

## Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic *Pseudomonas* infection of the lungs

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### Abstract

**Background**—A previous retrospective study suggested that a policy of regular anti-pseudomonal antibiotic treatment improved pulmonary function and increased survival in patients with cystic fibrosis chronically infected with *Pseudomonas* species. The results of a prospective multi-centre study to compare the effects on pulmonary function and mortality of three monthly elective anti-pseudomonal antibiotic treatment with conventional symptomatic treatment are reported.

**Methods**—Sixty patients with cystic fibrosis, chronically infected with *P aeruginosa*, were randomised to the two treatment arms (elective or symptomatic) and followed clinically at yearly reviews. The major end points were changes in forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC). Survival was a secondary end point.

**Results**—Patients in the symptomatic group received a mean of three antibiotic treatments each year and those in the elective group received four antibiotic treatments during each year of the study. No significant differences in FEV<sub>1</sub> and FVC were found between the two groups after three years. There was a statistically non-significant higher rate of deaths in the elective group (n = 4), three of which were associated with *B cepacia* infection, compared with the symptomatic group (n = 0). **Conclusions**—This study did not demonstrate an advantage of a policy of elective antibiotic treatment over symptomatic treatment in patients with cystic fibrosis chronically infected with *Pseudomonas* species.

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**Keywords:** cystic fibrosis; *Pseudomonas aeruginosa*; maintenance treatment; antibiotics

The prognosis for patients with cystic fibrosis has improved significantly over the past three decades.<sup>1,2</sup> In the 1960s the median survival age was about six years compared with the current median survival age of over 30 years.<sup>2</sup> The care of patients in specialised centres, improved

nutrition, and the aggressive treatment and control of respiratory infection are considered to be the main reasons for this improvement.<sup>3,4</sup> Patients with cystic fibrosis have frequent infections during the first decade due mainly to *Staphylococcus aureus* and *Haemophilus influenzae*.<sup>5</sup> By the end of the second decade the lungs of most patients become colonised with *Pseudomonas aeruginosa* and, in some cases, *Burkholderia cepacia*.<sup>5–7</sup> Aggressive antibiotic treatment after the first sputum isolation of *P aeruginosa* can postpone chronic infection but usually this organism is regularly isolated from sputum culture.<sup>8,9</sup> Once established, this infection causes respiratory exacerbations which usually respond to treatment with anti-pseudomonal antibiotics such as ureidopenicillins, aminoglycosides, third or fourth generation cephalosporins, and carbapenems.<sup>10,11</sup> When patients develop an exacerbation of symptoms, treatment with appropriate antibiotics results in a significant improvement in symptoms and pulmonary function and in a reduction in systemic markers of the inflammatory response such as C reactive protein and neutrophil elastase  $\alpha_1$ -antitrypsin complexes.<sup>12</sup>

In 1976 the Danish Cystic Fibrosis Centre began treating patients colonised with *P aeruginosa* with a regimen of two week courses of intravenous antibiotics given every three months regardless of their clinical state.<sup>13</sup> In a retrospective comparison of mortality with that occurring during the previous five years they found a reduction in deaths from about 10% to 2% per year and an improvement in five year survival from 54% to 82%.<sup>13</sup> This study was not prospective or randomised and a large proportion of the patients were children. During the period of the study there were several other changes in the management of cystic fibrosis that have been shown to improve survival—for example, the change from low to high fat diets.<sup>14</sup> As a result, survival of patients in most developed countries improved between 1970 and 1985 and it was difficult to assess how much this improvement was due to a change in antibiotic policy.<sup>1</sup>

Many centres now advocate regular three monthly antibiotic treatment without evidence of efficacy from a randomised controlled trial.<sup>15</sup> We have compared the three year outcome of regular three monthly elective antibiotic

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Table 1 Comparison of elective and symptomatic groups at entry

	Elective (n = 32, 16 male)	Symptomatic (n = 28, 13 males)
Age (years)	18 (9)	18 (8)
Height (cm)	157 (17)	155 (16)
(Z score)	-0.5 (1.0)	-0.4 (1.0)
Weight (kg)	47 (13)	47 (14)
(Z score)	-0.5 (1.0)	-0.3 (0.9)
Chrispin-Norman score	11 (5)	10 (4)
Shwachman score	68 (14)	74 (13)
FEV <sub>1</sub> (l)	1.7 (0.8)	1.9 (0.9)
FEV <sub>1</sub> (% predicted)	59 (24)	63 (25)
FVC (l)	2.6 (1.1)	2.6 (1.2)
FVC (% predicted)	72 (21)	74 (21)

Values are mean (SD).

