BRONCHIECTASIS

Longitudinal pulmonary function of childhood bronchiectasis and comparison with cystic fibrosis

J Twiss, A W Stewart, C A Byrnes


Background: Little has been published on the progression of non-cystic fibrosis bronchiectasis (BX), especially in childhood. Data are needed for prognosis and evaluation of the effectiveness of treatments. A study was undertaken to evaluate the change in lung function over time in children with BX, and to consider covariates and compare them with the local cystic fibrosis (CF) population.

Methods: Children with BX or CF and ≥3 calendar years of lung function data were identified from hospital clinics. Diagnosis was made by high resolution CT scans, sweat tests, and genetic studies. Lung function performed on a single plethysmograph between 6 and 15 years of age and ≥6 weeks after diagnosis was analysed longitudinally (linear mixed model). The impact of reference equation and “best annual” versus “all data” approaches were evaluated.

Results: There were 44 children in each of the BX and CF groups with an overall mean 5.7 calendar years follow up data. The estimated forced expiratory volume in 1 second (FEV1) in the BX group had an intercept of 68% predicted (Polgar) at 10 years of age which fell at a rate of 1.9% per annum using “best annual” data compared with 63% and 0.9% using “all data”. Those with post-infectious BX or chronic Haemophilus influenzae infection had more severe disease. In CF the FEV1 (“best annual”) intercept was 85% predicted with a slope of −2.9% per annum. The choice of reference equation affected the magnitude of the result but not the conclusions.

Conclusion: Children with BX have significant airway obstruction which deteriorates over time, regardless of analysis strategy or reference. Effective interventions are needed to prevent significant morbidity and adult mortality.

Knowledge of disease severity and progression is critical for clinicians, researchers, patients, and families. Bronchiectasis (BX), a chronic suppurative airway disease, causes significant morbidity and mortality. While often described as progressive, there has been little published to define or substantiate this and available evidence is in disagreement.1–4 Pulmonary function measurements are one way of defining lung disease severity and progression. They are non-invasive, safe, and reproducible. Forced expiratory volume in 1 second (FEV1) has been found to correlate with radiology and quality of life in those with BX.5–7 Obstructive lung disease in childhood BX has been described in case series but few have examined disease progression.8–12 Childhood cross sectional series have reported mean/median FEV1 values of 68–77% predicted.11–12 Karadag et al10 recently reported an overall improvement in lung function in 92 children and young adults from presentation to follow up at an estimated mean 4.7 years later (mean increase in FEV1 of 11% predicted). Sheehan et al11 reported a mean fall in FEV1 of 3.8% in adult patients relative to baseline over a variable interval of 6–74 months. Evans et al12 reported a decline in FEV1 of 3.0% per annum, but only in those chronically infected with Pseudomonas aeruginosa. Cherniak et al13 again in adult patients, reported a mean decline of 1.4% per annum over a mean period of just over 4 years. The decline in lung function correlated with the number of lower respiratory exacerbations. Studying disease progression in children is important as it is believed that a substantial proportion of the lifetime incidence of BX occurs in childhood and, given that BX is irreversible, early intervention is needed to minimise long term morbidity and mortality.13 The high incidence of BX recently reported in children in New Zealand and a number of international communities heightens the need for better understanding of this condition.14–16

This study aimed to determine whether, and at what rate, the lung function of children with established BX deteriorates. Recognising that methodological choices can have a significant impact on the results, we made concurrent analyses with several reference equations and two data selection strategies. In addition, a local peer group with cystic fibrosis (CF) provided a methodological control group, given similarities in lung pathology and its well described progression.

METHODS

Subjects
Children were identified from the Auckland Starship Children’s Hospital BX and CF clinics if they attended between 2000 and 2004. Inclusion criteria were a definitive diagnosis of BX or CF, ability to reliably perform lung function tests, and data in at least three calendar years. Diagnosis required evidence of BX on a high resolution computed tomographic (HRCT) scan or evidence of CF from a sweat test and/or genetic study. Individuals with progressive neuromuscular disease and studies subsequent to a lobectomy were excluded. Demographic data, aetiology of BX, asthma status, microbiological and radiological findings were recorded. Diagnostic HRCT scanning is avoided during acute exacerbations and is often performed after a period of treatment to maximise the quality and predictive value of the scans. The diagnosis is based on the criteria of Naidich.

