Author(s):
Date:
Question: Long term Macrolide compared to standard for Exacerbation Rate
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard	Relative (95% CI)	Absolute (95% CI)		
Exacerbations, (Liu et al 2014) (follow up: mean 6 months; assessed with: Time to first exacerbations (days))												
1 [1]	randomised trials	serious [a]	not serious	serious [b]	serious [c,d,e]	none	22	21	-	median **151 days to 1st exacerbation lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Exacerbation rate, (Serisier et al 2013) (follow up: mean 12 months; assessed with: Exacerbations per patient per year)												
1 [2]	randomised trials	serious [f]	not serious	not serious	not serious	none	59	58	-	mean **0.68 exacerbations per patient per year lower** (0 to 0)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation incidence, (Serisier et al 2013) (assessed with: Incidence rate ratio)												
1 [2]	randomised trials	serious [f]	not serious	not serious	not serious	none	59	58	-	mean **0.57 Incidence rate ratio higher** (0.42 higher to 0.77 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation rate, (Wong et al 2012) (follow up: 6 months; assessed with: Rate ratio)												
1 [3]	randomised trials	not serious	serious [g]	not serious	not serious	none	71	70	-	Rate Ratio **0.38 higher** (0.26 higher to 0.54 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation rate 6 months post treatment, (Wong et al 2012) (follow up: 12 months; assessed with: Rate Ratio)												
1 [3]	randomised trials	not serious	serious [g]	not serious	not serious	none	71	70	-	Rate Ratio **0.58 higher** (0.46 higher to 0.74 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation, Wong et al 2012 (follow up: 12 months; assessed with: Days to first exacerbation)												
1 [3]	randomised trials	not serious	serious [g]	not serious	not serious	none	71	70	-	median **154 days to first exacerbation more** (0 to 0)	⨁⨁⨁◯ MODERATE	IMPORTANT
Exacerbation rate, Altenburg et al 2013 (assessed with: Median difference of exacerbation rate)												
1 [4]	randomised trials	serious [h]	not serious	not serious	not serious	none	43	40	-	difference of median exacerbation rate per year **2 exacarbtions higher** (0 to 0)	⨁⨁⨁◯ MODERATE	IMPORTANT

Exacerbation rate, (Diego 2013) (follow up: 3 months; assessed with: Number in months)

1 [5]	randomised trials	very serious [a,i]	not serious	not serious	serious [c]	none	16	14	-	MD **1.1 exacerbations higher** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

Exacerbation, (Zhou et al 2014) (follow up: range 8 weeks to 12 months)

4 [6]	randomised trials	not serious	not serious	not serious	not serious	none	184	178	-	OR **0.39 higher** (0.25 higher to 0.63 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

Exacerbation, (Fan et al 2015)

5 [7]	randomised trials	serious [a]	not serious	serious [j]	not serious	none			**OR 0.55** (0.47 to 0.64)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Exacerbation, (Fan et al 2015) (follow up: range 6 months to 12 months; assessed with: Only in adults double blind trials)

3 [7]	randomised trials	not serious	not serious	not serious	not serious	none			**OR 0.55** (0.46 to 0.65)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT

Numbers with exacerbations, (Wu et al 2014)

7 [8]	randomised trials	not serious	not serious	not serious	not serious	none	106/232 (45.7%)	147/223 (65.9%)	**RR 0.70** (0.60 to 0.82)	**198 fewer per 1,000** (from 264 fewer to 119 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT

Exacerbation rate, Wu et al 2014

3 [8]	randomised trials	not serious	not serious	not serious	not serious	none	118	112	-	MD **1.01 exacerabations lower** (1.35 lower to 0.67 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT

Exacerbation rate, Anwar et al 2008

1 [9]	observational studies	serious [k]	not serious	not serious	not serious	strong association	44		-	mean **0.4 Exacerbations per month lower** (0 to 0)	⨁⨁◯◯ LOW	IMPORTANT

Exacerbation rate, Davies et al 2004

1 [10]	observational studies	serious [a,k]	not serious	not serious	not serious	strong association			-	mean **0.58 exacarbations per month lower** (0 to 0)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Open Label study
b. Oriental Population

c. Small Numbers
d. No confidence intervals
e. Had all been hospitalised
f. Unclear baseline exacerbation rates
g. Data for different definition of exacerbation gave a different result
h. Lower exacarbation rate in the treatment group at baseline
i. No Placebo
j. Paediatric data included
k. Not blinded