Z = standard deviation score; FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity.

treatment with that of antibiotic treatment given according to symptoms in a prospective randomised parallel group study over three years.

### Methods

The study began in 1991 when all cystic fibrosis centres in the UK were invited to enter patients. Patients aged eight years and over with cystic fibrosis from whom *P aeruginosa* had been isolated on three or more occasions during the previous 12 months were eligible for inclusion. Informed consent was obtained from patients and, in those under 16 years of age, from their parents. Patients with a history of hypersensitivity to antipseudomonal agents, those who were already on a regular treatment regimen of intermittent antibiotics, and those who had had less than two or more than four exacerbations during the previous year requiring intravenous antibiotics were excluded.

Patients who agreed to take part were then allocated by a central coordinating centre to receive elective antipseudomonal antibiotics every three months or to receive antibiotic treatment only when symptoms indicated. Allocation of treatment was by the method of minimisation using age, severity based on chest radiographic score, and treatment centre. Patients received treatment for 10–14 days with antipseudomonal antibiotics. The choice of antibiotic was based on the sensitivity of the individual patient's micro-organisms from the last available sputum culture. A table of guidance was given for treatment with antibiotics which included the ureidopenicillins, antipseudomonal third generation cephalosporins, carbapenems, aminoglycosides, monobactams, and ciprofloxacin. The choice of the place of treatment was left to the judgement of the individual clinician and patients. If a patient in the elective arm received a course of antibiotics for a symptomatic deterioration within four weeks of the planned elective treatment, that course was taken to be their elective treatment. The next course of elective treatment was given three months later. An exacerbation was not pre-defined in the protocol but left to the discretion of each centre.

Clinical and lung function data were collected at the time of entry and at the time of each annual assessment following entry to the study when patients were clinically stable. Chest radiographs were scored independently by a radiologist experienced in radiology in cystic fibrosis using the Chrispin-Norman system.

Weight, height, and spirometric values were recorded as actual values and as standardised values; percentage of predicted values for spirometry and number of standard deviations from the mean of healthy subjects for weight and height (Z score). A sputum sample was cultured for respiratory organisms including *H influenzae*, *S aureus*, *P aeruginosa* and *B cepacia* and in vitro sensitivity testing was performed using the disc diffusion method.

### DATA ANALYSIS

The effect of the treatment group on changes in the clinical outcome measures from entry to the study to three years after randomisation was analysed by analysis of covariance, with the entry value included as a covariate. The analysis was conducted according to the principle of intention to treat.

The target sample size for the study was 100 patients. It was anticipated that the standard deviation of the change in lung function, expressed as percentage predicted, would be between 10% and 15%. This would yield a standard error for the mean difference between the treatment groups of 2–3%. In practice, 60 patients were recruited, inflating the standard errors by 30% relative to that anticipated.

### Results

Sixty patients were entered from 15 cystic fibrosis centres, 32 of whom were randomised to the elective group and 28 to the symptomatic group. At the start of the study there were no appreciable differences between the two groups in any of the variables recorded (table 1). Both groups were receiving similar concomitant treatments such as antistaphylococcal antibiotics; 25% of patients in the elective group were taking nebulised antibiotics compared with 40% in the symptomatic group, while 41% of elective patients and 29% of symptomatic patients were taking regular inhaled bronchodilators. None of these differences was significant. There was no difference in the prevalence of pancreatic insufficiency, diabetes mellitus, significant renal or liver disease, allergic bronchopulmonary aspergillosis, *B cepacia* infection, or history of pneumothorax between the two groups at the time of entry into the study.

### ANTIBIOTIC TREATMENTS

The elective group received an average of four courses of antibiotics per year during the three years of follow up compared with an average of three courses per year in the symptomatic group (table 2). This difference was statistically significant in year 1 but not so in the subsequent two years.

In the elective group 25 of 30 patients during year 1, 26 of 31 in year 2, and 22 of 27 in year 3 received three or more courses of antibiotics

Table 2 Mean (SD) number of courses of antipseudomonal antibiotics in each year

	Elective	Symptomatic
Year 1	4.2 (1.7)	2.9 (1.5)
Year 2	4.1 (2.0)	3.3 (2.5)
Year 3	4.0 (2.0)	3.0 (2.0)