Abbreviations: BX, bronchiectasis; CF, cystic fibrosis; FEF25–75, forced expiratory flow 25–75%; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity
et al. and HRCT scans are scored using the modified Bhalla scoring system by a single paediatric radiologist (RM) with no clinical data. This score has been validated in adult and paediatric BX with values assigned to each lobe and the lingula as follows: bronchiectasis extent (0–3), bronchial wall dilatation (0–3) and thickness (0–3), presence of mucus in large (0–1) and small airways (0–1), air trapping (0–4), atelectasis (0–1), and consolidation (0–1) resulting in a worst possible score of 102. Post infectious aetiology required a history of significant pneumonia leading to hospital admission with oxygen requirement and/or ventilation. Chronic infection was defined as three or more positive growths within 1 year and more than 1 month apart. A diagnosis of asthma required both a physician diagnosis and an improvement in FEV₁ of at least 12% with bronchodilator relative to baseline.

**Pulmonary function**

Studies performed in children aged 6–15 years and conducted >6 weeks after HRCT diagnosis were reviewed. These included FEV₁ (primary outcome measure), forced vital capacity (FVC), forced expiratory flow 25–75% (FEF₂₅–₇₅), FEV₁/FVC ratio, total lung capacity (TLC), residual volume (RV), and RV/TLC. All studies were performed on a system 6200 Autobox DL Plethysmograph (Sensormedics Corporation, California, USA) by one of three paediatric respiratory technologists according to American Thoracic Society criteria.

**Statistical methods**

Polgar (primary reference), Knudson, Asher, Quanjer, and Wang reference equations were used to produce percentage of predicted values. “Best annual” analysis used each individual’s best result for each calendar year. “All data” analysis used all available data. A random coefficients model was made where the intercept and age at observation are assessed as random effects. Fixed effect variables were sex, ethnicity, infecting organism, and aetiology. SAS PROC MIXED version 8.2 (SAS Institute Inc) was used to obtain estimates and perform hypothesis tests for the mixed models. A nominal level of p = 0.05 was used to indicate statistical significance and 95% confidence intervals (CI) are provided. Gradients are expressed as change in absolute percent significance and 95% confidence intervals (CI) are provided. A nominal level of p = 0.05 was used to indicate statistical significance and 95% confidence intervals (CI) are provided. A nominal level of p = 0.05 was used to indicate statistical significance and 95% confidence intervals (CI) are provided. A nominal level of p = 0.05 was used to indicate statistical significance and 95% confidence intervals (CI) are provided. A nominal level of p = 0.05 was used to indicate statistical significance and 95% confidence intervals (CI) are provided.

**RESULTS**

Two hundred and nine children were identified (147 with BX, 62 with CF) but 121 (103 with BX, 18 with CF) were excluded (45 for being too young or developmentally delayed for reliable lung function and 56 who had <3 calendar years data in the age range too young (n = 18), too old (n = 17), too newly diagnosed (n = 9), insufficient attendance (n = 10), lobectomy (n = 1) or premature death (n = 1)). Finally, two had spinal muscular atrophy or a non-diagnostic HRCT scan. Those who were excluded had been diagnosed more recently (mean difference 2.1 years) and at a younger age (mean difference 1.4 years) than those included in the analysis. They were younger (mean difference 3.5 years) and a greater proportion were male (58%). Their ethnicity and disease aetiology were similar. Those excluded with CF were too young to have any or sufficient data. This left 44 children in each group (table 1).

More than twice as many studies were available in the CF population reflecting longer and more frequent follow up. The mean age at lung function testing (BX 10.7 years, CF 10.1 years) and the proportion of girls (BX 57%, CF 48%) were similar, but those with BX had been diagnosed at a significantly older age (mean 7.6 years v 1 month, p<0.0001), in part due to CF screening at birth. Most children with BX were of Pacific Peoples (57%) or Maori (27%) ethnicity while 91% of those with CF were NZ European. Half of those with BX had an identified cause with 16% attributed to past infection, 14% to primary immunodeficiency, and 14% were oncological disease sequelae (table 1).

Usual BX management included review by paediatric respiratory specialists 3–6 monthly, chest physiotherapy (percussion, active cycle of breathing or with positive end expiratory pressure devices) twice daily which was increased when unwell, and antibiotics only for exacerbations (oral or intravenous). Those with primary immunodeficiency received 3–5 weekly intravenous immunoglobulins and were on regular oral antibiotics for chest, sinus, and ear disease. General health measures such as optimising the social setting and financial support, immunisations, and encouraging exercise are also promoted.

