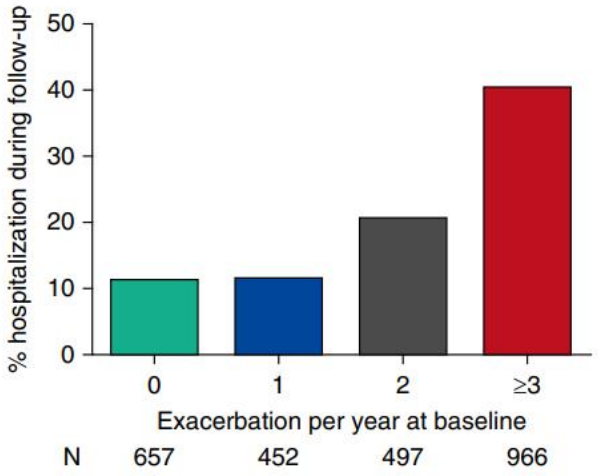
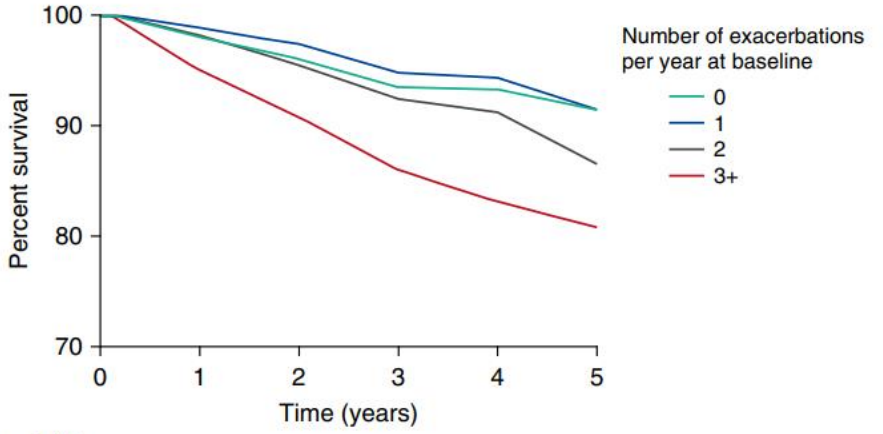


Figure 3. St. George's Respiratory Questionnaire (SGRQ) scores according to baseline exacerbation frequency ($P < 0.0001$ by Kruskal-Wallis test). IQR = interquartile range.





Numbers at risk

0	657	654	600	554	522	153
1	452	444	402	381	351	134
2	497	490	437	407	376	196
3 or more	966	958	836	771	694	365

Figure 4. Follow-up hospitalization rates and annual survival in groups on the basis of baseline exacerbations.

- **Frequent exacerbator phenotype** Associated with **Poor quality of life, Increased hospitalization & mortality**

Exacerbations as a Predictor of Mortality

ORIGINAL ARTICLE

The Bronchiectasis Severity Index
An International Derivation and Validation Study

James D. Chalmers[1], Pieter Goeminne[2], Stefano Aliberti[3], Melissa J. McDonnell[4,5], Sara Lonni[3], John Davidson[4], Lucy Poppelwell[1], Waleed Salih[1], Alberto Pesci[3], Lieven J. Dupont[2], Thomas C. Fardon[1], Anthony De Soyza[4,5], and Adam T. Hill[6]

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Table 3: Results of the Cox Proportional Hazard Regression Analysis for Mortality and Hospitalization

Severity Marker	HR (95% CI) for Hospital Admissions during Follow-up	HR (95% CI) for Mortality	Score Points
Age, yr			
<50	1.0 (reference)	1.0 (reference)	0
50–69	1.38 (0.73–2.56)	2.21 (0.28–17.5)	2
70–79	1.50 (0.79–2.82)	8.57 (1.15–63.63)	4
80+	1.76 (0.89–3.50)	23.16 (3.09–173.7)	6
BMI			
<18.5	1.23 (0.73–2.08)	2.25 (1.09–4.67)	2
18.5–25	1.0 (reference)	1.0 (reference)	0
26–29	0.90 (0.62–1.30)	0.91 (0.46–1.81)	0
30 or more	1.14 (0.76–1.70)	1.38 (0.68–2.81)	0
FEV_1 % predicted			
>80	1.0 (reference)	1.0 (reference)	0
50–80	1.17 (0.74–1.85)	1.34 (0.67–2.67)	1
30–49	1.40 (0.68–2.85)	1.58 (0.72–3.46)	2
<30	1.52 (1.03–2.25)	4.47 (1.60–12.53)	3
Hospital admission before study			
No	1.0 (reference)	1.0 (reference)	0
Yes	13.5 (9.40–19.46)	2.43 (1.30–4.53)	5
Exacerbations before the study			
0	1.0 (reference)	1.0 (reference)	0
1–2	1.67 (0.78–3.58)	1.78 (0.80–3.98)	0
3 or more	2.25 (0.89–5.70)	2.03 (1.02–4.03)	2
MRC dyspnea score			
1–3	1.0 (reference)	1.0 (reference)	0
4	2.42 (1.66–3.52)	1.05 (0.50–2.20)	2
5	2.69 (1.59–4.53)	1.15 (0.50–2.63)	3
Pseudomonas colonization			
No	1.0 (reference)	1.0 (reference)	0
Yes	2.16 (1.36–3.43)	1.58 (0.75–3.34)	3
Colonization with other organisms			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.66 (1.12–2.44)	1.10 (0.54–2.24)	1
Radiological severity: ⩾3 lobes involved or cystic bronchiectasis			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.48 (1.02–2.15)	1.05 (0.57–1.94)	1

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; MRC = Medical Research Council.
All factors founded to be significantly associated with either mortality or hospital admissions were included in the derivation of the severity score.

Am J Respir Crit Care Med. 2014 Mar 1;189(5):576-85.

Management targeting treatable traits

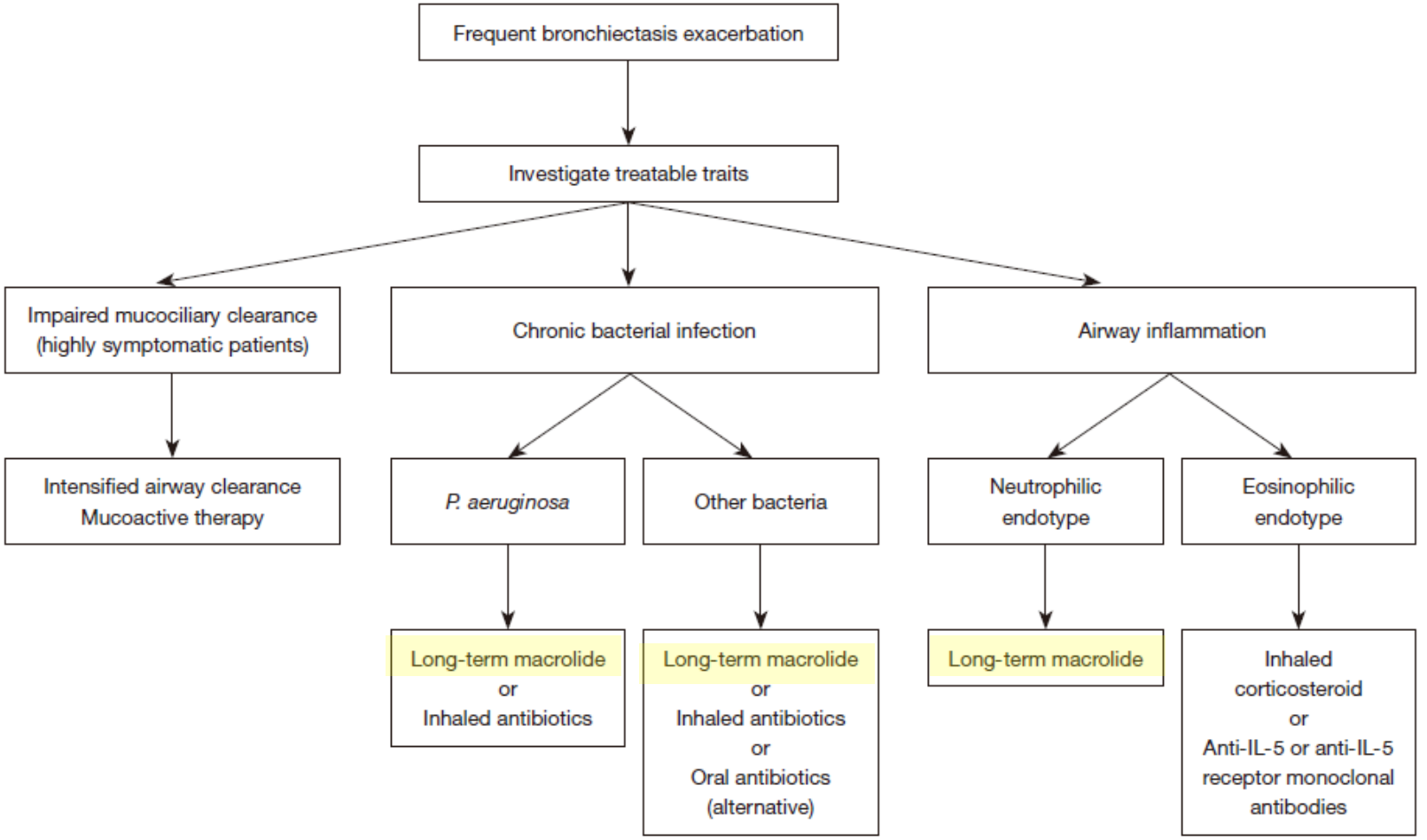

Figure 2 Management targeting treatable traits to prevent bronchiectasis exacerbations. IL, interleukin.

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2023 Australia/New Zealand guideline

Received: 13 October 2022 | Accepted: 18 January 2023
DOI: 10.1111/resp.14479

POSITION PAPER

Respirology WILEY

Thoracic Society of Australia and New Zealand (TSANZ) position statement on chronic suppurative lung disease and bronchiectasis in children, adolescents and adults in Australia and New Zealand

Long-term oral macrolides should be considered for patients with the frequent exacerbator phenotype (≥3 exacerbations requiring antibiotics in the preceding 12-months) and without contraindications to these agents. Such courses of macrolides should be for at least 6-months with regular assessments to determine if there is a clinical benefit. Those receiving longer courses should be reviewed regularly for adherence, development of adverse events (especially gastrointestinal and auditory) and emergent macrolide-resistant bacteria, and to determine risk versus benefit.

