# Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis

S P Conway, M N Pond, A Watson, C Etherington, H L Robey, M H Goldman

**Abstract**

***Background* – Patients with cystic fibrosis have received more intravenous antibiotic courses as median survival has steadily increased. A number of centres have adopted a policy of regular (three monthly) rather than on demand intravenous anti-pseudomonal antibiotics. More widespread bacterial antibiotic resistance has resulted from this increased antibiotic use. Most *Pseudomonas aeruginosa* strains remain fully sensitive to colistin but its use has been resisted owing to concerns about neurotoxicity and nephrotoxicity. A study was carried out to assess the safety and efficacy of intravenous colistin in the treatment of acute respiratory exacerbations in adult patients with cystic fibrosis.**

***Methods* – Patients with chronic *Pseudomonas aeruginosa* colonisation who presented with protocol defined respiratory tract exacerbations were randomised to receive treatment for 12 days with either colistin (2 MU tds intravenously) alone or with a second anti-pseudomonal antibiotic. Comparisons of the absolute values of respiratory function tests on days 1, 5, and 12 and of overnight oxygen saturation on days 1 and 12 were the primary outcome measures. Patient's weight, clinical and chest radiographic scores, and peripheral blood markers of inflammation were also documented. The effect of each treatment regimen individually was assessed by the change in clinical measurements from baseline values. Adverse renal effects were monitored by measurement of serum levels of urea and electrolytes, creatinine clearance, and ward urine testing. Neurotoxicity was monitored by direct questioning for symptoms.**

***Results* – Fifty three patients, 18 of whom entered the study twice, were enrolled. The mean forced expiratory volume in one second ($FEV_1$) increased significantly in both groups, mean forced vital capacity (FVC) only with dual therapy. Both groups showed a non-significant increase in overnight oxygen saturation. All patients showed clinical improvement. Thirty seven adverse neurological events (two severe) were reported in 33 patients in the monotherapy group and 37 (none severe) in 36 patients in the dual therapy group. One patient withdrew because of severe weakness and dizziness. All other adverse neurological events were well tolerated and resolved during or shortly after treatment. Significant changes were seen in mean serum urea levels in both groups, but in only four patients to a level above the normal range, and in creatinine clearance in the dual therapy group. At 24 month follow up no long term adverse consequences from intravenous colistin were found in patients who completed the study.**

***Conclusions* – Intravenous colistin is an effective treatment for *Pseudomonas aeruginosa* associated pulmonary exacerbations in patients with cystic fibrosis. Assessment of the individual effect of each treatment regimen suggests a greater efficacy when colistin is combined with a second antibiotic to which the pseudomonas shows in vitro sensitivity. Changes in renal function should be monitored.**

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Keywords: colistin, cystic fibrosis, *Pseudomonas aeruginosa*, nephrotoxicity, neurotoxicity.

**Regional Adult Cystic Fibrosis Unit, Seacroft Hospital, Leeds LS14 6UH, UK**
S P Conway
M N Pond
A Watson
C Etherington

**Pharmax Ltd, Bexley, Kent, UK**
H L Robey
M H Goldman

Correspondence to:
Dr S P Conway.

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Cohort survival curves from 1968 for children born with cystic fibrosis show an increasing life expectancy with a median survival presently of about 29 years[1 2] and an expected median survival for today's children of 40 years.[3] This success directly reflects better patient nutrition, better and individualised physiotherapy, and the advent of effective anti-pseudomonal antibiotics.[4] More frequent antibiotic usage inevitably has resulted in a greater prevalence of bacterial antibiotic resistance and patient hypersensitivity reactions.[5–9] Resistance of *Pseudomonas aeruginosa* to colistin is still unusual[7] but cystic fibrosis specialist physicians have resisted its prescription as a first line intravenous anti-pseudomonal antibiotic because of concerns regarding its reported nephrotoxicity and neurotoxicity.[10] Two recent reports, one an observational study in a small patient group[11] and the other using retrospective clinical data,[7] have suggested that reports of colistin toxicity were exaggerated. The aim of the present study was to establish the true incidence of colistin toxicity and its efficacy alone and in combination with a second anti-pseudomonal antibiotic in the treatment of respiratory exacerbations in adult patients with cystic fibrosis.

## Methods

Patients with a previous hypersensitivity reaction to colistin, neurological signs or symp-

toms, a history of renal impairment and those who were pregnant were excluded from the study. Over a nine month period all other patients who were chronically colonised with a colistin sensitive *Pseudomonas aeruginosa* were invited to enrol in the study if they satisfied four of the following criteria for an acute respiratory exacerbation: increased sputum volume, change in sputum colour from yellow to green, or pale to dark green, more frequent cough, increased dyspnoea or lethargy, decreased exercise tolerance or appetite, temperature >37°C, new infiltrates on chest radiography, new bacterial pathogen on sputum culture, deterioration in respiratory function tests, and increased focal signs on chest auscultation.

