Eradication treatment for *Pseudomonas aeruginosa* infection in adults with bronchiectasis: a systematic review and meta-analysis

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A meta-analysis of *Pseudomonas aeruginosa* eradication treatment in bronchiectasis reports successful eradication in 40% of cases at 12 months. The data suggest superior results with the inclusion of an inhaled antibiotic. https://bit.ly/3QDmIi8

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Abstract

Introduction: *Pseudomonas aeruginosa* is the most commonly isolated pathogen in bronchiectasis and is associated with worse outcomes. Eradication treatment is recommended by guidelines, but the evidence base is limited. The expected success rate of eradication in clinical practice is not known.

Methods: We conducted a systematic review and meta-analysis according to Meta-Analysis of Observational Studies in Epidemiology guidelines. PubMed, Embase, the Cochrane Database of Systematic Reviews and Clinicaltrials.gov were searched for studies investigating *P. aeruginosa* eradication treatment using antibiotics (systemic or inhaled) in patients with bronchiectasis. The primary outcome was the percentage of patients negative for *P. aeruginosa* at 12 months after eradication treatment. Cystic fibrosis was excluded.

Results: Six observational studies including 289 patients were included in the meta-analysis. Our meta-analysis found a 12-month *P. aeruginosa* eradication rate of 40% (95% CI 34–45%; p<0.00001), with no significant heterogeneity (I^2=0%). Combined systemic and inhaled antibiotic treatment was associated with a higher eradication rate (48%, 95% CI 41–55%) than systemic antibiotics alone (27%, 13–45%).

Conclusion: Eradication treatment in bronchiectasis results in eradication of *P. aeruginosa* from sputum in ∼40% of cases at 12 months. Combined systemic and inhaled antibiotics achieve higher eradication rates than systemic antibiotics alone.

Introduction

Bronchiectasis is associated with chronic respiratory bacterial infection, which perpetuates airway inflammation [1, 2]. *Pseudomonas aeruginosa* is the most frequent organism in severe bronchiectasis [3–7]. Chronically infected patients with *P. aeruginosa* have worse quality of life, increased exacerbations and hospital admissions, and poorer prognosis [8–10]. In cystic fibrosis patients, the role of *P. aeruginosa* eradication treatment is well defined and supported by a Cochrane review showing that early detection and eradication treatment, consisting of nebulised antibiotics with or without systemic antibiotics, could reduce the risk of chronic infection [11]. The European Respiratory Society (ERS) guidelines for adult bronchiectasis suggested that patient with a new isolation of *P. aeruginosa* should also be offered eradication antibiotic treatment, despite low quality of evidence [12]. Inhaled antibiotics have theoretical advantages over systemic therapies by delivering higher concentrations of drugs to the airway and achieving greater rates of clearance [13]; however, the best regimen to achieve successful eradication in bronchiectasis is currently unknown. A randomised trial of *P. aeruginosa* eradication in bronchiectasis is

needed. In the absence of such trials the best available evidence to inform clinical practice and to inform clinical trial design comes from observational studies.

We performed a systematic review and meta-analysis of observational studies to assess the overall efficacy of *P. aeruginosa* eradication therapy and also the effectiveness of different eradication strategies, in adults with bronchiectasis.

Methods

We performed a systematic review and meta-analysis of all studies of *P. aeruginosa* eradication therapies in patients with bronchiectasis according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Eligible publications were identified by searching MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. Search terms used were a combination of terms of *P. aeruginosa* (*Pseudomonas* OR *P. aeruginosa* or *aeruginosa*) AND (eradicat* OR clearance OR eliminat*) AND (bronchiectasis OR NCFB OR NCFBE OR BE). Studies were included from the inception of the database to December 2022. Studies were included if the patients were adults with stable bronchiectasis, diagnosed by high-resolution computed tomography [14], and underwent treatment aimed at *P. aeruginosa* eradication. Studies in cystic fibrosis or limited exclusively to specific aetiologies such as primary ciliary dyskinesia [15] were excluded. No language restrictions were applied. Data reported only in abstract form was not included. Authors were contacted for clarification or additional data in the event that data could not be extracted in the required format.

