While colonisation with *Burkholderia cepacia* in cystic fibrosis (CF) may carry a poor prognosis, different strains can vary in their pathogenicity. Previous studies have found it impossible to predict the outcome of such colonisation for individual patients, either because these studies had very few patients, or were short term, or failed to type the *B cepacia* strains.

In the UK one such important strain is epidemic ET12, an aggressive multiresistant form of *B cepacia* that is easily transmitted between CF patients, which falls into Genomovar III and is present in up to 50% of UK CF centres. In Liverpool 37 patients with CF colonised by this epidemic strain have attended the regional adult unit since its inception in 1993. We have followed the course of this cohort, providing us with a unique opportunity to assess the long term effect of colonisation with a single *B cepacia* strain on infected patients. We have compared the clinical progress of this group with that of the remaining CF patients in the clinic.

**METHODS**

**Data collection**

By December 1997 107 patients had attended the Liverpool adult CF clinic since its inception in 1993. All these patients formed the study population. Over this 5 year period data for age, sex, pulmonary function, body weight, and sputum microbiology were regularly recorded. For spirometric data, the best value was taken for each patient for every 6 month period, and for assessment of nutritional state, the best body mass index (BMI) for each patient was calculated for each calendar year. Where patients had attended the Liverpool adult clinic for less than this 5 year period, information was obtained by retrospective review of the case sheets from the referring hospital. Where patients had died, information was obtained for 5 years prior to death. Thus, complete data were available for all patients for the 5 year period up to December 1997 or death. For surviving patients the baseline data were those obtained in 1993 and final data were those in December 1997. For deceased patients the baseline data were those obtained immediately before death.

**Patients**

Thirty seven patients (35%) were colonised by UK epidemic (ET12) *B cepacia* (mean age 25.2 years (range 18–38), 20 men), 58 patients (54%) were colonised with *Pseudomonas aeruginosa* (mean age 27.8 years (range 17–43), 25 men), and 12 patients (11%) were not colonised either by ET12 *B cepacia* or *P aeruginosa* (mean age 22.4 years (range 18–27); five men). There was no difference between groups in age (*B cepacia* colonised mean
The mean rate of change in FEV1 in that subject over the 5 years preceding death or 1997 was constructed. Potential risk factors for death (table 2) but, given the significant univariate effect of age, this variable was included in the model to adjust risk factors for age. The relative risk of mortality from *B cepacia* colonisation was 4.0 (95% CI 1.6 to 11.2) compared with non-colonised patients.

In the survivor group we compared the effect of *B cepacia* colonisation on FEV1 over the 5 year study period (fig 1). No difference was seen in spirometric parameters between patients colonised with *B cepacia* and the remainder in 1993. Those patients colonised with *B cepacia* had an accelerated loss of lung function with time (\(-1.9 (0.7)\% \text{ predicted FEV1/year}\)) compared with the remaining patients (\(-0.3 (0.4)\% \text{ predicted/year}\); \(p<0.05\)).

In the deceased group the effect of colonisation with *B cepacia* on spirometric data over the 5 year period before death was studied (fig 2). At baseline *B cepacia* colonised patients had a significantly higher FEV1, than the remaining patients (mean 53.3\% predicted \(v\) 34.6\% predicted, \(p=0.007\)). However, while both subgroups had worsening pulmonary function with time the remaining 70 patients (9%) (four men) died during the study period, all of whom were colonised by *P aeruginosa*. Univariate predictors of mortality included age at 1993 and baseline FEV1, with a trend towards nutritional status (table 1). Following the time varying covariate Cox proportional hazards analysis, only a lower FEV1, and colonisation with *B cepacia* were identified as significant factors for death (table 2) but, given the significant univariate effect of age, this variable was included in the model to adjust risk factors for age. The relative risk of mortality from *B cepacia* colonisation was 4.0 (95% CI 1.6 to 11.2) compared with non-colonised patients.

### Table 1

Demographic characteristics of the study group stratified by death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n=88)</th>
<th>Dead (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonised with <em>B cepacia</em> in 1993 (%)</td>
<td>22 (19)</td>
<td>39 (7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Colonised with <em>B cepacia</em> (%)</td>
<td>28 (24)</td>
<td>68 (13)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean (SE) age in 1993</td>
<td>19.6 (0.6)</td>
<td>23.8 (1.4)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sex (male, [n])</td>
<td>53 (46)</td>
<td>47 (9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean (SE) baseline FEV1 in 1993 (%)</td>
<td>68.6 (2.5)</td>
<td>43.2 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SE) baseline BMI in 1993 (%)</td>
<td>20.6 (0.3)</td>
<td>19.5 (0.5)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in 1 second; BMI = body mass index.

