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A Comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonisation on prognosis in adult bronchiectasis

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1 Rationale:

2 Eradication and suppression of *Pseudomonas aeruginosa* is a key priority in national guidelines for
3 bronchiectasis, and is a major focus of drug development and clinical trials. An accurate estimation
4 of the clinical impact of *P. aeruginosa* in bronchiectasis is, therefore, essential.

5 Methods

6 Data from 21 observational cohort studies comparing patients with *P. aeruginosa* colonisation to
7 those without were pooled by random effects meta-analysis with data collected for key longitudinal
8 clinical outcomes of mortality, hospital admissions, exacerbations and lung function decline along
9 with cross sectional outcomes such as quality of life.

10 Measurements and main results:

11 Studies included 3683 patients. *P. aeruginosa* was associated with a highly significant and consistent
12 increase in all markers of disease severity including mortality (odds ratio (OR) 2.95, 95% CI 1.98-4.40;
13 $p < 0.0001$), hospital admissions (OR 6.57, 95% CI 3.19-13.51; $p < 0.0001$) and exacerbations (mean
14 difference 0.97 per year, 95% CI 0.64-1.30; $p < 0.0001$). Patients with *P. aeruginosa* also had worse
15 quality of life using the St Georges Respiratory Questionnaire (mean difference 18.2 points, 95% CI
16 14.7-21.8; $p < 0.0001$). There were also large differences in lung function and radiological severity.

17 Definitions of colonisation were inconsistent but findings were robust irrespective of the definition
18 used.

19 Conclusion: *P. aeruginosa* is associated with an approximate 3-fold increased risk of death and an
20 increase in hospital admissions and exacerbations in adult bronchiectasis.

21

22

23 Primary source of funding: European Bronchiectasis Network (EMBARC)

24

25 **Introduction**

26 Bronchiectasis is a chronic inflammatory lung disease characterised by recurrent cough, sputum
27 production and recurrent respiratory tract infections.(1) Failure of the mucociliary escalator and
28 innate antimicrobial defences leads to chronic bacterial colonisation of the airways.(2) Bacteria
29 provoke an inflammatory response that can further drive airways inflammation and airway
30 structural damage leading to the well described “vicious cycle” of bronchiectasis.(2,3)

31 While the majority of patients with bronchiectasis may be colonised with organisms that are upper
32 airway commensals such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, a proportion of
33 patients become colonised with the opportunistic pathogen *Pseudomonas aeruginosa*.(4-6)

34 In cystic fibrosis (CF) bronchiectasis, it is well established that *P. aeruginosa* colonisation leads to a
35 more rapid deterioration in lung function and earlier mortality.(7) Consequently, *P. aeruginosa*
36 eradication is standard care in European CF centres.(8,9) The capability of *P. aeruginosa* to form
37 biofilms provide it with physical and chemical protection from the immune system and reduces its
38 exposure to systemically delivered antibiotics.(10,11) *P. aeruginosa* has the ability to rapidly adapt to
39 chronic infection in the lung and readily develops antimicrobial resistance. Management of *P.*
40 *aeruginosa* therefore represents a significant clinical challenge.

41 In bronchiectasis, conflicting data have been published on the independent contribution of *P.*
42 *aeruginosa* to long term prognosis and there remains a question of whether *P. aeruginosa* drives
43 disease progression or is simply a marker of existing severe disease.(12,13) Determining the
44 importance of *P. aeruginosa* to bronchiectasis morbidity and mortality is important, as there are few
45 evidence based treatments for bronchiectasis.(14) Current therapeutic development is heavily
46 influenced by CF and is therefore largely targeted towards treatment of *P. aeruginosa*
47 infection.(15,16) Therefore from clinical, drug development and regulatory perspectives it is
48 important to have a comprehensive understanding of the impact of *P. aeruginosa* on outcomes in
49 bronchiectasis.

50 We therefore undertook a systematic review to determine whether colonisation with *P. aeruginosa*
51 influences future prognosis and/or is associated with cross-sectional features of severity.