The primary outcome of interest was eradication of *P. aeruginosa* defined as absence of growth on culture at 12 months [14]. Secondary efficacy end-points were frequency of exacerbations, frequency of hospitalisations for severe exacerbations, proportion of patients with at least one exacerbation, proportion of patients with at least one hospitalisation for a severe exacerbation and quality of life. Safety end-points were adverse events and bacterial resistance in sputum. Study eligibility assessment and data extraction was performed by two observers with discrepancies resolved by consensus.

Random-effects meta-analysis was used to pool individual studies. Effect estimates were pooled by the inverse of their variance and are presented as pooled effect estimates (incidence rates) with corresponding 95% confidence intervals. Heterogeneity was assessed using I^2. Meta-analysis was performed using RevMan (version 5.4; Cochrane Collaboration) and MedCalc (version 20.015; MedCalc Software, Ostend, Belgium). The review was registered on www.crd.york.ac.uk/prospero/ (identifier CRD42021287027).

Results

212 unique studies were identified across the database searches and six single-centre studies were selected for the meta-analysis: three retrospective [16–18] and three prospective studies including one randomised controlled trial [19–21], corresponding to a total of 287 patients (figure 1). In the randomised controlled trial by Orriols *et al.* [21], patients were initially treated with systemic intravenous antibiotics for 2 weeks, followed by nebulised antibiotic for 3 months in the interventional arm or placebo in the other arm. Therefore, both arms were treated as independent studies for the analysis purpose: the interventional arm defined as “combined systemic and inhaled antibiotics”, and the placebo arm as “systemic antibiotics”.

All the studies reported at least one eradication regimen using systemic and nebulised antibiotics, and two retrospective studies included some schemes only with systemic or inhaled antibiotics [16, 18]. The included retrospective studies reported the use of several eradication regimens, ranging from three to eight [16–18] (table 1). Colistin was the selected inhaled antibiotic in four studies [17–20] and tobramycin was used in two studies [16, 21]. Different devices were used for administration of inhaled antibiotics (*e.g.* nebulisers with inhalation solution or dry powder) and adherence data were not described.

The duration of studies’ follow-up varied from 12 to 36 months, with treatment periods ranging from 2 weeks to 12 months. Two studies provided data on the timing from first detection of *P. aeruginosa* to initiating eradication treatment. In these two studies, the eradication treatment was started within the first month from initial detection of *P. aeruginosa* [16, 21]. Spontaneous sputum samples were obtained during regular outpatient clinics visits and bacteriological analysis were performed. In 50% of the studies, the eradication treatment was started after at least two sputum samples isolating *P. aeruginosa* [17–19]; however, one study recruited patients promptly after the first isolation of *P. aeruginosa* [21]. In the study by Suarez-Cuartin *et al.* [20], serum anti-*P. aeruginosa* IgG levels were also used to detect a new isolation of the organism. One study allowed patients who were free of *P. aeruginosa* for ⩾2 years to be included (documented by five or more negative samples) [18]. Long-term macrolide use was reported in two studies, ranging from 63% to 69% of the patients included [18, 19].

