ORIGINAL ARTICLE

Increased treatment requirements of patients with cystic fibrosis who harbour a highly transmissible strain of *Pseudomonas aeruginosa*

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Background: A group of patients who harbour the same highly transmissible strain of *Pseudomonas aeruginosa* were identified at a cystic fibrosis (CF) centre. Isolates of this strain display a number of unusual phenotypic features including resistance to most typical antipseudomonal antibiotics. A study was undertaken to see if there was a difference in treatment requirements between CF patients with chronic infection with their own unique *P aeruginosa* strains (group 1) and those who harbour a highly transmissible strain (group 2).

Methods: Data on treatment requirements for the year 2000 were collected from the case records of CF patients with chronic *P aeruginosa* infection who had received inpatient treatment. Patients co-infected with *Burkholderia cepacia* or other highly transmissible strains of *P aeruginosa* were excluded.

Results: There were 2/56 and 3/22 deaths in groups 1 and 2, respectively; these patients were excluded from the analysis. No difference was found between the two groups for mean age, % predicted forced expiratory volume in 1 second (FEV_1), % predicted forced vital capacity (FVC), and body mass index. Patients in group 2 had a greater median (range) number of intravenous antibiotic days (60 (17–216) *v* 33 (4–237) days; p=0.01), inpatient days (39 (7–183) *v* 16 (1–172) days; p<0.01), and inpatient episodes (3 (1–9) *v* 2 (1–6); p<0.01), and more respiratory exacerbations (mean (SD) 8.2 (3.4) *v* 6.1 (3.2); p=0.01).

Conclusions: Patients who harbour the highly transmissible *P aeruginosa* strain have a greater treatment burden than patients with CF who harbour their own unique strains. These findings support the need for microbiological surveillance for highly transmissible *P aeruginosa* and the implementation of infection control measures to prevent cross infection.

Chronic *Pseudomonas aeruginosa* infection can lead to a worsening in clinical state and increased mortality for patients with cystic fibrosis (CF).[1–3] Concern has recently arisen following reports of spread of multiresistant strains of *P aeruginosa* among patients with CF, including at our own adult centre.[4–7] How much *P aeruginosa* cross infection contributes to morbidity and mortality is, at present, unknown. The provision of resources for microbiological surveillance and implementation of infection control measures including segregation to prevent cross infection remains controversial.[8] We have studied the treatment requirements of two groups of CF patients with chronic *P aeruginosa* infection—those who harbour their own unique strains and those who harbour a highly transmissible strain.

METHODS

Patients with chronic *P aeruginosa* infection who attend the Manchester Adult CF Centre were included in the study if they had received inpatient treatment with intravenous antibiotics during the year 2000. Patients were grouped on the basis of typing results of *P aeruginosa* isolates from sputum samples as outlined in our previous study.[5] Briefly, bacterial fingerprinting of *P aeruginosa* isolates by pyocin typing and pulsed field gel electrophoresis identified a number of patients at our centre who harboured a highly transmissible strain. This strain was genomically distinct from another strain of *P aeruginosa* associated with cross infection at other UK CF centres.[4 6] The patients with CF were divided into two groups: those who harbour unique *P aeruginosa* strains (group 1) and those who harbour the Manchester epidemic *P aeruginosa* (group 2).[5] Patients co-infected with *Burkholderia cepacia* or other highly transmissible strains of *P aeruginosa* such as the Alder Hey epidemic strain[4] were excluded.

The results of antibiotic sensitivity patterns of *P aeruginosa* from disc sensitivity tests were noted. Multiresistance for *P aeruginosa* was defined as resistance to at least two of the three major classes of usual antipseudomonal antibiotics (β-lactam antibiotics, aminoglycosides, quinolones).

The regime for treating an exacerbation with intravenous antibiotics was identical for both groups. Patients were treated with a combination of at least two antibiotics with ceftazidime and tobramycin used as first line treatment; however, adjustments were made to the regime on the basis of in vitro sensitivity of the isolate and the patient's allergies to antibiotics. The duration of treatment was based upon clinical response.

The age, percentage predicted forced expiratory volume in one second (FEV_1), percentage predicted forced vital capacity (FVC), and body mass index (BMI) were calculated at the patient's first visit of the year 2000 to the CF centre. The number of days of intravenous antibiotic treatment (inpatient and home combined), number of infective pulmonary exacerbations requiring treatment with oral or intravenous antibiotics, and the number of clinic visits were calculated for the year 2000. The numbers of inpatient episodes and total number of inpatient days were also recorded, but hospital admissions for causes unrelated to respiratory exacerbations were excluded.