52

53 **METHODS**

54 The present study was a systematic review and meta-analysis conducted and reported according to
55 MOOSE (meta-analysis of observational studies in epidemiology) guidelines.(17)

56 **Search Criteria**

57 The study was based on a search of the PUBMED database for articles evaluating the prognostic
58 impact of colonisation with *P. aeruginosa*. The following search strategy was used: ("Pseudomonas"
59 OR "aeruginosa") AND ("bronchiectasis") followed by ("prognosis" or "mortality") and
60 ("bronchiectasis"). The search included articles published between January 1980 and January 2015.
61 No language criteria were applied. Full articles of potentially appropriate abstracts were reviewed.
62 Only peer reviewed data were included. Conference abstracts were excluded. The search was
63 repeated in EMBASE and Web of Science to obtain any articles missed by the initial search. The
64 search strategy was supplemented by reviewing of the reference lists, bibliographies including the
65 British Thoracic Society guidelines and investigator files.

66

67 **Data extraction**

68 Non relevant studies were excluded based on review of the title and abstract. Article reviewing was
69 performed independently by two investigators ((two out of SF, ,MM, AHL, SA and JC) who conducted
70 data extraction and quality assessment from studies meeting the inclusion criteria. All investigators
71 have experienced of meta-analysis and training in literature review. Any disagreement between
72 investigators was resolved independently by a third investigator. Additional unpublished data were
73 obtained from study authors where possible. Where data were presented only as medians, means
74 with standard deviation were estimated according to the formula of Hozo et al.(18)

75

76

77 **Study inclusion and exclusion criteria**

78 All studies were considered eligible if they fulfilled the following criteria: original publications;
79 inclusion of a cohort of patients with computed tomography diagnosed bronchiectasis not due to
80 cystic fibrosis; inclusion of patients with *P. aeruginosa* colonisation and a comparator population
81 without *P. aeruginosa* colonisation; reporting of one of the study outcomes which were determined
82 *a priori* (described below).

83 Definitions of *P. aeruginosa* colonisation were obtained from the source studies and were not pre-
84 specified.

85 As the aim of this study was to compare *P. aeruginosa* colonised patients compared to non-
86 colonised patients, we excluded any studies which provided data only for a single population. We
87 also excluded case reports; review articles, editorials and letters without original data.

88

89 **Study outcomes**

90 **Primary analysis**

91 Our hypothesis was that *P. aeruginosa* colonisation would be associated with globally worse clinical
92 outcome when compared to patients without *P. aeruginosa* colonisation. **Outcomes were split into**
93 **longitudinal clinical outcomes determined during follow-up, and cross-sectional outcomes.** The
94 primary **longitudinal** outcome was all-cause mortality. Secondary outcomes were: hospital
95 admissions, **exacerbation frequency**, decline in forced expiratory volume in 1 second (FEV₁) and the
96 prognostic impact of *P. aeruginosa* eradication therapy.

97 **Cross sectional outcomes were:** FEV₁ % predicted, forced vital capacity (FVC), radiological
98 involvement and quality of life (QoL). A descriptive analysis of the methods of defining *P. aeruginosa*
99 colonisation in the literature was also considered a pre-specified secondary end-point.

100 Anticipating that studies would have different lengths of follow-up to determine survival, we pre-
101 specified that data could be pooled where equal follow-up was demonstrated between *P.*
102 *aeruginosa* colonised and non-colonised patients.

103

104 **Quality assessments**

105 The quality of each study was independently assessed according to the criteria described by Hayden
106 et al, which are widely used for assessing the quality of observational studies in meta-
107 analysis.(19,20) The agreement between the two reviewers (two of SF, AHL and JC) was measured
108 using the kappa statistic. Publication bias was determined by visual inspection of funnel plots and
109 Eggers test.

110

111 **Sensitivity analysis**

112 A priori we identified possible factors that may be major sources of bias and planned subanalyses for
113 the follow; 1) Analysis according to different definitions of *P. aeruginosa* colonisation e.g single
114 isolate versus multiple isolatins; 2) Comparison of *P. aeruginosa* vs *H. influenzae* colonised patients
115 compared to comparisons of *P. aeruginosa* colonised vs non-colonised patients; 3) Data derived
116 from high quality and prospective studies.

117

118 **Statistical analysis**

119 The primary outcome of the relationship between *P. aeruginosa* colonisation and mortality was
120 displayed as odds ratios (OR) with 95% confidence intervals (95% CI). ORs were pooled using a
121 Mantel-Haenszel random effects model. The same analysis was used for hospital admissions.

122 Continuous variables such as quality of life, lobar involvement, pulmonary function tests and
123 exacerbations were compared by pooling mean differences by the inverse of their variance. As
124 above, random effects meta-analysis was used due to expected heterogeneity between studies. To
125 analyse for possible effect modifiers, such as study quality or definitions of colonisation, we
126 compared OR's using interaction testing as described.