All study participants had had cystic fibrosis confirmed by two diagnostic sweat tests and/or gene typing. Patients were randomised to receive colistin sulphomethate 2 MU (160 mg) three times daily, either alone (monotherapy) or with a second intravenous anti-pseudomonal antibiotic (dual therapy), administered according to the manufacturer's recommendations. The second antibiotic was chosen according to the patient's most recent sputum bacterial sensitivity patterns. Potentially nephrotoxic antibiotics were excluded. Colistin was administered in 50 ml of physiological saline over 30 minutes. Patients were permitted to enter the study a second time provided that at least 28 days had passed since the first participation. All patients who enrolled twice received the alternative treatment arm on their second entry. No alterations were made to patients' routine therapy during the study period other than temporarily stopping any nebulised antibiotic inhalations.

Patients were monitored during 12 days of intravenous antibiotic treatment. Sputum samples were obtained twice weekly for microscopy, culture, and sensitivity testing. Primary outcome measures were comparisons of lung function, the forced expiratory volume ($FEV_1$) in the first second of the forced vital capacity (FVC) on days 1, 5, and 12 and of mean overnight oxygen saturation ($Sao_2$) on days 1 and 12. The former were performed after the morning physiotherapy session and the latter recorded on an Ohmeda Biox 3740 oximeter. Secondary outcome measures were comparisons with the in-house clinical score,[12] blood white cell and percentage neutrophil count, and serum C-reactive protein levels. The effect of mono and dual treatment regimens individually was assessed as the change in clinical measurement from baseline values and also included patient weight, the Shwachman-Kulczycki (SK) score of overall clinical status,[13] and the Chrispin-Norman (CN)[14] and Northern[15] chest radiograph scores.

Renal function was monitored by measurement of serum levels of urea and electrolytes and urine multistix testing on days 1, 5 and 12, and by estimation of creatinine clearance on days 1 and 12.

Adverse neurological events were actively sought by asking patients on days 2, 3, 5, and 12 about the occurrence and/or persistence of any new symptoms of dizziness, numbness, tingling, unsteadiness, incoordination, or weakness. All possible adverse events were recorded.

Blood was sampled for measurement of steady state trough and peak colistin levels 30 minutes before and 15 minutes after the 14.00 hour dose on day 5 in patients receiving colistin monotherapy. The assay, a standard microbiological agar technique with *Bordatella bronchiseptica* as the test organism, cannot be interpreted when a second intravenous antibiotic has been administered.

Laboratory safety and efficacy data and radiological assessments were blinded. Symptom questionnaires were conducted by a third party unaware of the patients' randomisation.

*Table 1 Details of patient withdrawals from the study*

| *Antibiotic therapy* | *Day of withdrawal* | *Reason for withdrawal* | *Withdrawal colistin related* |
|---|---|---|---|
| Monotherapy | 5 | Patient wanted two antibiotics | No |
| Monotherapy | 3 | Colistin resistance | No |
| Monotherapy | 2 | Dizziness and weakness | Probably |
| Monotherapy | 4 | Skin rash | Possibly |
| Monotherapy | 5 | Difficult venous access | No |
| Dual therapy | 8 | Died (terminal CF) | No |
| Dual therapy | 5 | Diagnosed pregnant | No |
| Dual therapy | 5 | Increased facial spots | No |
| Dual therapy | 5 | Difficult venous access | No |

*Table 2 Mean (SD) demographic and clinical data on entry into study*

| | *Monotherapy (n=36)* | *Dual therapy (n=35)* |
|---|---|---|
| Age (years) | 21.7 (4.2) | 21.2 (4.25) |
| Sex | 17F:19M | 12F:23M |
| Weight (kg) | 54.4 (9.1) | 54.4 (10.7) |
| BMI ($kg/m^2$) | 19.7 (2.2) | 19.4 (2.8) |
| $FEV_1$ (% predicted) | 43.3 (16.6) | 45.8 (21.8) |
| FVC (% predicted) | 64.8 (22.2) | 61.8 (24.8) |
| Overnight $Sao_2$ | 92.2 (2.6) | 92.2 (2.6) |
| Clinical score | 8.9 (3.6) | 9.2 (3.4) |
| SK score | 60 (15.4) | 59 (16.5) |
| CN score | 25.1 (5.7) | 24.7 (6.2) |
| Northern score | 12.6 (3.0) | 12.8 (3.3) |

BMI = body mass index; $FEV_1$ = forced expiratory volume in one second; FVC = forced vital capacity; $Sao_2$ = oxygen saturation; SK score = Shwachman-Kulczycki score; CN score = Chrispin-Norman score.