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Author(s):
Date:
Question: Long term Macrolide compared to standard care for QoL
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
SGRQ, (Liu et al 2014) (follow up: mean 6 months; Scale from: 0 to 100)												
1 [1]	randomised trials	serious [a]	not serious	serious [b]	serious [c,d,e]	none	22	21	-	mean **11.1 lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
SGRQ, (Serisier et al 2013) (follow up: mean 12 months; Scale from: 0 to 100)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [f]	none	59	58	-	median **2.9 SGRQ lower** (7.3 lower to 1.6 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
SGRG, (Wong et al 2012) (follow up: 6 months; Scale from: 0 to 100)												
1 [3]	randomised trials	not serious	not serious	not serious	serious [f]	none	71	70	-	MD **3.25 SGRQ lower** (7.21 lower to 0.72 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
SGRQ 6 months post treatment, (Wong et al 2012) (follow up: 12 months; Scale from: 0 to 100)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**1.82 SGRQ higher** (0.27 lower to 6.32 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
SGRQ, (Altenburg et al 2013) (follow up: 12 months; assessed with: SGRQ decrease per 6 months; Scale from: 0 to 100)												
1 [4]	randomised trials	not serious	not serious	not serious	not serious	none	43	40	-	difference in reduction in SGRQ over 6 months **4.03 SGRQ lower** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT
SGRQ, Diego 2013 (follow up: 3 months; Scale from: 0 to 100)												

1 [5]	randomised trials	very serious [a,g]	not serious	not serious	serious [c]	none	16	14	-	MD **12 SGRQ lower** (21.6 lower to 2.39 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

SGRQ, Zhuo et al 2014 (follow up: range 6 months to 12 months; Scale from: 0 to 100)

3 [6]	randomised trials	not serious	serious [h]	not serious	not serious	none	173	168	-	MD **1.9 SGRQ lower** (7.01 lower to 3.2 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT

SGRQ, (Fan et al 2015) (Scale from: 0 to 100)

[7]	randomised trials	not serious	serious [h]	not serious	serious [f]	none			-	WMD **5.39 lower** (9.88 lower to 0.89 lower)	⨁⨁◯◯ LOW	IMPORTANT

SGRQ, (Wu et al 2014) (Scale from: 0 to 100)

5 [8]	randomised trials	not serious	serious [h]	not serious	serious	none			-	MD **5.39 SGRQ lower** (0.88 lower to 9.89 lower)	⨁⨁◯◯ LOW	IMPORTANT

5 Point Score, (Davies et al 2004) (assessed with: Cough/Fatigue/Exercise Tolerance/Wheeze/Breathlessness)

1 [9]	observational studies	very serious [c,g]	not serious	not serious	not serious	none	5 point score for multiple symptoms including sputum, cough, fatigue, exercise, wheeze and breathlessness. Statistically significant improvement for all.				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Open-label
b. Oriental population
c. Small study
d. No Confidence intervals
e. Had all been hospitalised
f. wide confidence intervals
g. no placebo
h. High I2 value