127 Statistical heterogeneity was assessed using the Cochran Q (χ^2) test and the Higgins I² tests. For the
128 Cochran Q test, p<0.1 was considered to represent significant heterogeneity. For the Higgins test, I²
129 <25% indicated low heterogeneity, 25–50% moderate and >50% severe heterogeneity. Analyses
130 were conducted using Review Manager 5 (Cochrane Collaboration) and SPSS version 21 for windows
131 (Chicago, IL, USA).

132

133

134

135

136 **RESULTS**

137

138 The results of the literature review are shown in figure 1. The majority of studies were rejected
139 because they did not deal specifically with patients with bronchiectasis not due to CF or did not
140 evaluate severity or outcomes. Of 55 articles selected as relevant, 21 studies had valid data for
141 inclusion and were pooled in the meta-analysis.(6,12,13,21-36) One study contained data for 5
142 cohorts and each cohort was considered separately for the purposes of this analysis on the basis that
143 they were independent cohorts (total 25 cohorts).(24)

144

145

146 Characteristics of the 21 included studies are shown in table 1. 10 studies were from the UK
147 (12,21,23,24,26,28,31,32) and overall 16 cohorts were from Europe. There were no cohorts from
148 North America.

149

150 Definitions of chronic *P. aeruginosa* colonisation were highly heterogeneous. The most frequent
151 definition used was 2 positive cultures at least 3 months apart over 12 months. 5 studies reported
152 patients with a single positive culture as “colonised”. In all, 8 different methods of defining *P.*
153 *aeruginosa* colonisation were identified in addition to 3 studies where the definition was not stated.
154 According to the quality assessment, 6 studies were rated as high quality, 8 as intermediate, and 7 as
155 low quality (Kappa 0.73). None of the analyses showed evidence of publication bias.

156

157 The total number of patients studied was 3683 with a rate of *P. aeruginosa* colonisation (according
158 to study definitions) of 21.4%. Comparator populations were almost universally mixed populations
159 of bronchiectasis not colonised with *P. aeruginosa*.

160

161 **Impact of *P. aeruginosa* on longitudinal outcomes**

162 **Primary outcome: All-cause Mortality**

163 Mortality was available as an outcome in 8 cohorts (24-27) of which 5 cohorts were derived from a
164 single study (24). Follow-up duration ranged from 1 year to 14 years. **Mortality for patients with *P.***
165 ***aeruginosa* ranged from 7.7% at 1 year, 13.6% at 2 years to 30-50% at 5 years. Corresponding**
166 **mortality rates for patients without *P. aeruginosa* were 0% at 1 year, 7% at 2 years and 9-15% at 5**
167 **years.** All studies showed a higher risk of mortality associated with *P. aeruginosa* colonisation. The
168 pooled OR for mortality was 2.95 (95% CI 1.98-4.40; p<0.0001). Heterogeneity tests were not
169 statistically significant. This is shown in figure 2.

170 Sub-analyses confirmed this association in high quality studies (OR 3.64, 95% CI 1.75-7.55; p=0.0005,
171 n=1433), prospective studies and excluding studies with <3 (OR 2.82, 95% CI 1.94-4.11; p<0.0001,
172 n=1994) and >6 years follow-up (OR 3.14, 95% CI 1.83-5.33; p<0.0001, n=1894).

173

174 **Hospital admissions**

175 This analysis included 7 cohorts with 1628 participants (23,24,29). Hospital admission rates for
176 patients with *P. aeruginosa* varied from 41% at 1 year to 75% at 4 years. Corresponding hospital
177 admission rates in patients without *P. aeruginosa* were 15% at 1 year and 28.5% at 4 years. *P.*
178 *aeruginosa* was associated with a marked increase in the risk of hospital admissions – pooled OR
179 6.57 (95% CI 3.19-13.51; p<0.0001). There was significant heterogeneity which was not resolved on
180 limiting studies by quality, prospective design or length of follow-up. Insufficient data was available
181 to evaluate additional impacts such as length of hospital stay or economic impacts of hospitalisation.
182 Data are shown in figure 3.