Before commencing long-term macrolides;

(a) seek specialist advice,

(b) ensure NTM infection is excluded in patients capable of providing a sputum specimen,

(c) perform an electrocardiogram in adults to determine their QTc interval (an electrocardiogram should also be ordered in children/adolescents when there is a history of acute cardiac events, if there is a family history of prolonged QT syndrome and/or arrhythmias, or if already receiving QT prolonging medication), and

(d) warn adults that macrolides may adversely affect their hearing, and if confirmed the antibiotic will be discontinued.

2017 Saudi Thoracic Society guideline

Macrolides (Long-term, Low-dose) (A)

- ↓ Exacerbations, sputum volume
- Attenuates the decline in pulmonary function
- ↑ Quality of life (QoL)

Indications (A)

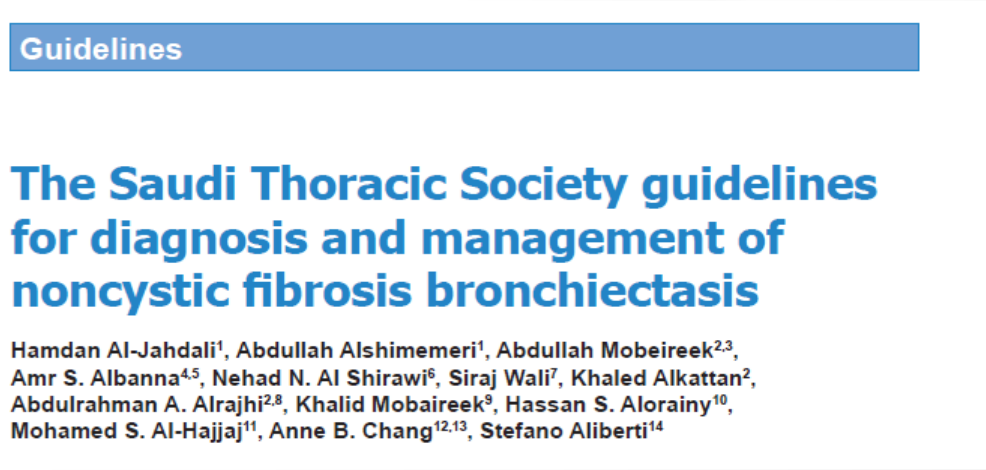
- Moderate–severe bronchiectasis with ≥3 exacerbations/year or ≥2 hospitalizations in past year

Risks (D)

- Bacterial resistance
- Cardiotoxicity

Before Starting (D)

- Rule out **MAC** (sputum culture)
- Obtain **ECG** in adults (QT interval)


Guidelines

The Saudi Thoracic Society guidelines for diagnosis and management of noncystic fibrosis bronchiectasis

Hamdan Al-Jahdali[1], Abdullah Alshimemeri[1], Abdullah Mobeireek[2,3], Amr S. Albanna[4,5], Nehad N. Al Shirawi[6], Siraj Wali[7], Khaled Alkattan[2], Abdulrahman A. Alrajhi[2,8], Khalid Mobaireek[9], Hassan S. Alorainy[10], Mohamed S. Al-Hajjaj[11], Anne B. Chang[12,13], Stefano Aliberti[14]

Ann Thorac Med . 2017 Jul-Sep;12(3):135-161.

2017 Spanish guideline

Macrolides in Bronchiectasis

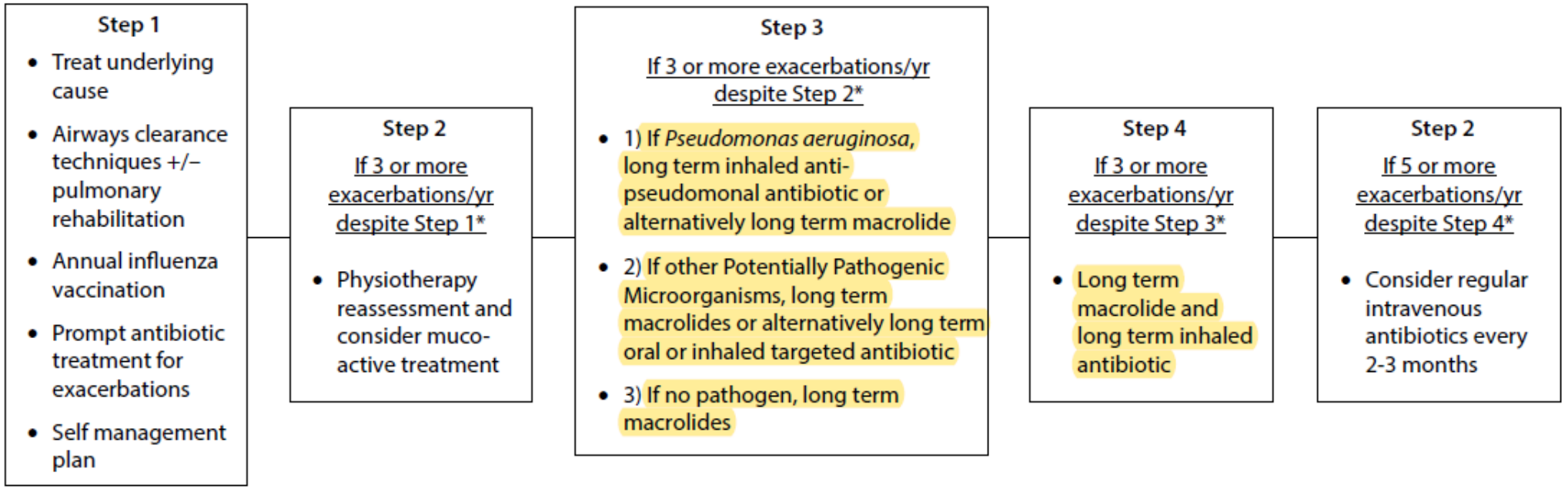
- **Clinical Benefits** *(Strong recommendation, high-quality evidence)*
  - Anti-inflammatory & anti-biofilm effects
  - ↓ Exacerbations & sputum volume
  - ↑ Quality of Life
  - Attenuates lung function decline
- **Indication:** Stable BE with ≥2 annual exacerbations despite optimal appropriate treatment
- **Considerations:** Common in chronic bronchial infection (esp. *P. aeruginosa*) with abundant sputum / poor control despite antibiotic treatment
- **Preferred regimen:** Azithromycin 500 mg, 3×/week
- **Adverse effects:** Mainly GI, usually transient
- **Before starting:**
  - ECG (QT prolongation)
  - Lab tests (liver function)
  - Mycobacterial culture
- **Risk:** ↑ Resistance to macrolide-sensitive pathogens
- **Clinical efficacy:** re-evaluated every 6 months based on the decrease in number of exacerbations

2019 BTS guideline

Thorax
An international journal of RESPIRATORY MEDICINE

BRITISH THORACIC SOCIETY GUIDELINE FOR BRONCHIECTASIS IN ADULTS

British Thoracic Society Bronchiectasis in Adults Guideline Development Group



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.

Figure 2 Stepwise management.

2017 ERS guideline

European Respiratory Society guidelines for the management of adult bronchiectasis

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

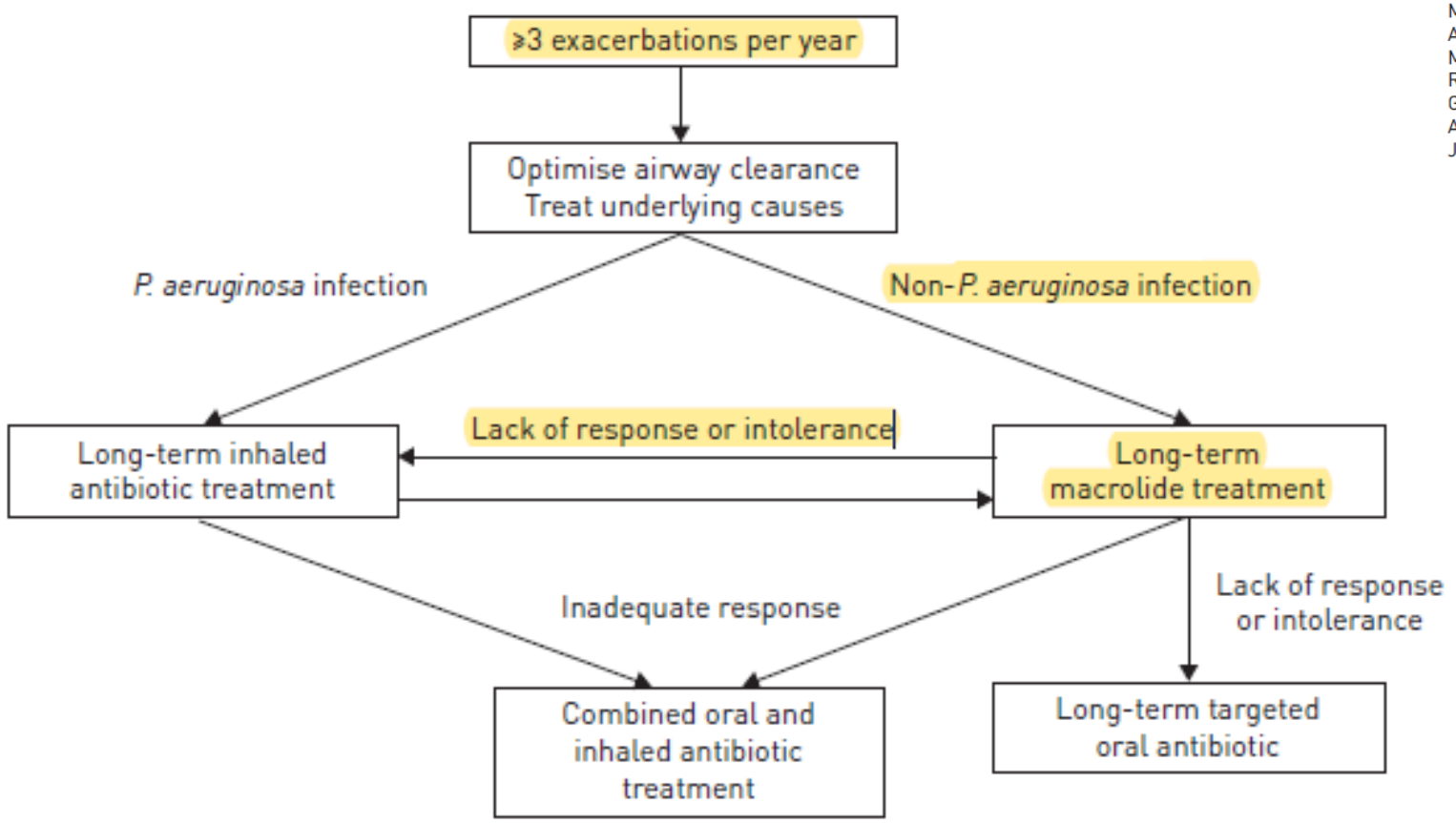


FIGURE 4 Summary of recommendations for long-term antibiotic treatment.

