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Outcome for patients colonised with *Burkholderia cepacia* in a Birmingham adult cystic fibrosis clinic and the end of an epidemic

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Abstract

***Background* – There has been increasing concern since 1979 about the emergence of *Pseudomonas cepacia* (*Burkholderia cepacia*) in patients with cystic fibrosis in the UK and elsewhere. Colonisation of the sputum has been shown to be associated with increased morbidity and mortality. Evidence suggests person to person transmission and some centres have segregated those colonised with *B cepacia* from other patients with cystic fibrosis. The outcome of patients colonised by *B cepacia* has been studied, together with the effects of strict segregation.**

***Methods* – The outcome in 18 patients with sputum colonised by *B cepacia* was compared with that in age, sex, and severity matched controls with no evidence of *B cepacia* colonisation by a retrospective case note study.**

***Results* – No differences between cases or controls were found in the 24 month period prior to colonisation by *B cepacia* in lung function, number of days in hospital, or outpatient visits. Colonisation led to an increased rate of loss of lung function and utilisation of hospital services. There was an increase in the numbers of transplants and deaths amongst the cases. Since 1992 there have been only three new cases of *B cepacia* colonisation and the incidence and prevalence of the organism has fallen dramatically since segregation commenced.**

***Conclusions* – *B cepacia* appears to be linked to the decline in colonised individuals. There was no evidence that colonisation occurred in patients declining for other reasons. *B cepacia* colonisation confers a worse prognosis than *Pseudomonas aeruginosa* alone. Segregation appears to limit the spread of the organism from infected individuals to other patients with cystic fibrosis.**

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Keywords: cystic fibrosis, *Pseudomonas cepacia*, outcome

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Patients with cystic fibrosis usually become colonised with *Pseudomonas aeruginosa* as they get older; however, a newer organism has recently given cause for concern. *Burkholderia cepacia* (previously *Pseudomonas cepacia*) is a ubiquitous environmental pathogen that causes a variety of infections in patients with diminished defences.[1] Colonisation of the respiratory tract with *B cepacia* in patients with cystic fibrosis has been recognised since 1979,[2] and has been associated with significant morbidity and mortality with up to one third of patients dying within six months and a further third experiencing a significant loss of lung function.[3 4]

The first report of isolation of *B cepacia* in the United Kingdom from a patient with cystic fibrosis who subsequently died was in 1986.[5] Whilst infection may occur de novo in some patients, there is increasing evidence of person to person transmission[5–8] – for example, by inhalation of contaminated aerosol droplets[9] or direct contact through hand shaking.[10] It is generally accepted that acquisition of *B cepacia* should be avoided[11–13] and the French Cystic Fibrosis Association (AFLM) has declared, in a multinational consensus, that "the cystic fibrosis patient infected with *Pseudomonas cepacia* is currently the major source of *Pseudomonas cepacia* for other cystic fibrosis patients".[14] For these reasons patients colonised with *B cepacia* have been segregated by our unit since 1988 by provision of separate wards and outpatient clinics.

We have compared our experience of patients colonised with *B cepacia* with matched controls in whom *B cepacia* has not been isolated, and have attempted to ascertain whether acquisition is incidental to an increased rate of decline due to other factors or whether colonisation itself leads to the observed decline. We further report the end of an epidemic of new cases by a policy of both in-hospital and social segregation.

Methods

The population comprised 167 patients who had ever attended the Adult Cystic Fibrosis Unit at Birmingham Heartlands Hospital between 1989 and 1993 whose outcome was known. The cases included 18 patients from whom *B cepacia* was isolated from one or more sputum samples and identified from the time of the first isolation of the organism (the "colonisation date"). Data were collected for 24 months before this and six months thereafter. Insufficient data were available on two cases and 16 were studied. Sixteen patients from whom *B cepacia* had never been isolated were identified and matched for age, sex, and within 10% of the forced vital capacity (FVC ± 10%) at the beginning of the study, 24 months before

Table 1 Mean (range) of data in cases colonised with B cepacia (nine men) and B cepacia negative controls

	Colonised patients	*Controls*	*p value*
Age	25·5 (21–33)	26·5 (19–36)	NS
%FEV_1	41·4 (21–98)	49·9 (23–78)	NS
%FVC	69 (29–116)	60·6 (31–119)	NS
%IBW	81 (54–98)	90 (72–104)	<0·05
Genotype			
dF508/dF508	9/14	10/15	
dF508/other	3/14	4/15	
Unavailable	2/14	1/15	
Microbiology			
P aeruginosa alone	8/15	12/15	
P aeruginosa + *Staph aureus*	5/15	2/15	
Staph aureus alone	1/15	—	

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IBW = ideal body weight.