183

184

185 **Exacerbations per year**

186 All available data were presented as mean exacerbations per patient per year. The 9 cohorts which
187 recorded this information gave a pooled increased frequency of just under 1 exacerbation per
188 patient per year – mean difference 0.97 (95%CI 0.64-1.30; p<0.0001) with no significant
189 heterogeneity.(6,23,24,29,30) This is shown in figure 4. No significant differences in effect were
190 observed in high quality studies, prospective studies or in sub-analyses based on the definition of *P.*
191 *aeruginosa*.

192

193 **Lung function decline**

194 There were limited data available on lung function decline. One study reported lower lung function
195 in PA colonised patients but no differences in long term lung function decline.(13) Another study
196 reported a mean decline of 52ml per year in *P. aeruginosa* patients(12) with a further study
197 reporting a mean decline of 123ml per year.(38) The available data included only 41 patients with *P.*
198 *aeruginosa* colonisation. Consequently no attempt was made to pool the data.

199

200 **Pseudomonas eradication treatment**

201 No randomised studies of *P. aeruginosa* eradication treatment were identified. A non-randomised
202 observational study (n=30) reported an initial eradication success rate of 80%, and 43% after a
203 median of 6 months.(39) This was associated with a reduction in exacerbations from 3.93 per year to
204 2.03 per year. No control population was available for comparison with no data on the spontaneous
205 clearance rate that would have occurred without treatment.

206

207

208 **Cross sectional association between *P. aeruginosa* and markers of severe disease**

209 **Patient characteristics**

210 *In cross-sectional studies we observed that patients with *P. aeruginosa* infection were on average 3*
211 *years older than non-colonised patients (mean difference 3.1 years, 95% CI 0.9-5.4,p=0.007, I²=48%).*
212 *Interestingly there was a statistically significant association between male gender and *P. aeruginosa**
213 *colonisation, OR 1.39 95% CI 1.09- 1.75, p=0.009, I²=0%.*

214 **Quality of life**

215 The only data that were available for QoL used the St.Georges Respiratory Questionnaire (SGRQ).

216 The SGRQ is a validated questionnaire in patients with bronchiectasis that has been widely used with

217 an accepted increment of 4 points demonstrating clinical significance.(37) 4 studies reported data
218 for SGRQ, with a mean difference of 18.2 points (95% CI 14.7-21.8; p<0.0001, n=1041).(22,24,28)
219 There was no heterogeneity between studies ($I^2=0\%$). No data were available for other
220 questionnaires, including the QoL-Bronchiectasis questionnaire.

221

222 **Lung Function- FEV₁ and FVC**

223 As expected, patients with *P. aeruginosa* colonisation had worse cross-sectional lung function
224 compared to patients without *P. aeruginosa*. 17 studies reported valid data for FEV₁ with all showing
225 worse lung function in the *P. aeruginosa* group ranging from -1.4% to -29%.
226 (6,12,13,21,22,24,28,29,30,31,33,34,36) The pooled mean difference was 15.0% (95% CI -18.7 to -
227 11.3; p<0.0001). There was significant heterogeneity but this was no longer statistically significant
228 after excluding 1 study that defined *P. aeruginosa* presence by PCR.(6) 9 cohorts presented data for
229 FVC with a pooled mean difference of -9.4% (95% CI -14.3 to -4.5%;p=0.005, n=1453).
230 (12,24,28,29,33,34)

231

232 **Radiological severity**

233 Although multiple severity scoring systems have been utilised in bronchiectasis, the only variable
234 which was studied in more than one study was the number of lobes involved on CT. This data were
235 available in 9 cohorts.(24,29,30,32,34,35) The mean difference between *P. aeruginosa* colonised and
236 non-colonised was 1.4 lobes (95% CI 0.93-1.86; p<0.0001). Nevertheless all studies reported worse
237 radiological severity in *P. aeruginosa* colonised patients.

238 **Sensitivity analyses**

239 Limiting the analysis to only those studies that used the most robust definition of *P. aeruginosa*
240 colonisation, requiring at least 2 positive sputum samples over a 12 month period, showed very

241 similar results to the primary analysis with ORs for mortality of 3.46, 95% CI 1.96-.6.08; p<0.0001;
242 hospital admissions 7.22, 95% CI 2.88-18.09; p<0.0001 and exacerbations mean difference 0.87, 95%
243 CI 0.59-1.15; p<0.0001 (p>0.5 when comparing odds ratios using interaction testing compared to the
244 overall cohort).