References

1. Liu, J., Zhong, X., He, Z., Wei, L., Zheng, X., Zhang, J., Bai, J., Zhong, W., Zhong, D.. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. Mediators of Inflammation; 2014.
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Author(s):
Date:
Question: Long term Macrolide compared to standard care for drug monitoring/side effects/toxicity
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Nausea, Liu et al 2014 (follow up: mean 6 months; assessed with: Patient reported)												
1 [1]	randomised trials	serious [a]	not serious	serious [b]	serious [c,d]	none	5/22 (22.7%)	0/21 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	NOT IMPORTANT
Allergic Response, Liu et al 2014 (follow up: mean 6 months; assessed with: events; Scale from: 0 to infinite)												
1 [1]	randomised trials	serious	not serious	serious	serious	none	1	0	-	total **1 rash more** (0 to 0)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
QTc, Serisier et al 2013 (follow up: 12 months; assessed with: change in QTc)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [e]	none	59	58	-	**0** (0 to 0)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Nausea, Serisier et al 2013 (follow up: 12 months)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	0/59 (0.0%)	3/58 (5.2%)	not estimable		⨁⨁⨁⨁ HIGH	NOT IMPORTANT
GI, Wong et al 2012 (follow up: 12 months)												
1 [3]	randomised trials	not serious	not serious	not serious	serious	none	19/71 (26.8%)	9/70 (12.9%)	not estimable		⨁⨁⨁◯ MODERATE	IMPORTANT
Diarrhoea, Altenburg et al 201 (follow up: 12 months; assessed with: Patient who suffered diarrhoea)												
1 [4]	randomised trials	not serious	not serious	not serious	serious [e]	none	9/43 (20.9%)	1/40 (2.5%)	not estimable		⨁⨁⨁◯ MODERATE	IMPORTANT
Rash, ALtenburg et al 201 (follow up: 12 months; assessed with: Patients affected)												
1 [4]	randomised trials	not serious	not serious	not serious	not serious	none	8/43 (18.6%)	4/40 (10.0%)	not estimable		⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Chest pain, Altenburg et al 2013 (follow up: 12 months; assessed with: patient reported)												
1 [4]	randomised trials	not serious	not serious	not serious	serious [e]	none	1/43 (2.3%)	1/40 (2.5%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Nausea, Altenburg et al 2013 (follow up: 12 months; assessed with: Patients affected)												
1 [4]	randomised trials	not serious	not serious	not serious	serious	none	6/43 (14.0%)	6/40 (15.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Fatigue, Altenberg et al (follow up: 12 months)												

1 [4]	randomised trials	not serious	not serious	not serious	serious	none	1/43 (2.3%)	0/40 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Abdominal pain, Altenburg et al 2013 (follow up: 12 months; assessed with: patients affected)												
1 [4]	randomised trials	not serious	not serious	not serious	not serious	none	8/43 (18.6%)	1/40 (2.5%)	not estimable		⨁⨁⨁⨁ HIGH	IMPORTANT
Auditory, Altenburg et al 2013 (follow up: 12; assessed with: post-study questionnaire)												
1 [4]	randomised trials	serious [f]	not serious	not serious	serious [e]	none	5/43 (11.6%)	4/40 (10.0%)	not estimable		⨁⨁◯◯ LOW	NOT IMPORTANT
All adverse events, zhou et al 2014 (follow up: range 6 months to 12 months)												
3 [5]	randomised trials	not serious	not serious	not serious	not serious	none	94/173 (54.3%)	97/168 (57.7%)	not estimable		⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Nausea/Vomiting, Zhuo et al 2014 (follow up: range 6 months to 12 months)												
3 [5]	randomised trials	not serious	not serious	not serious	not serious	none	15/173 (8.7%)	14/168 (8.3%)	not estimable		⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Diarrhoea, Zhou et al 2014 (follow up: range 6 months to 12 months)												
2 [5]	randomised trials	not serious	not serious	not serious	not serious	none	22/114 (19.3%)	5/110 (4.5%)	not estimable		⨁⨁⨁⨁ HIGH	IMPORTANT
Abdominal discomfort, Zhou et al 2014 (follow up: range 6 months to 12 months)												
2 [5]	randomised trials	not serious	not serious	not serious	not serious	none	13/144 (9.0%)	2/110 (1.8%)	not estimable		⨁⨁⨁⨁ HIGH	IMPORTANT
Headache, Zhou et al 2014 (follow up: range 6 months to 12 months)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [e]	none	3/114 (2.6%)	5/110 (4.5%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Rash, Zhou et al 2014 (follow up: range 8 weeks to 12 months)												
2 [5]	randomised trials	not serious	not serious	not serious	serious [e]	none	9/54 (16.7%)	4/50 (8.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Nausea/Vomiting, Fan et al 2015												
3 [6]	randomised trials	not serious	not serious	not serious	not serious	none	15/173 (8.7%)	14/168 (8.3%)	not estimable		⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Diarrhoea, Fan et al 2015												
3 [6]	randomised trials	not serious	not serious	not serious	not serious	none	26/126 (20.6%)	5/122 (4.1%)	**OR 5.36** (2.06 to 13.98)	**145 more per 1,000** (from 40 more to 333 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Headache, Fan et al 2015												

3 [6]	randomised trials	not serious	not serious	not serious	serious [e]	none	4/173 (2.3%)	5/168 (3.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT

Sinusitis, Fan et al 2015

2 [6]	randomised trials	not serious	not serious	not serious	serious [e]	none	4/130 (3.1%)	4/128 (3.1%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT

Rash, Fan et al

2 [6]	randomised trials	not serious	not serious	not serious	serious [e]	none	9/54 (16.7%)	4/50 (8.0%)	**OR 2.17** (0.66 to 7.99)	**79 more per 1,000** (from 26 fewer to 330 more)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT

Adverse events, Wu et al (assessed with: All adverse events)

4 [7]	randomised trials	not serious	not serious	not serious	not serious	none	95/183 (51.9%)	97/179 (54.2%)	**RR 0.96** (0.82 to 1.12)	**22 fewer per 1,000** (from 98 fewer to 65 more)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Open-label
b. Oriental population
c. small study
d. No confidence intervals
e. small number of events
f. post-study questionnaire

References

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Author(s):
Date:
Question: Long term macrolide compared to standard care for exercise capacity/tolerance
Setting: Bronchiectasis
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	long term macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Activity, Liu et al 2014 (follow up: mean 6; assessed with: SGRQ- Activity; Scale from: 0 to 100)												
1 [1]	randomised trials	serious	not serious	serious	serious	none	22	21	-	mean **4.4 SGRQ- Activity lower** (0 to 0)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Exercise capacity, Serisier et al 2013 (assessed with: 6MWT)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	59	58	-	median **3.55 metres higher** (17.6 lower to 24.7 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Exercise capacity, Wong et al 2012 (follow up: 6 months; assessed with: 6MWT)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	mean **10.52 metres higher** (26.15 higher to 5.12 lower)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Exercise capacity, Wong et al 2012 (follow up: 12 months; assessed with: 6MWT)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**6.48 metres higher** (24.22 higher to 11.28 lower)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Activity, Wong et al 2012 (follow up: 6 months; assessed with: SGRQ- Activity)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**1.58 SGRQ- Activity lower** (7.31 lower to 4.12 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Activity, Wong et al 2012 (follow up: 12 months; assessed with: SGRQ- Activity)												

1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**2.71 SGRQ-Activity higher** (3.37 lower to 8.79 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT

Activity, Diego et al 20133 (follow up: 3 months; assessed with: SGRQ-Activity; Scale from: 0 to 100)

1 [4]	randomised trials	very serious [a,b]	not serious	not serious	serious	none	16	14	-	MD **0.1 SGRQ-Activity higher** (0 to 0)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No placebo
b. Open label

References

1. Liu, J., Zhong, X., He, Z., Wei, L., Zheng, X., Zhang, J., Bai, J., Zhong, W., Zhong, D.. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. Mediators of Inflammation; 2014.
2. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
3. Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H., Milne, D., Fergusson, W., Tuffery, C., Sexton, P., Storey, L., Ashton, T.. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet; 2012.
4. Diego, A. D., Milara, J., Martinez-Moragon, E., Palop, M., Leon, M., Cortijo, J.. Effects of long-term azithromycin therapy on airway oxidative stress markers in non-cystic fibrosis bronchiectasis. Respirology; 2013.

Author(s):
Date:
Question: Long term Macrolide compared to standard care for Hospital Admission rate
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Admission rate, Serisier et al 2013												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	59	58	-	mean **0.02 Hospital admissions per patient lower** (0 to 0)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Admissions, Wong et al 2012 (follow up: 12 months; assessed with: Bronchiectasis related admissions)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [a]	none	1/71 (1.4%)	3/70 (4.3%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Admission rate, Altenburg 2013 (follow up: 12 months; assessed with: admissions to hospital)												
1 [3]	randomised trials	not serious	not serious	not serious	serious [a]	none	1/43 (2.3%)	2/40 (5.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT

CI: Confidence interval

Explanations

a. Wide confidence intervals

References

1. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
2. Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H., Milne, D., Fergusson, W., Tuffery, C., Sexton, P., Storey, L., Ashton, T.. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet; 2012.
3. Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H., Koppers, R. J., van der Werf, T. S., Boersma, W. G.. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA; 2013.