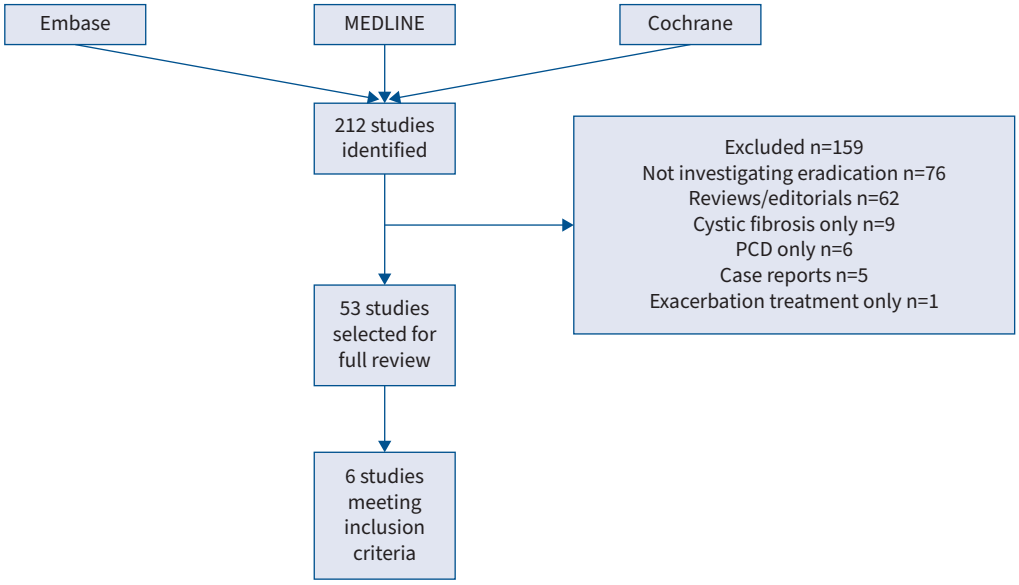

FIGURE 1 Flow chart for the results of the systematic review. PCD: primary ciliary dyskinesia.

Our meta-analysis found a 12-month *P. aeruginosa* eradication rate of 40% (95% CI 34–45%; p<0.00001), with no significant heterogeneity (I^2=0%) (figure 2).

Five studies provided data allowing a subgroup analysis to test whether the specific antibiotic regimen ("combined systemic and inhaled antibiotics" or "systemic antibiotics") modifies the effect of *P. aeruginosa* eradication. There were insufficient data for a direct comparison with inhaled antibiotics alone. The eradication rate for combined therapy was 48% (95% CI 41–55%), while systematic antibiotics alone provided an efficacy estimate of 27% (13–45%) (figure 3). The test of subgroup interaction was statistically significant (p=0.01). In the subgroup of systemic antibiotics, at least four different regimens and treatment durations were used, including oral, intravenous or combination antipseudomonal antibiotics [18, 21]. However, a smaller number of trials and participants contributed data for the systemic antibiotics subgroup (two studies, 27 patients) [18, 21].

Exacerbation outcomes were reported in few studies with different end-points as the number of exacerbations or hospitalisations pre- and post-eradication therapy, expressed as the mean number of antibiotic courses and hospital admissions, respectively [17, 19], or the number of patients experiencing at least one exacerbation and hospital admissions, expressed as a percentage [16]. Despite the scarce data extracted from two studies [17, 19], we found a significantly reduction in exacerbation rate post-eradication (mean difference −0.91 exacerbations over 12 months, 95% CI −1.64 to −0.17; p=0.02; I^2=0%), without affecting the hospitalisation rate. Pieters *et al.* [16] also described a significant reduction in exacerbation frequency, expressed as percentage of patients experiencing an exacerbation, in the year after eradication compared to the year before eradication (p=0.011). Hospital admission rates remained unchanged.

There were no data concerning quality of life pre- and post-eradication treatment. Orriols *et al.* [21] only compared the quality of life between interventional and placebo arms, using the St George's Respiratory Questionnaire (SGRQ). No significant difference between arms was achieved in the mean change of SGRQ score.

Adverse effects related to nebulised antibiotics were described in four studies [17–19, 21]. Adverse events leading to drug discontinuation, such as bronchospasm or drug intolerance, were reported in five patients using tobramycin [21] and five patients using colistin [17, 18].

The impact of eradication treatment on the development of antibiotic resistance has not been studied extensively. Orriols *et al.* [21] did not describe the emergence of tobramycin-resistant *P. aeruginosa*, and did not describe a higher rate of other opportunistic micro-organisms in patients treated with tobramycin compared to those receiving placebo. White *et al.* [17] reported fully sensitive *P. aeruginosa* in most

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TABLE 1 Characteristics of included studies