Statistical analysis was performed using SPSS statistical package version 9.0 (SPSS Inc, Chicago, Illinois, USA). The two groups were compared using a two sample *t* test and the Mann-Whitney U test.

Table 1 Demographic data and treatment requirements of adult CF patients with chronic infection by unique (group 1) and highly transmissible strains (group 2) of *P aeruginosa*

	Group 1 (n=56)	Group 2 (n=22)	p value
Age	25.6 (7.2)	26.6 (7.4)	NS
FEV_1 (% pred)	55.1 (19.3)	54.9 (18.0)	NS
FVC (% pred)	75.4 (19.2)	75.3 (20.4)	NS
Body mass index	21.2 (2.8)	20.6 (3.4)	NS
Outpatient episodes*	10 (2–26)	9.5 (3–32)	NS
Inpatient episodes*	2 (1–6)	3 (1–9)	0.005
Inpatient days*	16 (1–172)	39 (7–183)	0.003
IV antibiotic days*	33 (4–237)	60 (17–216)	0.01
Respiratory exacerbations	6.1 (3.2)	8.2 (3.4)	0.01

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.
Results expressed as mean (SD) or *median (range).

RESULTS

There were 56 patients (33 male) and 22 patients (10 male) in groups 1 and 2, respectively; two patients died in group 1 and three in group 2. A multiresistant *P aeruginosa* isolate was identified in sputum samples on at least one occasion during the year 2000 for 28 (50%) of the 56 patients in group 1 and 20 (91%) of the 22 patients in group 2. There was no difference between the two groups in mean age, % predicted FEV_1, % predicted FVC, and body mass index. There were, however, significant differences between the two groups in median number of days receiving intravenous antibiotics (p=0.01), inpatient episodes (p=0.005), inpatient days (p=0.003), and mean number of respiratory exacerbations (p=0.01; table 1).

DISCUSSION

This study has examined the differences in treatment requirements between patients with CF who have chronic *P aeruginosa* infection with their own unique strains and those who harbour a highly transmissible strain. Patients who harbour the highly transmissible *P aeruginosa* strain had more respiratory exacerbations and a greater requirement for intravenous antibiotics and inpatient treatment.

The emergence and spread of highly transmissible strains of *P aeruginosa* is, at present, a topic of great concern and controversy among CF physicians.[8] Isolates of highly transmissible strains may display unusual phenotypic features, including antibiotic resistance.[4–6] Most (20/22) of the isolates from patients in group 2 were found to be multiresistant; however, *P aeruginosa* strains from 50% (28/56) of the patients in group 1 were also found to exhibit antibiotic resistant phenotypes. Although the increased morbidity seen in patients in group 2 may be a reflection of the difficulty in treating a multiresistant strain, it is also possible that highly transmissible strains possess other properties that allow adaptation to and spread among CF patients, and which make them more difficult to treat. We have previously described two "*Pseudomonas* naïve" patients who acquired initial infection with the highly transmissible *P aeruginosa* strain.[5] In both cases the recommended eradication regimes failed and the patients developed chronic infection.[9] There are also reports of superinfection by a highly transmissible strain at another UK CF centre.[6] In addition, there is a suggestion from an Australian CF centre that another highly transmissible strain may be associated with increased virulence.[10]

The two groups in the current study were well matched in terms of spirometric parameters and body mass index. However, it is still not clear whether infection by the highly transmissible strain is the cause of the increase in treatment requirements or a marker for CF patients who require a high intensity of treatment. The contact density of cases may be important in determining the risk of cross infection, therefore highly transmissible strains may be more likely to spread among inpatients, selecting CF patients who already have increased treatment requirements. We therefore limited the patients in the study to those who have received inpatient treatment with intravenous antibiotics during the year 2000.

The CF Trust advocates surveillance for highly transmissible strains of *P aeruginosa*.[11] This study shows that there may be resource implications associated with spread of infection by multiresistant highly transmissible *P aeruginosa* strains and an increased morbidity for the CF patient. These findings support the need for microbiological surveillance for *P aeruginosa* cross infection and the implementation of cross infection control measures to limit spread of highly transmissible strains.

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