### Table 2

Time varying Cox proportional hazards analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (decreasing) per unit % predicted change</td>
<td>1.10</td>
<td>1.06 to 1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colonisation (present in 1993 or acquired)</td>
<td>7.92</td>
<td>2.65 to 23.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years) in 1993 (covariate)</td>
<td>1.08</td>
<td>0.99 to 1.18</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### RESULTS

Thirteen of 37 patients (35%) (five men) colonised by UK epidemic ET12 *B cepacia* died during the study period, and six of the remaining 70 patients (9%) (four men) died during the study period, all of whom were colonised by *P aeruginosa*. Univariate predictors of mortality included age at 1993 and baseline FEV1, with a trend towards nutritional status (table 1). Following the time varying covariate Cox proportional hazards analysis, only a lower FEV1, and colonisation with *B cepacia* were identified as significant factors for death (table 2) but, given the significant univariate effect of age, this variable was included in the model to adjust risk factors for age. The relative risk of mortality from *B cepacia* colonisation was 4.0 (95% CI 1.6 to 11.2) compared with non-colonised patients.

In the survivor group we compared the effect of *B cepacia* colonisation on FEV1 over the 5 year study period (fig 1). No difference was seen in spirometric parameters between patients colonised with *B cepacia* and the remainder in 1993. Those patients colonised with *B cepacia* had an accelerated loss of lung function with time (\(-1.9 (0.7)\% \text{ predicted FEV1/year}\)) compared with the remaining patients (\(-0.3 (0.4)\% \text{ predicted/year}\); \(p<0.05\)) over the 5 year study period.

In the deceased group the effect of colonisation with *B cepacia* on spirometric data over the 5 year period before death was studied (fig 2). At baseline *B cepacia* colonised patients had a significantly higher FEV1, than the remaining patients (mean 53.3\% predicted \(v\) 34.6\% predicted, \(p=0.007\)). However, while both subgroups had worsening pulmonary function with time.

![Figure 1](http://www.thoraxjnl.com)

Figure 1 Subgroup FEV1 data for surviving patients from 1993 to 1997 showing that *B cepacia* colonised patients lose lung function at an accelerated rate (\(-1.9\% \text{ predicted/year}\)) compared with non-colonised patients (\(-0.3\% \text{ predicted/year}\); \(p<0.05\)). *Psa* = *Pseudomonas aeruginosa*; *Bc* = *Burkholderia cepacia*.
Figure 2. Subgroup FEV1 data for deceased patients for 5 years prior to death showing that B cepacia colonised patients had better lung function 5 years before death than the non-colonised patients but had a greater loss over time (−6.2% predicted per year versus −1.9% predicted per year; p<0.05). Ps = Pseudomonas aeruginosa; Bc = Burkholderia cepacia.

(p<0.01), the patients colonised with B cepacia had a greater rate of decline in spirometric data (−6.2 (1.3)% predicted FEV1/year) than those not colonised with B cepacia (−1.9 (1.0)% predicted FEV1/year; p<0.05) such that, at death, both subgroups had similar lung function.

DISCUSSION

There has been a marked improvement in survival in CF and over 80% of patients now survive childhood. Indeed, it is estimated that those patients born in 1990 can expect to live until at least 40 years of age, and the median survival is already 31 years. While there is little doubt that patients cared for in specialist centres receive optimum care, 95% of patients still die from respiratory failure caused by chronic pulmonary sepsis, usually due to Pseudomonas aeruginosa.

Previous workers have shown that increasing bacterial lung colonisation in CF is associated with increasing morbidity and mortality, and for this reason intensive antibiotic treatment regimes are advocated. While in some paediatric CF centres B. aeruginosa colonisation rates are low, adult colonisation rates are still over 60%. More recently an aggressive new multiresistant respiratory pathogen in the form of B cepacia has appeared in the CF population. This was first described as an opportunistic organism in CF in 1972, and its prevalence increased in North America following this. Epidemic B cepacia strains which can be easily transmitted between CF patients were first described in the USA in 1984, and by 1989 such a strain (ET12) had entered the UK CF population. We have recently shown that this strain is capable of cross-colonising CF patients already infected with B cepacia, often with fatal consequences, and can also colonise non-CF relatives causing serious morbidity. In 1993 this epidemic strain was present in up to 50% of CF centres in the UK, although in many centres only a few patients were infected. Since then the introduction of strict segregation policies and the deaths of colonised patients have decreased the prevalence of this organism, and recent epidemiological surveys have revealed that 3.2% of American, 5% of European, and 6% of UK patients with CF are colonised with B cepacia. Despite this, in our centre we still have a prevalence rate of 35%, although we have had no new cases for 3 years.