### ANALYSIS OF DATA

Statistical analysis was by Student's *t* test (paired for intragroup changes and unpaired for intergroup changes), ANOVA, $\chi^2$, Mann-Whitney U test, and Wilcoxon signed rank test as appropriate, using the C-Stat program (Cherwell Scientific, UK). All baseline data for patients who withdrew from the study were evaluated. Exit assessment data for these patients was generated by the process of last data carried forward. This process was also used for incomplete data sets and all data were analysed by intention to treat.

## Results

Fifty three patients were enrolled into the study. Eighteen patients entered the study twice, nine initially to the monotherapy group and nine initially to the dual therapy group. Thirty six treatments were with intravenous colistin alone, and 35 with colistin and another anti-pseudomonal antibiotic (aztreonam, azlocillin, piperacillin, ceftazidime, imipinem, or ciprofloxacin). Four patients in the monotherapy

*Table 3 Mean laboratory and clinical data*

| *Measured parameter* | *Day 1* | | | *Day 5* | | | *Day 12* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Monotherapy* | *Dual therapy* | *p value* | *Monotherapy* | *Dual therapy* | *p value* | *Monotherapy* | *Dual therapy* | *p value* |
| $FEV_1$ (l) | 1.52 | 1.62 | NS | 1.58 | 1.87 | NS | 1.66 | 1.92 | NS |
| SD | 0.68 | 0.78 | | 0.75 | 0.93 | | 0.82 | 0.89 | |
| FVC (l) | 2.44 | 2.34 | NS | 2.45 | 2.74 | NS | 2.56 | 2.93 | NS |
| SD | 1.04 | 1.0 | | 1.04 | 1.05 | | 1.21 | 1.12 | |
| Overnight $Sao_2$ | 92.2 | 92.2 | NS | | | | 92.7 | 93.0 | NS |
| Clinical score | 9 | 9 | NS | 7 | 7 | NS | 7 | 6 | NS |
| White blood cell count | 10.3 | 11.1 | NS | 10.4 | 7.4 | <0.01 | 9.0 | 7.9 | NS |
| % neutrophil count | 70.8 | 71.8 | NS | 70.6 | 62.3 | <0.01 | 63.4 | 60.5 | NS |
| % patients with normal C-reactive protein | 58.3 | 45.7 | NS | | | | 58.3 | 84.5 | <0.05 |

p values are given for dual therapy versus monotherapy.

*Table 4 Changes in mean (SD) renal function values with treatment (NR = normal ranges)*

| | *Monotherapy group* | | | *Dual therapy group* | | |
|---|---|---|---|---|---|---|
| | *Day 1* | *Day 12* | *p value* | *Day 1* | *Day 12* | *p value* |
| Urea (mmol/l) (NR 2.5–7.1) | 3.6 (0.8) | 4.2 (1.1) | <0.01 | 3.8 (1) | 4.6 (1.3) | <0.01 |
| Creatinine (mmol/l) (NR 50–140) | 70 (16) | 72 (13) | NS | 73 (10) | 71 (14) | NS |
| Creatinine clearance (ml/min) (NR 80–120) | 109 (54) | 94 (29) | NS | 109 (42) | 91 (34) | < 0.01 |

group missed between one and five doses of colistin (total 12 doses missed), two patients in the dual therapy group missed three doses of colistin, and one patient missed four doses (total 10 doses missed). The reasons for missing intravenous drug doses were as follows: patient not on the ward (7), refused new intravenous line towards end of treatment (5), no reason given (5), left early on final day because sitting national school examinations the next day (3), drug not signed as given or not given on chart (2). Coexisting pathogens were isolated from monotherapy and dual therapy treatment courses, respectively, as follows: *Staphylococcus aureus*, 20 and 13; *Candida albicans*, 8 and 3; *Aspergillus fumigatus*, 2 and 2; *Haemophilus influenzae*, 0 and 2. Five patients in the monotherapy group and four in the dual therapy group withdrew from the study (table 1). Two of these withdrawals were related to an adverse event – severe weakness and dizziness (probably colistin related) and a minor localised skin rash (possibly colistin related).