Macrolides in Bronchiectasis – Key RCTs

	EMBRACE Wong et al: (2012)	BAT Altenburg et al(2013)	BLESS Serisier et al(2013)
n (Intervention vs Placebo)	n=141 (71 vs 70)	n=83 (43 vs 40)	n=117 (59 vs 58)
Population	New Zealand, 3 centers (2008–2009)	Netherlands, 14 hospitals (2008–2010)	Australia, single centers (2008–2011)
Macrolide regimen	Azithromycin 500 mg 3×/wk	Azithromycin 250 mg daily	Erythromycin 400 mg bid
Duration	6 mo + 6 mo obs.	12 mo + 3 mo run-out	12 mo
Key inclusion criteria	≥1 exacerbation in prior year	≥3 exacerbations; sputum culture(+) before baseline	≥2 exacerbations; daily sputum production
Main Results (exacerbation frequency ↓)	0.59 vs 1.57 (P<0.0001)	0.84 vs 2.05 (P<0.001)	1.29 vs 1.97 (P=0.003)
Other Findings	benefit persisted 6 mo post-treatment	benefit lost after cessation	
Macrolide resistance ↑			28% ↑ macrolide-resistant streptococci

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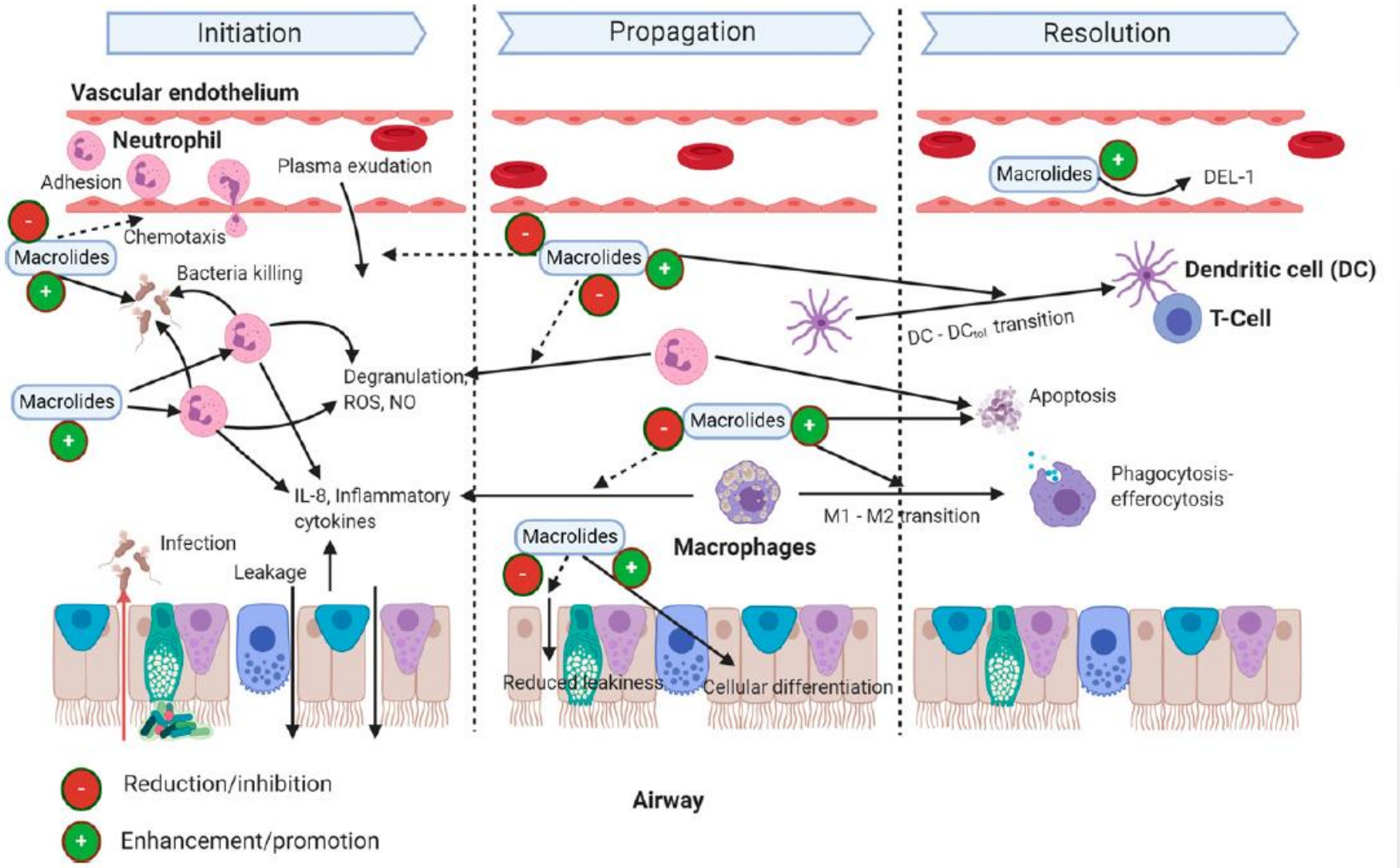
Functional Role of Macrolides



Pharmacol Rev . 2021 Oct;73(4):233-262.

The Role of Macrolides in BE

ORIGINAL RESEARCH

Macrolide Treatment Inhibits *Pseudomonas aeruginosa* Quorum Sensing in Non–Cystic Fibrosis Bronchiectasis

An Analysis from the Bronchiectasis and Low-Dose Erythromycin Study Trial

Lucy D. Burr[1,4], Geraint B. Rogers[2], Alice C.-H. Chen[1], Brett R. Hamilton[3], Gertruida F. Pool[3], Steven L. Taylor[2], Deon Venter[3], Simon D. Bowler[4], Sally Biga[5], and Michael A. McGuckin[1]

[1]Immunity, Infection and Inflammation Program, Mater Research Institute, University of Queensland, Translational Research Institute, Wooloongabba, Queensland, Australia; [2]South Australian Health and Medical Research Institute Infection and Immunity Theme, School of Medicine, Flinders University, Adelaide, Australia; and [3]OMICS, Pathology Department, [4]Department of Respiratory Medicine, and [5]Department of Microbiology, Mater Health Services, South Brisbane, Queensland, Australia

ORCID ID: 0000-0003-4010-3787 (L.D.B.).

Background:

- **Quorum sensing (QS):** a bacterial communication system regulating virulence factor production and biofilm formation. Macrolide antibiotics have effects beyond antibacterial action, including anti-inflammatory and QS inhibitory properties in vitro.

Objective:

- To determine whether long term low-dose erythromycin inhibits P. aeruginosa quorum sensing within the airways of patients with non–cystic fibrosis bronchiectasis.

Methods

- Analysis was performed on induced sputum from P. aeruginosa–positive subjects at recruitment to the BLESS(Bronchiectasis and Low-Dose Erythromycin Study) trial and after 48 weeks of treatment with erythromycin or placebo.
- Assessments: QS-related gene expression in sputum samples

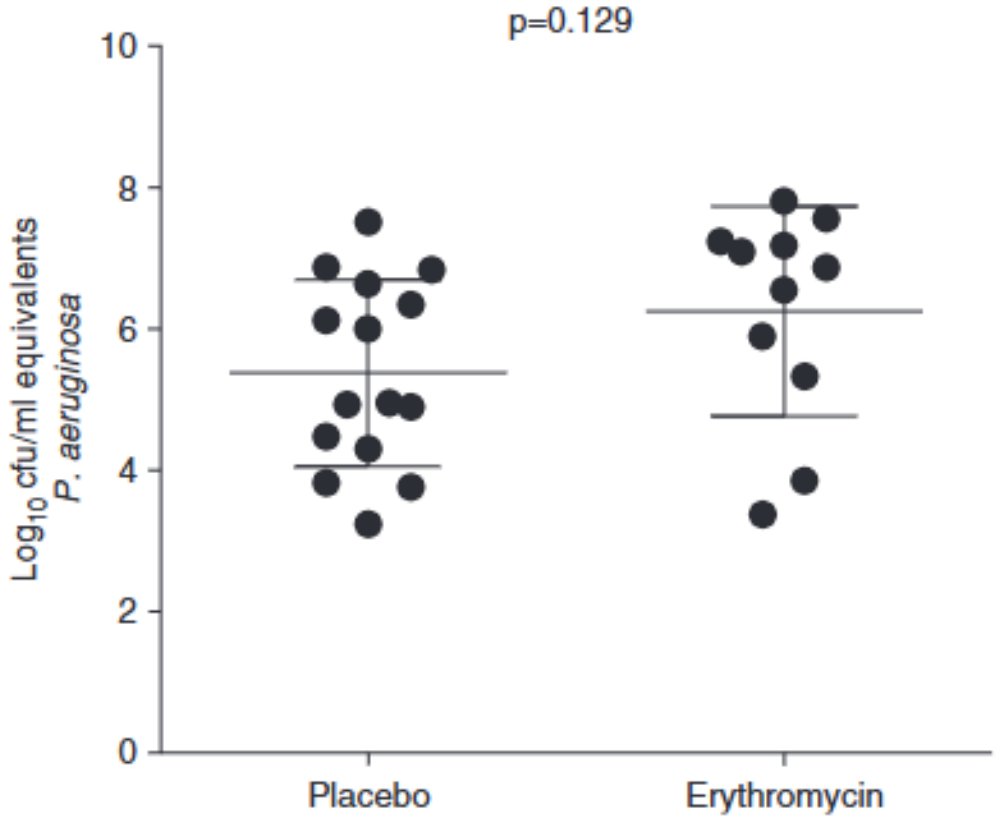


Figure 2. Total *Pseudomonas aeruginosa* bacterial load. *P. aeruginosa* bacterial load in induced sputum from patients treated with low-dose erythromycin for 48 weeks compared with placebo determined by quantitative reverse transcriptase–polymerase chain reaction (PCR) amplification of *oprL*. *P. aeruginosa* levels were determined by comparison to a standard curve, which was simultaneously generated in the same PCR reaction. Points represent Log_{10} cfu/ml of duplicate measures. *Horizontal bars* represent mean values for each set of conditions; *error bars* represent SD. *P* value from unpaired *t* test shown.