Colonisation with B cepacia can have several clinical outcomes, varying from relatively asymptomatic carriage to a rapid fulminant pneumonia and death. While it is recognised that colonisation with B cepacia is a poor prognostic indicator in CF, previous studies have given a confused picture of the consequences of such colonisation for individual patients. For example, while some workers have suggested that patients with poorer lung function are more likely to be colonised with B cepacia, others have suggested the reverse. While it is generally accepted that the level of lung function before acquisition undergoes a greater decline following colonisation, furthermore, other workers have suggested that B cepacia colonisation has much less impact on patients if they survive the first year of colonisation.

These conflicting results may be due to the fact that most previous studies were short term or contained few patients. Furthermore, it is now known that different strains of B cepacia vary not only in their transmissibility but also in their pathogenicity. Previous studies almost certainly lacked these factors and the different strains of B cepacia are more difficult to define since reliable strain typing has only recently become available. Thus, predicting the outcome of B cepacia colonisation in the CF population has not previously been possible.

For the first time, therefore, we have been able to assess the effect of a single epidemic B cepacia strain on the clinical course of a substantial group of CF patients over a prolonged time period. We did not attempt to ascertain the date of first B cepacia colonisation of our patients for two reasons. Firstly, most of these patients were already colonised when they first came to our unit, and it may not be possible to determine colonisation status reliably prior to this. In the early 1990s many laboratories were unaware that this organism was a potential pathogen and routine culture for B cepacia was not available in many hospitals. Furthermore, reliable B cepacia culture requires expertise and inexperienced microbiology laboratories may misreport samples. Indeed, a recent survey of US CF centres found that 20% of samples labelled as B cepacia were, in fact, other organisms. Thus, in our patients a positive B cepacia culture at first attendance at our unit in 1993 is unlikely to represent the date of colonisation. Secondly, it has been shown that patients may be colonised with B cepacia for a variable length of time before the organism can be reliably grown from sputum, such that the date of acquisition even where B cepacia is suspected is impossible to determine. However, since the Liverpool adult CF unit opened in 1993, we have assiduously looked for B cepacia in the sputum of our patients and genotyped every strain, demonstrating that since this time their colonisation status is assured.

While on univariate analysis it appears that age and possibly nutritional status may be important factors determining mortality, when subjected to time related multivariate analysis the contribution of these factors as predictors of death was subsumed. In our patients this technique confirmed that a time related deterioration in lung function together with colonisation with epidemic B cepacia are the only independent predictors of death. By looking back at these factors for 5 years in our patients who subsequently died, we have shown that, although B cepacia colonised patients had much higher baseline spirometric values than non-colonised patients, their FEV1 was still much lower than either group of survivors at 1993. This suggests that the level of pulmonary function at B cepacia acquisition may be an important predictor of survival in patients with CF. Furthermore, these patients had a greatly accelerated loss of lung function over the 5 year period, confirming the pathogenicity of this organism. The apparent wide variation in clinical outcome that occurs in response to colonisation with B cepacia remains unclear, but possible explanations include host immunological response or interaction with other colonising organisms.

As expected, the non-colonised patients who died appear to have had long standing poor pulmonary function with a mean FEV1 of less than 40% predicted. It has always been assumed that even patients with CF who are well cared for would have a steady decline in lung function, and it is therefore reassuring to find that, with modern treatment, stable adult patients can be maintained with minimal loss of lung function.

While it has been suggested that nutrition plays an important part in maintaining the health of patients with CF, there...
is little evidence that weight gain diminishes the number of respiratory exacerbations or improves spirometric parameters or survival. In keeping with this, univariate analysis showed that BMI had only a weak correlation with survival. This suggests that the most important factor indicating survival in CF patients is lung function, and that nutritional state merely reflects this.

Thus, in our clinic most non-

B cepacia colonised patients remain stable with little deterioration in pulmonary function and a constant nutritional status. Only six of these patients died during the study period compared with 13 in the epidemic B cepacia group, giving a fourfold excess risk of mortality from ET12 B cepacia colonisation. Conversely, while our results show the risks associated with epidemic (ET12) B cepacia colonisation, the effect of colonisation by non-epidemic B cepacia strains is unknown. Several European studies have suggested that B cepacia colonisation is of less importance, possibly because these patients were largely colonised by other (non-ET12) B cepacia strains which may be less harmful.

Our results illustrate the threat posed to patients with CF from epidemic ET 12 B cepacia and confirm the need to segregate these patients from the remainder of the CF population.

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