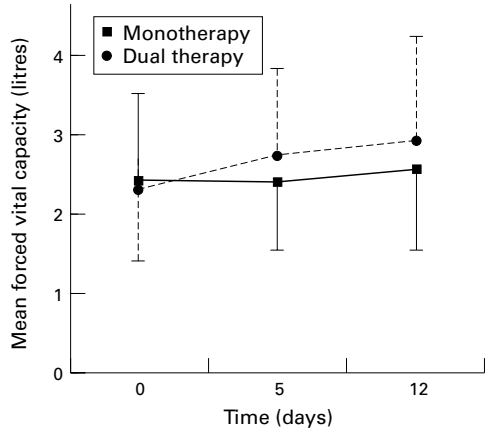


*Figure 1 Mean forced vital capacity in monotherapy and dual therapy groups.*

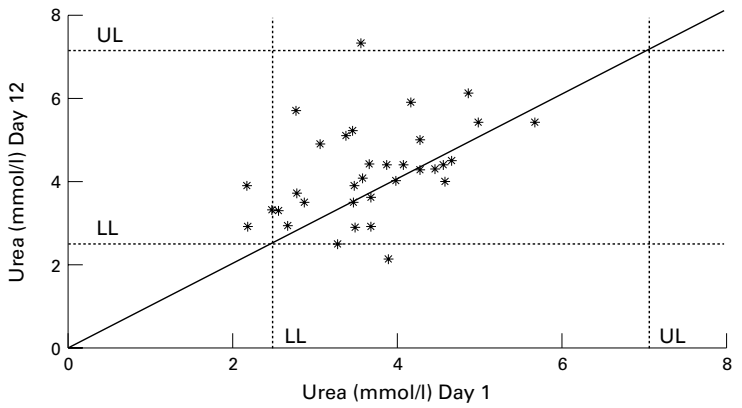


*Figure 2 Blood urea levels Day 1 versus Day 12 in monotherapy group*

All patients showed clinical improvement and resolution of their acute respiratory exacerbation. At entry to the study there were no significant differences between the monotherapy and dual therapy groups for baseline measurements of either primary or secondary outcome measures (table 2). Analysis of the changes at 12 days showed no significant differences between the groups except that more patients who received dual therapy had a normal serum level of C-reactive protein (table 3).

The following changes occurred in both treatment groups: a significant fall in the clinical score at days 5 and 12 ($p<0.01$), a significant rise in the SK score at day 12 ($p<0.01$ in the monotherapy group and $p<0.05$ in the dual therapy group), no significant change in the CN and Northern chest radiographic scores, and a non-significant rise in mean overnight $Sao_2$. The mean (95% CI) values for the increase in the latter were 0.53 (−0.15 to 1.2) for the monotherapy group and 0.81 (−0.20 to 1.83) for the dual therapy group. The total white cell count fell significantly with dual therapy from $11.1 \times 10^9$/l to $7.9 \times 10^9$/l ($p<0.01$) and showed a non-significant fall with monotherapy from $10.3 \times 10^9$/l to $9.0 \times 10^9$/l ($p=0.053$). Both treatment regimens showed a significant increase in $FEV_1$ from day 0 to 12

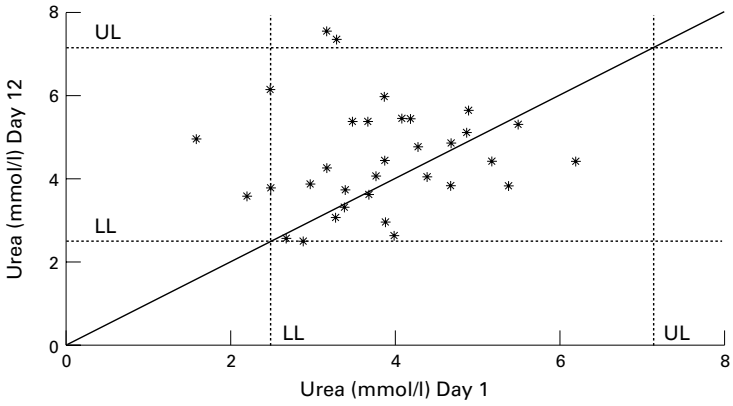


*Figure 3 Blood urea levels Day 1 versus Day 12 in dual therapy group (uppermost asterisks represent two patients with identical pretreatment and post-treatment urea values).*

