Online material
Manuscript: European Respiratory Society (ERS) Guidelines for the Management of Adult Bronchiectasis

Systematic review

An experienced external librarian designed and ran a search strategy using MeSH terms and keywords for each clinical question, in collaboration with the methodologists. More details are shown in the online supplemental material.

The PubMed platform was used to search MEDLINE. The Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) were also searched. The search was limited to English language and used a hierarchical approach: we first looked for systematic reviews and subsequently for randomized clinical trials. In the absence of these designs, observational studies were also searched. All searches were performed systematically through July 2015.

The search retrieved 3,038 records, after removal of duplicates. After excluding 2,834 citations through title and abstract screening, 204 references were assessed in full-text by at least two authors who determined inclusion by consensus; disagreements were resolved by consultation to guideline panel chairs. All authors monitored the literature up to December 2016 and identified 3 additional relevant references. A total of 48 references were included in the evidence summaries.

Assessment of the level of evidence and degree of recommendations

The panel selected outcomes of interest for each clinical question a priori, based on their relative importance to adult patients with bronchiectasis and to clinical decision making. Following the GRADE approach, outcomes were rated as “not important”, “important” or “critical” for clinical decision making through an online vote of the entire panel. Only outcomes that were

considered important or critical were subsequently used to formulate recommendations. Three patient representatives also rated the outcomes and only outcomes also considered important by patients were included.

A methodology group composed of the chairs (EP and JDC) and two members (PCG and MJM) extracted the data in duplicate from relevant publications reporting important or critical outcomes and pooled them, whenever applicable, using RevMan 5 software version 5.3. The process of literature search, data extraction and reporting were supervised by two experienced ERS methodologists.

We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations [1]. This approach specifies four categories of quality (high, moderate, low and very low) that are applied to a body of evidence and not on individual studies. The body of evidence was evaluated based primarily on risk of bias, precision, consistency, directness of evidence and risk of publication bias.

Recommendations are graded as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation[2].

Evidence summaries of findings (SoF tables) and Evidence to Decisions (EtD) frameworks were generated by the methodology group for each clinical question using the GRADEpro Guideline Development Tool [3]. Based on these formats, the panel formulated the clinical recommendations and decided on their strength by

consensus and, if required, by voting. Following the GRADE approach, strong recommendations are worded as “we recommend”, while conditional recommendations are worded as “we suggest”.

Evidence summaries of findings (SoF tables)

PICO question 1:

Is the application of current SEPAR/BTS recommendations about aetiological testing panel of BE beneficial for their clinical management in comparison with no aetiological diagnosis (only CT scan evidence of bronchiectasis)?

Setting: secondary care
Bibliography: Anwar GA *et al.*, Respir Med. 2013;107(7):1001-7; Lonni S. et al. Ann Am Thorac Soc. 2015 Dec;12(12):1764-70; Pasteur MC *et al.*, Am J Respir Crit Care Med. 2000;162(4 Pt 1):1277-84; Shoemark A *et al.*, Respir Med. 2007;101(6):1163-70.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aetiological testing**	**No aetiological testing**	**Relative (95% CI)**	**Absolute (95% CI)**		
CRITICAL OUTCOME REPORTED IN THE STUDIES INCLUDED IN THE ANALYSIS: change in clinical management of bronchiectasis												
4	observational studies	very serious [1]	serious [2]	serious [3]	not serious	none	1762	-	not estimable	263/1762 (15%) From 7% to 37%	VERY LOW	CRITICAL
CRITICAL AND IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED IN THE ANALYSIS: number of hospitalizations, number of exacerbations, quality of life, FEV1%, FEV1 L, FVC %, FVC L, Mortality, costs, adverse events												
Not assessed									not estimable		-	

CI: Confidence interval

1. Non-controlled studies, retrospective studies mixed with prospective.
2. Wide range of effect estimates
3. Non-homogeneous set of tests across studies, some tests not matching the pre-defined set of tests, paediatric data for 2 of the 5 studies

PICO question 2:

Are courses of 14-21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult BE patients with an acute exacerbation?

Setting: Outpatients and inpatients

Bibliography: Bilton D et al. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of Pseudomonas aeruginosa infection in adult bronchiectasis. Chest. 2006 ;130(5):1503-10.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	14-21 days courses of systemic antibiotics	<14 day courses of systemic antibiotics	Relative (95% CI)	Absolute (95% CI)		
CRITICAL OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: sputum volume, antibiotic resistance, mortality, quality of life, time to next exacerbation												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: cough, breathlessness, adverse events, exercise tolerance, successful eradication.												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
IMPORTANT OUTCOMES REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: Bacterial load (mean difference in cfu/ml between groups)												
1	randomised trials	very serious [1]	not serious	serious [2]	serious [3]	none	43	40	-	MD **0.23 cfu/ml higher** (1.55 lower to 2.01 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
FEV1 (difference in litres) **Note:** we used liters since there is no literature evaluable on % of predicted. No MID is available in the literature but we internally assumed 100ml as for COPD (Donohue et al. COPD. 2005 Mar;2(1):111-24.)												
1	randomised trials	very serious [1]	not serious	serious [2]	serious [3]	none	43	40	-	MD **0.01 Litres higher** (0.51 lower to 0.53 higher)	⊕◯◯◯ VERY LOW	IMPORTANT

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

1. The trial did not directly compare 14 days vs 7 days of treatment, we have extracted outcomes at these stages from the presented data. Therefore, we cannot be sure what results would have been obtained had antibiotics been discontinued in the 7 day group. In addition, we have pooled results from arms receiving 2 different treatments
2. Not a direct comparison between antibiotics stopped at day 7 vs antibiotics stopped at day 14
3. Wide confidence intervals that includes both clinically relevant benefit and clinically relevant harm

PICO question 3:

Is an eradication treatment beneficial for treating BE patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?

Setting: Outpatient care
Bibliography: Orriols et al. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration. 2015;90(4):299-305. White et al. Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis., Respir Med. 2012;106(3):356-60.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eradication treatment	standard care	Relative (95% CI)	Absolute (95% CI)		
Eradication of *Pseudomonas aeruginosa* at 12 months (proportion of patients with *Pseudomonas*)												
2	observational studies	very serious [1]	not serious	serious [2]	not serious	publication bias strongly suspected strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient [2]	34/58 (58.6%)	58/58 (100.0%)	**RR 15.73** (3.15 to 78.63)	**Not provided**	⨁◯◯◯ VERY LOW	CRITICAL
Exacerbation frequency following eradication treatment												
1	observational studies	very serious [1]	not serious	serious [3]	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [2]	Reduced exacerbation frequency from mean 3.93 to 2.09 in the year following eradication treatment				⨁◯◯◯ VERY LOW	CRITICAL
FEV1% change following eradication treatment Note: no MID available in the literature. We internally assumed 5% change												
1	observational studies	very serious [4]	not serious	serious [3]	not serious	publication bias strongly suspected [2]	28	28	-	MD **0.19 % higher** (1.89 lower to 2.27 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eradication treatment	standard care	Relative (95% CI)	Absolute (95% CI)		
Quality of life (change in the SGRQ total score at 12 months following eradication) Note: lower SGRQ score equals improved quality of life												
1	observational studies	very serious [4]	not serious	serious [3]	serious [5]	publication bias strongly suspected strong association all plausible residual confounding would reduce the demonstrated effect [2]	28	28	-	MD **8.46 units lower** (18.44 lower to 1.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Antibiotic resistance (number of patients with resistant pathogens at end of treatment)												
2	observational studies	very serious [6]	serious [7]	serious [4]	serious [5]	publication bias strongly suspected [2]	4/39 (10.3%)	0/39 (0.0%)	**RR 9.00** (0.54 to 149.50)	**Not provided**	⨁◯◯◯ VERY LOW	CRITICAL
CRITICAL OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: sputum purulence, bacterial load, side effects related to eradication treatment, mortality												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: cough, fatigue, breathlessness, exercise tolerance.												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

1. Studies are before and after, with no control group to indicate the rate of spontaneous Pseudomonas clearance. Definition of eradication is absence of P. aeruginosa in sputum at 12 months
2. Before and after design
3. Not directly evaluating eradication vs no eradication
4. Before and after data extracted from a study comparing two methods of eradication not directly addressing the question of eradication vs no eradication
5. 95% CI includes the possibility of no improvement or a substantial improvement
6. One study only evaluated tobramycin sensitivies. Presence of resistance can only be evaluated in positive cultures at end of treatment.
7. No resistance in one study and 4/10 in another, due to different methods/definitions of resistance