Author(s):
Date:
Question: Long term Macrolide compared to standard care for Lung function
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
FEV1, Serisier et al 2013 (follow up: mean 12 months; assessed with: Decline in FEV1%predicted)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	59	58	-	mean **2.2 %predicted reduction lower** (0.01 lower to 4.3 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
FEV1, Wong et al 2012 (follow up: 6 months; assessed with: FEV1- Prebronchodilators)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	change in baseline **0.04 litres higher** (0.03 lower to 0.12 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
FEV1, Wong et al 2012 (follow up: 6 months; assessed with: FEV1- Post Bronchodilator)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	difference in change from baseline **0.07 litres higher** (0.03 lower to 0.15 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
FEV1, Wong et al 2012 (follow up: 12 months; assessed with: FEV1- Pre bronchodilator)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	difference of change from baseline **0.04 litres higher** (0.02 lower to 0.11 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
FEV1, Wong et al (follow up: 12 months; assessed with: FEV1- postbronchodilator)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	difference in change from baseline **0.07 litres higher** (0.01 lower to 0.15 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT

FEV1, Altenburg 2013 (follow up: 12 months; assessed with: Rate of change per 3 months)

1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	43	40	-	**1.13 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT

FVC, Altenburg et al 2013 (follow up: 12 months; assessed with: Rate of change per 3 months)

1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	43	40	-	**1.63 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT

FEV1, Diego 2013 (follow up: 3 months; assessed with: Changes after 3 months)

1 [4]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	none	16	14	-	Mean difference of change of FEV1 **0.02 litres more** (0 to 0)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

FEV1, Fan et al 2015 (assessed with: Changes in FEV1)

4 [5]	randomised trials	not serious	not serious	not serious	not serious	none	109	105	-	WMD **0.02 L more** (0 to 0.04 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

FEV1, Fan et al 2015 (assessed with: Change in FEV1% Pred)

3 [5]	randomised trials	not serious	not serious	not serious	not serious	none	115	110	-	WMD **1.52 %pred higher** (0.49 higher to 2.56 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

FVC, Fan et al 2015 (assessed with: Change in FVC)

3 [5]	randomised trials	not serious	serious [d]	not serious	not serious	none	98	95	-	WMD **0.05 litres higher** (0.03 lower to 0.13 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT

FEV1, Wu et al 2014 (assessed with: Change in FEV1)

5 [6]	randomised trials	serious	not serious	not serious	not serious	none			-	MD **0.02 L higher** (0 to 0.04 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

FEV1, Anwar et al 2008 (assessed with: FEV1)

1 [7]	observational studies	serious [e]	not serious	not serious	not serious	none	29		-	mean **0.083 litres higher** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

FEV1, Anwar et al 2008 (assessed with: FEV1 %predicted)

1 [7]	observational studies	serious [e]	not serious	not serious	not serious	none	29		-	mean **3.5 % higher** (0 to 0)	⨁◯◯◯ VERY LOW	

Lung function, Davies et al 2004

1 [8]	observational studies	serious [b]	not serious	not serious	not serious	none	Improvement in all parameters of lung function but stats not described except for TLCO (p=0.01)				⨁◯◯◯ VERY LOW	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No Placebo
b. Open label
c. Small study
d. High I2
e. Not blinded

References

1. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
2. Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H., Milne, D., Fergusson, W., Tuffery, C., Sexton, P., Storey, L., Ashton, T.. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet; 2012.
3. Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H., Koppers, R. J., van der Werf, T. S., Boersma, W. G.. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA; 2013.
4. Diego, A. D., Milara, J., Martinez-Moragon, E., Palop, M., Leon, M., Cortijo, J.. Effects of long-term azithromycin therapy on airway oxidative stress markers in non-cystic fibrosis bronchiectasis. Respirology; 2013.
5. Fan, L. C., Lu, H. W., Wei, P., Ji, X. B., Liang, S., Xu, J. F.. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infectious Diseases; 2015.
6. Wu, Q., Shen, W., Cheng, H., Zhou, X.. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirology; 2014.
7. Anwar, G. A., Bourke, S. C., Afolabi, G., Middleton, P., Ward, C., Rutherford, R. M.. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Respiratory Medicine; 2008.
8. Davies, G., Wilson, R.. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. Thorax; 2004.