245

246 8 cohorts provided data that could be used to directly compare the outcomes of patients colonised
247 with *P. aeruginosa* versus *Haemophilus influenzae*. The findings were highly consistent with the main
248 analysis, with an increase in mortality associated with *P. aeruginosa* (OR 4.00, 95% CI 2.28-7.02;
249 p<0.001), increased rate of hospital admissions (OR 6.75, 95% CI 3.98-11.45; p<0.001), increased
250 exacerbations (mean difference 0.99 (95% CI 0.54-1.43; p<0.0001) and low FEV₁ (mean difference -
251 11.4, 95% CI -14.8 to -7.9; p<0.0001).

252 DISCUSSION

253 The management of bronchiectasis patients with *P. aeruginosa* colonisation is challenging and a
254 large proportion of the current therapeutic development in bronchiectasis is focussed towards
255 management of *P. aeruginosa* infection.(14-16) In particularly there are intensive efforts in the field
256 of inhaled antibiotics to develop a licensed therapy for *P. aeruginosa* infection in
257 bronchiectasis.(15,16) Therefore an accurate assessment of the prognostic impact of *P. aeruginosa*
258 in bronchiectasis is important for clinicians, for drug developers and for regulators. This analysis
259 provides a detailed insight into the impact that *P. aeruginosa* colonisation has on key clinical
260 outcomes in bronchiectasis. **In addition, *P. aeruginosa* colonisation was associated with multiple**
261 **cross-sectional markers of disease severity. It can therefore be said that *P. aeruginosa* is both a**
262 **marker of severe disease, and is associated with a worse long term prognosis.** Bronchiectasis has
263 historically been a neglected condition, described in the ERS white book as one of the most
264 neglected diseases in respiratory medicine.(40) As a result, there have been few large cohort studies.
265 The value of meta-analysis therefore is to combine the available data from existing small studies to
266 give a more accurate estimate of the disease impact.

267 The most striking finding within this analysis is the impact of *P. aeruginosa* on all-cause mortality.
268 Our analysis identifies a 3-fold increase in the risk of death with *P. aeruginosa* colonisation. *P.*
269 *aeruginosa* **was also associated with a** greatly increased the risk of hospital admissions and
270 exacerbation frequency by a rate of 1 exacerbation per patient per year. This finding was robust
271 regardless of the definition used and was consistent across all cohorts. These results strengthen the
272 view that patients with *P. aeruginosa* require specific treatment to reduce the risk of long term
273 morbidity and mortality and that *P. aeruginosa* colonisation status should play a key role in the
274 assessment of disease severity.(14)

275 The increased exacerbation frequency and hospital admissions demonstrates a measurable
276 healthcare cost **associated with** *P. aeruginosa* colonisation. Each additional exacerbation results in

277 further antibiotic use with associated risks and side-effects as well as increased potential for the
278 development of antimicrobial resistance. Exacerbations are associated with reduced productivity
279 through absence from work and are associated with poorer QoL and potential lung function
280 decline.(24,38,41) Hospital admissions may reflect more severe exacerbations or the development
281 of resistance to oral antibiotic agents necessitating intravenous antibiotic therapy.(24) The ability of
282 *P. aeruginosa* to develop antibiotic resistance is inevitably enhanced by repeated antibiotic
283 exposure.(29)

284 **Our analyses of quality of life, lung function and radiological severity were cross-sectional and can**
285 **therefore only be considered hypothesis generating in terms of the impact of *P. aeruginosa* on these**
286 **outcomes over the long term. Nevertheless** the impact on QoL demonstrated in this analysis is
287 striking. The 18 point decrement in the SGRQ demonstrated in patients with *P. aeruginosa*
288 colonisation reflects a dramatic worsening of QoL. Given our observation that patients with *P.*
289 *aeruginosa* had reduced lung function and more widespread radiological disease on imaging it is
290 difficult to determine what proportion of this difference in QoL is directly attributable to *P.*
291 *aeruginosa*. All of the analyses described herein are subjective to the same limitation, that *P.*
292 *aeruginosa* may be to some extent a reflection of the severity of underlying disease rather than a
293 directly cause of disease progression. The only way to conclusively prove or quantify the
294 independent effects of *P. aeruginosa* on outcome is likely to be through a large randomised
295 controlled trial of *P. aeruginosa* eradication treatment which has been highlighted as a clear priority
296 for the bronchiectasis research community.(42) Demonstrating that mortality, hospital admissions,
297 exacerbations, QoL and lung function are improved or cease to decline after successful eradication
298 would clearly demonstrate the independent impact of *P. aeruginosa*. **A strength of our analysis is**
299 **that it provides the most precise estimates to date of *P. aeruginosa* prevalence and impact in order**
300 **to power future trials.**

301 Current national guidelines for bronchiectasis recommend eradication treatment for new isolation of
302 *P. aeruginosa*, largely based on recommendations for CF.(8,14,43) Data in bronchiectasis is limited to
303 date and further research is greatly needed.