PICO question 4:

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

Setting: Secondary care
Bibliography: (1) Mandal P, et al. Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. Lancet Respir Med. 2014 Jun;2(6):455-63. (2) Hernando R, et al. Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. Int J Clin Pharm. 2012 Aug;34(4):644-50. (3) Tsang KW, et al. Inhaled fluticasone in bronchiectasis: a 12-month study. Thorax. 2005 Mar;60(3):239-43.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-term (> 3 months) anti-inflammatory treatment**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Exacerbations (number of patients with at least one exacerbation)												
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	36/61 (59.0%)	39/62 (62.9%)	**RR 0.99** (0.76 to 1.30)	**6 fewer per 1000** (from 151 fewer to 189 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of Life (QoL): SGRQ total score change (units) Note: lower score indicates better QoL; MID fixed at 4 points reduction in total score												
2	randomised trials	serious [1]	not serious	not serious	serious [3]	none	61	62	-	MD **0.91 higher** (4.51 lower to 6.33 higher)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
3	randomised trials	very serious [4]	not serious	not serious	not serious	none	20/110 (18.2%)	7/106 (6.6%)	**RR 2.75** (1.21 to 6.25)	**116 more per 1000** (from 14 more to 347 more)	⊕⊕◯◯ LOW	CRITICAL
Sputum purulence after treatment Note: no MID available in the literature. We internally assumed 1 unit in scale from 0 to 8 points (Murray MP, et al. Eur Respir J 2009;34:361e64.**)**												
1	randomised trials	serious [5]	not serious	not serious	serious [6]	none	43	43	-	MD **0.2 more** (0.94 fewer to 1.34 more)	⊕⊕◯◯ LOW	IMPORTANT
FEV1 (% change) Note: no MID available in the literature. We internally assumed 5% change												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-term (> 3 months) anti-inflammatory treatment	no treatment	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [4]	not serious	not serious	not serious [7]	none	104	105	-	MD **0.02 lower** (0.18 lower to 0.14 higher)	⨁⨁◯◯ LOW	IMPORTANT
FVC (% change) Note: no MID available in the literature. We internally assumed 5% change												
2	randomised trials	serious [8]	not serious	not serious	not serious [9]	none	61	62	-	MD **0.68 lower** (4.13 lower to 5.49 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Sputum volume change (ml) Note: no MID available in the literature. We internally assumed 10ml or 25% change from baseline												
1 [10]	randomised trials	serious [5]	not serious	not serious	serious [11]	none	43	43	-	MD **1 ml lower** (6.56 lower to 4.56 higher)	⨁⨁◯◯ LOW	IMPORTANT
Resistance (not reported)												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

1. Mandal: Placebo was not matched to atorvastatin in appearance. Hernando: withdrawals not further specified.
2. Wide confidence interval that includes both clinical relevant benefit and harm; minimal important difference in relative risk = 20%.
3. Wide confidence interval that includes both appreciable benefit and harm; minimal important difference for SGRQ=4
4. Mandal: The placebo was not matched to atorvastatin in appearance. Tsang: probably no allocation concealment and significant baseline differences (cough, dyspnea). Hernando: withdrawals not further specified
5. Tsang had probably no allocation concealment (unclear). Withdrawals not further specified in the trials. Baseline differences for cough and dyspnea.
6. Wide confidence interval that includes both appreciable benefit and harm; minimal important difference for sputum purulence = 1 unit
7. Although the confidence interval is wide and includes the null effect, it does not include clinical relevant benefit or harm; minimal important difference for FEV1% = 5%
8. Mandal: Placebo was not matched to atorvastatin in appearance.
9. Wide confidence interval that includes both limited benefit and harm; minimal important difference for FVC% = 5%
10. Change as reported by the author
11. Although the confidence interval is wide and includes the null effect, it does not include clinical relevant benefit or harm. minimal important difference for sputum volume = 10 ml

PICO question 5:

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

Setting: Secondary care

Bibliography. ***Oral****: Lourdesamy, AI et al.* Respirology *2014; 19: 1178–1182. LiuJ et al.* Mediators Inflamm. *2014, Serisier DJ et al. (BLESS)* JAMA *2013; 309: 1260–1267 2013, Altenburg J et al. (BAT)* Jama *2013; 309: 1251–1259, De Diego A et al.* Respirology *2013; 18: 1056–1062, Wong C et al. (EMBRACE)* Lancet *2012; 380: 660–667, Cymbala AA et al.* Treat. Respir. Med. *2005; 4: 117–122., Currie DC et al.* QJM *1990; 76: 799–816., MRC* Br Med J. *1957; Aug 3; 255–259.* ***Inhaled****: Tabernero E et al.* Rev. española Geriatr. y Gerontol. *2015; 50: 111–115, Haworth CS et al.* Am. J. Respir. Crit. Care Med. *2014; 189: 975–982, Barker AF et al.* Lancet Respir. Med. *2014; 2: 738–749, Serisier DJ et al.(ORBIT2)* Thorax *2013; 68: 812–817, Murray MP et al.* Am. J. Respir. Crit. Care Med. *2011; 183: 491–499., Drobnic ME et al.* Ann. Pharmacother. *2005; 39: 39–44., Orriols R et al.* Respir. Med. *1999; 93: 476–480.*

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long term antibiotics (≥ 3 months)**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Change in sputum volume after study intervention (ml) Note: no MID available in the literature. We internally assumed 10ml or 25% change from baseline												
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	60	65	-	MD **1.53 higher** (5.15 lower to 8.21 higher)	⊕⊕◯◯ LOW	CRITICAL
No. of patients with a reduction in sputum purulence after study intervention (based on 4-point sputum colour chart)												
1	randomised trials	not serious	not serious	not serious	very serious [3]	none	15/27 (55.6%)	1/30 (3.3%)	**RR 16.67** (2.36 to 117.89)	**522 more per 1,000** (from 45 more to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
No. of patients with exacerbations during study follow-up												
10	randomised trials	not serious	serious [4]	not serious	not serious	none	231/596 (38.8%)	300/593 (50.6%)	**RR 0.72** (0.58 to 0.89)	**142 fewer per 1,000** (from 56 fewer to 212 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to first exacerbation (days)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long term antibiotics (≥ 3 months)**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	serious	none	-	-	**HR 0.34** (0.20-0.58)	**0 fewer per 1,000** (from 0 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Severity of exacerbations = No of patients requiring hospitalisation												
6	randomised trials	not serious	not serious	serious [5]	serious [2]	none	19/424 (4.5%)	24/423 (5.7%)	**RR 0.82** (0.41 to 1.64)	**10 fewer per 1,000** (from 33 fewer to 36 more)	⨁⨁◯◯ LOW	CRITICAL
No. patients with successful eradication at 12-month follow-up												
3	randomised trials	serious [6]	not serious	not serious	serious [2]	none	34/90 (37.8%)	6/93 (6.5%)	**RR 8.05** (0.43 to 151.11)	**455 more per 1,000** (from 37 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
No. of patients with resistance at end of treatment												
7	randomised trials	not serious	not serious	not serious	serious [2]	none	43/216 (19.9%)	23/232 (9.9%)	**RR 2.02** (1.09 to 3.75)	**101 more per 1,000** (from 9 more to 273 more)	⨁⨁⨁◯ MODERATE	CRITICAL
No. of patients with adverse events												
11	randomised trials	not serious	serious [4]	not serious	not serious	none	381/595 (64.0%)	320/586 (54.6%)	**RR 1.19** (1.03 to 1.37)	**104 more per 1,000** (from 16 more to 202 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Change in SGRQ (units) Note: lower score indicates better QoL; MID fixed at 4 points reduction in total score												
7	randomised trials	not serious	serious [4]	not serious	serious [2]	none	301	293	-	MD **3.47 lower** (8.51 lower to 1.56 higher)	⨁⨁◯◯ LOW	CRITICAL

Change in exercise tolerance as measured by 6-minutes walk test (6MWD) at end of intervention (m) Note: MID according to literature (1) is 24,5 mt (Lee AL, et al. Respir Med. 2014 Sep;108(9):1303-9.)												
3	randomised trials	not serious	not serious	not serious	serious [2]	none	206	150	-	MD **7.61 higher** (8.75 lower to 23.97 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in FEV1% predicted (%) Note: no MID available in the literature. We internally assumed 5% change												
4	randomised trials	serious [7]	not serious	not serious	not serious	none	141	137	-	MD **1.99 higher** (1.96 lower to 5.94 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mortality												
13	randomised trials	not serious	not serious	not serious	serious [2]	none	18/686 (2.6%)	10/681 (1.5%)	**RR 1.54** (0.75 to 3.15)	**8 more per 1,000** (from 4 fewer to 32 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in bacterial density at 4 weeks (expressed as log^{10} cfu/mL or cfu/g) Note: MID fixed at 2 log units (Am J Respir Crit Care Med. 2012 Oct 1;186(7):657-65.)												
2	randomised trials	not serious	not serious	not serious	serious [2]	none	93	93	-	MD **2.45 lower** (5.29 lower to 0.38 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in mMRC Dyspnoea score **Note: we assumed MID at 1 point change**												
1	randomised trials	serious [8]	not serious	not serious	not serious	none	16	14	-	MD **0.5 lower** (0.62 lower to 0.38 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: cough, fatigue.												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR**: Hazard ratio.