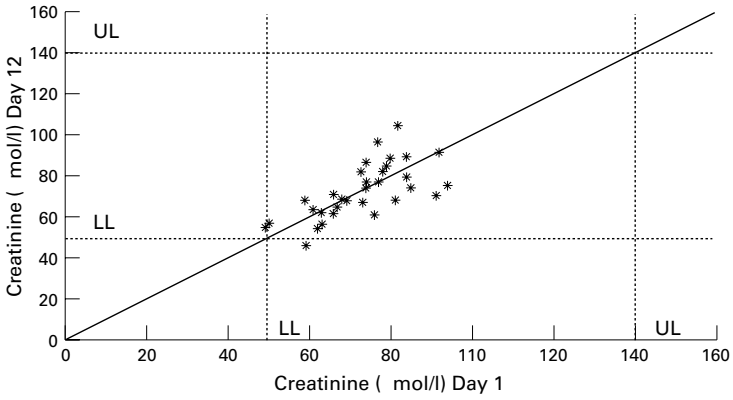


*Figure 4 Serum creatinine levels Day 1 versus Day 12 in monotherapy group.*

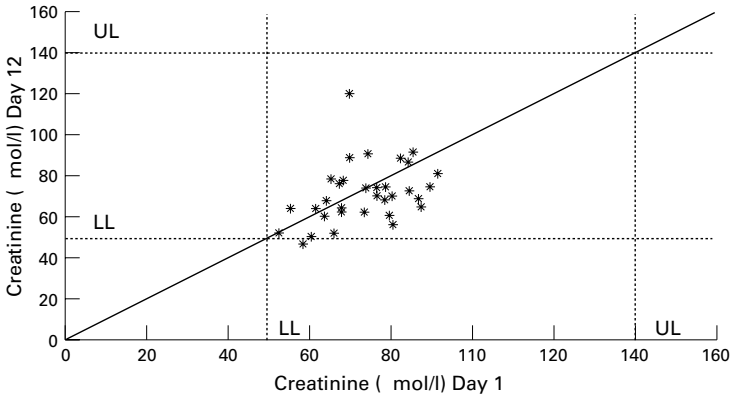


*Figure 5 Serum creatinine levels Day 1 versus Day 12 in dual therapy group.*

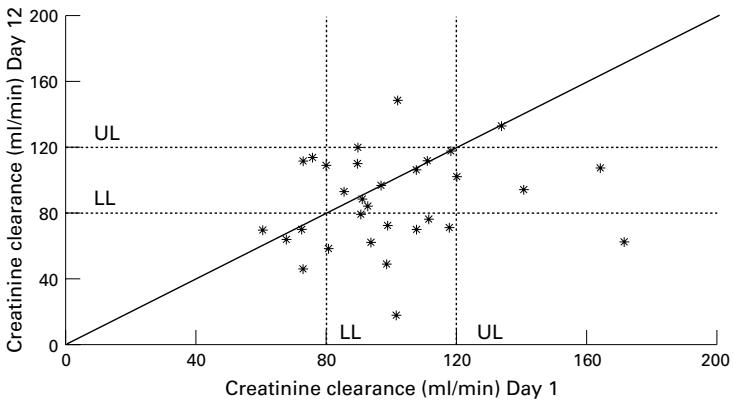


*Figure 6 Creatinine clearance Day 1 versus Day 12 in monotherapy group.*

(p<0.01), with a mean (95% CI) increase of 0.11 (0.03 to 0.2) for the monotherapy group and 0.31 (0.19 to 0.42) for the dual therapy group. Only patients in the dual therapy group showed a significant improvement in FVC (p<0.01, fig 1) with a mean (95% CI) value of 0.12 (−0.06 to 0.29) for the monotherapy group and 0.6 (0.4 to 0.8) for the dual therapy group. The mean weight increased by 1.52 kg with dual therapy (p<0.01) and showed a non-significant increase with monotherapy of 0.36 kg (p=0.16).

There was a statistically significant rise in blood urea levels at day 12 in both treatment groups and a significant fall in creatinine clearance in the dual therapy group. Neither group showed a statistically significant rise in serum creatinine levels (table 4, figs 2–7). The mean (95% CI) increases in blood urea and serum creatinine levels, respectively, were 0.57 (0.21 to 0.93) and 3.0 (−1.67 to 7.67) for monotherapy and 0.83 (0.26 to 1.4) and −5.85 (−14.13 to 2.43) for dual therapy. No toxic effect was detected during therapy on urine multistix testing on days 5 and 12.

Thirty seven adverse neurological events (dizziness, numbness, tingling, incoordination, unsteadiness, muscle weakness) were reported in 33 patients in the monotherapy group as a result of direct enquiries on four separate days (2, 3, 5, and 12). Only one patient described the symptoms of dizziness and muscle weakness as severe and withdrew from the study. In the dual therapy group 37 adverse neurological events were reported in 36 patients. None was described as severe. All "mild" and "moderate" symptoms were well tolerated and resolved during or shortly after treatment. None of these patients required a change in their antibiotic therapy. No clinically significant non-neurological event with a "possible" or "probable" relationship to colistin therapy occurred in either group.

Optimal peak blood levels of colistin lie between 10 and 15 μg/ml.[16] Twenty three paired blood samples were collected for assay of colistin levels from patients in the monotherapy group. The mean trough level was 2.3 μg/ml and the mean peak level was 12.3 μg/ml. Eleven peak levels were below 10 μg/ml but only seven of these were less than 9 μg/ml and only two values were unexpectedly low at 5.1 and 5.2 μg/ml. Only one patient had very high levels (>25 μg/ml) but experienced no toxic effects.