Table 2 Mean (SD) rates of decline in lung function and body weight before and after colonisation

	Colonised patients	*Controls*	*p value*
FEV_1 (ml/month)			
Before	−6·8 (20)	−8·99 (16·1)	NS
After	−29·2 (56)	+7·0 (28·6)	<0·05
p value	NS	<0·05	
FVC (ml/month)			
Before	−5·5 (29)	−3·6 (24·6)	NS
After	−41·4 (66)	+16·5 (46·2)	<0·02
p value	<0·05	NS	
Weight (kg/month)			
Before	+0·079 (0·215)	+0·082 (0·204)	NS
After	−0·072 (0·655)	−0·009 (0·267)	NS
p value	NS	NS	

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

Table 3 Mean (SD) outpatient attendance and inpatient days before and after colonisation

	Colonised patients	*Controls*	*p value*
Outpatient visits per 6 months			
Before	3·2 (1·5)	2·8 (1·26)	NS
After	4·7 (1·8)	3·5 (1·76)	NS
p value	<0·01	NS	
Hospital inpatient days per 6 months			
Before	9·7 (10)	11·7 (19·6)	NS
After	36·3 (17)	11·8 (14·5)	<0·001
p value	<0·001	NS	

the "colonisation date" of their respective controls.

B cepacia strains were isolated with a standard selective medium used since 1989 and identified by techniques described elsewhere.[15] Isolates identified in our laboratory were confirmed by the Central Public Health Laboratory, Colindale, London, UK. Details of the microbiological methods including ribotyping and pulsed gel electrophoresis by the clamped homogenous electric field (CHEF) technique, which included the typing of 17 of the 18 patients, have been described previously.[8]

OUTCOME MEASURES

At each hospital attendance the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and body weight were routinely measured and recorded in the notes. Results were expressed as percentage predicted lung function (%FEV_1, %FVC)[16] and percentage ideal body weight (%IBW).[17] Rates of change were expressed as ml/month and kg/month for lung function and weight, respectively. The number of outpatient visits over the 30 month period was expressed as attendances per six months and the number of hospital inpatient days for treatment of pulmonary exacerbations was expressed as the number of days per six months. The dates of transplantation or death were noted.

STATISTICAL ANALYSIS

The clinical data were considered to be normally distributed and were analysed between groups with the Student's *t* test and before and after colonisation with the paired *t* test. Variations between the group trends were analysed with interaction plots. Comparison of proportional outcomes was with the χ^2 test (Yates' correction).

Results

MATCHING OF CASES AND CONTROLS

There were 16 patients (nine men) in each group with similar cystic fibrosis genotypes and sputum microbiology (table 1). No significant differences were found between the two groups in age, lung function (%FEV_1, %FVC) or body weight (table 2), nor were there any differences in the rate of decline of FEV_1, FVC, or body weight, or the number of outpatient visits or inpatient days per six months in the two years prior to the colonisation date (table 3).

CHANGES AFTER COLONISATION

Lung function (table 2)

After the colonisation date both FEV_1 ($p<0·05$) and FVC (p = NS) were increased in the control group while in the *B cepacia* group lung function was reduced (FVC, $p<0·05$; FEV_1, p = NS). Since case numbers were small with large variability in lung function both within and between patients, standard deviations were large and significant trends may have been masked. Analysis of variance between pairs within the groups over the whole study to produce an interaction plot revealed significant differences in the trends with loss of both FVC ($p<0·01$) and FEV_1 ($p=0·02$) in the *B cepacia* group compared with small increases in lung function in the controls.

Body weight (table 2)

Despite attempted matching, the control group was significantly heavier than the *B cepacia* group. Both groups gained weight before the colonisation date and began to lose it thereafter. Although the *B cepacia* group gained less and went on to lose weight more rapidly, no significant difference in the rates or trends were revealed by the interaction plot, both groups showing a small loss over the study.

Outpatient attendances and inpatient days (table 3)

Following the colonisation date the number of outpatient visits rose in both groups, but significantly so only in the *B cepacia* group ($p<0·01$). The number of inpatient days rose sharply in the *B cepacia* group ($p<0·001$), with no change in the control group.

Table 4 Outcome following colonisation as at December 1994 (survival in months)

	Colonised patients			*Controls*		
	No.	*%*	*Mean (range)*	*No.*	*%*	*Mean (range)*
All patients	18*			16		
Alive	7	39%	56 (35–91)	11	69%	42 (12–89)
Dead	11*	61%	10 (1–33)	5	31%	33 (-5–76)
Transplanted	7† (4 died)	39%	22 (1–40)	2 (1 died)	12%	26 (22–30)

* Including two patients on whom serial data were incomplete.
† One patient with incomplete data was transplanted and died after two weeks.

Outcomes (table 4)
Of the 18 patients colonised with *B cepacia*, seven have been transplanted at a mean of 22 (range 0·5–40) months after colonisation. Three died within a month of surgery due to *B cepacia* septicaemia, three remain alive at 59 (41–87) months after transplantation, and the seventh died after eight months from an unrelated cause. Of the 11 not transplanted, four are alive at 37 (35–39) months and seven died at 13 (2–33) months, all from overwhelming *B cepacia* infection. Two patients succumbed whilst on full ventilation awaiting transplantation. Of the controls, two have been transplanted at 22 and 30 months. One died at 13 months, the other is alive at 12 months. Ten patients are alive at 44 (29–89) months *without transplantation* and four have died 33 (–5–76) months after colonisation.