1. Baseline sputum in treatment groups was much higher than control which could affect results
2. Wide CI that includes appreciable benefit and harm
3. Effect size driven by a single study with few events
4. Heterogeneity remained high on subgroup analyses for type of antibiotic and duration of treatment
5. Hospitalization may not always be related to severity depending on the healthcare system and reasons for hospitalization

6. Inconsistencies in methods of assessing eradication
7. 2 of 4 studies included were considered to have high risk of bias, negative effect driven by one study only
8. Effect size driven by a single open-label study with few events

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

Setting: Secondary care
Bibliography: Bilton D et al. *Thorax* 2014; 69: 1073–1079; Bilton D et al. *Chest* 2013; 144: 215; Nicholson CHH et al *Respir. Med.* 2012; 106: 661–667.; Kellett F et al. *Respir. Med.* 2011; 105: 1831–1835; O'Donnell AE et al. *Chest* 1998; 113: 1329–1334.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall long-term mucolytics	no treatment	Relative (95% CI)	Absolute (95% CI)		
Change in SGRQ (units) Note: lower score indicates better QoL; MID fixed at 4 points reduction in total score												
2	randomised trials	not serious	not serious	serious [1]	serious [2]	none	464	340	-	MD **1.81 lower** (3.59 lower to 0.02 lower)	⊕⊕◯◯ LOW	CRITICAL
Annual exacerbation rate (exacerbations/patient/year)												
1	randomised trials	not serious	not serious	serious [1]	not serious	none	233	228	**Rate Ratio 0.92** (0.78 to 1.08) [3]		⊕⊕⊕◯ MODERATE	CRITICAL
Time to first exacerbation (days)												
1	randomised trials	not serious	not serious	serious [1]	not serious	none	233	228	**HR 0.78** (0.63 to 0.96) [3]		⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events												

2	randomised trials	not serious	not serious	serious [1]	serious [2]	none	89/464 (19.2%)	58/340 (17.1%)	**RR 1.13** (0.84 to 1.53)	**22 more per 1,000** (from 27 fewer to 90 more)	⊕⊕◯◯ LOW	CRITICAL
Changes in FEV1 % predicted												
1	randomised trials	not serious	not serious	serious [1]	serious [2]	none	233	228	-	MD **7.56 higher** (19.69 lower to 34.81 higher)	⊕⊕◯◯ LOW	IMPORTANT
Changes in FVC % predicted												
1	randomised trials	not serious	not serious	serious [1]	serious [2]	none	233	228	-	MD **15.85 higher** (37.08 lower to 68.78 higher)	⊕⊕◯◯ LOW	IMPORTANT
IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: Sputum volumen (ml), sputum purulence												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

1. Potential therapeutic benefit from low dose mannitol placebo which may reduce effect size.
2. Wide CI that includes appreciable benefit and harm
3. As reported in Bilton 2014
4. No data reported

PICO question 7:
Is long-term bronchodilator treatment (≥3 months) compared to no treatment beneficial for adult bronchiectasis patients?

Setting: Inpatients and outpatients with bronchiectasis
Bibliography: Martinez-Garcia MA et al. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest 2012;141(2):461-468

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long acting bronchodilators	no bronchodilators	Relative (95% CI)	Absolute (95% CI)		
Exacerbations (total number of exacerbations over 12 months)												
1	randomised trials	very serious [1]	not serious	very serious [2]	serious [3]	none	4/20 (20.0%)	7/20 (35.0%)	**RR 0.57** (0.16 to 1.46)	**151 fewer per 1,000** (from 161 more to 294 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Severe exacerbations (total number of patients requiring hospitalization over 12 months)												
1	randomised trials	very serious [1]	not serious	very serious [4]	serious [3]	none	1/20 (5.0%)	3/20 (15.0%)	**RR 0.34** (0.04 to 2.38)	**99 fewer per 1,000** (from 144 fewer to 207 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	randomised trials	very serious [1]	not serious	serious [5]	serious [3]	none	1/20 (5.0%)	7/20 (35.0%)	**RR 0.15** (0.02 to 0.93)	**298 fewer per 1,000** (from 24 fewer to 343 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life (SGRQ total score) Note: lower score indicates better quality of life												
1	randomised trials	very serious [1]	not serious	very serious [4]	serious [3]	none	20	20	-	MD **4.57 lower** (12.38 lower to 3.24 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Breathlessness Note: transition dyspnoea index, higher indicates reduced breathlessness												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long acting bronchodilators	no bronchodilators	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [1]	not serious	very serious [5]	serious [3]	none	20	20	-	MD **1.29 higher** (0.4 higher to 2.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
FEV1 (ml difference) **Note:** we used liters since there is no literature evaluable on % of predicted. No MID is available in the literature but we internally assumed 100ml as for COPD (Donohue et al. COPD. 2005 Mar;2(1):111-24.)												
1	randomised trials	very serious [1]	not serious	very serious [4]	very serious [3]	none	20	20	-	MD **14 lower** (84.14 lower to 56.14 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

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

1. The Cochrane review identified significant limitations with the conduct of this trial, including inadequate blinding, inadequate or misleading description of the methodology and other potential sources of bias
2. Indirect as compared two different doses of inhaled corticosteroid and so effects cannot be said to be due to the LABA. Also only reported number of individuals with events in a low exacerbation population which provides only indirect evidence of the effect of LABA on overall frequency of exacerbations.
3. Wide confidence interval that includes the possibility of clinically relevant benefit or harm
4. Not a direct evaluation of LABA, but also has two different doses of ICS
5. Unable to evaluate if any of the adverse effects are directly due to the LABA

PICO question 8:

Are surgical interventions more beneficial compared to standard (non surgical) treatment for adult bronchiectasis patients?

Setting: Secondary care
Bibliography: Fan LC, et al. Efficiency and safety of surgical intervention to patients with Non-Cystic Fibrosis bronchiectasis: a meta-analysis. Sci Rep. 2015 Dec 2;5:17382.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	non-surgical	Relative (95% CI)	Absolute (95% CI)		
Mortality												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery**	**non-surgical**	**Relative (95% CI)**	**Absolute (95% CI)**		
29	observational studies	very serious [1]	not serious	serious [2]	not serious	none				**Rate: 0.014** (0.008 to 0.025)	⨁◯◯◯ VERY LOW	CRITICAL
Morbidity (Adverse Events)												
26	observational studies	very serious [1]	not serious	serious [2]	not serious	none [3]				**Rate: 0.162** (0.125 to 0.198)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (symptomatic changes defined as reduction of preoperative symptoms or alleviation)												
26	observational studies	very serious [1]	not serious	very serious [4]	not serious	none				**Rate: 0.202** (0.173 to 0.231)	⨁◯◯◯ VERY LOW	CRITICAL
CRITICAL OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: Exacerbations, hospitalizations												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: Time to next exacerbation, FEV1 (% change), FVC (% change), Exercise tolerance (changes in 6 minute walking distance or incremental walk test)												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

1. Observational studies without control groups. Different surgical interventions. Different stages of disease. No control for underlying medication. Selection bias (only patients with suspected improvement might have been included).
2. Although meta-analysis has sub-analysis on adults, children were included in those papers (judging by age distribution)
3. Funnel plot of 33 studies (adult and children) evaluating the morbidity of resection on bronchiectasis appeared to be symmetrical upon visual examination (Supplementary. The data suggested that there was no evidence of publication bias.
4. Included studies from both children and adults.