	Study type	Study population	Duration of follow-up for outcomes months	Antibiotic regimen(s)	Inhaled antibiotic	Primary outcome	Secondary outcomes
Blanco-Aparicio (2019) [19]	Prospective	67	12	(Ciprofloxacin oral 750 mg twice daily for 3 weeks OR tobramycin 5 mg·kg^{-1} + antipseudomonal β-lactam *i.v.* for 2 weeks) AND inhaled colistin 1 MU twice daily for 12 months	Colistin	*P. aeruginosa* eradication from sputum	Number of exacerbations and hospital admissions in the year pre- and post-eradiation, safety
Suarez-Cuartin (2017) [20]	Prospective	38	12	(Ciprofloxacin oral for 2 weeks + antibiotics *i.v.* for 2 weeks) AND inhaled colistin for 3 months	Colistin	Specific anti-*P. aeruginosa* IgG measurement to identify chronic *P. aeruginosa* infection	*P. aeruginosa* eradication from sputum and correlation with anti-*P. aeruginosa* IgG levels as a marker of treatment response, disease severity (BSI and FACED scores), and quality of life (SGRQ)
Orriols (2015) [21]	Prospective (randomised controlled trial)	28	15	(Ceftazidime + tobramycin *i.v.* for 2 weeks) AND inhaled tobramycin twice daily for 3 months OR placebo for 3 months	Tobramycin	*P. aeruginosa* eradication from sputum (intervention *versus* placebo)	Number of exacerbations and hospital admissions in interventional *versus* placebo arms; quality of life (SGRQ), safety, development of antibiotic resistance
White (2012) [17]	Retrospective	30	14.3	*i.v.* regimen: gentamicin 4 mg·kg^{-1} *i.v.* + ceftazidime 2 g, thrice daily for 2 weeks followed by inhaled colistin 1 MU twice daily for 3 months ± ciprofloxacin 500 mg twice daily for 3 months OR Oral regimen: ciprofloxacin 500 mg twice daily for 3 months + inhaled colistin 2 MU twice daily for 3 months	Colistin	*P. aeruginosa* eradication from sputum	Number of exacerbations and hospital admissions in the year pre- and post-eradiation, safety, development of antibiotic resistance, lung function
Pieters (2019) [16]	Retrospective	60	36	(Ciprofloxacin oral for 3 weeks OR ciprofloxacin oral for 2 weeks OR *i.v.* antibiotics) AND inhaled tobramycin for 1–3 months OR ciprofloxacin oral for 2 weeks	Tobramycin	*P. aeruginosa* eradication from sputum	Proportion of patients with at least one exacerbation and hospital admission in the year pre- and post-eradiation, lung function

Continued

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TABLE 1 Continued

	Study type	Study population	Duration of follow-up for outcomes months	Antibiotic regimen(s)	Inhaled antibiotic	Primary outcome	Secondary outcomes
Vallières (2017) [18]	Retrospective	64	12	(Ciprofloxacin ⩽3 weeks OR ciprofloxacin >3 weeks OR antibiotic *i.v.* 2 weeks OR ciprofloxacin + antibiotic *i.v.*) AND inhaled colistin for 3 months OR Inhaled colistin for 3 months OR Ciprofloxacin OR Ciprofloxacin + antibiotic *i.v.* OR antibiotic *i.v.*	Colistin	*P. aeruginosa* eradication from sputum	Safety

MU: mega-units; *P. aeruginosa*: *Pseudomonas aeruginosa*; BSI: Bronchiectasis Severity Index; FACED: F: forced expiratory volume in 1 s, A: age, C: chronic colonisation by *P. aeruginosa*, E: radiological extension, D: dyspnoea; SGRQ: St George's Respiratory Questionnaire.

Study	Eradication n	Subjects n	Weight %	Eradication rate %
Blanco-Aparicio	27	67	23.7	40 (28–53)
Orriols (1)[#]	6	11	2.3	55 (23–83)
Orriols (2)[#]	5	17	9.2	29 (10–56)
Pieters	25	60	20.1	42 (29–55)
Suarez Cuartin	20	38	8.3	53 (36–69)
Vallières	23	64	27.1	36 (24–49)
White	13	30	9.4	43 (26–63)
Pooled	119	287	100	40 (34–45)