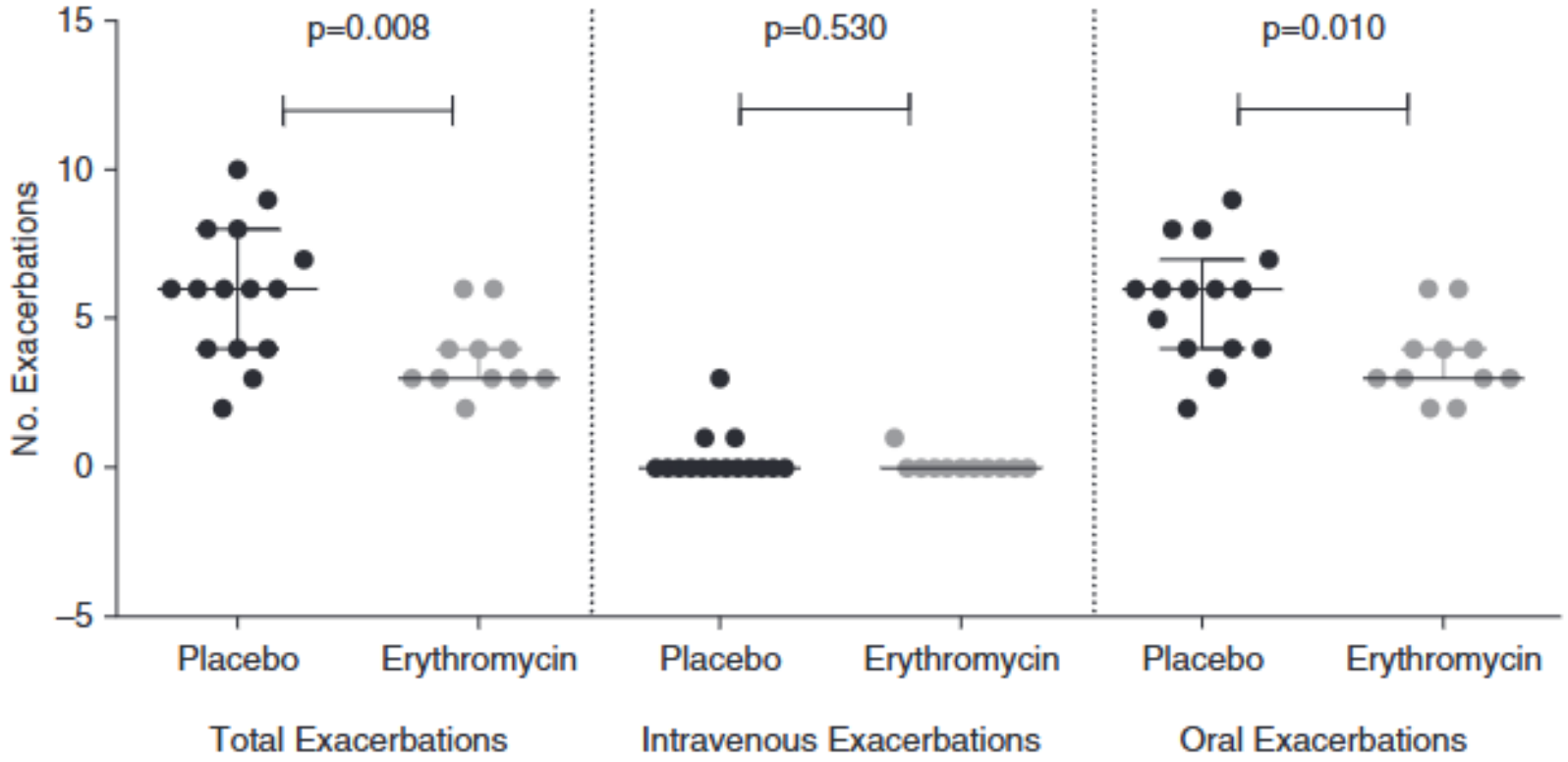


Figure 3. Pulmonary exacerbations. Pulmonary exacerbations in subjects after 48 weeks of either erythromycin or placebo therapy. Points represent number of exacerbations per individual subject. *Horizontal bars* represent median values. *P* value from Mann-Whitney *U* test shown.

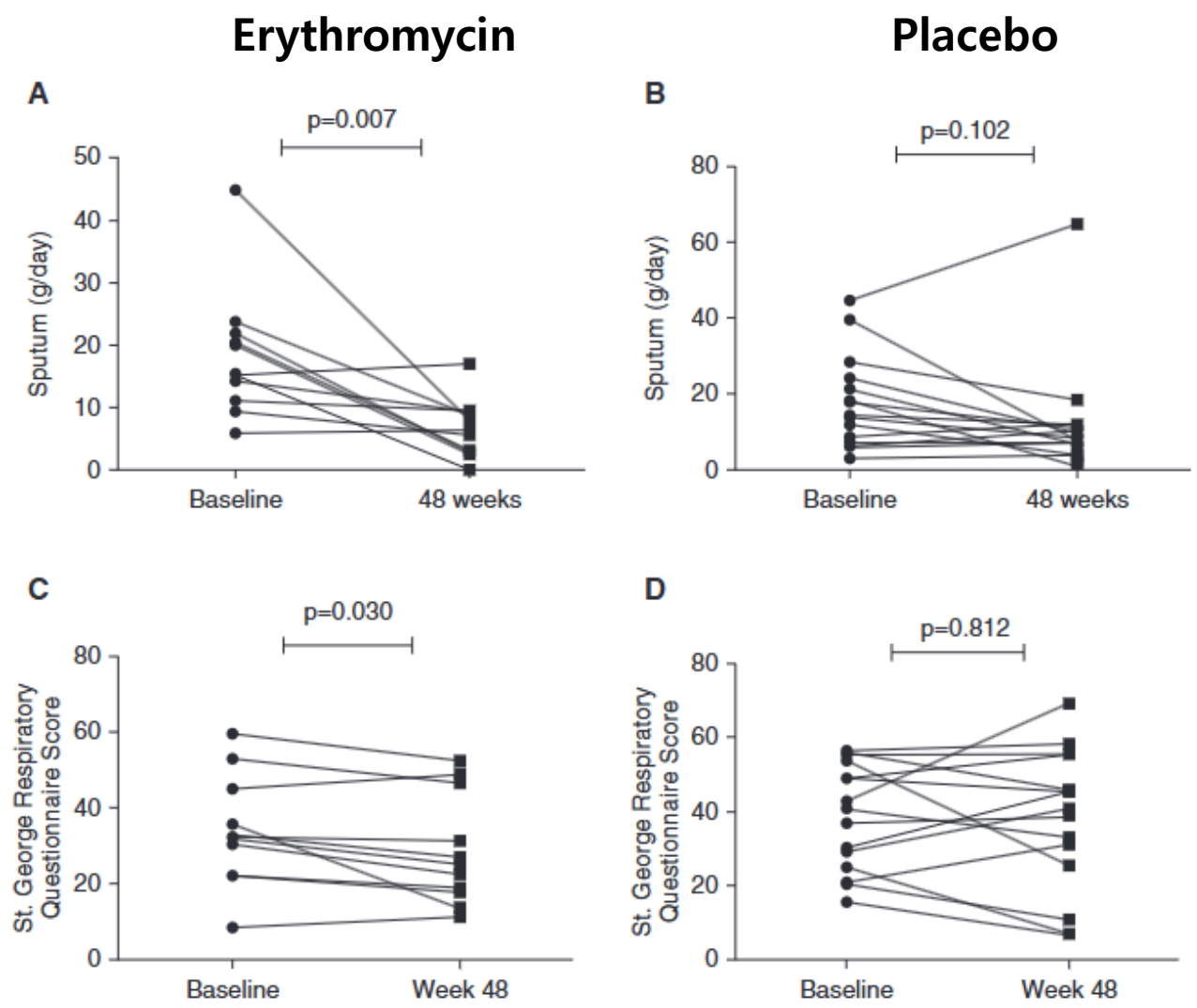
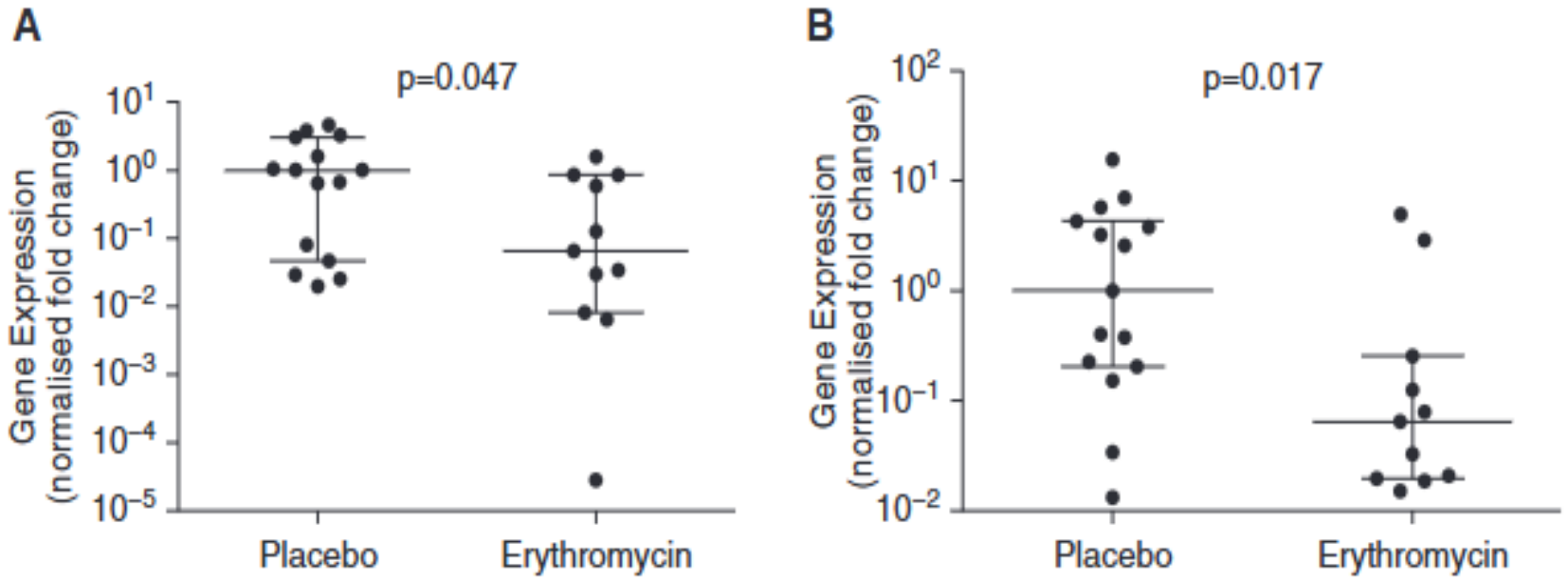