PICO question 9:
Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than standard treatment (with no physiotherapy) in adult bronchiectasis patients?

Setting: primary and secondary care; outpatients
Bibliography: Newall, C., et al. Thorax 60(11): 943-948.(2005).; Lee, A. L., et al. (2014). Respir Res 15: 44.; Liaw, M. Y., et al. (2011). Clin Rehabil 25(6): 524-536.; Nicolini, A., et al. BMC Pulm Med 13: 21. (2013).; Figueiredo, P. H., et al. Physiother Res Int 17(1): 12-20.(2012); Guimaraes, F. S., et al. Rev Bras Fisioter 16(2): 108-113.(2012).; Murray, M. P., et al. Eur Respir J 34(5): 1086-1092. (2009).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Physiotherapy**	**no physiotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
QoL- SGRQ total score differences Note: lower score indicates better QoL; MID fixed at 4 points reduction in total score												
2	randomised trials	not serious	serious [1]	not serious	serious [2]	none	25	22	-	MD **5.67 fewer** (13.88 fewer to 2.54 more)	⨁⨁◯◯ LOW	CRITICAL
Number of patients with at least 1 exacerbation (at 12-month follow-up)												
1	randomised trials	serious [3]	not serious	not serious	serious [2]	none	12/42 (28.6%)	18/43 (41.9%)	**RR 0.68** (0.38 to 1.24)	**134 fewer per 1.000** (from 100 more to 260 fewer)	⨁⨁◯◯ LOW	CRITICAL
Exercise capacity-6-minutes walk test (6MWT) Note: MID according to literature (1) is 24,5 mt (Lee AL, et al. Respir Med. 2014 Sep;108(9):1303-9.)												
1	randomised trials	not serious	not serious	not serious	serious [2]	none	13	13	-	MD **41.23 more** (39.05 fewer to 121.51 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Exercise capacity- Incremental shuttle walk test (ISWT) differences Note: MID according to literature (1) is 35 mt (Lee AL, et al. Respir Med. 2014 Sep;108(9):1303-9.)												
2	randomised trials	not serious	not serious	not serious	not serious	none	49	48	-	MD **73.15 more** (45.51 more to 100.8 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Cough (LCQ) 9 weeks Note: a higher score indicates a better quality of life as consenquence of impact of cough; MID is 1.3 (Raj AA, et al. Handb Exp Pharmacol. 2009;(187):311-20.)												
1	randomised trials	not serious	not serious	not serious	not serious	none	42	43	-	MD **0.1 fewer** (0.95 fewer to 0.75 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Cough (LCQ)- 12 months Note: a higher score indicates a better quality of life as consenquence of impact of cough; MID is 1.3 (Raj AA, et al. Handb Exp Pharmacol. 2009;(187):311-20.)												
1	randomised trials	serious [3]	not serious	not serious	not serious	none	42	43	-	MD **4.4 fewer** (5.66 fewer to 3.14 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Dyspnoea expressed as BORG scale Note: MID was fixed at 1 point according to literature in other respiratory diseases (COPD, etc.). mMRC was discarded as referred to daily life more than to current situation.												
1	randomised trials	not serious	not serious	not serious	serious [2,4]	none	33	-	-	SMD **0.15 fewer** (0.92 fewer to 0.62 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

FEV1 (l) **Note:** we used liters since there is no literature evaluable on % of predicted. No MID is available in the literature but we internally assumed 100ml as for COPD (Donohue et al. COPD. 2005 Mar;2(1):111-24.)											
3	randomised trials	not serious	serious [1,5]	not serious	serious [2]	none	33	23	-	MD **0** (0.17 fewer to 0.18 more)	⨁⨁◯◯ LOW	IMPORTANT
FVC (l) Note: we use liters since there is no literature evaluable on % of predicted. No MID is available in the literature but we internally assumed 150ml											
3	randomised trials	not serious	serious [1,6]	not serious	serious [2]	none	33	23	-	MD **0.13 more** (0.01 fewer to 0.26 more)	⨁⨁◯◯ LOW	IMPORTANT
Sputum volume (end of treatment) **Note:** No MID is available in the literature but we internally assumed 10ml or 25% reduction from baseline.											
3	randomised trials	not serious	serious [7]	not serious	not serious	none	32	19	-	MD **4.67 lower** (12.83 lower to 3.48 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Anxiety (HADS) 9 weeks (end of treatment) **Note:** No MID is available in the literature but we internally assumed 1.5 from COPD (Puhan et al. Health Qual Life Outcomes. 2008 Jul 2;6:46.)											
1	randomised trials	not serious	not serious	not serious	serious [2,8]	none	42	43	-	MD **0.6 more** (0.78 fewer to 1.98 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Anxiety (HADS) at 12-month follow-up. **Note:** No MID is available in the literature but we internally assumed 1.5 from COPD (Puhan et al. Health Qual Life Outcomes. 2008 Jul 2;6:46.)											
1	randomised trials	serious [3]	not serious	not serious	serious [2,8]	none	42	43	-	MD **0.3 fewer** (1.59 fewer to 0.99 more)	⨁⨁◯◯ LOW	IMPORTANT
Depression HADS 9 weeks (end of treatment) **Note:** No MID is available in the literature but we internally assumed 1.5 from COPD (Puhan et al. Health Qual Life Outcomes. 2008 Jul 2;6:46.)											
1	randomised trials	not serious	not serious	not serious	serious [2,8]	none	37	39	-	MD **0.3 higher** (0.99 lower to 1.59 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Depression (HADS) at 12-month follow-up **Note:** No MID is available in the literature but we internally assumed 1.5 from COPD (Puhan et al. Health Qual Life Outcomes. 2008 Jul 2;6:46.)											

1	randomised trials	serious [3]	not serious	not serious	serious [2,8]	none	30	25	-	MD **0.2 fewer** (1.75 fewer to 1.35 more)	⨁⨁◯◯ LOW	IMPORTANT
CRITICAL AND IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED FOR THE ANALYSIS: Hospitalizations; Physical activity; adverse events, treatment burden, fatigue - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	-

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

1. overlap of CI
2. Estimate of effect includes both appreciable benefits to harms
3. large number of patients lost of follow up
4. small sample size from one study not powered for Borg
5. high heterogeneity I^2 92%
6. heterogeneity for this outcome is 77%
7. heterogenous interventions since IMT and CPT are different: only CPT is directed at increase expectoration and it does
8. largely far from MID of 1.5

Evidence to Decisions (EtD) frameworks

Criteria (factors that should be considered) for making the decision

Judgements that the panel members must make in relation to each criterion

Research evidence to inform each of those judgements

Additional considerations that inform or justify each judgement; Other evidence, such as estimates from routinely collected data; Plausible consequences or logical reasons for anticipating that the intervention might be (or not be) acceptable to key stakeholders or might be difficult to implement.

PICO question 1:

Is the application of current SEPAR/BTS recommendations about aetiological testing panel of BE beneficial for their clinical management in comparison with no aetiological diagnosis (only CT scan evidence of bronchiectasis)?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The evidence is provided only by 5 observational studies that were not designed to answer the question posed by PICO1. Nonetheless it is likely that considering the existence of treatable causes of bronchiectasis, an aetiological panel of tests may change clinical management in a variable percentage of adult patients as suggested by these studies. Despite the relatively low number of patients whose management could potentially change the relative effect of the intervention may be substantial in case of immunoglobulin deficit for instance or surgically intervenable conditions (fistulae, big

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't k now	hernia, etc.) Almost none or minimal side effects are reported for the tests usually performed for aetiological diagnosis of BE. Radiological exposure risk for CT scan or venipuncture for blood tests, spirometry etc. Another potential source of undesirable effects, although uncommon, could be false positive and false negative related to specificity/sensitivity of each test used for the aetiological diagnosis. Overall trivial undesirable effects can be expected individually.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	Due to lack of good quality scientific evidence
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	Wide variability and uncertainty is always expected due to heterogeneity of the disease and to minimal quality of evidence related to this intervention (aetiological testing). However younger patients or patients whose aetiology is not known ("idiopathic bronchiectasis") may give a greater value to aetiological testing due to potential implications in the clinical management and future outcomes of the disease.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Some benefit can be expected for a subgroup of patients while minimal or no adverse events can be expected.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	If they do not find any evidence, they should note the lack of evidence and record any plausible assumptions as additional considerations. Some of the tests (immunological tests, etc) can be quite expensive and costs can be a considerable limit of feasibility in some centres or countries. On the other hand only few cases may be associated with some savings when etiological testing is followed by a clear reduction in infections and complications related to bronchiectasis and their cause.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Equity / Acceptability / Feasibility: The application of aetiological testing and the consequent change in management may be a source of inequity if these tests and facilities are not available everywhere.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes, since patients and physicians would both be willing to have a correct aetiological diagnosis in order to optimize clinical management and long-term outcomes of some patients with bronchiectasis due to modifiable conditions. However, the subgroups of patients who would benefit and the criteria to identify patients susceptible of this improvement are not clear nowadays.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are some limits related to costs, availability and organization of local settings and feasibility of this intervention may be very variable although generally acceptable.

