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Supplementary appendix

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Online supplement for:

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

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Search terms used

Medline

("Macrolide*" or "azithromycin" or "erythromycin" or "clarithromycin" or "roxithromycin") and ("bronchiectasis" or "non-cystic fibrosis bronchiectasis" or "non-CF bronchiectasis" or "NCFB") and ("randomized controlled trial" or "RCT")

Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials

randomized controlled trial [pt] or controlled clinical trial [pt] or randomized [tiab] or placebo [tiab] or drug therapy [sh] or randomly [tiab] or trial [tiab] or groups [tiab] and macrolide [tiab] or azithromycin [tiab] or erythromycin [tiab] or roxithromycin [tiab] or clarithromycin [tiab] and bronchiectasis [tiab]

EMBASE

randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR
allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti OR trial:ti and macrolide OR azithromycin OR erythromycin OR roxithromycin OR clarithromycin AND bronchiectasis

Supplementary tables and figures

Table E1shows the risk of bias assessment for the three studies. Studies were rated as low risk of bias across all domains.

The primary analysis of frequency of exacerbations showed an incident rate ratio of 0.49 95% CI 0.36-0.66,p<0.0001. Sensitivity analyses including removing baseline adjustment for age, sex and FEV_1, removing the offset and controlling for study as a random effect produced very similar results, table E2.

Further analysis of the exacerbation data shows that exacerbation reductions were evident across all groups based on prior exacerbation frequency. Absolute rates of exacerbation were higher with higher baseline exacerbation frequency. The event based number needed to treat were less than 2 for all subgroups (Table E3).

Forest plots in the main manuscript summarise the results of the change in SGRQ and FEV_1 from baseline to the end of study. The numerical data are shown in table E4 below.

Several trials of macrolides were identified by the literature search that did not meet the inclusion criteria due to short duration, a comparator that was not placebo or enrolment of a paediatric population. These studies are summarised in the table E5 below. A summary of the major results is listed below. The majority of these trials found evidence to support the efficacy of macrolides using different endpoints.

The two stage meta-analysis results are shown below in figure E1. They confirm the results of the 1 stage meta-analysis.

Study	**Sequencing generation**	**Allocation concealment**	**Blind of participants and personnel**	**Blind of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**
BAT- Altenburg 2013	Low	Low	Low	Low	Low	Low	Low
BLESS- Serisier 2013	Low	Low	Low	Low	Low	Low	Low
EMBRACE- Wong 2012	Low	Low	Low	Low	Low	Low	Low

Table E1. Risk of bias assessment

	Incident rate ratio and 95% CI	**p-value**
Primary analysis	0.49 95% CI 0.36-0.66	<0.0001
No baseline adjustment	0.49 95% CI 0.36-0.66	<0.0001
Removing off-set	0.50 95% CI 0.37-0.59	<0.0001
Controlling for study as a random effect	0.49 95% CI 0.36-0.66	<0.0001

Table E2. Sensitivity analysis of the primary outcome

Baseline exacerbation rate	Annual Mean exacerbation frequency Macrolide group	Annual Mean exacerbation frequency Placebo group	Number needed to treat
1-2 per year	0.32	1.00	1.5
3 per year	0.77	1.35	1.7
4 or more per year	1.14	2.11	1.0

Table E3. Absolute risk reductions in the macrolide and placebo groups (N=341 pooled across 3 studies).