**Lung function**

The “best annual” strategy produced an estimated FEV₁ of 68% predicted Polgar (95% CI 63 to 72) at 10 years of age with a slope of −1.9% (95% CI −0.9 to −2.9) per annum (table 2). FVC was abnormal (79%; 95% CI 74 to 83, p<0.0001) but did not change with time (p = 0.19). The FEF₂₅–₇₅ and FEV₁/FVC ratio both fell significantly with time (−2.6% and −1.1% respectively, both p<0.0001). Assigned aetiology had a significant impact on the intercept (p = 0.02) but not on the slope (p = 0.69). Those with post-infectious...
aetiology had the most severe disease and those with a post-oncological aetiology were the least severe (intercept 51% and 74%, respectively, at age 10). Sex and ethnicity were not statistically significant determinants of disease severity or progression. Asthma predicted a slower decline (−2.7% v −0.6%, p = 0.05, table 3).

In the previous year those with BX had a mean lowest RV of 149% predicted and mean highest TLC of 109% predicted. Longitudinally, the RV/TLC ratio was raised but static at 0.35 (slope −0.001, p = 0.87). Compared with the lung volumes reported by Landau in 1974, a greater proportion of our population had smaller lung volumes (TLC<80%; 8% v 0% and VC<80%; 46% v 14%) and were hyperinflated (RV/TLC>0.3: 47% v 31%).

Alternative lung function analyses
Using all available data, the estimated FEV₁ for BX was 63% predicted (95% CI 58 to 68) at 10 years age with a slope of −0.9% (95% CI −0.1 to −1.6) per annum. Lung function parameters had lower intercepts and less rapid decline using this strategy. Nominal significance was not affected except for the difference in rate of decline with asthma which became non-significant (p = 0.08).

The Knudsen, Asher, Wang and Quanjer reference ranges all produced FEV₁ (“best annual” strategy) intercepts that were abnormal (76%, 72%, 78% and 74% respectively, all p<0.0001) and fell significantly with age (−1.9, −1.3, −1.7, −1.7 respectively, all p<0.001). Repeat analysis with these reference ranges affected the magnitude of sex and ethnicity estimates but not the nominal significance of the results.

Comparison with CF
Using best annual data, the FVC, FEV₁ and FEF₂₅₋₇₅% estimates in children with CF were 93% (95% CI 89 to 98), 85% (95% CI 80 to 89), and 79% (95% CI 82 to 91) predicted Polgar respectively at 10 years of age. The slopes were −1.7% (95% CI −0.8 to −2.6), −2.9% (95% CI −2.0 to −3.8), and −2.5% (95% CI −1.6 to −3.4) per annum, respectively. When all the data were included, the estimates had FVC, FEV₁ and FEF₂₅₋₇₅% intercepts of 86% (95% CI 82 to 91), 77% (95% CI 73 to 81), and 68% (95% CI 61 to 76). The respective slopes were −1.6% (95% CI −0.8 to −2.4), −2.5% (95% CI −1.7 to −3.4), and −1.9% (95% CI −1.1 to −2.7) per annum. All intercepts were significantly higher in children with CF than in those with BX (all p<0.001). The decline in lung function was more rapid in all estimates but was only significantly different in the “all data” analyses of FVC and FEV₁ (both p = 0.02, fig 1).

DISCUSSION
The children in our study with established childhood BX had significant airway obstruction that progressed over time as determined by pulmonary function testing. This is consistent with the current understanding of BX and emphasises the need for effective and early intervention strategies.

The pattern of pulmonary function in BX was similar to that seen in CF, characterised by intrathoracic airway obstruction of the medium to small airways and hyper-inflation indicated by increased RV and reduced FEV₁ and FEF₂₅₋₇₅%. The principal outcome was an FEV₁ estimate of 68% or 63% predicted (Polgar) at 10 years age with a slope of −1.9% or −0.9% per annum depending on the strategy used (“best” or “all data”, respectively). Other measures of obstructive disease (FEF₂₅₋₇₅% and FEV₁/FVC) were also reduced and progressively declined. Lung volume studies indicated that TLC was normal but RV and the RV/TLC ratio were increased. There was wide variability in individual

### Table 2 Lung function estimates for BX (Polgar reference)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Intercept at age 10 (95% CI)</th>
<th>Slope (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best annual (All data)</td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>79% (74 to 83)</td>
<td>−0.7% (−1.7 to +0.3)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>68% (63 to 72)</td>
<td>−2.9% (−2.9 to −0.9)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (% predicted)</td>
<td>61% (53 to 68)</td>
<td>−2.6% (−3.9 to −1.4)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>76% (72 to 82)</td>
<td>−1.5% (−1.5 to −0.7)</td>
</tr>
<tr>
<td></td>
<td>All data</td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>74% (70 to 78)</td>
<td>−0.0% (−1.0 to +1.0)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>68% (63 to 72)</td>
<td>−2.9% (−2.9 to −0.9)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (% predicted)</td>
<td>63% (58 to 68)</td>
<td>−1.6% (−1.6 to −1.1)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>74% (70 to 79)</td>
<td>−1.4% (−1.4 to −0.3)</td>
</tr>
</tbody>
</table>