Is the application of current SEPAR/BTS recommendations about aetiological testing panel of BE beneficial for their clinical management in comparison with no aetiological diagnosis (only CT scan evidence of bronchiectasis)?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest the minimum bundle of aetiological tests in adults with a new diagnosis of bronchiectasis *(conditional recommendation, very low quality of evidence)* is: 1. Differential blood count 2. Serum immunoglobulins (total IgG, IgA, IgM)				

	3. Testing for allergic bronchopulmonary aspergillosis (ABPA) It is expected that sputum culture is undertaken for monitoring purposes of bacterial infection. Mycobacterial culture may be helpful in selected cases where non-tuberculous mycobacteria (NTM) is suspected as an aetiological cause of bronchiectasis. Additional tests may be appropriate in response to specific clinical features, or in patients with severe or rapidly progressive disease.
JUSTIFICATION	These tests can considerably change the future management of bronchiectasis by indicating specific therapeutic interventions such as immune therapy (Ig replacement) steroid or antifungal treatment, CFTR correctors, specific antibiotic therapies in case of NTM or other respiratory infections. These therapies have shown a good benefits/side effects overall balance and can significantly modify clinical history of patients. Minimal undesirable effects are described in association with these tests and potential benefits are expected for some patients. However, the lack of strong scientific evidence in the literature makes this recommendation conditional.
SUBGROUP CONSIDERATIONS	Patients with immunodeficiencies, anatomic deformities that are surgically intervenable, ABPA and NTM infections
IMPLEMENTATION CONSIDERATIONS	Strategies to stratify the risk of a specific underlying condition leading to development of bronchiectasis may help in individualising the aetiological testing and in saving.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Strategies to improve easiness and costs of testing (e.g. alternatives for cilia beating like nasal NO be more researched, or other potentially easier tests) Identification of easy and cheap but reliable markers of specific aetiologies that may deserve specific tests (i.e. dyskinesia, etc.)

PICO question 2

Are courses of 14-21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult BE patients with an acute exacerbation?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	There is no evidence of benefit favouring either 14-21 days or shorter courses of antibiotic therapy. The only data comes from an indirect comparison of response at day 7 vs day 14 in patients that all received 14 days antibiotic treatment. We were unable to identify any significant adverse effects attributable to prolonged or to shorter courses of antibiotic treatment.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't k now	

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	This data is very low quality and is indirect as described above. There is no data available for the majority of end-points. Data were available for bacterial load and FEV1 which were rated as important but not critical outcomes. These are, to a large extent, surrogate outcomes of more important critical outcomes such as subsequent quality of life and time to the next exacerbation. No data were available for these outcomes, therefore any conclusions based on surrogate outcomes must be appropriately weak.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	Patients will generally place a higher value on hard clinical outcomes like quality of life, and a lower value on outcomes such as bacterial load and FEV1 which are surrogates.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ● Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The evidence does not support a conclusion in favour of either treatment regime.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Prolonged antibiotic therapy in the context of a hospitalized exacerbation may carry moderate to large costs, but prolonged oral antibiotic therapy is likely to carry negligible costs. There is no formal data available on the cost-effectiveness of either antibiotic strategy.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Equity / Acceptability / Feasibility: There is no evidence of an impact on health equity
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Data suggests that 14-days antibiotic treatment is considered standard. It is recommended for all exacerbations by national guidelines like the British Thoracic Society guidelines, and has been used in several publications testing the impact of treatment of exacerbations (Chalmers et al AJRCCM 2012, Murray et al ERJ 2009). There is no evidence to show that shorter courses would be acceptable to stakeholders.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no	Yes, and evidence suggests both 14-21 days and shorter courses of antibiotic therapy are administered in clinical practice for a variety of conditions without any practical barriers.

	○ Probably yes ● Yes ○ Varies ○ Don't know	

Are courses of 14-21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult BE patients with an acute exacerbation?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ●	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics (*conditional recommendation, very low quality of evidence*).				
JUSTIFICATION	Standard practice and the available studies have all used treatment of exacerbations for 14 days. I the absence of evidence to show that this practice is harmful or that the alternative practice is more beneficial, the guideline committee has recommended that for the majority of exacerbations treatment should be with 14 days of an appropriate antibiotic. The guideline committee recognizes that shorter courses may be appropriate for some patients and recommended that further evidence on shorter course therapy should be a research priority.				
SUBGROUP CONSIDERATIONS	Patients with an acute exacerbation of bronchiectasis Adults Antibiotics chosen based on prior microbiology testing and targeted towards the causative pathogen The majority of data comes from patients with severe exacerbations and *P. aeruginosa* infection				
IMPLEMENTATION CONSIDERATIONS	Including strategies to address any concerns about the acceptability and feasibility of the intervention				

	Further research assessing the optimal duration of antibiotics is recommended.
MONITORING AND EVALUATION	Suggestions for monitoring including any important indicators that should be monitored and any needs for further evaluation Sputum culture should be performed at the onset of an exacerbation to ensure antibiotic treatment is appropriate and targeted to the causative pathogen. Antibiotic treatment should be revised based on the results of a sputum culture.
RESEARCH PRIORITIES	Randomized controlled trials comparing prolonged vs shorter course antibiotic treatments for exacerbations of bronchiectasis should be conducted. Such trials should include or focus on outpatients where the majority of burden of disease is focussed.

PICO question 3:
Is an eradication treatment beneficial for treating BE patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Moderate proportion of patients achieve clearance of *P. aeruginosa* at 12 months (approx. 40%) but proportion that would achieve this without treatment is unknown. Reduction in exacerbation frequency reported is clinically relevant. Indirect evidence from cystic fibrosis suggests that the intervention is beneficial.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't k now	Poor quality evidence, but there is a reported increase in antimicrobial resistance.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High	All evidence is of very quality and is indirect, with no randomized comparisons between eradication vs no eradication treatment.

	○ No included studies	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The EMBARC priorities survey and discussion with the patient advisory group suggests oatients place a high value on eradication of *P. aeruginosa* and reduction in exacerbations. There is uncertainty about how to define “eradication”.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The overall balance may be in favour of the intervention as there is 1) Low quality evidence in favour of successful eradication and reduced exacerbations 2) minimal evidence of harm. In addition, there is clear evidence of poor outcomes associated with the persistence of *P. aeruginosa* in patients with bronchiectasis (Finch An Am Thorac Soc 2015). This impacts on the risk of NOT performing the intervention. The guideline development group all rated the relevant outcomes of eradication of *Pseudomonas aeruginosa* and reduction in exacerbations as being important or critical. Understanding the benefit of *P. aeruginosa* eradication treatment was rated the most important clinical research priority by a recent EMBARC survey (Aliberti, ERJ 2016).

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There is no literature published on this but we assume by practical observations/assumptions that a moderate cost is associated with administration of intravenous and/or inhaled antibiotics which were used in the two studies considered in this section.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Equity / Acceptability / Feasibility:** There is no evidence of an impact on health equity
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is recommended in national consensus guidelines such as those from the British Thoracic Society and SEPAR. In the EMBARC registry, 2/3 of patients with *P. aeruginosa* isolation have received eradication treatment, suggesting a widespread use of the intervention in clinical practice. On the opposite side, there are some physicians who do not advocate the intervention.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no	The intervention is feasible, but requires monitoring of sputum cultures to identify *P. aeruginosa* infection and the ability to readily administer intravenous and/or nebulised antibiotic treatments.