Figure 4. Clinical outcomes. (*A*, *B*) Sputum weight (g/d) at baseline and either after 48 weeks of erythromycin treatment (*A*), or after 48 weeks of placebo (*B*). (*C*, *D*) St. George's Respiratory Questionnaire at baseline and either after 48 weeks of erythromycin treatment (*C*), or after 48 weeks of placebo (*D*). A 4-point change represents a clinically significant difference. All points represent individual patient values. *P* value from paired *t* test shown.

LasR expression

PqsA expression



Conclusion: Bronchiectasis receiving long-term, low-dose erythromycin, without a reduction in bacterial load, representing a potential mechanism(inhibition of P. aeruginosa quorum sensing) of therapeutic impact beyond a classical antimicrobial or anti-inflammatory pathway.

ARTICLES
https://doi.org/10.1038/s41591-021-01289-7
nature medicine
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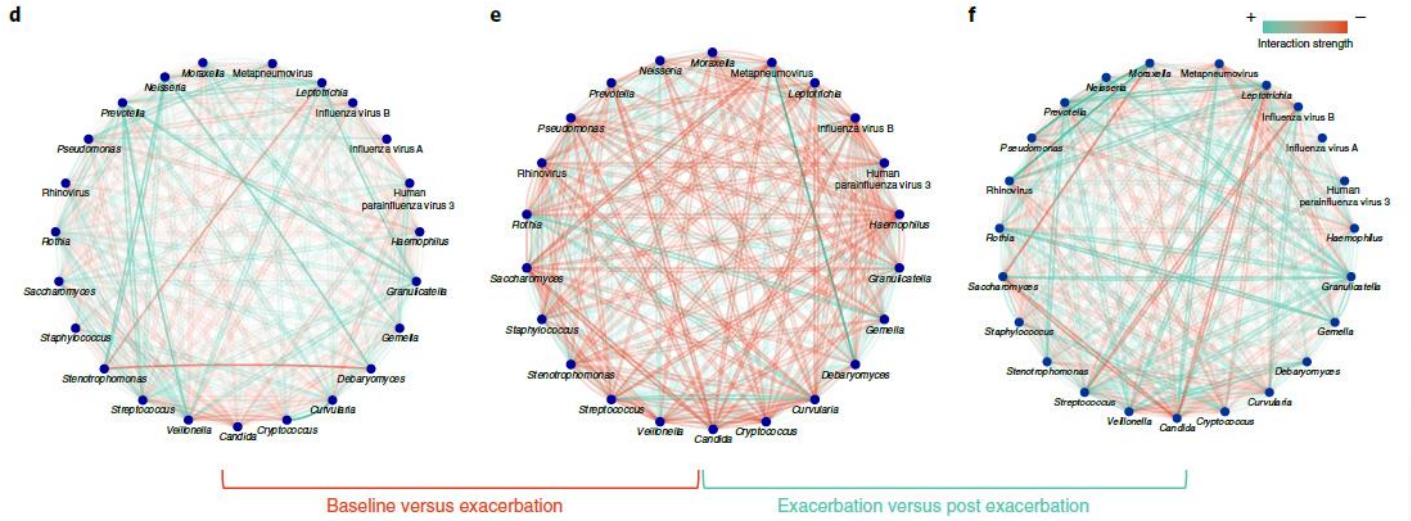
Integrative microbiomics in bronchiectasis exacerbations

Micheál Mac Aogáin[1,12], Jayanth Kumar Narayana[1,12], Pei Yee Tiew[1,2], Nur A'tikah Binte Mohamed Ali[1], Valerie Fei Lee Yong[1], Tavleen Kaur Jaggi[1], Albert Yick Hou Lim[3], Holly R. Keir[4], Alison J. Dicker[4], Kai Xian Thng[1], Akina Tsang[1], Fransiskus Xaverius Ivan[1], Mau Ern Poh[5], Martina Oriano[6,7], Stefano Aliberti[6,7], Francesco Blasi[6,7], Teck Boon Low[8], Thun How Ong[2], Brian Oliver[9,10], Yan Hui Giam[4], Augustine Tee[8], Mariko Siyue Koh[2], John Arputhan Abisheganaden[3]



- **Interactome:** Microbial networks influence disease activity. Exacerbations are associated with increased negative interactions within the microbiome.

- **Antibiotics:** provide benefit not only via direct antimicrobial activity but also by
  - Modifying the interactome
  - Reducing pathogen virulence indirectly

Contents

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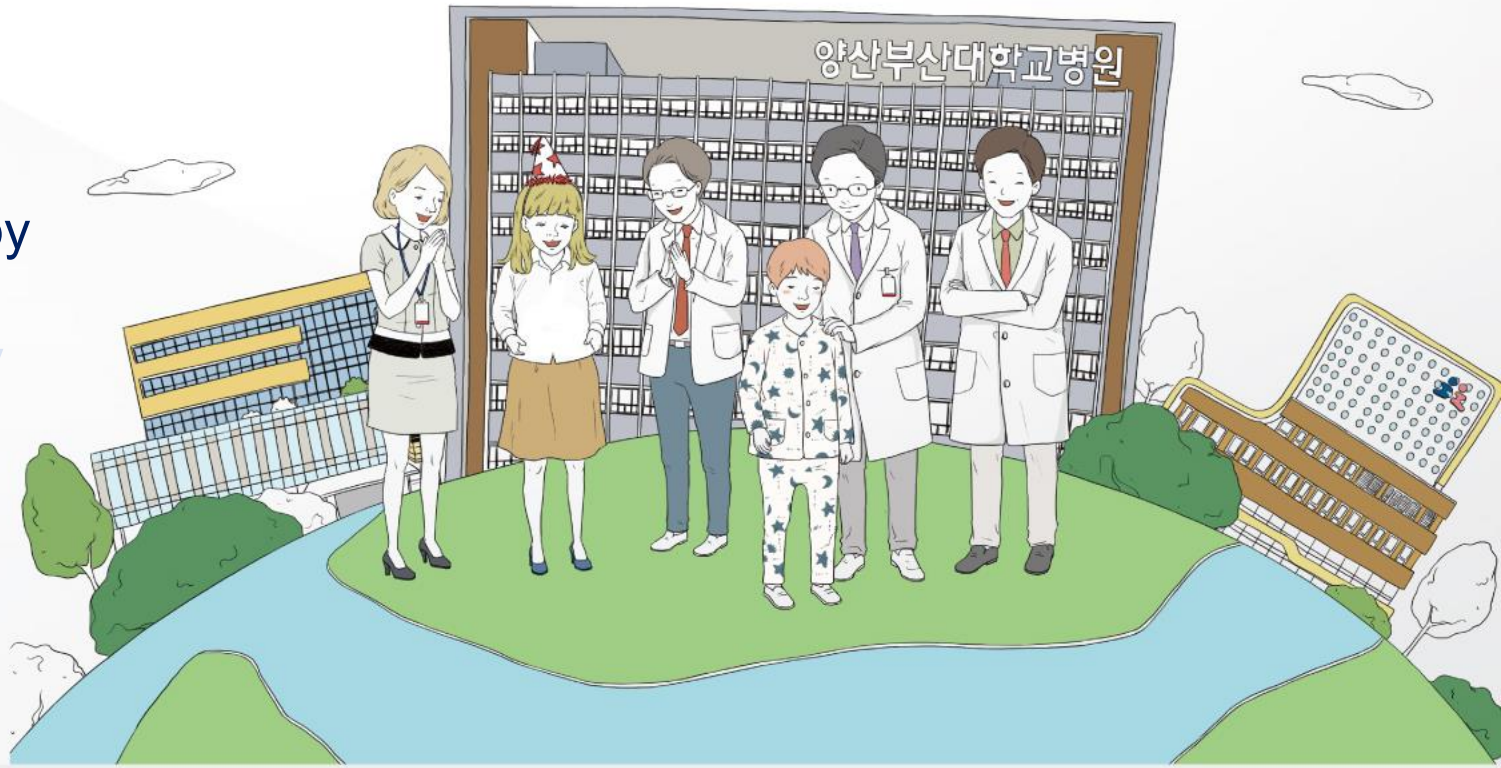

Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

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

- **Design:** Double-blind RCTs, placebo-controlled, adult bronchiectasis (non-CF) (2000-2018)
- **Primary outcome:** Frequency of exacerbations needing antibiotics
- **Secondary outcomes:**
  - Time to first exacerbation
  - Change in QoL (SGRQ)
  - Change in FEV_1

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

Key RCT of Macrolide Use in BE

	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**

Analysis of Exacerbation Frequency

- Macrolide reduced the frequency of exacerbations (IRR: 0·49, 95% CI 0·36 to 0·66; p<0·0001).