Author(s):
Date:
Question: Long term Macrolide compared to standard care for Microbiological resistance
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Resistant Streptococci, Serisier et al 2013 (follow up: mean 12 months; assessed with: macrolide resistance oropharyngeal strep)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	59	58	-	difference **25.5 %macrolide resistant strep more** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT
Resistance, Wong et al 2012 (follow up: 6 months; assessed with: Occurence of resistance)												
1 [2]	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	2/46 (4.3%)	0/45 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	NOT IMPORTANT
Resistance, Altenburg et al 2013 (follow up: 12 months; assessed with: Macrolide resistant pathogens tested)												
1 [3]	randomised trials	serious [c]	not serious	not serious	not serious	none	53/60 (88.3%)	29/112 (25.9%)	not estimable		⨁⨁⨁◯ MODERATE	IMPORTANT
Resistance, Fan et al 2015												
3 [4]	randomised trials	serious [d]	not serious	not serious	not serious	none			**OR 16.83** (7.26 to 38.99)	**17 fewer per 1,000** (from 39 fewer to 7 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Resistance, Anwar et al 2008												
1 [5]	observational studies	serious [e]	not serious	not serious	not serious	none			not estimable		⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No planned or consistent testing of macrolide resistance
b. Wide confidence intervals
c. Not clear which samples tested for resistance
d. issues from the BAT study which is the main data source
e. Not clear if same number of samples pre and post treatment

References

1. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
2. Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H., Milne, D., Fergusson, W., Tuffery, C., Sexton, P., Storey, L., Ashton, T.. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet; 2012.
3. Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H., Koppers, R. J., van der Werf, T. S., Boersma, W. G.. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA; 2013.
4. Fan, L. C., Lu, H. W., Wei, P., Ji, X. B., Liang, S., Xu, J. F.. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infectious Diseases; 2015.
5. Anwar, G. A., Bourke, S. C., Afolabi, G., Middleton, P., Ward, C., Rutherford, R. M.. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Respiratory Medicine; 2008.

Author(s):
Date:
Question: Long term Macrolide compared to standard care for Sputum volume/colour/character
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Sputum weight, Serisier et al 2013 (follow up: mean 12 months; assessed with: median 24 hr weight in grams)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	59	58	-	median **4.3 grams lower** (7.8 lower to 1 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Sputum volume, Diego et al 2013 (follow up: 3 months; assessed with: mls/day)												
1 [2]	randomised trials	very serious [b,c]	not serious	not serious	serious [d]	none	16	14	-	MD **6.8 mls lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Sputum Colour, Diego et al 2013 (follow up: 3 months; assessed with: Scale; Scale from: 0 to 15)												
1 [2]	randomised trials	very serious [b,c]	not serious	not serious	serious [d]	none	16	14	-	MD **0.1 Colour Scale higher** (0 to 0)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Sputum Volume, Fan et al 2015												
4 [3]	randomised trials	serious [b,c]	serious [e]	not serious	not serious	none			-	MD **7.38 mls lower** (12.9 lower to 1.85 lower)	⨁⨁◯◯ LOW	IMPORTANT
Sputum Volume, Wu et al 2014												
2 [4]	randomised trials	serious	not serious	not serious	not serious	none			-	MD **10.76 mls lower** (12.7 lower to 8.83 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Sputum volume, Anwar et al 2008 (assessed with: <15mls sputum/daily)												
1 [5]	observational studies	serious [f]	not serious	not serious	serious [g]	strong association	18/50 (36.0%)		not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Sputum, Davies et al 2004 (assessed with: 5 point scale)												

1 [6]	observational studies	serious [c]	not serious	not serious	not serious	none	Unvalidated 5 point scale suggested improvement in these symptoms	⊕OOO VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. wide confidence
b. No placebo
c. open label
d. Small study
e. High i2 value
f. not blinded
g. Imprecise volume definition

References

1. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
2. Diego, A. D., Milara, J., Martinez-Moragon, E., Palop, M., Leon, M., Cortijo, J.. Effects of long-term azithromycin therapy on airway oxidative stress markers in non-cystic fibrosis bronchiectasis. Respirology; 2013.
3. Fan, L. C., Lu, H. W., Wei, P., Ji, X. B., Liang, S., Xu, J. F.. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infectious Diseases; 2015.
4. Wu, Q., Shen, W., Cheng, H., Zhou, X.. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirology; 2014.
5. Anwar, G. A., Bourke, S. C., Afolabi, G., Middleton, P., Ward, C., Rutherford, R. M.. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Respiratory Medicine; 2008.
6. Davies, G., Wilson, R.. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. Thorax; 2004.