	● Probably yes ○ Yes ○ Varies ○ Don't know	

Is an eradication treatment beneficial for treating BE patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest that adults with bronchiectasis with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment (*conditional recommendation, very low quality of evidence*). We suggest not routinely offering eradication antibiotic treatment to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa* (*conditional recommendation, very low quality of evidence*)				
JUSTIFICATION	Average 40% rate of eradication of *P. aeruginosa* with eradication treatment. Weak evidence of reduced exacerbations after eradication treatment. Indirect evidence from cystic fibrosis suggests benefit. Strong evidence of poor prognosis associated with *P. aeruginosa* infection and minimal evidence of harms associated with the intervention.				
SUBGROUP CONSIDERATIONS	Symptomatic patients Adults New isolation of *P. aeruginosa* Patients with chronic infection and those already receiving suppressive antibiotic treatments were excluded.				
IMPLEMENTATION CONSIDERATIONS	Including strategies to address any concerns about the acceptability and feasibility of the intervention				

	Prompt identification of *P. aeruginosa* requires sputum monitoring when clinically stable as part of standard care Facilities to administer intravenous antibiotics as an outpatient will reduce the cost implications of eradication treatment The one study that commented on the practice recommended a second sputum sample to exclude spontaneous clearance prior to attempted eradication (White et al, 2012) The quality of evidence is low and further research is also needed on potential side effects of eradication therapies and, particularly, the emergence of resistances or new infections.
MONITORING AND EVALUATION	Suggestions for monitoring including any important indicators that should be monitored and any needs for further evaluation Repeat sputum cultures should be performed to confirm eradication of *P. aeruginosa* following the intervention and at 12 months post-intervention. Failure of *P. aeruginosa* eradication should prompt evaluation of whether the patient would benefit from chronic suppressive antibiotic therapy (dealt with in a different section).
RESEARCH PRIORITIES	A randomized controlled trial comparing eradication treatment with no eradication treatment in patients with new isolation of *P. aeruginosa* infection should be performed. The primary outcome should be a clinical outcome (exacerbations, quality of life).

PICO question 4:
Is long-term (≥ 3 months) anti-inflammatory treatment compared to no treatment beneficial for treating adult bronchiectasis patients?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For all investigated clinical variables, the effect of anti-inflammatory treatment had only minimal effect and with wide confidence intervals that includes both clinical benefit and harm. The effect of anti-inflammatory treatment never reached the minimal important difference for each of those variables (FEV1%, FVC%, exacerbations, SGRQ, sputum volume and sputum purulence) On the other hand, a clinical significant effect of anti-inflammatory treatment on adverse events was perceived with a significant higher number of adverse events in the treatment group versus placebo.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't k now	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	Overall quality of evidence is mainly low due to serious risk of bias that could be attributed to several factors such as: placebo not being similar to treatment in appearance, no allocation concealment, no specification of withdrawals and significant baseline differences in one trial for certain variables.

VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The St Georges Respiratory Questionnaire was not developed specifically for bronchiectasis and so there is some uncertainty about its value as a measure to prove the effectiveness of treatments in bronchiectasis. The measure used for exacerbations (number of patients with events) is clinically important, but the study did not consider other measures of exacerbation frequency. The main outcomes are probably all valuable to all patients. Maybe FVC% and FEV1% as well as sputum purulence might be less important from a patients perspective.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ● Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The significant number of adverse events with limited clinical benefit not reaching minimal important difference, causes a choice towards the alternative.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings	There are no data on this topic but as the benefit of the investigated anti-inflammatory treatments are low and adverse events are significantly higher, a moderate cost might be real. The investigated anti-inflammatory treatment are not expensive.

	○ Varies ○ Don't know	
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No evidence to suggest an impact on health equity. The higher number of adverse events however is an important factor.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Currently, the investigated anti-inflammatory treatments had significant higher adverse events with no important clinical benefit. However, an important part of the adverse events was driven by high dose statins. Therefore, we cannot say that it is definitely not acceptable but rather probably not acceptable with current evidence.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes	The investigated anti-inflammatories are widely available and are sometimes used in this patient population for a variety of reasons.

	○ Varies ○ Don't know	

Is long-term (≥ 3 months) anti-inflammatory treatment compared to no treatment beneficial for treating adult bronchiectasis patients?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ●	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• We suggest not routinely offering treatment with inhaled corticosteroids to adults with bronchiectasis (*conditional recommendation, low quality of evidence*). • We recommend not offering statins for the treatment of bronchiectasis (*strong recommendation, low quality of evidence*). • We recommend not to discontinue inhaled corticosteroid treatment in adults with asthma or COPD following the diagnosis of bronchiectasis (Best practice advice, indirect evidence).				
JUSTIFICATION	No relevant clinical improvement was noticed for all outcome variables in the treatment group versus placebo with significant increased adverse events. Evidence is of low quality due to serious risk of bias and imprecision.				
SUBGROUP CONSIDERATIONS	A large part of the increased adverse events are driven by the statin trial. Adverse events subgroup analysis excluding the Mandal et al. trial (only including Hernando et al. 2012 and Tsang et al. 2005) showed a RR 2.30 CI 95% [0.74,7.19] as compared to 2.75 CI 95% [1.21, 6.25] with all three trials.				
IMPLEMENTATION CONSIDERATIONS	We recommend randomized controlled trials of inhaled corticosteroids in bronchiectasis who are naïve to inhaled corticosteroid therapy. Inhaled corticosteroid use is, however, already widely used in bronchiectasis. In those already				

	treated with inhaled corticosteroids and no clear history of asthma or COPD a randomized controlled trial of inhaled corticosteroid withdrawal may help define true utility of this widely prescribed therapy.
MONITORING AND EVALUATION	Careful monitoring of adverse events is needed when patients with bronchiectasis receive anti-inflammatory treatment.
RESEARCH PRIORITIES	The conclusion of this research question does not imply a generalisation towards all anti-inflammatory treatments nor does this conclusion discourage research for future anti-inflammatory treatments. More research and larger trials are needed looking at other anti-inflammatory treatments. Researchers should carefully consider to investigate the effect of the highest tolerated dose, side-effects and duration of treatment.

PICO question 5:
Is long-term antibiotic treatment (≥3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Long term antibiotics (≥ 3 months) compared to no treatment for adult patients with bronchiectasis significantly improved several important measures of disease severity including no. of exacerbations, time to first exacerbation, sputum purulence and breathlessness. On the other hand, a clinical significant effect of long term antibiotics on adverse events and mortality was noted with a significantly higher number of adverse events in the treatment group versus placebo.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	Overall quality of evidence is moderate primarily due to the wide confidence intervals of the results demonstrating appreciable benefit and harm.
	Is there important uncertainty about	The current research evidence (EMBARC roadmap for patients) and the patients

VALUES	**or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	advisory board suggest that patients give high value to long term antibiotic treatment that may reduce the number of exacerbations and/or hospitalizations in patients with bronchiectasis Patients seem to prefer oral antibiotics in comparison to inhaled antibiotics due to ease of administration and reduced time to administer treatment and enable travel. Most value is attributed to exacerbations and quality of life as opposed to other variables such as lung function which would be less noticeable to patients in an everyday setting. However, patients are increasingly concerned about potential adverse events and resistance with medication and do not want to benefit from short-term gains at the expense of potential long-term consequences of treatment.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The overall balance of 1) positive effects in reduction in no. of exacerbations, time to first exacerbation, sputum purulence and breathlessness, 2) a significant but generally accepted adverse event and resistance profile, and 3) patients' values, probably favours the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No cost-effectiveness studies were identified that compared the use of long term antibiotics (≥ 3 months) compared to no treatment for adult patients with bronchiectasis or other treatments. It is anticipated that that a moderate cost reduction is associated with long term antibiotic treatment due to a reduction in number of exacerbations and hospitalisations for severe exacerbations in this group.

EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Equity / Acceptability / Feasibility:** There is no literature published on this but it is assumed that treatment with long term antibiotics may be limited by local access to inhaled antibiotics, which is very dependent on individual country's health care system organization and economy. *An overall decision to remove this section may be taken by the panel if we agree there is no sufficient information to comment on this.*
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes, since patients and physicians would both be willing to accept long term antibiotics as an intervention but further information is needed on optimum regimes, doses, and duration of treatment where possible plus the potential increase in adverse events and resistance may somewhat reduce their overall acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no major issues limiting feasibility apart from costs and organization of tolerance trials and follow-up of inhaled antibiotics in some countries (particularly in developing countries).