## Discussion

Intravenous antibiotic therapy is usually necessary in moderate to severe acute pulmonary exacerbations of cystic fibrosis associated with chronic *Pseudomonas aeruginosa* infection. Improvement in respiratory function significantly correlates with decreased sputum *P aeruginosa* density,[4 17] appropriate antibiotic treatment providing quantifiable additional benefit to treatment with bronchodilators and physiotherapy alone.[4] Therapeutic regimens involving more frequent parenteral antibiotic administration, and patients' greater antibiotic

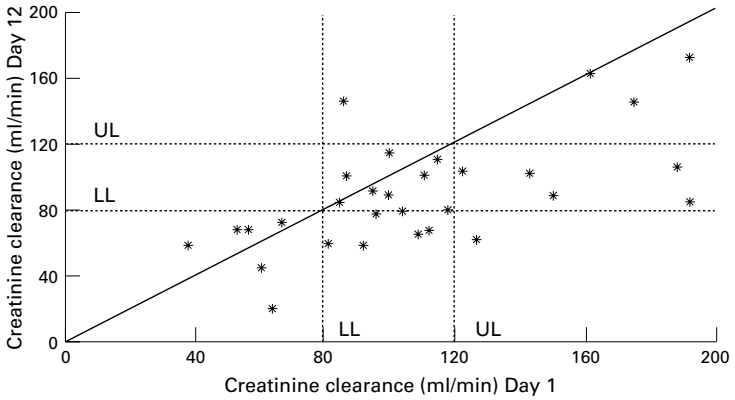


*Figure 7 Creatinine clearance Day 1 versus Day 12 in dual therapy group.*

exposure as a result of greater longevity have resulted in increasing pseudomonal antibiotic resistance.[5 7 18] Colistin has continued to show in vitro efficacy[7 8 19] but has not been readily used parenterally because of concerns about its reported nephrotoxicity (increased serum creatinine and blood urea, acute renal failure and acute tubular necrosis)[10 20–22] and neurotoxicity (paraesthesiae, muscle weakness, dizziness, confusion, and respiratory insufficiency secondary to neuromuscular blockade).[10 20–24] Reported experiences of adverse reactions to colistin are, however, variable,[22 24–26] do not include patients with cystic fibrosis, and are reversible when colistin is stopped or the dose reduced, even when very large doses have been used.[10 20 21] Because of the complexity of the patient's underlying illness, some of the adverse events documented might have been wrongly attributed to colistin.[10]

Bosso *et al* observed only one case of reversible renal toxicity in a study of 21 courses of intravenous colistin in 19 patients with cystic fibrosis.[11] In a large prospective study we have shown a significant rise in mean serum urea levels, a significant fall in mean creatinine clearance only when colistin is used in conjunction with a second intravenous anti-pseudomonal antibiotic, but no significant change in mean serum creatinine values or urine multistix tests. Of the parameters measured, creatinine clearance most closely reflects glomerular filtration rate. It is, however, the most difficult to document accurately and the wide variability in results possibly reflects problems in obtaining complete urine collections from ambulatory young adult patients. In both groups there was a mean fall in creatinine clearance of 16.5%. Whilst most of the values fell, eight of 32 (25%) with monotherapy and five of 29 (17%) with dual therapy increased. Only one patient in the monotherapy group showed a marked fall in creatinine clearance from a normal pretreatment value. At the end of the study the mean serum urea level, though showing a statistically significant rise, remained within the normal laboratory range (<7.1 mmol/l) and only four individual patients had a level above this upper limit (7.3 (A), 7.4 (B), and 7.6 (C and D) mmol/l).

We have looked for evidence of long term nephrotoxicity from intravenous colistin. Since the end of the study the above four patients have received, respectively, 9, 11, 17, and 6 further treatment courses including colistin. Mean serum urea (mmol/l) and creatinine (μmol/l) levels before and after these treatments were: patient A, 5.3, 5.9, 63, 55; patient B, 6.3, 9.0, 96, 76; patient C, 4.4, 5.1, 89, 91; patient D, 2.5, 4.2, 61, 67. All showed a rise in urea levels but these remained within the normal laboratory range except for patient B. The latter was in respiratory failure with cor pulmonale.

The 53 patients in the study had received a further 393 intravenous treatment courses which included colistin from the end of the study to 31 December 1996. The mean admission and discharge serum urea and creatinine levels for these 393 treatments were, respectively, 4.0 and 4.7 mmol/l, 71 and 69 μmol/l. The study and follow up data show some adverse effect of colistin on renal function, but this is probably not of clinical importance. Colistin appears to be safe in the treatment of acute respiratory exacerbations in adult patients with cystic fibrosis, but renal function should be monitored before and during its use. Colistin should not be used in combination with other potentially nephrotoxic antibiotics nor in patients with pre-existing renal impairment.

Bosso *et al* recorded six minor neurological events but all patients were able to continue with treatment.[11] Only two patient withdrawals in our study were related to adverse drug reactions, and only one was classified as severe. A total of 37 adverse neurological events were described in each patient group over the study period but, with the exception of the single patient who withdrew from the study, they were well tolerated, did not necessitate any reduction in the dose of colistin, and resolved during or shortly after the end of treatment. There were no clinically significant non-neurological events associated with colistin administration.

