Efficacy of *Pseudomonas aeruginosa* Eradication Regimens in Bronchiectasis

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Patients with bronchiectasis and chronic infection with *Pseudomonas aeruginosa* have more frequent pulmonary exacerbations and hospital admissions, reduced quality of life and survival, in comparison to those who are *P. aeruginosa* free [1]. Guidelines published by the British Thoracic Society recommend treatment to eradicate *P. aeruginosa* when first isolated in respiratory tract samples of people with bronchiectasis [2]. However, the best regimen to achieve eradication and how successful eradication is determined are not known.

At the Northern Ireland Regional Respiratory Centre (Belfast, United Kingdom), the preferred eradication regimen is a combination of oral ciprofloxacin (for 6 weeks), and nebulised colistimethate sodium (for 3 months)[3]. However, this regimen is varied, according to patient experience (e.g. drug allergy and/or intolerance), clinician judgement and the antimicrobial susceptibility profile of the *P. aeruginosa* isolate. Therefore, the aims of this study were to determine if the eradication regimens used differed in their efficacy, in order to optimise and standardise clinical practice.

Adult patients with bronchiectasis who underwent treatment aimed at *P. aeruginosa* eradication between 1 January 2007 and 31 December 2014 were identified from the clinical database. Historical data were collected from medical notes. *P. aeruginosa* eradication was considered successful if all (and at least 3) bacteriologic cultures from respiratory samples collected during the 6-month period following the eradication attempt were negative for *P. aeruginosa*. Patients who remained on chronic (>3 months) nebulised antibiotics were excluded from the analysis, as this treatment could suppress bacterial growth and overestimate eradication success rate. In order to select patients with recent acquisition of *P.*

aeruginosa, we included only those who had never grown *P. aeruginosa* or those who were free of this bacteria for at least 2 years (and documented by 5 or more negative samples) before the eradication trial. All patients had a second confirmatory sample collected prior to initiation of eradication therapy.

Sixty-four (64) patients who had at least one eradication attempt were identified. Their mean (SD) age was 64 (1.6) years, 58% (n=37) were male, and 63% (n=39/62) of patients were receiving azithromycin 500 mg thrice weekly. Forced expiratory volume in one second (FEV_1) was 1.70 (0.15) litres and Forced vital capacity 2.89 (0.19) litres.

Eighty-four percent of patients (n=54) received an eradication regimen that included nebulised colistimethate sodium (table 1). The most frequent regimen used was the combination of nebulised colistimethate sodium with oral ciprofloxacin, prescribed for at least 3 weeks (n=27, 42%).

Overall, the eradication success rate at 6 months was 52% (n=33) and 70% (n=23) of these patients remained *P. aeruginosa* free for at least 1 year. Treatment combinations including nebulised colistimethate sodium were more effective (n=31/54, 57%) than those with systemic antibiotics alone (n=2/10, 20%) (Student t-test, p=0.04).

Intravenous anti-pseudomonal antibiotics (n=9/18, 50%) were not superior to oral ciprofloxacin (n=21/35, 60%) in the subgroup of patients who also received nebulised antibiotics as part of their regimen (table 1). Additionally, prolonged courses of oral ciprofloxacin (> 3 weeks) were no more efficient than shorter treatment periods (n=15/27, 56% vs n=6/8, 75%).

The study population was stratified according to eradication outcome (success versus failure). Demographic and clinical data of both groups were compared in order to identify factors that could have impacted eradication outcome. Age, gender, lung function and duration of infection prior to eradication

were similar between groups. However, chronic azithromycin use was more frequent amongst patients who successfully cleared *P. aeruginosa* infection (75% vs 47%, p=0.04).

This study suggests that eradication regimens combining nebulised and systemic antibiotics are more efficient for *P. aeruginosa* eradication than treatment without inhaled antibiotic. This finding supports results recently published by Orriols *et al*. [4]. In that study, the authors randomised 35 patients who recently acquired *P. aeruginosa* infection to receive 2 weeks of intravenous antibiotics (ceftazidime and tobramycin), followed by either 3 months of nebulised tobramycin or placebo. They found that the interval for recurrence of *P. aeruginosa* infection was extended in the tobramycin group and that the treatment arm had a reduced number of exacerbations and hospitalisations during the follow-up period. However, one third of patients in the tobramycin group experienced bronchospasm. In our cohort, respiratory symptoms associated with nebulised colistimethate sodium were infrequent as only 2 patients had to discontinue the inhaled treatment prematurely. Although consistent with our findings, results from Orriols' study must be interpreted cautiously due to the small sample size and limitations in study design and reporting.

The potential benefit conferred by azithromycin on *P. aeruginosa* eradication needs further investigation. Azithromycin may contribute to biofilm disruption, and may augment the action of anti-pseudomonal antibiotics [5-7] .

In conclusion, this study suggests the superiority of a combination of systemic (oral or intravenous) and inhaled antibiotics in the initial eradication treatment of *P. aeruginosa* infection in bronchiectasis patients, in comparison to systemic antibiotics only. Considering the literature gap addressing *P. aeruginosa* eradication in this population, these findings should inform the design of appropriate randomised clinical trials, to determine the best therapeutic approach, including the role of macrolides, in the treatment of new infections with *P. aeruginosa* in people with bronchiectasis.

Table 1: Frequency and efficacy of antibiotics used as first-line eradication regimens.

Treatment	Nebulised colistimethate sodium (3 months) &					No nebulised colistimethate sodium		
	Cipro (≤3 weeks)	Cipro (>3 weeks)	IVs (2weeks)	Cipro + IVs	Nil else	Cipro	IVs	Cipro + IVs
Patients, *n*	8	27	13	5	1	6	2	2
Success, *n* (%)	6 (75)	15 (55.5)	7 (54)	2 (40)	1 (100)	1 (17)	0 (0)	1 (50)
Total	**31/54 (57%)**					**2/10 (20%)**		

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