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

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention	**Conditional** recommendation **against** the intervention	Conditional recommendation for either the intervention or the alternative	**Conditional** recommendation **for** the intervention	**Strong** recommendation **for** the intervention
	○	○	○	●	○
RECOMMENDATION	We suggest offering long-term antibiotic treatment for adults with bronchiectasis who have three or more exacerbations per year (*conditional recommendation, moderate quality evidence*). See more details in the main manuscript. Remarks: The type of antibiotic chosen should be tailored to each individual patient according to their baseline symptom profille (frequency and severity of exacerbations), microbiological status and patient preferences. Combined treatment with oral and inhaled antibiotics or combinations of inhaled antibiotics may be considered in selected cases.				
JUSTIFICATION	Clear significant benefit in the reduction of exacerbations, increased time to first exacerbation and improved breathlessness and sputum purulence with non-significant benefits in several other measures of disease severity, such as improved exercise capacity and QoL. Acceptable adverse events and resistance pattern are to be considered in the overall balance.				
SUBGROUP CONSIDERATIONS	**Subgroup analyses performed where appropriate number of studies included:** **Oral versus inhaled antibiotics:** No significant differences for sputum volume, QoL or exercise tolerance. Inhaled antibiotics were associated with a bigger reduction in no. of exacerbations and hospitalisations, higher eradication rates at 12 months (1 study only), lower resistance at end of treatment, a lower adverse event profile and a lower mortality rate compared to oral antibiotics. Oral antibiotics were associated with a bigger change in FEV1% compared to inhaled antibiotics but still not relevant (<5%) in clinical practice. **Pseudomonas Aeruginosa eradication:** Data for this at 12 months was only available in 3 studies. Effect much higher with inhaled versus oral antibiotics. **Per type of drug:** Data for no. of exacerbations suggests AZLI followed by erythromycin then colistin is better at reducing no. of exacerbations. Data for adverse events suggests AZLI associated with lowest AE profile and highest SAE profile. Highest AE associated with roxithromycin (single study). Lowest SAE profile associated with erythromycin (BLESS). Data available for mortality suggests colistin is associated with the lowest mortality compared to all other drugs. Further sub-analyses can be provided on request.				

IMPLEMENTATION CONSIDERATIONS	Larger superiority studies should potentially be considered in the future to determine optimum treatment types, dosages, durations and combinations. Also health-economic analyses would surely be help in determining the economic impact and potential benefits of long term prophylactic therapy (considering on the other side costs due to exacerbations/hospitalizations)
MONITORING AND EVALUATION	Patients with more severe disease characterised by older age, worse lung function, chronic PA infection, worse symptoms, reduced QoL/exercise tolerance, increased comorbidities etc may benefit from more strict long term monitoring (potentially different benefits and harms)
RESEARCH PRIORITIES	Health economic studies Superiority studies comparing different doses or duration or different antibiotics

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

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A small reduction in SGRQ QoL was noted but this not reach the minimum clinically important difference of 4 units. A small but clinically insignificant improvement in annual exacerbation rate and a significant improvement in time to first exacerbation were noted; however, these findings were limited to one study only. A significant improvement in FEV1% and FVC% was noted, both of which reached the MID of 5%. No data on sputum volume or purulence was available. An increase in no. of patients with adverse events was noted at end of treatment with a wide confidence interval that included both clinical benefit and harm.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	Long term mucoactive treatment (≥ 3 months) compared to no treatment for adult patients with bronchiectasis can significantly improve several important measures of disease severity including lung function parameters FEV1% predicted and FVC% predicted with a slightly elevated but acceptable adverse event profile. Overall quality of evidence is mainly low due to potential therapeutic effects of low dose drug given as placebo and wide confidence intervals that included both clinical benefit and harm.
	Is there important uncertainty about	The current research evidence (EMBARC roadmap for patients) and the patients'

VALUES	**or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	advisory board suggest that patients give intermediate value to long term mucoactive treatment that may reduce the number of exacerbations or time to exacerbation in patients with bronchiectasis. However, patients do admit difficulties with administration of such treatment and limiting factors such as time constraints and difficulty with travel.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The overall balance of 1) increase in time to first exacerbation, improvement in FEV1% and FVC% predicted, and a small but clinically insignificant improvement in SGRQ QoL, 2) a generally accepted adverse event profile, and 3) patients' values, probably favours the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No cost-effectiveness studies were identified that compared the use of long term mucoactive treatment (≥ 3 months) compared to no treatment for adult patients with bronchiectasis or other treatments. It is anticipated that that a moderate cost reduction is associated with long term mucoactive treatment due to a reduction in number of exacerbations and potential healthcare utilisation in this group as a result of treatment.

EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Equity / Acceptability / Feasibility:** There is no literature published that suggests an impact on health equity but certain treatments may not be available in developing countries.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes, since patients and physicians would both be willing to accept long term mucoactive treatment as an intervention but further information is needed on optimum regimes, doses, and duration of treatment where possible plus the potential increase in adverse events may somewhat reduce their overall acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no major issues limiting feasibility apart from costs and acceptability, and potentially limited availability particularly in developing countries.

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

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest offering long-term inhaled mucoactive treatment (≥ 3 months) in adult patients with bronchiectasis who have difficulty in expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms (*weak recommendation, low quality evidence*). We recommend not to offer recombinant human DNase to adult patients with bronchiectasis (*strong recommendation, moderate quality evidence*) Remarks: The type of mucoactive therapy chosen should be tailored to each individual patient according to their baseline symptom profille (frequency and severity of exacerbations), baseline lung function and patient preferences.				
JUSTIFICATION	Significant benefit in the increased time to first exacerbation and improved lung function with non-significant benefits in several other measures of disease severity, such as reduction in exacerbation frequency and QoL.				
SUBGROUP CONSIDERATIONS	Subgroup analyses were performed where appropriate, however limited due to the small number of studies and lack of reported outcomes.				
IMPLEMENTATION CONSIDERATIONS	Larger superiority studies incorporating health-economic analyses should potentially be considered in the future to determine optimum treatment types, dosages, durations and combinations.				
MONITORING AND EVALUATION	Patients with more severe disease characterised by older age, worse lung function, chronic PA infection, worse symptoms, reduced QoL/exercise tolerance, increased comorbidities etc may benefit from stricter long-term monitoring (potentially different benefits and harms).				
RESEARCH PRIORITIES	Health economic studies Superiority studies comparing different doses or duration or different mucoactive therapies.				

PICO question 7:

Is long-term bronchodilator treatment (≥3 months) compared to no treatment beneficial for adult bronchiectasis patients?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	If real, the effects would be clinically relevant as a >4 unit improvement in the SGRQ and a >1 unit improvement in the Transitional dyspnoea index would be above the minimum clinically important difference. Nevertheless, the confidence intervals are wide and quality of evidence is very low, therefore these effects cannot be expected with any certainty.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't k now	Although the available evidence provides little data on this point, the known safety profile of long acting bronchodilators in other populations suggests no clinically important risk.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	All evidence is of very low quality and is indirect, and comes from only one study. Data is only available for the comparison of long acting beta-agonist/inhaled corticosteroid versus high dose inhaled corticosteroid. No randomized controlled trial data was available for anti-muscarinics.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	The St Georges Respiratory Questionnaire was not developed specifically for bronchiectasis and so there is some uncertainty about its value as a measure to

	○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	prove the effectiveness of treatments in bronchiectasis. The transitional dyspnoea index has similarly been developed for other conditions and is applied to bronchiectasis without validation or modification for disease specificity. The measure used for exacerbations (number of patients with events) is clinically important, but the study did not consider other measures of exacerbation frequency and the population had a very low rate of exacerbations.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ● Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The evidence suggests the possibility of clinically relevant effects but from very low quality evidence. The data in bronchiectasis and the known safety profile of long acting bronchodilators suggests no clinically important safety issue. The evidence therefore does not favour the routine use of inhaled bronchodilators, but would not favour withholding these if deemed to be clinically indicated.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Most inhaled long acting bronchodilators carry a moderate cost

EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Equity / Acceptability / Feasibility: There is no evidence of an impact on health equity
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	EMBARC registry data shows that these medications are the most widely used treatments for bronchiectasis in Europe.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, the medications are widely available and require no specialised services. It is recommended that patients are trained in appropriate inhaler technique.

Is long-term bronchodilator treatment (≥3 months) compared to no treatment beneficial for adult bronchiectasis patients?