### Table 3 Univariate subgroup analysis of BX (Polgar reference)

<table>
<thead>
<tr>
<th>Group</th>
<th>% predicted FEV₁ at 10 years intercept (Best annual [All data])</th>
<th>% predicted FEV₁ slope (Best annual [All data])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>73% (68%)</td>
<td>−1.4% (−0.7%)</td>
</tr>
<tr>
<td>Post-infectious</td>
<td>51% (49%)</td>
<td>−0.8% (−0.3%)</td>
</tr>
<tr>
<td>(p&lt;0.0001)*</td>
<td></td>
<td>−2.8% (−1.7%)</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td>64% (58%)</td>
<td>−2.4% (−0.7%)</td>
</tr>
<tr>
<td>Post-oncology</td>
<td>74% (73%)</td>
<td>−2.4% (−0.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>71% (65%)</td>
<td>−1.9% (−0.6%)</td>
</tr>
<tr>
<td>(p = 0.02)</td>
<td></td>
<td>−1.9% (−1.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>63% (60%)</td>
<td>−1.9% (−1.1%)</td>
</tr>
<tr>
<td>(p = 0.31)*</td>
<td></td>
<td>−1.9% (−1.1%)</td>
</tr>
<tr>
<td>Pacific ethnicity</td>
<td>69% (65%)</td>
<td>−0.9% (−1.0%)</td>
</tr>
<tr>
<td>(p = 0.60)</td>
<td></td>
<td>−2.2% (−0.9%)</td>
</tr>
<tr>
<td>M氧asi ethnicity</td>
<td>63% (59%)</td>
<td>−0.9% (−0.0%)</td>
</tr>
<tr>
<td>(p = 0.76)*</td>
<td></td>
<td>−2.2% (−0.9%)</td>
</tr>
<tr>
<td>European ethnicity</td>
<td>68% (61%)</td>
<td>−0.9% (−0.0%)</td>
</tr>
<tr>
<td>No chronic organism</td>
<td>73% (68%)</td>
<td>−2.2% (−2.1)</td>
</tr>
<tr>
<td>(p = 0.02)</td>
<td></td>
<td>−1.3% (−0.6)</td>
</tr>
<tr>
<td>Chronic H influenzae</td>
<td>60% (54%)</td>
<td>−1.3% (−0.6)</td>
</tr>
<tr>
<td>(p = 0.41)*</td>
<td></td>
<td>−1.3% (−0.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>63% (57%)</td>
<td>−0.6% (−0.0)</td>
</tr>
<tr>
<td>(p = 0.16)</td>
<td></td>
<td>−2.7% (−1.4)</td>
</tr>
<tr>
<td>No asthma</td>
<td>70% (66%)</td>
<td>−0.9% (−1.4)</td>
</tr>
<tr>
<td>(p = 0.08)*</td>
<td></td>
<td>−2.7% (−1.4)</td>
</tr>
</tbody>
</table>

*Between group interactions.
inhaled corticosteroids for bronchodilator responsiveness have not (as yet) been found to improve lung function. In due to different management (such as higher inhaled differences (less severe disease), and part may possibly be Turkish population was, however, substantial—part will be following initial treatment by only studying lung function study specifically attempted to exclude the improvement seen aetiologies, severity, and management practices. Ascribed BX aetiology had a significant influence on severity. Post-infectious BX had the worst pulmonary function and oncological sequelae disease the best. We did not detect significant differences in rates of decline between aetiologies although there was a consistent trend for those with primary immunodeficiency to decline faster. We speculate that those with post-infectious BX had an originally severe pulmonary insult with subsequent progression due solely to existing BX, while those with adaptive immunodeficiencies may have greater progression due to persistent underlying vulnerabilities. Chronic Haemophilus influenzae infection was a marker for more severe disease but we did not detect more rapid decline. Ethnic disparity exists in many BX populations including our own with the highest incidence in Pacific peoples; however, we did not detect significant differences in severity or progression.\textsuperscript{3, 13}

The CF group was included because of its well described progressive suppurative lung disease and as a methodological control. Estimates for the CF population showed a decline of 2–3% per annum consistent with other studies and reinforces the validity of our analysis strategy.\textsuperscript{27} Compared with the BX population, those with CF had milder obstruction but lung function appeared to decline more rapidly (only statistically significant with “all data” analysis). Pulmonary function may be worse in those with BX due to a severe initial insult and/or delayed diagnosis. In a previous study of the same community Edwards et al. reported symptom onset at a median age of 1 year but HRCT diagnosis at a median of 8 years. Lack of appropriate early treatment may have contributed to the severity of the disease.