	Change in SGRQ from baseline to end of study	p-value	P-interaction	Change in FEV1 from baseline to end of study (mL)	p-value	p-interaction
Overall effect	2.93 (0.03-5.83)	0.048	n/a	67 (-22 to 112)	0.14	n/a
Age groups						
<50 years	-0.4 (-7.2 to 6.5)	0.91		-38 (-363 to 288)	0.82	
50-69 years	3.2 (-0.4 to 6.9)	0.085	0.024	95 (-19 to 209)	0.10	0.16
70 years or more.	4.6 (-1.6 to 10.7)	0.15		81 (5 to 158)	0.038	
Sex						
male	1.5 (-2.3 to 5.3)	0.44		86 (-73 to 245)	0.29	
female	5.6 (1.0 to 10.2)	0.016	0.24	65 (-43 to 173)	0.24	0.91
Prior exacerbation						
1-2 per year	-2.1 (-7.4 to 3.2)	0.44		5 (-191 to 200)	0.96	
3 per year	7.2 (1.4 to 13.1)	0.015	0.81	163 (37 to 290)	0.011	0.88
4 or more per year	3.0 (-1.4 to 7.3)	0.18		44 (-89 to 178)	0.52	
Smoking status						
Never	2.4 (-0.9 to 5.6)	0.16		79 (-45 to 203)	0.21	
Former	4.8 (-0.9 to 10.5)	0.10	0.62	74 (-35 to 182)	0.19	0.90
Current	Not estimable	n/a		Not estimable	n/a	
Inhaled corticosteroid use						
Yes	4.2 (0.3 to 8.1)	0.034		112 (39 to 185)	0.003	
No	0.8 (-3.3 to 4.9)	0.70	0.097	4 (-207 to 215)	0.97	0.097
Body mass index at baseline*						
<21	6.9 (-3.7 to 17.6)	0.20		152 (14 to 291)	0.031	
21-24.9	1.0 (-2.4 to 4.5)	0.57		54 (-99 to 206)	0.49	
25-29.9	3.3 (-4.4 to 11.0)	0.40	0.35	1 (-122 to 123)	0.98	0.40
30 or more	9.0 (3.6 to 10.7)	0.001		104 (-0.4 to 231)	0.059	
Aetiology						
idiopathic and post-infective	1.8 (-1.3 to 4.9)	0.26		19 (-72 to 110)	0.68	
Other	7.2 (0.4 to 14.1)	0.038	0.035	286 (-11 to 583)	0.062	0.026
Baseline C-reactive protein*						
<2mg/L	5.0 (0.4 to 9.6)	0.034		21 (-73 to 115)	0.66	
2-5mg/L	1.7 (-3.0 to 6.4)	0.48		103 (-132 to 338)	0.39	
5.1-10mg/L	2.9 (-2.5 to 8.3)	0.30	0.49	-73 (-265 to 119)	0.46	0.61
>10mg/L	7.2 (0.7 to 13.6)	0.029		253 (119 to 388)	<0.001	
Baseline FEV1*						
>80% predicted	4.3 (0.2 to 8.5)	0.040		103 (-12 to 210)	0.080	
50-79% predicted	2.1 (-2.3 to 6.6)	0.35		25 (-153 to 203)	0.78	
<50% predicted	5.5 (-0.1 to 11.2)	0.056	0.73	53 (-41 to 147)	0.27	0.35
SGRQ total score						
<30	2.6 (-0.7 to 5.9)	0.13		19 (-108 to 147)	0.77	
30-49	5.0 (-0.5 to 9.4)	0.028		83 (-78 to 244)	0.31	
50 or more	0.7 (-6.0 to 7.5)	0.84	0.40	122 (-68 to 311)	0.21	0.17
Pseudomonas aeruginosa						
Yes	3.6 (-2.8 to 10.0)	0.28		171 (-128 to 469)	0.26	
No	3.2 (0.8 to 6.4)	0.045	0.88	41 (-48 to 130)	0.37	0.33

Table E4. Subgroup effects of macrolide treatment in the one-step IPD meta-analysis. For quality of life, positive values indicate improvement in quality of life.

Author	Population	N	Comparison	Duration	Summary of results
Cymbala 2005	Adults	12	Azithromycin vs no intervention	Crossover trial with 6 months of each intervention	Reduced exacerbations and 24-hour sputum volume with azithromycin
Diego 2013	Adults	36	Azithromycin vs no intervention	3 months	No effect of azithromycin on oxidative stress
Koh 1997	Children	25	Roxithromycin vs placebo	12 weeks	Roxithromycin may reduce airway hyperresponsiveness compared to placebo
Liu 2012	Adults	50	Roxithromycin +ambroxol vs no intervention	6 months	Significantly improved dyspnoea and radiological severity of disease
Liu 2014	Adults	52	Roxithromycin vs no intervention	6 months	Reduced sputum neutrophils with macrolide treatment
Lourdesamy 2014	Adults	78	Azithromycin vs placebo	3 months	Reduced sputum volume and improved St Georges Respiratory Questionnaire score with azithromycin
Tsang 1999	Adults	21	Erythromycin vs placebo	8 weeks	Improved FEV1, FVC and 24 hour sputum volume with erythromycin
Valery 2013	Children	89	Azithromycin vs placebo	Up to 24 months	Reduced exacerbation frequency with azithromycin but also increased carriage of resistant bacteria.
Yalcin 2006	Children	34	Clarithromycin vs no intervention	3 months	Clarithromycin was associated with improved IL-8, total cell count and neutrophil ratio in BAL, and reduced daily sputum production.

Table E5. Randomized controlled trials of macrolide antibiotics which were not included in the meta-analysis.