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ●	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest not routinely offering long-acting bronchodilators for adult patients with bronchiectasis (*conditional recommendation, very low quality of evidence*) We suggest to offer long acting bronchodilators for patients with significant breathlessness on an individual basis (*weak recommendation, very low quality of evidence*). We suggest using bronchodilators before physiotherapy, including inhaled mucoactive drugs, as well as before inhaled antibiotics, in order to increase tolerability and optimize pulmonary deposition in diseased areas of the lungs (good practice point, indirect evidence). We suggest that the diagnosis of bronchiectasis should not affect the use of long acting bronchodilators in patients with comorbid asthma or COPD (Good practice point, indirect evidence).				
JUSTIFICATION	Long acting bronchodilators have weak evidence supporting their use, but appear to be safe and well tolerated. It is therefore reasonable to suggest their use in patients with significant breathlessness and impaired quality of life (where the reported improvements in SGRQ or TDI could be clinically important) but not for routine use. As there is high quality evidence from randomized controlled trials in COPD and asthma supporting the use of inhaled bronchodilators it is important that the bronchiectasis guidelines do not discourage the use of these drugs in this patient population.				
SUBGROUP CONSIDERATIONS	Symptomatic patients Adults The majority of patients in the single trial had airflow obstruction (fev1 mean 60% predicted) Excluded smokers and patients with COPD				

	Although the only available data is for long acting beta agonists, there is no reason to favour Long acting beta agonists over long acting antimuscarinics or dual bronchodilators.
IMPLEMENTATION CONSIDERATIONS	Including strategies to address any concerns about the acceptability and feasibility of the intervention Assessment of symptoms of breathlessness should be part of the evaluation of patients with bronchiectasis Spirometry should be performed at diagnosis to identify patients with airflow obstruction Patients should be evaluated for the presence of co-morbid COPD and asthma
MONITORING AND EVALUATION	Suggestions for monitoring including any important indicators that should be monitored and any needs for further evaluation As the benefits of long acting bronchodilators appear to be primarily symptomatic, following a trial of inhaled bronchodilators, patients should be evaluated for evidence of benefit and the drug discontinued if there is no symptomatic evidence of benefit.
RESEARCH PRIORITIES	If relevant Randomized controlled trials of inhaled bronchodilators in bronchiectasis are required.

PICO question 8:
Are surgical interventions more beneficial compared to standard (non surgical) treatment for adult bronchiectasis patients?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Surgery offers a small benefit for quality of life with low mortality but with appreciable morbidity. Moreover, the intervention group is prone to selection bias where only patients with suspected improvement are included in the intervention group.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A surgical intervention causes increased adverse events.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall quality of evidence is very low due to the observational nature of the trials included in the meta-analysis. There are no randomised controlled trials and the observational data is without a control group and included both different surgical interventions and different stages of the disease.
	Is there important uncertainty about	Selection bias of the intervention group (patients with more symptoms or who

VALUES	**or variability in how much people value the main outcomes?** ● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	are probably more responsive of surgical intervention were included. No "randomization".) It's not sure to what extent some patients will find certain outcome measures from the studies important. Lung function might be of little interest in a patient who mainly complains about sputa all day long but isn't really short of breath. Moreover, certain outcome measures where described loosely.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ● Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	There's increased improvement of symptoms but with a similar increase in adverse events in this selected patient population with no control group. As the evidence is of very low quality and as different surgical procedures were compared the balance favours non-surgical interventions to be more beneficial. No direct comparison was made to a non-surgical intervention, therefore the alternative probably favours the surgical intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Surgical interventions with hospitalization and possible adverse events might cause a large cost in resource as compared to non-surgical interventions. There was no data on therapies started or continued or tapered after surgical intervention, therefore the surgical intervention needs to be considered an extra cost on top of normal/standard non-surgical treatment. No data on QALY's. There is however a small percentage of mortality, but no comparison with a control group.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There's no data to support reduced or increased inequity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Surgical interventions showed the possibility of overall improvement in symptoms with increased risk of adverse events and with a small risk of death.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Surgical interventions are already being performed in many centres.

Are surgical interventions more beneficial compared to standard (non surgical) treatment for adult bronchiectasis patients?

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ●	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	We suggest not offering surgical treatments for adult patients with bronchiectasis with the exception of patients with localised disease and a high exacerbation frequency despite optimisation of all other aspects of their bronchiectasis management (*weak recommendation, very low quality of evidence*).				
JUSTIFICATION	Very low quality data showing only a moderate improvement in symptoms with some patients even deteriorating in symptoms. Moreover, considerable adverse events and some mortality.				
SUBGROUP CONSIDERATIONS	Although an "adult sub-analysis" was performed, this sub-analysis included patients under the age 18 years. According to the intervention. According to the output of the surgeon (number of interventions/year; high vs low)				
IMPLEMENTATION CONSIDERATIONS	When planning a patient for a surgical intervention, all non-surgical interventions should be considered and when no more non-surgical interventions are at hand, careful selection of the patient is needed.				
MONITORING AND EVALUATION	Careful monitoring of adverse events and pre –and post-intervention objective measurements of QOL.				
RESEARCH PRIORITIES	More research is needed on surgical interventions. Although a randomized trial is not feasible from an ethical point of view, future trials should include a matched control population with meticulous description of other treatments used in both populations. Important other issues to tackle: The definition of symptomatic improvement was different across trials and no validated outcome measures were used. Because different interventions were pooled, data on adverse events need to be interpreted with care.				

	As these data tackle surgical interventions, data on number of interventions per surgeon per year might be of relevance but were not present in the meta-analysis. As there was no control group, adverse events and symptomatic improvement has to be interpreted with caution.

PICO question 9:

Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than standard treatment (with no physiotherapy) in adult bronchiectasis patients?

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Moderate improvement in exercise capacity (iswt> mid of 35mt) and a non significiant trend to improved quality of life (sgrq) No relevant side effects are excepted based on the publications since the interventions are usually not aggressive or tailored at individual capacity.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't k now	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High	Physio interventions can significantly improve exercise capacity with a good safety profile

	○ No included studies	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The current research evidence (EMBARC roadmap for patients) and the patients advisory board suggest that patients give high value to physiotherapy in order to improve QoL, autonomy, symptoms and exercise capacity; less value is given to lung function
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	The overall balance of 1) positive effects of exercise capacity,2) limited or none undesired side effects and 3) patients values favours the intervention

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There is no literature published on this but we assume by practical observations/assumptions that a moderate cost is associated with physio interventions
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Equity / Acceptability / Feasibility: There is no evidence of an impact on health equity but a different access to respiratory physiotherapy could favour some imbalance between different patients
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes, since patients and physicians would easily accept it but administrative and economic limitations may reduce their acceptability (health-economic considerations)
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no	We don’t see any big issues limiting feasibility apart from economic considerations (see costs and acceptability) that may limit contracting physiotherapists and use of dedicate spaces

	● Probably yes ○ Yes ○ Varies ○ Don't know	

Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than standard treatment (with no physiotherapy) in adult bronchiectasis patients?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• We suggest that patients with chronic productive cough or difficulty to expectorate sputum should be taught an airways clearance technique (ACT) by a trained respiratory physiotherapist to perform once or twice daily (*weak recommendation, low quality of evidence*). • We recommend that adult patients with bronchiectasis and impaired exercise capacity should participate in a pulmonary rehabilitiation program and take regular exercise. All interventions should be tailored to the patient's symptoms, physical capability and disease characteristics (*strong recommendation*, *high quality of evidence).*				
JUSTIFICATION	Clear benefit (>MID) for ISWT and cough questionnaire in stable adult BE patients with no adverse events.				
SUBGROUP CONSIDERATIONS	Symptomatic patients Adult and stable patients Patients with reduced exercise tolerance may benefit particularly from rehab protocols Patients with increased cough and sputum production (bronchorrhea) may benefit from both rehab protocols and				

	airways drainage interventions No clear differences have been observed in the literature across potential age classes or gender, presence of any chronic bronchial infection, FEV1 etc.
IMPLEMENTATION CONSIDERATIONS	Including strategies to address any concerns about the acceptability and feasibility of the intervention Larger series or health-economic studies may be required in the future
MONITORING AND EVALUATION	Suggestions for monitoring including any important indicators that should be monitored and any needs for further evaluation Patients with worse lung function or chronic bronchial infection or older age may benefit a more strict long term monitoring with physio interventions (potentially differential benefits and harms)
RESEARCH PRIORITIES	If relevant Subgroup analysis of more severe patients according to lung function, age, presence of chronic bronchial infection, and according to different aetiologies of bronchiectasis