Author(s):
Date:
Question: Long term macrolide compared to standard care for Symptom improvement/Symptom score
Setting: Bronchiectasis
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	long term macrolide	standard care	Relative (95% CI)	Absolute (95% CI)		
Symptoms, Liu et al 2014 (follow up: 6 months; assessed with: SGRQ-Symptom)												
1 [1]	randomised trials	serious	not serious	serious	serious	none	22	21	-	mean **4.7 SGRQ-Sympt lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Symtoms, Serisier et al 2013 (follow up: mean 12 months; assessed with: Leicester Cough Questionnaire)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	59	58	-	median **0.79 LCQ higher** (0.2 lower to 1.8 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Symptoms, Serisier et al 2013 (follow up: mean 12 months; assessed with: SGRQ-Symptoms score)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	59	58	-	median **5.3 SGRQ-Symptoms lower** (12.6 lower to 2.1 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Symptoms, Wong et al 2012 (follow up: 6 months; assessed with: SGRQ- Symptoms score)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**6.7 SGRQ lower** (13.37 lower to 0.04 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Symptoms, Wong et al 2012 (follow up: 12 months; assessed with: SGRQ- Symptoms score)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	71	70	-	**1.82 SGRQ-Symptoms higher** (0.27 lower to 6.32 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT
Symptoms, Altenburg et al 2013 (follow up: 12 months; assessed with: LRTI-VAS- decrease per 3 months; Scale from: 0 to 50)												
1 [4]	randomised trials	not serious	not serious	not serious	not serious	none	43	40	-	**1.05 LRTI-VAS lower** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT
Symptoms, Diego et al 2013 (follow up: 3 months; assessed with: Borg; Scale from: 0 to 10)												

1 [5]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	none	16	14	-	MD **0.5 Borg lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

Symptoms, Diego et al 2013 (follow up: 3 months; assessed with: SGRQ-symptoms)

1 [5]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	none	16	14	-	MD **30 SGRQ symptoms lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

Symptoms, Fan et al 2015 (assessed with: SGRQ-Symptom Score)

[6]	randomised trials	not serious	not serious	not serious	very serious [d]	none			-	WMD **13.38 SGRQ lower** (30.62 lower to 3.86 higher)	⨁⨁◯◯ LOW	NOT IMPORTANT

Symptom, Wu et al 2014 (assessed with: Dyspnoea scale)

2 [7]	randomised trials	serious	not serious	not serious	not serious	none			-	MD **0.31 MRC lower** (0.42 lower to 0.2 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No Placebo
b. Open label
c. Small study
d. large confidence intervals

References

1. Liu, J., Zhong, X., He, Z., Wei, L., Zheng, X., Zhang, J., Bai, J., Zhong, W., Zhong, D.. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. Mediators of Inflammation; 2014.
2. Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B., Biga, S., Schlebusch, S., Dash, P., Bowler, S. D.. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA; 2013.
3. Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H., Milne, D., Fergusson, W., Tuffery, C., Sexton, P., Storey, L., Ashton, T.. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet; 2012.
4. Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H., Koppers, R. J., van der Werf, T. S., Boersma, W. G.. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA; 2013.
5. Diego, A. D., Milara, J., Martinez-Moragon, E., Palop, M., Leon, M., Cortijo, J.. Effects of long-term azithromycin therapy on airway oxidative stress markers in non-cystic fibrosis bronchiectasis. Respirology; 2013.
6. Fan, L. C., Lu, H. W., Wei, P., Ji, X. B., Liang, S., Xu, J. F.. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infectious Diseases; 2015.
7. Wu, Q., Shen, W., Cheng, H., Zhou, X.. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirology; 2014.

Author(s):
Date:
Question: Long term Macrolides compared to standard care to reduce mortality
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term Macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Death, Altenburg et al 2013 (follow up: 12 months)												
1 [1]	randomised trials	not serious	not serious	not serious	serious	none	0/43 (0.0%)	0/40 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	NOT IMPORTANT

CI: Confidence interval

References

1. Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H., Koppers, R. J., van der Werf, T. S., Boersma, W. G.. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA; 2013.