BRIEF COMMUNICATION

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

D. P. Steinfort and C. Steinfort

Respiratory Department, Geelong Hospital, Melbourne, Victoria, Australia

Key words
colistin, chronic obstructive pulmonary disease, bronchiectasis, nebulized, Gram-negative.

Correspondence
Daniel P. Steinfort, 233 George Street, Fitzroy, Vic. 3065, Australia. Email: dsteinfort@yahoo.com

Received 29 May 2006; accepted 7 August 2006.
doi:10.1111/j.1445-5994.2007.01404.x

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. 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 cat-ionic 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
concerns about serious neurotoxicity and nephrotoxicity, but it has been reconsidered with the advent of multdrug-resistant *Pseudomonas* and *Acinetobacter* spp. and has been used to successfully treat nosocomial pneumonia due to multdrug-resistant Gram-negative bacteria in ventilated patients through both nebulized and systemic administration. Recent studies, including those of treatment durations of more than 4 weeks, 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. 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 spirometric volumes). Our findings are consistent with findings in CF where use of inhaled colistin (together with oral ciprofloxacin) in CF populations when compared with controls and to a far lower rate 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. 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. The use of azithromycin has been suggested to work through a similar mechanism although it is associated with a significant rate of adverse effects. Similarly, adverse effects during short-term nebulized tobramycin therapy for bronchiectasis were noted in 85% of patients.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>No. patients</th>
<th>14 idiopathic bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean treatment duration (months)</td>
<td>41 (range 6–116, ±25.6)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>69 (±10.2)</td>
</tr>
<tr>
<td>Sputum microbiology, n&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>14</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>6</td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td>4</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4</td>
</tr>
<tr>
<td><em>Escherichia coli</em>, <em>Haemophilus influenzae</em>, MAC, <em>Moraxella</em> spp.</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>1</sup>Standard deviation. <sup>2</sup>All patients had *Pseudomonas* spp. or *S. maltophilia* isolated from the sputum. COPD, chronic obstructive pulmonary disease. MAC, mycobacterium *aurantium* complex.
Long-term nebulized colistin in bronchiectasis

Table 2 Results—comparison between pre and post treatment outcomes

<table>
<thead>
<tr>
<th></th>
<th>Precolist†</th>
<th>Post-colistin§</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, mL (range)</td>
<td>1070 (350–1950)</td>
<td>1020 (350–1900)</td>
<td>0.400</td>
</tr>
<tr>
<td>Decline in FEV&lt;sub&gt;1&lt;/sub&gt;, mL/year (range)</td>
<td>104 (25–325)</td>
<td>44 (–100 to 280)</td>
<td>0.035</td>
</tr>
<tr>
<td>FVC, L (range)</td>
<td>2.0 (1.0–3.6)</td>
<td>1.9 (1.0–3.3)</td>
<td>0.295</td>
</tr>
<tr>
<td>Decline in FVC, mL/year (range)</td>
<td>110 (0–500)</td>
<td>48 (–200 to 160)</td>
<td>0.033</td>
</tr>
<tr>
<td>Frequency of admission, n/year (range)</td>
<td>1.1 (0–7)</td>
<td>0.84 (0–4)</td>
<td>0.493</td>
</tr>
<tr>
<td>Quality of life</td>
<td>3.6</td>
<td>6.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

†Precolist: FEV<sub>1</sub> and FVC refer to spirometric values recorded immediately before commencement of colistin. Frequency of admissions, quality of life and decline in FEV<sub>1</sub> and FVC refer to the period from registration in the clinic database until immediately before commencement of colistin. §Post-colistin: FEV<sub>1</sub> and FVC refer to spirometric values recorded at the conclusion of the study. Frequency of admission, quality of life and decline in FEV<sub>1</sub> 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<sup>13</sup> or prolonged parenteral administration.<sup>14</sup> Long-term use of nebulized colistin in CF has resulted in minimal resistance<sup>13</sup> and resistant isolates in non-CF populations remain very rare.<sup>18</sup>

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<sub>1</sub> and our results suggest that improved disease control in our patients has achieved a similar benefit.<sup>19</sup>

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.

References

12. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagou ME. Aerosolized colistin for the...


14 Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infect Dis 2005; 5: 1.