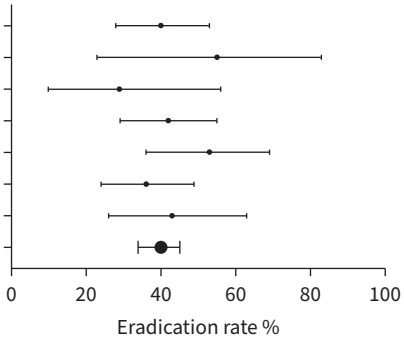

FIGURE 2 Forest plot of *Pseudomonas aeruginosa* eradication rate in sputum at 12 months [16–21]. [#]: two arms of the Orriols *et al.* [21] study, which were treated as separate cohorts for the purposes of analysis.

patients with re-culture; four patients developed antibiotic resistance to one or two antibiotics, not significantly affecting the future treatment options.

Discussion

Our systematic review and meta-analysis reports the rates of eradication of *P. aeruginosa* with antimicrobial agents to be 40% in bronchiectasis patients. These estimates are potentially biased by the observational nature of the contributing studies and it is not known what percentage of patients would have achieved eradication spontaneously without antibiotic treatment due to the lack of a control population.

"When and how should *P. aeruginosa* be eradicated in patients with bronchiectasis and whether eradication results in better outcomes" was identified as the key research priority in the research roadmap published by the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) [22]. The ERS guidelines recommended different antibiotic regimens for eradication treatment in case of a new isolation of *P. aeruginosa*, although the best scheme is still unknown [12]. Our pooled analysis suggests superiority of a combination of systemic and inhaled antibiotics compared to systemic antibiotics alone. Eradication treatment resulted in clinical benefits, with a significant reduction in the exacerbation rate post-eradication compared to pre-eradication, but without influencing the rates of hospitalisation. These data could be considered clinically meaningful given the important impact of exacerbations in quality of

Study	Eradication n	Subjects n	Weight %	Eradication rate %
Blanco-Aparicio	27	67	33.3	40 (28–53)
Orriols	6	11	5.9	55 (23–83)
Suarez-Cuartin	20	38	19.1	53 (36–69)
Vallières	30	53	26.5	57 (42–70)
White	13	30	15.2	43 (26–63)
Pooled[#]	96	199	100	48 (41–55)
Orriols	5	17	62.1	29 (10–56)
Vallières	2	10	37.9	20 (3–56)
Pooled[¶]	7	27	100	27 (13–45)

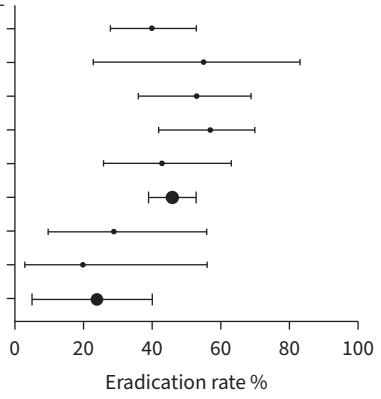

FIGURE 3 Forest plot of *Pseudomonas aeruginosa* eradication rate in sputum at 12 months. [#]: pooled eradication rate for systemic plus inhaled antibiotics, [¶]: pooled eradication rate for populations treated with systemic antibiotics only.

life, hospitalisation risk and mortality [23–26]. Caution should be exercised in interpreting these exacerbation reductions, since in the absence of a control group these may reflect regression to the mean. Use of eradication regimes was well tolerated, with a low proportion of treatment-emergent adverse effects or adverse effects leading to discontinuation of antibiotics.