Pulmonary function is one measure of impairment and has been validated against radiology and quality of life.\textsuperscript{3, 5–7} However, comparing individuals or groups over time is complicated in childhood by lung growth, puberty, sex, ethnicity, and the statistical model used. Reference equations based on “healthy” populations have been developed to predict appropriate volumes and flow rates. As these use different data sources and statistical models, they may introduce artifacts that influence estimates. The choice of formula has been found to affect both intercept and slope significantly.\textsuperscript{10–12} Infective exacerbations usually reflect a reversible deterioration and their inclusion may be inappropriate in determining progression. The use of an individual’s best result (“best annual”) is one strategy used to eliminate exacerbation data and may give a better estimate of disease progression. “All data” analysis includes more data (power) and may better reflect “everyday” lung function. There is no one ideal predictor equation or data selection technique for our data, so we made concurrent analyses with several formulae and two data selection strategies. Results that are consistent regardless of methodology are likely to be true findings. Polgar was the primary reference used because of its wide use nationally and internationally, including the Australasian CF registry and previous cross sectional case studies.\textsuperscript{9–11} It is, however, based on a compilation of models from five different studies with relatively few individuals and takes no account of age, ethnicity or sex for FEV\textsubscript{1}. The Asher reference is based on an Auckland population (\textless\textasciitilde14 years of age only) and attempts to account for ethnicity and sex.\textsuperscript{25} It is closest to meeting ATS recommendations for reference choice but is only used in our centre and does not cover the entire age range.\textsuperscript{28} The Knudson formula has wide use in the US, including the CF Foundation.\textsuperscript{22} Quanjer (Western Europe) and Wang (US Six Cities Study) are based on large populations and specifically attempt to account for puberty.\textsuperscript{26, 27} Intercept and slope did vary according to the equation used, but our conclusions are robust to choice of formula. This remained true when analysing the influence of ethnicity and sex. The best annual strategy produced estimates with higher intercepts and more rapid deterioration as has been found in CF studies.\textsuperscript{29} This did not affect our conclusions except that the difference in rate of decline in FEV\textsubscript{1} between BX and CF was only found to be statistically significant in the “all data” analysis.

Longitudinal pulmonary function typically has characteristics which cause problems with traditional statistical methods, including missing and irregularly timed data, informative censoring due to deaths, discharges, and transfers, and correlation between repeated measures, perhaps explaining the more frequent use of cross sectional strategies.\textsuperscript{37} Mixed model analysis overcomes these problems, is particularly suited for analysing continuous correlated

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**Figure 1** Linear mixed model estimates for FEV\textsubscript{1} in children with bronchiectasis (BX, —) and cystic fibrosis (CF, ——) using the Polgar reference. The “best annual” strategy involves using only the highest FEV\textsubscript{1} for each calendar year while the “all data” strategy uses all available data.
outcomes, and provides an estimation and hypothesis testing while simultaneously modelling both population and subject specific effects. It has been used previously in longitudinal pulmonary function studies in patients with CF. Using this technique, longitudinal analysis has greater statistical power and is more robust to model selection. Cross sectional data are subject to cohort bias, are less efficient, and may be less suited to study of disease progression. The main limitations of this study are the relatively small number of individuals and the fact that it is a retrospective review. Environmental factors such as housing and tobacco smoke exposure were not considered. A previous study estimated that 58% of these households had one or more smoker.

The inclusion and exclusion criteria may introduce a bias and potentially a cohort effect. These children had severe extensive disease (based on HRCT scanning) and our results reflect their effect on treatment in one centre rather than the natural history of BX.

We conclude that the pulmonary function of children with BX declines significantly over time, despite treatment. This finding was replicated with all reference equations (Asher, Knudson, Polgar, Quanjer, or Wang) and analysis methods ("all data" or "best annual") used. Aetiology had a significant impact on severity which may indicate an opportunity to target screening and treatments. The abnormality seen show a similar pattern to CF with evidence of intrathoracic airway obstruction and hyperinflation. Children with CF had less severe lung function but this may decline more rapidly. Overall, we found that most children with BX will finish lung growth and enter adulthood with significant obstructive lung disease giving rise to the high morbidity and mortality associated with this condition in young NZ adults. BX warrants greater attention with a focus on prevention and better interventions. If adult morbidity and mortality is to be moderated, this intervention needs to occur in childhood.

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