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BRIEF COMMUNICATION

Effect of long-term nebulized colistin on lung function and quality of life in patients with chronic bronchial sepsis

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Abstract

Recurrent Gram-negative bacterial infection is a significant cause of death in patients with bronchiectasis and severe chronic obstructive pulmonary disease (COPD). Nebulized colistin in cystic fibrosis has shown maintenance of pulmonary function and improved symptom scores. We prospectively followed 18 patients with chronic bronchial sepsis treated with nebulized colistin 30 mg daily. Mean decline in forced expiratory volume in 1 s was significantly slower following commencement of inhaled colistin (44 mL/year vs 104 mL/year, $P = 0.035$). Mean decline in forced vital capacity was also significantly slower following commencement of colistin (48 mL/year vs 110 mL/year, $P = 0.033$). Patient-reported quality of life improved following commencement of colistin (3.6 vs 6.2, $P = 0.001$). No patient had isolates resistant to colistin. No side-effects were reported by patients in the cohort. Use of inhaled colistin in the treatment of bronchiectasis and severe (COPD) in patients with recurrent Gram-negative infections is safe. Inhaled colistin may improve quality of life and slow decline in forced expiratory volume in 1 s and forced vital capacity.

Recurrent infective exacerbations in bronchiectasis and chronic obstructive pulmonary disease (COPD) are a major cause of death and in COPD constitute most of the cost burden.[1] Ongoing inflammation and damage of lung tissue in bronchiectasis and COPD result in accelerated decline in lung function.

Colonization by *Pseudomonas* is a feature of bronchiectasis in adult populations and is known to adversely affect quality of life and increase hospital admission rate.[2] *Pseudomonas* spp. and *Stenotrophomonas maltophilia* become significant pathogens in COPD patients with severe airflow limitation (forced expiratory volume in 1 s (FEV_1) <40% predicted).[3] There is significant clinical overlap between patients with severe COPD and bronchiectasis, with studies showing that up to 50% of COPD patients have associated lower lobe bronchiectasis and that this is associated with higher rates of colonization with pathogenic organisms and severe COPD exacerbations.[4]

Prophylactic macrolides in adult bronchiectasis have produced improvements in lung function and other clinical parameters[5] and short-term azithromycin in advanced COPD lowers the rates of infective exacerbations and hospital admissions.[6]

Despite data showing that short-term inhaled tobramycin or gentamicin in bronchiectasis produces significant respiratory improvement, both functionally and subjectively, to date there are no data for long-term nebulized prophylactic antibiotic therapy in bronchiectasis or COPD.[7,8]

In this study we examine the utility of long-term nebulized colistin in patients with COPD and non-cystic fibrosis (CF) bronchiectasis. Colistin is a bactericidal cationic cyclic polypeptide antibiotic active against Gram-negative bacteria, including *Pseudomonas aeruginosa* and *S. maltophilia*.[9] Resistance to colistin in *P. aeruginosa* is rare and far less common than to other antipseudomonals.[10] Use of colistin had previously been abandoned because of

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concerns about serious neurotoxicity and nephrotoxicity,[11] but it has been reconsidered with the advent of multidrug-resistant *Pseudomonas* and *Acinetobacter* spp. and has been used to successfully treat nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in ventilated patients through both nebulized and systemic administration.[12,13] Recent studies,[12,13] including those of treatment durations of more than 4 weeks[14], indicate considerably less toxicity than was reported in older studies.

No previous studies have examined its efficacy in non-CF chronic bronchial sepsis. It is used as an inhalational agent in CF patients where maintenance of pulmonary function as well as improved symptom scores and inflammatory parameters have been shown.[15] On this basis, we added nebulized colistin 30 mg daily (in 2 mL of saline or salbutamol solution) to the treatment regimen of clinic patients with either bronchiectasis (defined by computed tomography scan) or severe COPD (defined by FEV_1<40% predicted), as well as repeated isolates of multidrug-resistant Gram-negative bacteria in sputum cultures with the following clinical features:

- High rates of infective exacerbations or exacerbations requiring admission to hospital
- Difficulty with symptom control
- High volume of sputum production in between exacerbations

Before commencing colistin, spirometry had been measured at multiple clinic visits with spirometry values recorded on a mean 9.4 occasions per patient. Patients commenced on colistin were prospectively identified and their progress observed by regular review approximately every 6 months. Clinic and spirometric data were recorded at each clinic visit.

All 18 patients on nebulized colistin were contacted by mail and agreed to be included in the study. Patient characteristics at the conclusion of the study are shown in Table 1.

Lung function, as calculated by spirometry (post-bronchodilator FEV_1 and forced vital capacity, FVC) was recorded during stable periods following discharge from hospital. Sputum microbiology was obtained from clinic records. Patients completed a quality-of-life questionnaire using a visual analogue scale at the conclusion of the study, retrospectively in assessment of the period before commencement of colistin and a second assessment with respect to their current quality of life.

Values from each patient before commencement of colistin were compared with those while continuing inhaled colistin, obtained subsequent to completion of 6 months' therapy. The period of time over which the information was examined ranged from 2 years to 11 years for precolistin values and 6–116 months for post-colistin values. Statistical analysis was carried out by StatView for Windows 5.0.1 (SAS Institute Inc., Cary, NC, USA) using a paired *t*-test.