To our knowledge, this is the first systematic review and meta-analysis providing evidence of *P. aeruginosa* eradication effectiveness. The data reported here suggest that eradication therapy is slightly less effective than has been reported in cystic fibrosis [27–29]. The EPIC trial in children with cystic fibrosis with a first isolation of *P. aeruginosa* compared four randomised regimens in 304 patients with efficacy over the 18-month study period of between 57% and 74% [29]. In the ELITE trial, 66% and 69% of patients receiving two different eradication regimens were free of *P. aeruginosa* at 27 weeks [27], and an observational study by Cohen-Cymberknoh *et al.* [28] found an eradication success rate of 72% across seven cystic fibrosis centres. Therefore, the majority of studies suggest a higher eradication success rate in cystic fibrosis compared with bronchiectasis. Cystic fibrosis has undergone a major change with the introduction of highly effective modulator therapy, and it is currently unknown how the effectiveness of eradication treatment may be impacted [30, 31]. Any explanation for the different effectiveness seen in bronchiectasis and cystic fibrosis would be speculative, but would include the lower frequency of sputum sampling in bronchiectasis, such that *P. aeruginosa* infection in people with bronchiectasis may represent previous undetected chronic infection. The older age and greater comorbidity of the patient population [32–34] in bronchiectasis and lower use of comedication such as macrolides, DNAse and other therapies including airway clearance may also be relevant [35].

Most studies in our meta-analysis were retrospective and limited to small samples. The only randomised controlled trial was not designed to study the efficacy of *P. aeruginosa* eradication; rather, it aimed to assess whether inhaled antibiotic after a systemic course of antibiotics was superior compared to systemic therapy alone [21]. Several therapeutic regimens of systemic (oral and intravenous) and/or inhaled antibiotics were used, with different doses and treatment durations. Another possible limitation was that the patient selection was not homogenous with regard to timing of *P. aeruginosa* infection. In three studies, the eradication treatment was started after at least two sputum samples isolating *P. aeruginosa*. Nevertheless, Blanco-Aparicio *et al.* [19] did not report significant differences in eradication rate as a function of the number of previous positive sputum cultures (two or at least three), suggesting that eradication could be attempted both when *P. aeruginosa* is recent and if there is long-term infection. The studies were heterogeneous in terms of some end-points, reporting data in a format that could not be extracted and analysed, such as exacerbation and hospitalisation outcomes. We identified no data in children with bronchiectasis, and so this represents a further evidence gap [36, 37]. Our data suggest that a regimen including nebulised antibiotics achieves greater rates of clearance of *P. aeruginosa* that systemic treatment alone, although this should be interpreted with caution given the small number of patients involved. Nevertheless, this supports the current ERS recommendation to offer combined systemic and inhaled antibiotics for eradication.

Despite its limitations, this meta-analysis provides evidence that *P. aeruginosa* eradication may be effective. There remains limited evidence in many key areas of bronchiectasis care [38–40]. There is an unmet need of a prospective randomised study of *P. aeruginosa* eradication therapy, compared to no eradication treatment. Furthermore, a randomised controlled trial comparing combined systemic and inhaled antibiotics *versus* systemic antibiotic course *versus* inhaled antibiotics only should be performed to determine the best strategy for eradication therapy. Our estimates of the expected efficacy and tolerability will be useful for the design of these trials.

Provenance: Submitted article, peer reviewed.

Conflict of interest: M. Shteinberg reports grants or contracts from GSK and Trudell pharma; consulting fees from AstraZeneca, Boehringer Ingelheim, Dexcel, Kamada, Synchrony Medical, Trumed, and Zambon; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Boehringer Ingelheim, and Kamada; support for attending meetings or travel from Boehringer Ingelheim, AstraZeneca, and Kamada; participation on a Data Safety Monitoring Board or Advisory Board for Bonus Biotherapeutics, Boehringer Ingelheim, and AstraZeneca; leadership or fiduciary role in other board, society, committee, or advocacy groups with Israeli Pulmonology Society, Israeli Society for Tuberculosis and Mycobacterial Diseases, and EMBARC as unpaid management board member, and the *European Respiratory Journal* and *Chest* as an unpaid Editorial board member; and receipt of equipment, materials, drugs, medical writing, gifts or other services from Trudell Medical International. J.D. Chalmers reports grants or contracts from

Grifols; consulting fees from Antabio, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Grifols, Insmed, Janssen, Novartis, Pfizer, and Zambon; and leadership or fiduciary roles as Chair of European Respiratory Society (ERS) Bronchiectasis Guideline Task Force, Chief Editor of the *European Respiratory Journal*, and Chair of EMBARC Clinical Research Collaboration. All other authors have nothing to disclose.

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