	Number of participants (intervention vs placebo)	Incident rate ratio (95% CI)	p value	$p_{interaction}$ value
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

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

Analysis of Time to First Exacerbation

- Macrolide improved the time to first exacerbation (adjusted HR 0·46, 0·34 to 0·61; p<0·0001)

	HR (95% CI)	p value	$p_{interaction}$ value
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

Effect of Macrolide in QoL

- Macrolide improved QOL measured by the SGRQ (mean improvement 2·93 points, 0·03 to 5·83; p=0·048).

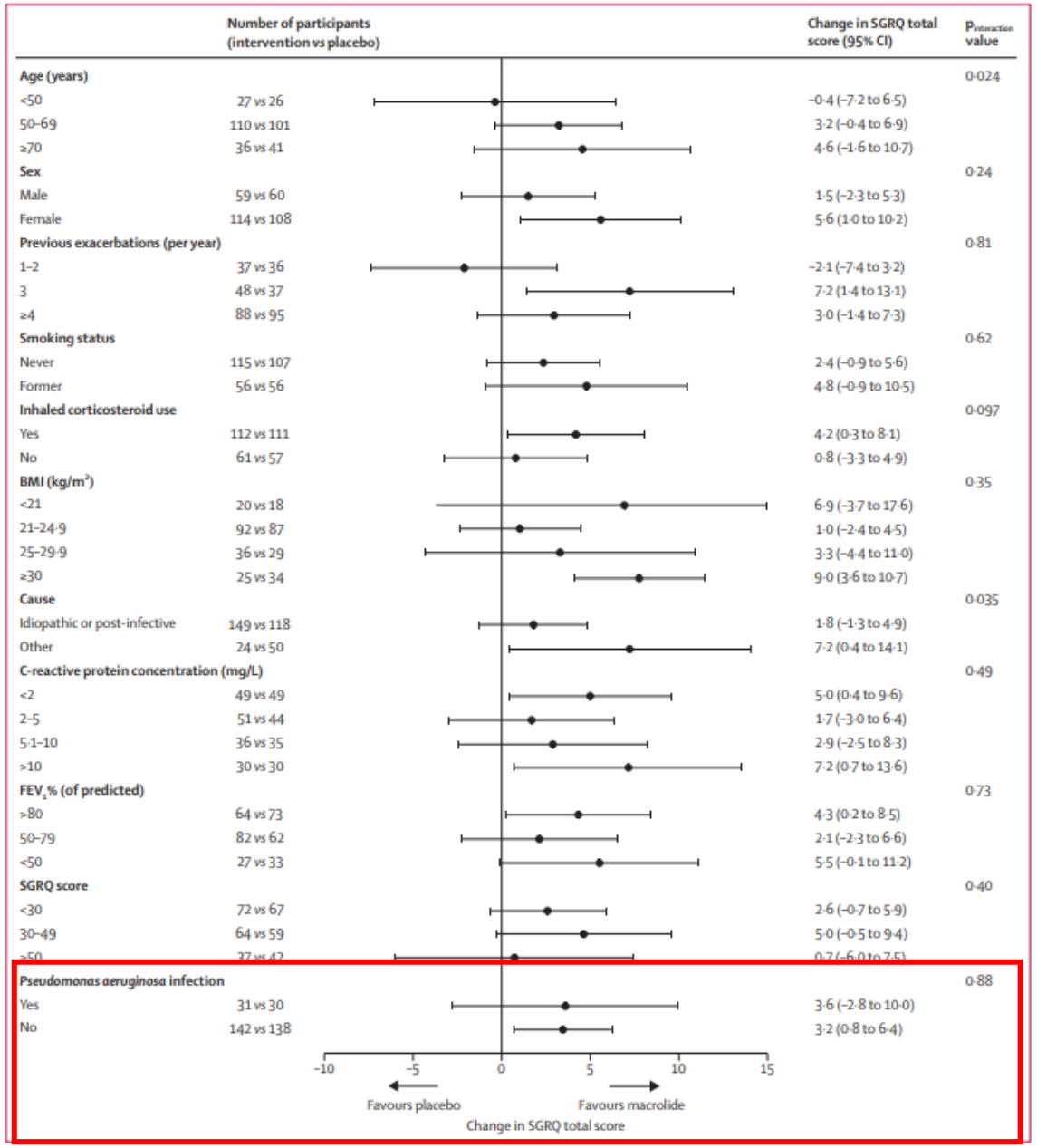

Figure 2: **Forest plot of the effect of macrolide treatment on the change in quality of life**
The change in quality of life was assessed using the SGRQ total score in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). Values for change in 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.

Effect of Macrolide in FEV_1

- Macrolides were not associated with a significant improvement in FEV_1 (67 mL at 1 year, –22 to 112; p=0·14).

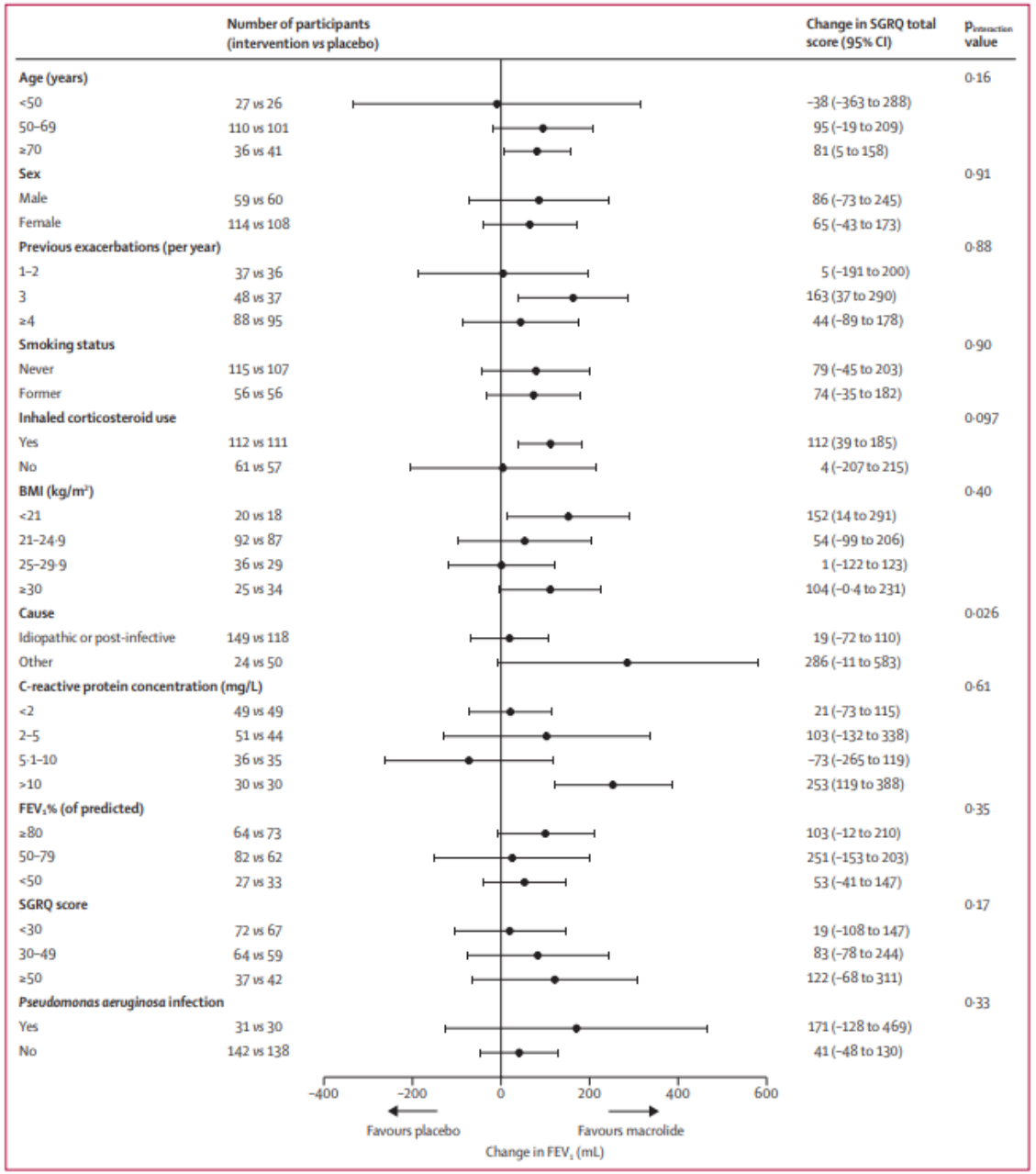

Figure 3: **Forest plot of the effect of macrolide treatment on the change in FEV_1**
The change in FEV_1 was assessed in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). BMI=body-mass index. Values for change in FEV_1 and the associated 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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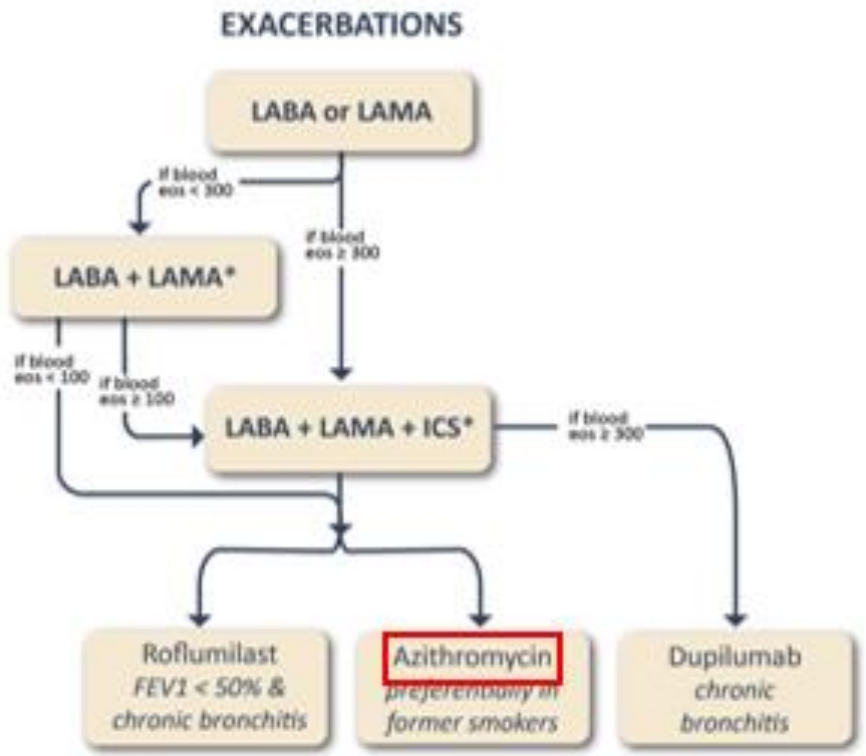
ORIGINAL RESEARCH

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



Purpose

- Long-term macrolide treatment is recommended for COPD patients with frequent exacerbations.
- Aim: Compare the effect of long-term azithromycin between **bronchiectasis patients with chronic airflow obstruction (CAO)** and **COPD patients without bronchiectasis**.