Table 1 Patient characteristics

No. patients	14 idiopathic bronchiectasis 4 severe COPD/chronic infective bronchitis
Mean treatment duration (months)	41 (range 6–116, ±25.6†)
Mean age (years)	69 (±10.2†)
Women (%)	66
Sputum microbiology, *n*‡	
Pseudomonas aeruginosa	14
Stenotrophomonas maltophilia	6
P. fluorescens	4
Staphylococcus aureus	4
Escherichia coli, *Haemophilus influenzae*, *MAC*, *Moraxella* spp.	1

†Standard deviation. ‡All patients had *Pseudomonas* spp. or *S. maltophilia* isolated from the sputum. COPD, chronic obstructive pulmonary disease. MAC, mycobacterium arium complex.

Spirometry was obtained at regular clinic visits using a Vitalograph spirometer (Vitalograph, Buckingham, UK), which was calibrated fortnightly with a 2-L syringe. Spirometric and quality-of-life assessment results are recorded in Table 2. Three patients (16.6%) showed improved FEV_1 over the study period. No resistance to colistin was recorded among bacterial isolates obtained and three patients showed clearance of *Pseudomonas* spp. from sputum isolates on culture carried out at the end of the study period.

No side-effects were reported by patients in the cohort. One patient ceased colistin because of perceived ineffectiveness.

The results show that the use of colistin significantly slowed the decline of FEV_1 and FVC and improved patient-reported quality of life. The mechanism is likely to be control of chronic bronchial sepsis with subsequent reduction in inflammation-mediated deterioration in spirometric volumes. Our findings are consistent with findings in CF where use of inhaled colistin (together with oral ciprofloxacin) in CF populations when *P. aeruginosa* infection was first documented led to significantly better lung function, when compared with controls and to a far lower rate of chronic *Pseudomonas* colonization.[16] Colonization with *Pseudomonas* spp. in bronchiectasis has been shown to stimulate a neutrophilic inflammatory mediator response proportionate to bacterial load, thereby worsening existing lung disease.[17] The use of azithromycin has been suggested to work through a similar mechanism although it is associated with a significant rate of adverse effects.[5] Similarly, adverse effects during short-term nebulized tobramycin therapy for bronchiectasis were noted in 85% of patients.[7]

Table 2 Results–comparison between pre and post treatment outcomes

	Precolistin†	Post-colistin‡	*P*-value
FEV_1, mL (range)	1070 (350–1950)	1020 (350–1900)	0.400
Decline in FEV_1, mL/year (range)	104 (25–325)	44 (–100 to 280)	0.035
FVC, L (range)	2.0 (1.0–3.6)	1.9 (1.0–3.3)	0.295
Decline in FVC, mL/year (range)	110 (0–500)	48 (–200 to 160)	0.033
Frequency of admission, *n*/year (range)	1.1 (0.1–7)	0.84 (0.0–4)	0.493
Quality of life	3.6	6.2	0.001

†Precolistin: FEV_1 and FVC refer to spirometric values recorded immediately before commencement of colistin. Frequency of admissions, quality of life and decline in FEV_1 and FVC refer to the period from registration in the clinic database until immediately before commencement of colistin.‡Post-colistin: FEV_1 and FVC refer to spirometric values recorded at the conclusion of the study. Frequency of admission, quality of life and decline in FEV_1 and FVC refer to the period from commencement of colistin until the conclusion of the study.

We noted no adverse effects and in recent case series of colistin use, no significant toxicity was seen following i.v. doses of greater than 240 mg/24 h[13] or prolonged parenteral administration.[14] Long-term use of nebulized colistin in CF has resulted in minimal resistance[13] and resistant isolates in non-CF populations remain very rare.[18]

This is the first report of use of colistin in non-CF adult patients and we are not aware of any studies examining nebulized antibiotic use in over such a prolonged period and the fact that no adverse effects were observed over such a period is noted. We do acknowledge some limitations to our study. It is a small cohort study with historical self-controls making broad conclusions difficult on the basis of our findings. Spirometric measurements, although carried out at regular clinic visits, were not recorded at standardized intervals and have not been carried out over uniform periods of time. Assessment of quality of life was recorded retrospectively and may be prone to recall bias and our visual analogue scale has not been validated for chronic respiratory illness. However, we note that recent comparisons of successive cohorts of CF patients have indicated that improvements in care have resulted in a slowing in decline of FEV_1 and our results suggest that improved disease control in our patients has achieved a similar benefit.[19]

Our cohort indicates nebulized colistin is an effective, well-tolerated and safe therapy in patients with chronic lung disease colonized by susceptible multidrug-resistant Gram-negative spp. Its use may be considered in patients with poor symptom control or frequent hospital admissions, which often result in rapid decline in lung function. Further prospective randomized studies are required to confirm its beneficial effect on lung function and quality of life and to examine its effect on the rate of infective exacerbations in both severe COPD and bronchiectasis. Additional areas of interest include its effect on the rate of infective exacerbations and on sputum microbiology, including possible role in eradication of *P. aeruginosa* in patients with persisting colonization despite prolonged antimicrobial therapy.

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