304 Important gaps in the literature identified through this analysis include an absence of data available
305 outside Europe and Australasia with a large proportion of included data from the UK; broad,
306 representative registries for patients with bronchiectasis are needed internationally. Few studies
307 examining lung function decline were identified, and those that were found were small with
308 inconsistent results. We would recommend further large studies of lung function decline in
309 bronchiectasis. There is a lack of data describing the impact of organisms other than *P. aeruginosa* in
310 bronchiectasis and in particular comparing the outcomes of *P. aeruginosa* colonised patients with
311 those colonised with the most common bronchiectasis pathogens such as *H. influenzae* or *Moraxella*
312 *catarrhalis*. Such data would be valuable as recent reports suggest that these patients do have a
313 worse outcome compared to non-colonised patients, but to a lesser extent than *P. aeruginosa*.(24)
314 For example in the Bronchiectasis Severity Index, 3 points are awarded to patients with *P.*
315 *aeruginosa* colonisation and 1 point to patients colonised with other pathogens.(24) For this meta-
316 analysis, we were able to identify 8 cohorts with data to compare outcomes between *P. aeruginosa*
317 and *H. Influenzae* colonised patients and these confirmed the significantly worse clinical outcomes
318 associated with *P. aeruginosa*.

319 There is a need from both a clinical and research perspective to define chronic bacterial colonisation
320 in bronchiectasis as this analysis identified 8 different methods of defining *P. aeruginosa*
321 colonisation in bronchiectasis studies. The most frequently used definition was 2 or more positive
322 cultures at least 3 months apart in 12 months. This should be standardised across studies to increase
323 our ability to generalise results between studies and healthcare systems. Our data were almost
324 entirely based on traditional bacterial culture and recent studies have increasingly used quantitative
325 PCR or characterisation of the microbiome through sequencing of the 16s ribosomal RNA subunit to

326 determine bacterial colonisation status.(6,36,44) This method is significantly more sensitive for the
327 detection of *P. aeruginosa* with Rogers et al. demonstrating very poor correlation between culture
328 and PCR for *P. aeruginosa* detection: 91/107 patients in this study were positive for *P. aeruginosa*
329 versus 31/107 by culture.(6) For this reason, further studies of the role of PCR in *P. aeruginosa*
330 detection and to confirm eradication, would be beneficial.

331 The word colonisation in this context is perhaps misleading. Colonisation implies a benign state
332 defined by absence of tissue invasion or tissue damage. The term 'chronic infection' may be more
333 appropriate given the clearly established association between the presence of bacteria and airway
334 inflammation and the worse clinical outcomes observed in the presence of *P. aeruginosa*.

335

336 In summary, *P. aeruginosa* colonisation is associated with increased mortality, hospital admissions
337 and exacerbations, and is associated with worse QoL. As such, new Isolation of *P. aeruginosa* should
338 be considered a highly significant clinical event and followed up with repeated cultures and attempts
339 to eradicate in line with guideline recommendations.