Table 3 Changes in clinical outcome measures from entry to end of year 3

	Elective	Symptomatic	Adjusted difference (95% CI)*	p value
FEV <sub>1</sub> (% predicted)	-5.7 (2.6)	-8.1 (3.4)	1.8 (-6.6 to 10.2)	0.67
FVC (% predicted)	-5.2 (2.3)	-6.3 (4.1)	1.0 (-8.3 to 10.4)	0.83
Shwachman score	-4.3 (2.3)	-6.1 (2.1)	1.7 (-4.7 to 8.1)	0.59
Chrispin-Norman score	-0.8 (0.8)	-1.0 (0.8)	0.4 (-1.7 to 2.6)	0.71
Height (SD score)	-0.11 (0.13)	0.05 (0.06)	-0.06 (-0.33 to 0.22)	0.67
Weight (SD score)	-0.06 (0.10)	0.03 (0.09)	-0.10 (0.38 to 0.18)	0.49
Weight/height (% predicted)	0 (1.5)	-0.8 (1.6)	0.8 (-1.4 to 3.0)	0.72

\*Adjusted for entry levels using an analysis of covariance. The signs are such that a positive value indicates that adjusted values are higher in the elective group at the end of year 3.

FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity.

compared with 18 of 28, 18 of 27, and 14 of 27, respectively, in the symptomatic group.

#### CLINICAL OUTCOMES

The changes in lung function, Shwachman score, Chrispin-Norman radiographic score, height and weight scores, and weight for height as a percentage of predicted at the end of three years are shown in table 3. There were no significant differences between the two groups in the changes in any of these measurements. At the end of year 1 patients in the elective group showed a slight improvement in lung function compared with the symptomatic group. This difference was not sustained after three years (fig 1).

#### WITHDRAWALS AND DEATHS

There were four deaths and five withdrawals in the elective group and no deaths and only one withdrawal in the symptomatic group. All deaths were due to respiratory failure secondary to cystic fibrosis. In the elective group three patients withdrew from the study because of the inconvenience of regular antibiotic treatments, one patient because of a heart and lung transplant, and one patient following pregnancy. The patient who withdrew in the symptomatic group did so at his own request. When the 19 patients in the elective group who completed three years of intermittent antibiotic treatment according to the protocol were compared with the symptomatic group there was also no significant difference in any clinical outcomes described.

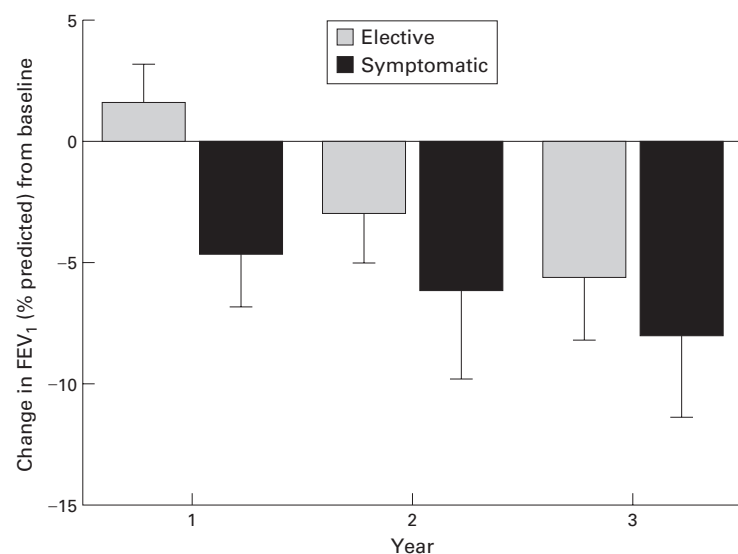


Figure 1 Changes in forced expiratory volume in one second (FEV<sub>1</sub>) at the end of each year following randomisation.

#### SPUTUM MICROBIOLOGY

There was no difference at entry to the study in the number of microbial isolates from sputum of *P. aeruginosa* which were multiresistant (resistant to three or more antipseudomonal antibiotics) in the elective group (n = 7) compared with the symptomatic group (n = 5). During the subsequent three years 31 isolates from 15 patients in the elective group and 31 isolates from 17 patients in the symptomatic group were due to organisms which were multiresistant. At entry *B. cepacia* was isolated from two patients in the elective group but none in the symptomatic group. Over the subsequent three years 11 isolates of *B. cepacia* were obtained from four patients in the elective group compared with 13 from five patients in the symptomatic group. In three of the patients in the elective group *B. cepacia* was isolated at the time of death. There was no difference in the prevalence of *S. aureus* and *H. influenzae* between the two groups.

#### Discussion

In the first three years of this study we have found no significant advantage of a policy of regular elective antibiotic treatment over symptomatic treatment in patients with cystic fibrosis and chronic infection of the airways. The main end points of spirometric lung function (FEV<sub>1</sub>, FVC) in the elective group and the symptomatic group were not different after three years. Other end points such as annual Chrispin Norman score, Shwachman score, and body weight were also not different during the period of study between the two groups.