Methods

- Retrospective study at a single referral hospital.
- A total of 59 patients (43 in bronchiectasis with CAO group vs 16 in COPD without bronchiectasis group)
- Included CAO patients who received azithromycin ≥12 weeks.
- Outcomes: **development of exacerbations** and **symptom improvement**.

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:** patients with ≥2 points decrement from the initial CAT score.

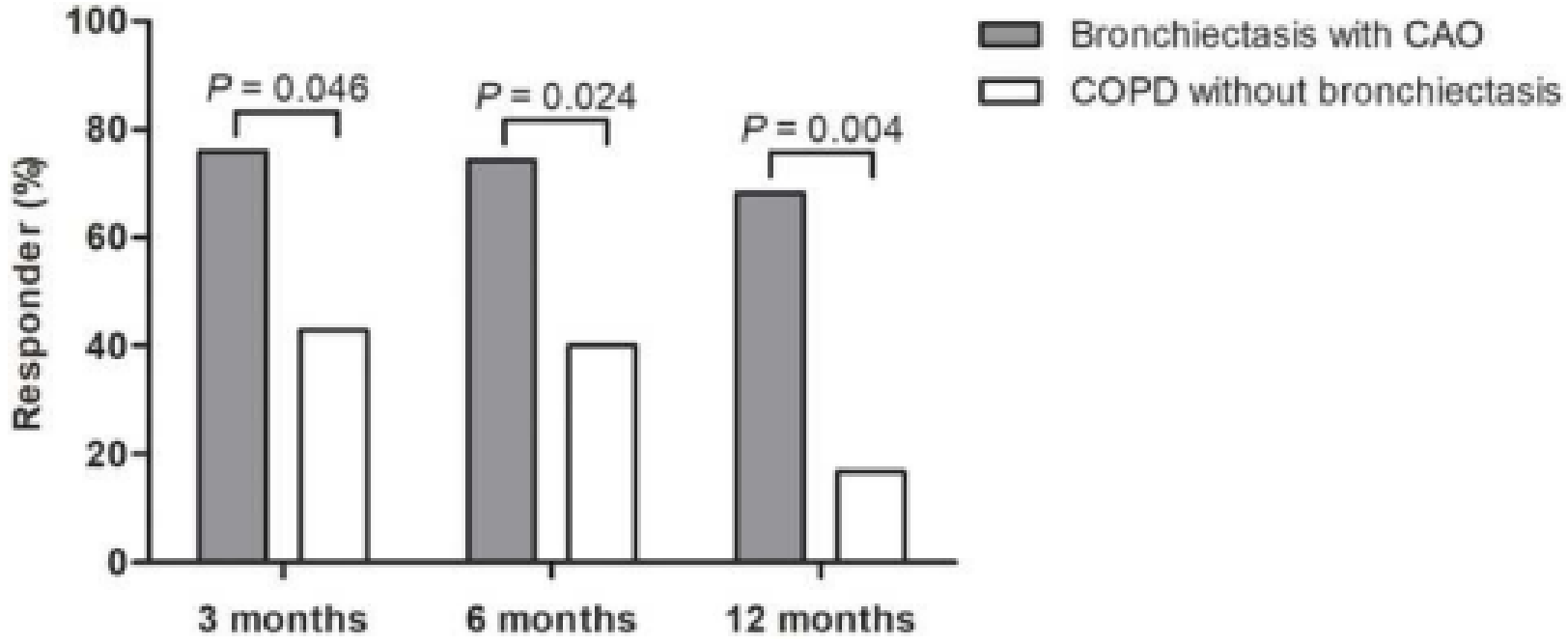


Figure 1 The proportion of symptomatic responders* after long-term azithromycin treatment. *Defined as patients with ≥2 points decrement from the initial COPD Assessment Test (CAT) score. CAT was measured in 43, 47, and 35 patients at 3, 6, and 12 months after initiation of azithromycin treatment.
Abbreviations: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

Conclusion: Bronchiectasis patients with CAO could benefit more from long-term azithromycin treatment than COPD patients without bronchiectasis.

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Safety concerns on long-term macrolide

Concerns of Long-term Macrolide Therapy

- ↑ *P. aeruginosa* abundance (BLESS trial, unclear significance)
- GI side effects
- QT prolongation, arrhythmia risk
- Tinnitus, hearing loss
- Resistant NTM risk

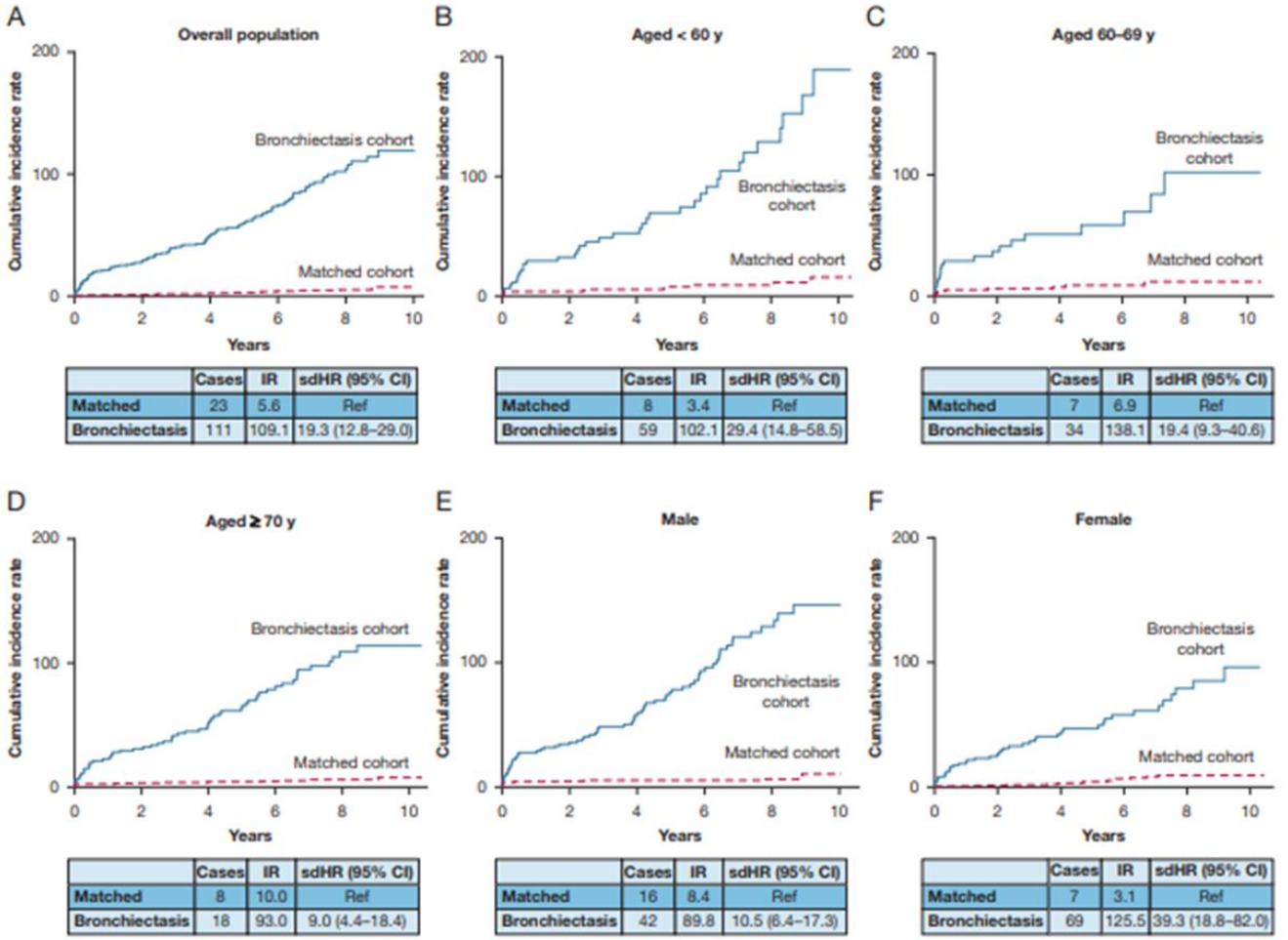
Monitoring Before/During Therapy

- Baseline ECG (QT interval)
- Sputum AFB culture (rule out NTM)
- Consider baseline audiogram
- Monitor GI tolerance, cardiac symptoms, sputum cultures

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

HR = hazard ratio; Ref = reference.

[a]Adjusted for age, sex, type of insurance, comorbidities, and use of inhaled corticosteroids, oral corticosteroids, and long-term macrolide.

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
R. GUO ET AL.