340

341 REFERENCES

- 342 1. Chalmers JD, Aliberti S, Blasi F. State of the art review: Bronchiectasis in Adults. *Eur Respir J*
343 2015; 45(5):1446-62.
- 344 2. Chalmers JD, Smith MP, McHugh B, Doherty C, Govan JRW, Hill AT. Short and long term
345 antibiotic therapy reduces airway and systemic inflammation in non-CF bronchiectasis. *Am J*
346 *Respir Crit Care Med*. 2012; 186(7):657-65.
- 347 3. Cole PJ. Inflammation: a two-edged sword--the model of bronchiectasis. *Eur J Respir Dis*
348 *Suppl* 1986;147:6–15.
- 349 4. Chalmers JD, McHugh BJ, Doherty CJ, Govan JR, Hill AT. Vitamin-D deficiency is associated
350 with chronic bacterial colonisation and disease severity in non-CF bronchiectasis. *Thorax*
351 2012; 68(1):39-47.
- 352 5. Whitters D, Stockley R. Immunity and bacterial colonisation in broncheictasis. *Thorax*
353 2012;67(11):1006-13.
- 354 6. Rogers GB, Zain NM, Bruce KD, Burr LD, Chen AC, Rivett DW, McGuckin MA, Serisier DJ. A
355 novel microbiota stratification system predicts future exacerbations in bronchiectasis. *Ann*
356 *Am Thorac Soc* 2014; 11(4):496-503.
- 357 7. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and
358 other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr*
359 *Pulmonol* 2002;34:91–100.
- 360 8. Döring G, Hoiby N; Consensus Study Group. Early intervention and prevention of lung
361 disease in cystic fibrosis: a European consensus. *J Cyst Fibros* 2004;3:67–91
- 362 9. Langton Hewer SC, Smyth A. Antibiotic strategies for eradicating Pseudomonas aeruginosa in
363 people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD004197.
- 364 10. Cullen L, McClean S. Bacterial adaptation during chronic respiratory infection. *Pathogens*
365 2015;4(1):66-89.

- 366 11. Chalmers JD, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-
367 cystic fibrosis bronchiectasis. *Mol Immunol* 2013;55:27–34.
- 368 12. Evans SA, Turner SM, Bosch BJ, Hardy CC, Woodhead MA. Lung function in bronchiectasis:
369 the influence of *Pseudomonas aeruginosa*. *Eur Respir J* 1996;9(8):1601-4.
- 370 13. Davies G, Wells AU, Doffman S, Watanabe S, Wilson R. The effect of *Pseudomonas*
371 *aeruginosa* on pulmonary function in patients with bronchiectasis. *Eur Respir J*
372 2006;28(5):974-9.
- 373 14. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis.
374 *Thorax* 2010; 65:suppl 1:i1-58.
- 375 15. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with
376 bronchiectasis and chronic *pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med*
377 2014; 189(8):975-82.
- 378 16. Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, Cipolla D, Bruinenberg
379 P, Gonda I. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis
380 (ORBIT-2): a randomised, double-blind, placebo-controlled trial. *Thorax* 2013;68(9):812-7.
- 381 17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe
382 TA, Thacker SB. Meta-analysis of observational studies in epidemiology. *JAMA*. 2000;
383 283:2008-2012.
- 384 18. Hozo SP, Djulbergovic B, Hozo I. Estimating the mean and variance from the median, range
385 and size of the sample. *BMC Med Res Methodol* 2005; 5:13.
- 386 19. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognostic studies in systematic
387 reviews. *Ann Intern Med* 2006; 144:427-437.
- 388 **20.** Chalmers JD, Rother C, Salih W, Ewig S. Healthcare associated pneumonia does not
389 accurately identify potentially resistant pathogens: a systematic review and meta-analysis.
390 *Clin Infect Dis* 2014; 58(3):330-9.
- 391 21. McDonnell MJ, Jary HR, Perry A, MacFarlane JG, Hester KL, Small T, Molyneux C, Perry JD,

- 392 Walton K, De Soyza A. Non cystic fibrosis bronchiectasis: a longitudinal retrospective
393 observational cohort study of Pseudomonas persistence and resistance. *Respir Med* 2014;
394 109(6):716-26.
- 395 22. Hernandez C, Abreu J, Jimenez A et al. Función pulmonar y calidad de vida en relación con la
396 colonización bronquial en adultos con bronquiectasias no debidas a fibrosis quística. *Med*
397 *Clin (Barc)* 2002;118(4):130-4
- 398 23. Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: a comprehensive profile of
399 a neglected disease. *Eur J Intern Med* 2003; 14(8):488-492.
- 400 24. Chalmers JD, Goeminne P, Aliberti S, McDonnell M, Lonni S, Davidson J, Poppelwell L, Salih
401 W, Pesci A, Dupont LJ, Fardon TC, De Soyza A, Hill AT. Derivation and validation of the
402 bronchiectasis severity index: an international multicentre observational study. *Am J Respir*
403 *Crit Care Med* 2014;189(5):576-85.
- 404 25. Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis
405 bronchiectasis: a prospective cohort analysis. *Respir Med* 2014;108(2):287-96.
- 406 26. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, Wilson R.
407 Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur*
408 *Respir J* 2009; 34(4):843-9.
- 409 27. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, Giron RM, Maiz Xarro L, de la Rosa
410 Carrillo D, Oliveira C. Multidimensional approach to non-cystic fibrosis bronchiectasis; the
411 FACED score. *Eur Respir J* 2014;43(5):1357-67.
- 412 28. Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum
413 bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J* 1997; 10:1754-
414 1760.
- 415 29. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study
416 in adult bronchiectasis. *Respir Med* 2007; 101:1633-1638
- 417 30. Tsang KW, Chan KN, Ho PL, Zheng L, Ooi GC, Ho JC, Lam W. Sputum elastase in steady state