These results differ from the retrospective study from Copenhagen reported by Szafl *et al* in 1983.<sup>13</sup> In most developed countries survival improved over that decade without the introduction of any change to elective antibiotic treatment.<sup>1-3</sup> The improvements in survival in the Danish study could reflect the impact of a dedicated cystic fibrosis centre, intervention with improved nutrition, and aggressive antibiotic treatment. The patients studied in the Copenhagen group were probably younger than in this current study. The mean age is not quoted but it is likely that it was 12 years compared with 18 years in our study. It is possible that younger patients may benefit from this treatment approach more so than adults. However, in the current study 42% of patients were under the age of 16 and there has been no suggestion that this younger subgroup behaves differently from older patients.<sup>8</sup> In the Copenhagen study it is not clear how long elective antibiotics were started after the first infection but it is stated that the duration of chronic infection did not differ between the elective and symptomatic groups in the study. A further difference in the Copenhagen study is that the retrospective control group received one course of antibiotics to three courses in the group treated with regular elective antibiotics.

In our prospective study elective antibiotics did not improve survival. There were more deaths in the patients treated with elective antibiotics than in the symptomatic group, but at three years this did not reach statistical significance. We have continued to collect data for up

to five years. There is now a significant difference in the number of deaths in the elective group ( $n = 8$ ) compared with those treated symptomatically ( $n = 1$ ,  $p < 0.04$ , Fisher's exact test). All the deaths were due to cardiopulmonary failure secondary to overwhelming lung infection. There was no evidence of increased antibiotic resistance in these patients or episodes of hypersensitivity. There were slightly more patients in the symptomatic group who had *B cepacia* infection. This organism is associated with reduced survival in patients with cystic fibrosis but does not account for the differences in mortality between the groups.<sup>17</sup>

No significant difference in the incidence of resistant bacteria was found during the study between the groups and no significant changes during the time of the study. There is no significant difference in the incidence of new cases of multi resistant organisms or new antimicrobial species such as *B cepacia* and *Stenotrophomonas maltophilia*. This may be because three years is too short a period of time to monitor changes in bacterial sensitivity to antibiotics.<sup>18</sup>

The lack of any difference in any of the clinical outcome measures may reflect the design of this study. Patients who entered the study had at least two exacerbations requiring intravenous antibiotics in the year prior to entry. The patients in the symptomatic arm of the study received an average of three courses of intravenous antibiotics whereas the patients in the elective arm received an average of four courses of antibiotics in each year. This suggests that many patients with cystic fibrosis require between three and four courses of antibiotics for respiratory exacerbations and the application of a policy of regular intravenous antibiotics may reflect the natural history of the disease.<sup>19</sup>

This study did not recruit the number of patients determined in the sample size calculation, and this reduced the power of the study to detect a difference between the treatment groups. There was a trend for patients in the elective arm to have a smaller reduction in FEV<sub>1</sub>, FVC, Shwachman score, and Crispin-Norman score compared with those treated symptomatically, but statistical significance was never reached. The trend towards a difference in spirometric values was seen mostly during the first year. This may reflect a treatment effect from the antibiotics or the early impact on lung function of more frequent admissions to hospital with extra physiotherapy and other hospital associated interventions.

There were significantly more withdrawals by patients treated in the elective arm than in those having symptomatic treatment. The major reason for withdrawal from the elective arm was the extra burden that regular antipseudomonal antibiotic treatment places on patients with cystic fibrosis. Ciprofloxacin was the only oral antipseudomonal drug available during the study. Most of the courses of antibiotics were given by the intravenous route. One patient withdrew from the elective arm because of poor venous access as a result of antibiotic induced thrombophlebitis.

The policy of elective antibiotic treatment has a significant cost implication. A course of

intravenous antibiotics given at home costs approximately £1000 and in hospital may cost over £3000.<sup>10,19</sup> It also has considerable implications for patients "costing" eight weeks each year to have the treatment. It is therefore important that sufficient evidence is available before committing resources and patients' time to this approach. In view of the fact that there was no significant difference between the elective and symptomatic group, and with the possibility of increasing resistance to antibiotics leading to limited therapeutic options, it would seem prudent to restrict the use of antibiotics to the treatment of infective exacerbations.

In summary, this study has shown no significant advantage in regular elective antibiotic treatment over symptomatic treatment in patients with cystic fibrosis with chronic infection with *P aeruginosa*. The apparent excess of deaths in the elective group is disturbing as there is no obvious explanation. It is important that further studies in younger patients are performed.

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