Due to the small numbers involved, a comparison of the proportions of deaths and transplanted patients between groups was not statistically significant; however, 61% of patients colonised with *B cepacia* have died compared with 31% of controls and 39% of colonised patients have required transplantation compared with 12·5% of controls.

Since the end of the study three further patients have been identified as having *B cepacia*, the last in January 1994; none have been transplanted, two are alive at eight and 21 months after colonisation, but one who had been in the control group acquired *B cepacia* and died within five months of colonisation.

Discussion

The impact of *B cepacia* colonisation on patients with cystic fibrosis has been similar in Canada,[6] the USA,[18] and the UK[8] and has already been described. The policy of segregation has been reported for *P aeruginosa* and is believed to have limited the spread of an epidemic multiresistant strain in one clinic.[19] Segregation of patients colonised with *B cepacia* has been advocated since 1986.[20]

In 1987 one of 52 patients in our adult cystic fibrosis clinic became colonised. In total 21 of 192 patients were affected up to December 1994. In-hospital segregation was initiated in 1988 but increasing incidence led to the recommendation of social segregation in 1991. Thereafter the incidence fell and a peak prevalence of 12 live patients among 143 (8·4%) was reached in 1993; numbers have since fallen to six in 152 following loss through death or transplantation.

Our experience shows that, of 21 patients, five died and two were transplanted within six months. Three died between 18 months and three years and five were transplanted in the same period. Of the seven transplanted patients three died of overwhelming *B cepacia* septicaemia within a month of surgery, in keeping with experience elsewhere of mortality rates up to 50% within the first postoperative month.[21] Six remain reasonably well over periods of five months to three years following colonisation.

Why *B cepacia* colonisation should apparently cause profound deterioration in some patients whilst others remain clinically unaffected has not been explained, hence the suggestion that *B cepacia* colonisation follows deterioration due to other causes. Having matched cases and controls as closely as possible and allowing for the slight difference in body weight, our experience suggests that those patients who go on to develop *B cepacia* colonisation are no different from controls with respect to age, sex, genotype, microbiology, or severity measured directly by lung function, or indirectly by assessing inpatient days or outpatient visits.

Within the 24 months prior to colonisation there was no evidence of early deterioration since the rates of change in lung function, weight, outpatient visits, and inpatient days were similar in each group. Separate analysis of each six month period also failed to show any difference in absolute values or trends for FEV_1, FVC, body weight, or outpatient visits prior to the colonisation date.

It is of interest that the mean $\%FEV_1$ and %FVC of the control group improved over the period of study in seven of the 16 patients; this may be accounted for by an improvement in the lung function in patients who have recently arrived in the adult clinic after institution of optimum respiratory care. This improvement is not seen in all patients and is eventually followed by the expected gradual decline.

The small rise in the number of inpatient days in the six months prior to colonisation in the *B cepacia* group is unexplained. It is unlikely that the organism was acquired in hospital since segregation was instituted early. A possible explanation is seen in a report that *B cepacia* identified at different clinics and ribotypically distinct from other local cases was cultured from two patients and found to be indistinguishable by ribotyping from an index case with whom they had had contact at a summer camp 12 and 24 months before their first positive cultures.[22] This suggests the possibility of inapparent transmission of the organism which may remain undetected until months later.

Most patients harbour individual "wild" strains of *B cepacia*; however, ribotyping techniques have identified strains in a number of UK centres which are indistinguishable, thus suggesting passage between clinics. This "epidemic" strain may be more transmissable and perhaps more virulent than the "wild" strains (T Pitt, Central Public Health Laboratory, personal communication). We compared 10 patients colonised with the "epidemic" strain and four with "wild" strains (four not available for ribotyping[8]). Seven of the 10 with the "epi-

demic" strain died as did three of the four with the "wild" strains. Four patients with the "epidemic" strain were transplanted; three died within a month, the fourth some months later due to an unrelated cause. None of the "wild" strains required transplantation.

Whilst it is not clear from our small number of patients whether there is an increased morbidity and mortality in those with the "epidemic" *B cepacia* strain, it is interesting to note that the three patients colonised and transplanted before the policy of segregation was instituted and before identification of the "epidemic" strain was possible have done remarkably well and are alive at 4·2–8·25 years after transplantation. They acquired their *B cepacia* a minimum of 18 months before the first isolation of the epidemic strain. The fourth patient acquired *B cepacia* 11 months before the first epidemic isolate and died five months later.

No factors were found to account for the increased rate of decline in lung function or the increased reliance on inpatient and outpatient services by the cases other than that they had become colonised with *B cepacia*. This study suggests that the increased morbidity and mortality after colonisation by *B cepacia* are directly due to the acquisition of this organism rather than to the opportunistic colonisation of patients who are already in decline.

Since transmission of *B cepacia* appears to occur from person to person, we believe our policy of in-hospital and recommended social segregation to be necessary to limit the spread, even though this has been difficult for patients, relatives, and staff. We are fortunate to have passed the peak of the epidemic but believe that we must continue to provide separate facilities at our centre and to give sympathetic advice and support when problems arise.

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