- 418 bronchiectasis. *Chest* 2000;117:420-426.
- 419 31. Hester KLM, MacFarlane JG, Tedd H, Jary H, McAlinden P, Rostron L, Small T, Newton JL, De
420 Soyza A. Fatigue in bronchiectasis. *Q J Med* 2012;105:235-240
- 421 32. Miszkiel KA, Wells AU, Rubens MB, Cole PJ, Hansell DM. Effects of airway infection by
422 *Pseudomonas aeruginosa*: a computed tomography study. *Thorax* 1997;52:260-264.
- 423 33. Ho PL, Chan KN, Ip MSM, Lam WK, Ho CS, Yuen KY, Tsang KW. The effect of *Pseudomonas*
424 *aeruginosa* infection on clinical parameters in steady-state bronchiectasis. *Chest*
425 1998;114:1594-1598.
- 426 34. Zheng L, Tipoe G, Lam WK, Ho JC, Shum I, Ooi GC, Leung R, Tsang KW. et al. Endothelin-1 in
427 stable bronchiectasis. *Eur Respir J* 2000;16:146-149.
- 428 35. Arsava BE, Coplu L. Does airway colonization cause systemic inflammation in bronchiectasis.
429 *Tuberk Toraks* 2011;59(4):340-347.
- 430 36. Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, Serisier DJ.
431 Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota
432 composition. *Thorax* 2013; 68(8):731-7.
- 433 37. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St.Georges Respiratory
434 Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):536-41.
- 435 38. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, Roman-Sanchez P, Soriano J.
436 Factors associated with lung function decline in adult patients with stable non-cystic fibrosis
437 bronchiectasis. *Chest* 2007;132(5):1565-72.
- 438 39. White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of
439 *Pseudomonas* eradication therapy in patients with non-cystic fibrosis bronchiectasis. *Respir*
440 *Med* 2012; 106(3):356-60.
- 441 40. Bronchiectasis. *The European Lung White Book* 2014; 15: 176-183.

- 442 41. Joish VN, Spilsbury-Cantalupo M, Operschall E, Luong B, Boklage S. Economic burden of non-
443 cystic fibrosis bronchiectasis in the first year after diagnosis from a US health plan
444 perspective. *Appl Health Econ Health Policy* 2013;11(3):299-304.
- 445 42. De Soyza A, Brown JS, Loebinger MR. Research priorities in bronchiectasis. *Thorax*
446 2013;68(7):695-6.
- 447 43. Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, Holland AE, O'Mara P,
448 Grimwood K. Chronic suppurative lung disease and bronchiectasis in children and adults in
449 Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Med J*
450 *Aust* 2015;202(1):21-3.
- 451 44. Tunney MM, Einarsson GG, Wei L, Drain M, Klem ER, Cardwell C, Ennis M, Boucher RC,
452 Wolfgang MC, Elborn JS. Lung microbiota and bacterial abundance in patients with
453 bronchiectasis when clinically stable and during exacerbation. *Am J Respir Crit Care Med*
454 2013; 187(10):1118-26.
- 455

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457 **Figure 1.** Flow chart illustrating the process and results of the literature review. Abbreviations: QoL=
458 quality of life; FEV₁= forced expiratory volume in 1 second.

459

460 **Figure 2.** Association between *P. aeruginosa* colonisation and mortality in bronchiectasis.

461 Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence
462 interval,

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465 **Figure 3.** Association between *P. aeruginosa* colonisation and hospital admissions in bronchiectasis.

466 Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval

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469 **Figure 4.** Exacerbation frequency comparing patients with and without *P. aeruginosa* colonisation.

470 Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval

471

472 **Figure 5.** FEV₁ % predicted compared between patients with *P. aeruginosa* colonisation and patients

473 without *P. aeruginosa* colonisation. Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV=

474 inverse variance, CI= confidence interval

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