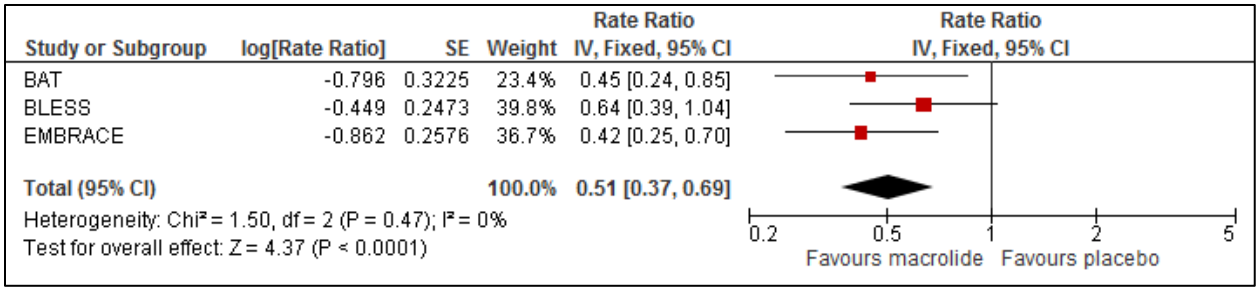

Figure E1- fixed effects two step meta-analysis of the primary outcome of frequency of exacerbations

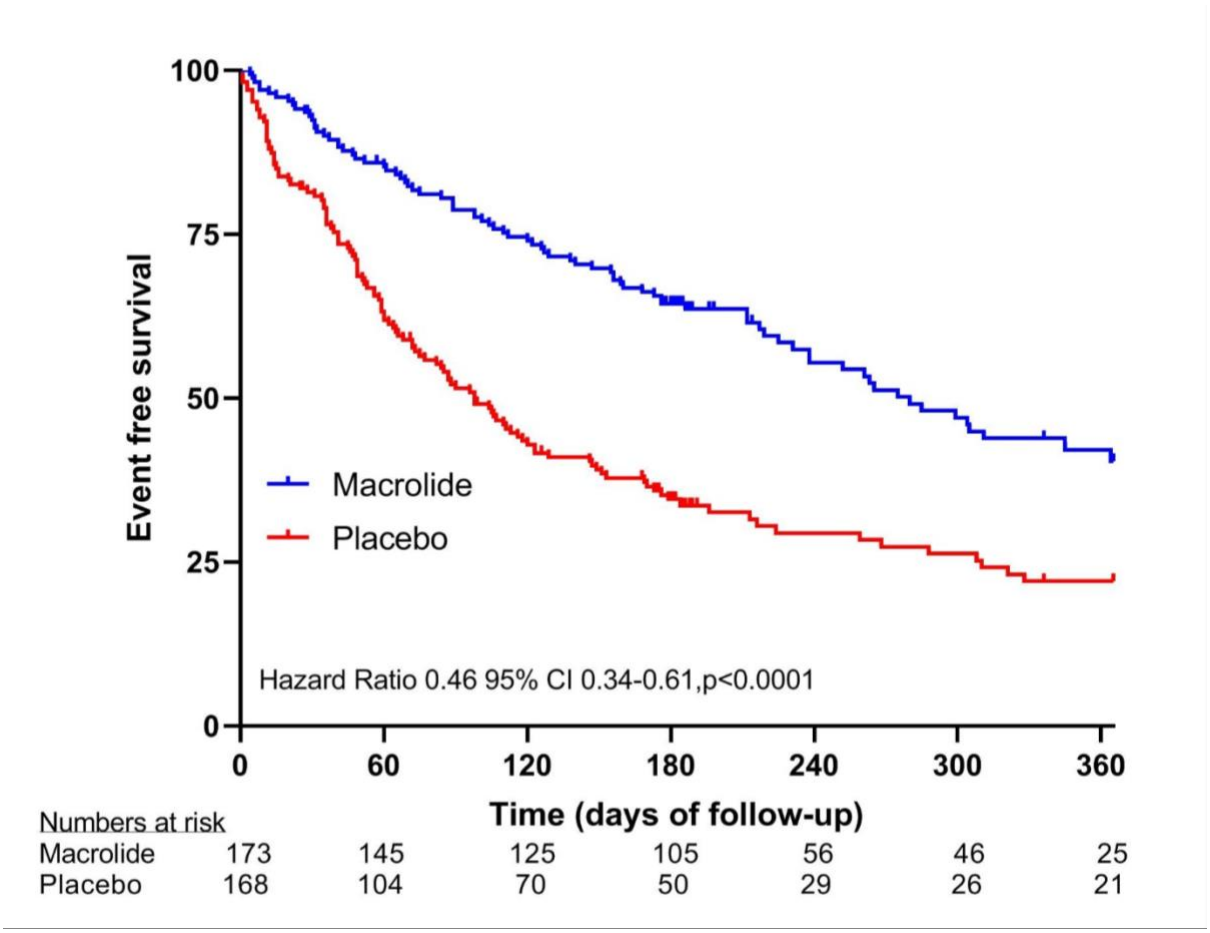

Figure E2. Time to first exacerbation survival curves for macrolide and placebo groups (n=3 studies).

References for Table E5.

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