Cardiovascular benefits and safety profile of macrolide maintenance therapy in patients with bronchiectasis

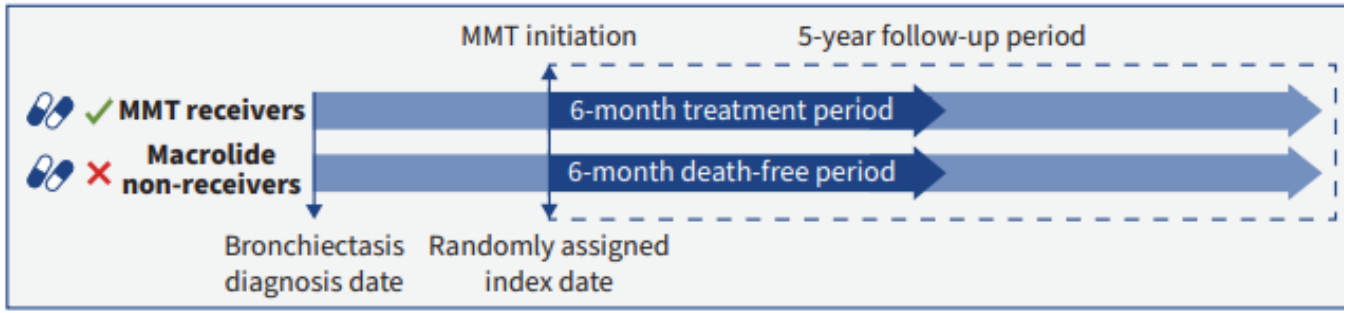
Ran Guo, Dennis Wat, Steven Ho Man Lam, Tommaso Bucci, Christopher Tze-Wei Tsang, An-Ping Cai, Yap-Hang Chan, Qing-Wen Ren, Jia-Yi Huang, Jing-Nan Zhang, Wen-Li Gu, Ching-Yan Zhu, Yik-Ming Hung, Freddy Frost, Gregory Y.H. Lip and Kai-Hang Yiu

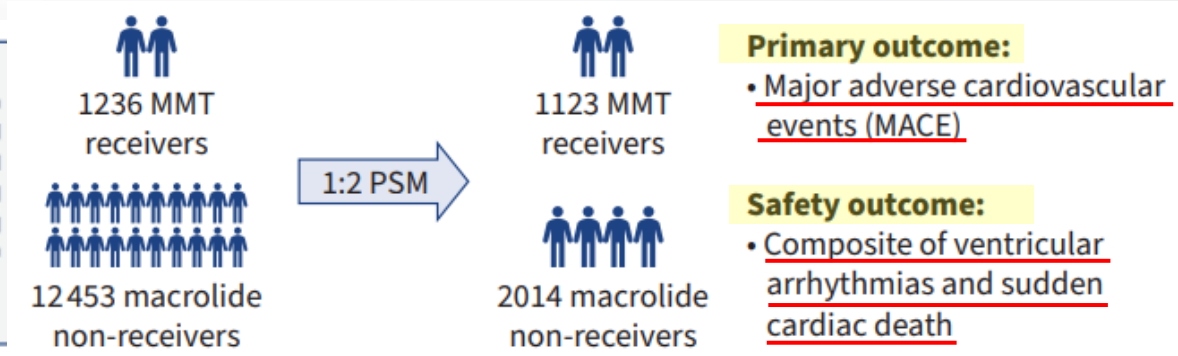
Background:

- bronchiectasis have a 3-fold increased risk of coronary heart diseases and a 5-fold elevated risk of stroke.
- This study aimed to evaluate the relationship between MMT and the incidence of cardiovascular adverse events, while also evaluating the associated risk of severe arrhythmia-related outcomes.

Method:

- territory-wide retrospective cohort study analyzed patients diagnosed with bronchiectasis in Hong Kong between 2001 and 2018.





	Events, n (incidence rate per 1000 person-years)		Hazard ratio (95% CI)	p-value
	MMT receivers	Macrolide non-receivers		
Primary outcome				
MACE	70 (16.38)	169 (24.11)	0.68 (0.52–0.90)	0.007
Secondary outcomes				
All-cause mortality	476 (109.95)	948 (132.04)	0.83 (0.74–0.93)	<0.001
Cardiovascular death	28 (6.47)	54 (7.52)	0.86 (0.54–1.35)	0.51
AMI	23 (5.33)	73 (10.28)	0.52 (0.33–0.83)	0.006
Stroke	32 (7.46)	79 (11.15)	0.61 (0.45–1.01)	0.059
Safety outcome				
Ventricular dysrhythmia or sudden cardiac death	31 (7.17)	55 (7.67)	0.93 (0.60–1.44)	0.746
Negative control outcome				
Hip fracture hospitalisation	27 (6.31)	53 (7.46)	0.85 (0.54–1.35)	0.496

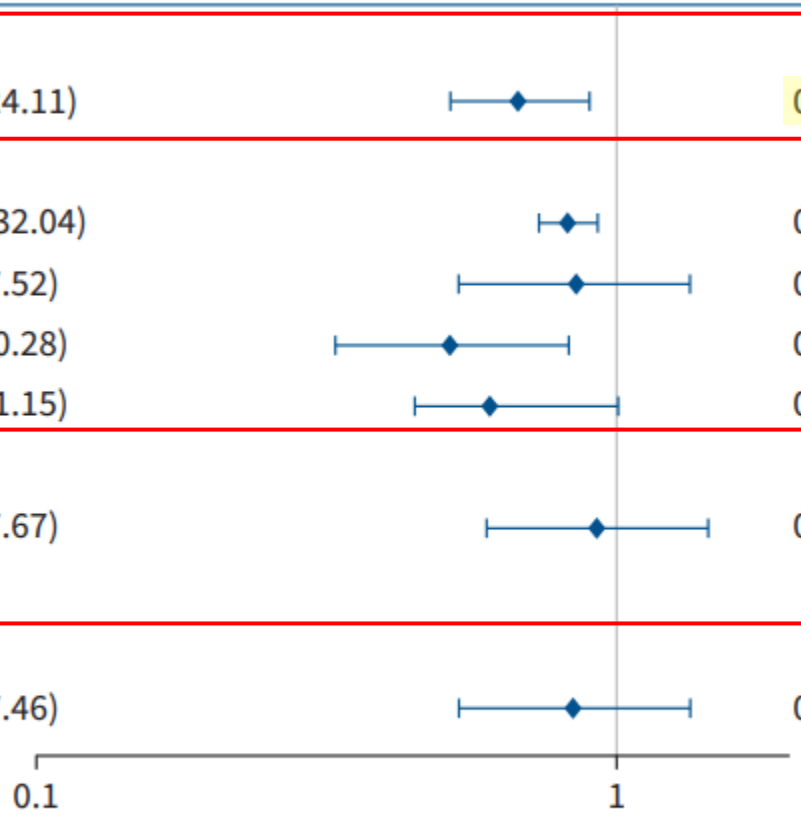
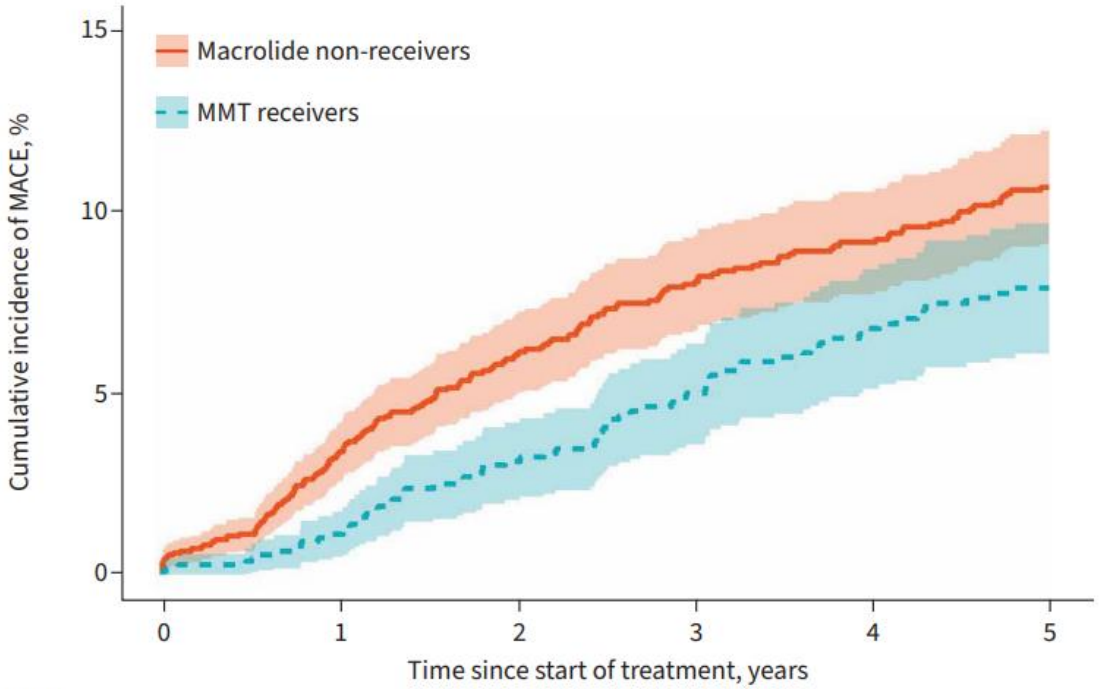


FIGURE 1 Outcomes in the 1:2 propensity score-matched macrolide maintenance therapy (MMT) receivers *versus* macrolide non-receivers. MACE: major adverse cardiovascular events; AMI: acute myocardial infarction.



At risk (n):						
Macrolide non-receivers	2014	1721	1407	1230	1104	1031
MMT receivers	1123	1034	889	781	690	628

FIGURE 2 Cumulative incidence of major adverse cardiovascular events (MACE) in the propensity score-matched cohort. MMT: macrolide maintenance therapy.

Conclusion: The administration of MMT in patients with bronchiectasis was associated with a significant reduction in the risk of MACE, without any evidence suggesting an increased risk of severe arrhythmia-related adverse events.

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Pusan National University Yangsan Hospital

Summary

Indications

- Recommended for patients with **frequent exacerbations (generally ≥3 per year)** despite optimal airway clearance and standard therapy.

Bright Side:

- Anti-inflammatory and immunomodulatory effects
- Reduces frequency of exacerbations
- improved quality of life

Dark Side:

- GI side-effects
- QT interval prolongation and arrhythmias
- Hearing loss, tinnitus
- Risk of resistant NTM & microbiome alteration

Before Prescribing – Check:

- Baseline ECG (QT interval)
- Baseline sputum AFB culture

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환자 내몸

경청해 주셔서 감사합니다.

Thank you for your attention