Intravenous colistin was shown to be effective in the treatment of pulmonary exacerbations in adult patients with cystic fibrosis, either as monotherapy or in combination with a second anti-pseudomonal antibiotic, as judged by primary (significant increases in $FEV_1$ and a non-significant rise in mean overnight $Sao_2$) and secondary (significant decreases in clinical scores and significant increases in SK scores) outcome measures. Treatment with colistin and another antibiotic produced a more rapid and greater improvement, with significant positive changes in FVC, mean weight, white blood cell count, and percentage of patients achieving a normal level of C-reactive protein. Previous studies have suggested an equal therapeutic response when only one antibiotic has been administered, but treatment numbers were smaller, drug dosage according to present recommendations suboptimal, treatment duration shorter, or monitoring less complete than in our study.[27–29] The greater increase in lung function shown by the dual therapy group may be more significant with repeated courses of

treatment, optimising the patient's respiratory capability and maximising performance between intravenous antibiotic treatments. Assuming that the lower values of C-reactive protein seen with dual therapy reflect less endobronchial inflammatory activity, treatment with two antibiotics might reduce the rate of attrition of lung function.

We can relate the improvement seen with colistin to that expected with conventional therapy by reference to our local data bank. In a 12 month period spanning the study 126 intravenous treatments which did not include colistin were administered for acute respiratory exacerbations of which 122 used two anti-pseudomonal antibiotics. $FEV_1$ data for the monotherapy study group showed a mean rise of 0.11 l. The corresponding changes for the 126 routine treatments and the dual therapy group were 0.19l and 0.3 l, respectively. Thus, colistin alone results in an improvement in $FEV_1$ similar to conventional combined therapy, and colistin in combination with a second antibiotic results in an even greater improvement. These data show that colistin is working alone and suggest that it confers an additional benefit when used in combination therapy.

The mean dose of colistin for all patients was 8.8 mg/kg/day (range 5.3–12.9). The manufacturers recommend 4 mg/kg/day up to 60 kg body weight, and 480 mg/day at 60 kg body weight or above – that is, a maximum of 8 mg/kg/day. Bosso *et al*[11] and Southern *et al*[7] used 6–8 mg/kg/day but did not measure blood colistin levels. Eleven of 23 measured peak colistin blood levels in this study fell below the target range of 10-15 μg/ml (mean colistin dose 9.2 mg/kg/day) although only two (colistin dose 9.6 and 8.0 mg/kg/day) were considered seriously low at 5.2 and 5.1 μg/ml. These results are consistent with the known abnormal drug disposition in cystic fibrosis and its interpatient variability, the low serum drug levels probably reflecting an increased volume of distribution and an increased renal and non-renal drug elimination.[30–32] Greater therapeutic efficacy might result from individual adjustment of colistin dosage according to measured serum levels. Unfortunately these are not routinely available.

With the increasing longevity of patients with cystic fibrosis and the concomitant increased use of anti-pseudomonal antibiotics, bacterial resistance has become more common and antibiotic choice, based on in vitro sensitivity testing, more limited. Resistance of *Pseudomonas aeruginosa* to colistin is unusual even after repeated use for the same patient. We have shown that intravenous colistin at a dose of 2 MU (160 mg) three times a day is effective in the treatment of *P aeruginosa* associated pulmonary exacerbations in adult patients with cystic fibrosis. This study also suggests that more rapid and/or greater improvement is achieved when colistin is prescribed in conjunction with a second antibiotic to which the pseudomonas also shows in vitro sensitivity. Colistin does cause changes in renal function. We have not found evidence of long term toxicity from our own clinical experience, but colistin should be used with care, and always with renal monitoring.

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1 Dodge JA, Morrison S, Lewis PA, Coles EC, Geddes D, Russell G, *et al*. Cystic fibrosis in the United Kingdom, 1968–88: incidence, population and survival. *Paediatr Perinatol Epidemiol* 1993;**7**:157–66.
2 Cystic Fibrosis Foundation. *Patient registry: 1991 Annual Data Report.* Bethesda, Maryland: 1992.
3 Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.
4 Regelmann WE, Elliott GR, Warwick WJ, Clawson CC. Reduction of sputum *Pseudomonas aeruginosa* density by antibiotics improves lung function in cystic fibrosis more than do bronchodilators and chest physiotherapy alone. *Am Rev Respir Dis* 1990;**141**:914–21.
5 Hoiby N, Heilesen A, Moller NE. Development of *Pseudomonas aeruginosa* strains resistant to carbenicillin, azlocillin, piperacillin and tobramycin during chemotherapy in cystic fibrosis patients. *Monogr Paediatr* 1981;**14**:103–7.
6 Pedersen SS, Koch C, Hoiby N, Rosendal K. An epidemic spread of multiresistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. *J Antimicrob Chemother* 1986;**17**:505–16.
7 Southern KW, Cunliffe CHE, McLaughlin SM, Haase EJ, Todd NJ, Littlewood JM. A review of the use of intravenous colistin in a regional cystic fibrosis unit. *European Cystic Fibrosis Conference, Madrid*, 1993: PD46.
8 Goldman M, Alcorn M. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by colistin. *European Cystic Fibrosis Conference, Madrid*, 1993: PD45.
9 Mouton JW, den Hollander JG, Horrevorths AM. Emergence of antibiotic resistance among *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. *J Antimicrob Chemother* 1993;**31**:919–26.
10 Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann Intern Med* 1970;**72**:857–68.
11 Bosso JA, Liptak CA, Seilheimer DK, Harrison GM. Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991;**25**:1168–70.
12 Conway SP, Miller MG, Ramsden C, Littlewood JM. Intensive treatment of *Pseudomonas* chest infection in cystic fibrosis: a comparison of tobramycin and ticarcillin, and netilmicin and ticarcillin. *Acta Pediatr Scand* 1985;**74**: 107–13.
13 Shwachman H, Kulczycki LL. Long-term study of 105 patients with cystic fibrosis: studies made over a 5 to 14 year period. *Am J Dis Child* 1958;**96**:6–15.
14 Chrispin AR, Norman AP. The systematic evaluation of the chest radiograph in cystic fibrosis. *Pediatr Radiol* 1974;**2**: 101–5.
15 Conway SP, Pond MN, Bowler I, Smith DL, Simmonds EJ, Joanes DN, *et al*. The chest radiograph in cystic fibrosis: a new scoring system compared with the Chrispin-Norman and Brasfield scores. *Thorax* 1994;**49**:860–2.
16 Froman J, Gross L, Curatola S. Serum and urine levels following parenteral administration of sodium colistimethate to normal individuals. *J Urol* 1970;**103**:210–4.
17 Smith AL, Redding G, Doershuk C, Goldmann D, Gore E, Hilman B, *et al*. Sputum changes associated with therapy for endobronchial exacerbation in cystic fibrosis. *J Pediatr* 1988;**112**:547–54.
18 Szaff M, Hoiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection. *Acta Paediatr Scand* 1983;**72**:651–7.
19 Blessing J, Maybury B, Lewiston N. Antimicrobial susceptibility of *Pseudomonas* from sputum of patients: 1975 to 1980. *Monogr Paediatr* 1981;**14**:115–9.
20 Walinsky E, Hines JD. Neurotoxic and nephrotoxic effects of colistin in patients with renal disease. *N Engl J Med* 1962;**266**:759–62.
21 Price DJE, Graham DI. Effects of large doses of colistin sulphomethate sodium on renal function. *BMJ* 1970;**4**: 525–7.
22 Cox CE, Harrison LH. Intravenous sodium colistimethate therapy of urinary tract infections: pharmacological and bacteriological studies. *Antimicrob Agents Chemother* 1970; **10**:296–302.
23 Gold GN, Richardson AP. An unusual case of neuromuscular blockade seen with therapeutic blood levels of colistin methanesulfonate. *Am J Med* 1966;**41**:316–21.
24 Olsen S, Madsen PO. Intravenous administration of sodium colistimethate in urinary tract infections. *Curr Ther Res* 1967;**9**:283–7.
25 Pines A, Raafat H, Plucinski K. Gentamicin and colistin in chronic purulent bronchial infections. *BMJ* 1967;**2**:543–5.
26 Halliday NP. *Pseudomonas* infection of the respiratory tract treated with colistin sulphomethate sodium. *Clin Trials J* 1967;**4**:771–5.
27 Parry MF, Neu HC, Merlino M, Gaerlan PF, Oref CN, Denning CR. Treatment of pulmonary infections in patients with cystic fibrosis: a comparative study of ticarcillin and gentamicin. *J Pediatr* 1977;**90**:144–8.
28 Michalsen H, Bergan T. Azlocillin with and without an aminoglycoside against respiratory tact infections in

children with cystic fibrosis. *Scand J Infect Dis* 1981; **29**(Suppl):92–7.
29 McLaughlin FJ, Matthews WJ, Strieder DJ, Sullivan B, Taneja A, Murphy P, *et al*. Clinical and bacteriological responses to three antibiotic regimens for acute exacerbations of cystic fibrosis: ticarcillin-tobramycin, azlocillin-tobramycin, and azlocillin-placebo. *J Infect Dis* 1983; **147**:559–67.
30 Kearns GL, Hilman BC, Wilson JT. Dosing implications of altered gentamicin disposition in patients with cystic fibrosis. *J Pediatr* 1982;**100**:312–8.
31 Prandota J. Clinical pharmacology of antibiotics and other drugs in cystic fibrosis. *Drugs* 1988;**35**:542–78.
32 Lindsay CA, Bosso JA. Optimisation of antibiotic therapy in cystic fibrosis patients. *Clin Pharmacokinet* 1993;**24**: 496–506.