Longitudinal pulmonary function of childhood bronchiectasis and comparison with cystic fibrosis

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Title Page.

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Longitudinal pulmonary function of childhood bronchiectasis and comparison with cystic fibrosis.

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Abstract:

Rational: Little has been published on the progression of non cystic fibrosis bronchiectasis (BX), especially in childhood. Data is necessary for prognosis and evaluation of the effectiveness of therapies.
Objectives: To evaluate the change in lung function over time in children with BX, consider covariates and compare them with the local cystic fibrosis (CF) population.
Methods: Children with BX or CF and ≥ three calendar years of lung function data were identified from hospital clinics. Diagnosis was made by high resolution computer tomography, sweat test 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.
Main results: The BX and CF groups each had 44 children with an overall mean 5.7 calendar years data. The FEV1 estimate in BX had an intercept of 68% predicted (Polgar) at ten years of age and fell at 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 and slope of -2.9% per annum. Reference equation choice affected result magnitude but not conclusions.
Conclusion: These children with BX had significant airway obstruction which deteriorated over time regardless of analysis strategy or reference. Effective interventions are needed to prevent significant morbidity and adult mortality.

INTRODUCTION:

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 disagrees.[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 one second (FEV1) has been found to correlate with radiology and quality of life in those with BX.[2,5-7] Case series describe obstructive lung disease in childhood BX but few examine progression.[8-12] Childhood cross sectional series have reported mean / median FEV1's of 68-77% predicted.[11,13,14] Karadag et al 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 11% increase in percent predicted FEV1).[3] Sheehan et al described a mean FEV1 fall of 3.8% in adult patients relative to baseline over a variable interval of 6 – 74 months.[15] Evans et al reported decline of 3.0% per annum but only in those chronically infected with pseudomonas aeruginosa.[1] Cherniak et al, again in adult patients, reported a mean decline of 1.4% per annum over mean period of just over 4 years.[4] Decline correlated with the number of lower respiratory exacerbations. Studying childhood progression is important as it is believed that a substantial proportion of the lifetime incidence of BX occurs in childhood and, given BX is irreversible, early intervention is needed to minimize long term morbidity and mortality.[16] The high incidence of BX recently reported in NZ children and a number of international communities heightens the need for better understanding of this condition.[13,17-19]

This study aims to determine whether, and at what rate, the lung function of children with established BX deteriorates. Recognizing that methodological choices can have significant impact on results, we made concurrent analyses with a variety of 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; definitive diagnosis of BX or CF, ability to reliably perform lung function testing; with data in at least three calendar years. Diagnosis required evidence of BX on high resolution computer tomogram (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. Demographics, aetiology of BX, asthma status, microbiology and radiology were recorded. Diagnostic HRCT is avoided during acute exacerbations and are often performed after a period of therapy to maximize the quality and predictive value of scans. Diagnosis is based on the criteria of Naidich et al[20] and HRCTs are scored using the modified Bhalla by a single paediatric radiologist (RM) with no clinical data.[6,21,22] This score has been validated in adult and paediatric bronchiectasis and assigns a value 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.[6,21] Post infectious aetiology required a history of significant pneumonia requiring hospital admission with oxygen requirement and/or ventilation. Chronic infection was defined as 3 or more positive growths within one year and more than 1 month apart. Asthma designation required both physician diagnosis and an improvement in FEV1 of at least 12% with bronchodilator relative to baseline.[23]

Pulmonary function:

Studies performed between age 6 and 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% (FEF_{25-75}), FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV) and RV/TLC. All studies were done on a system 6200 Autobox DL Plethysmograph (Sensormedics Corporation, California, USA) by one of three paediatric respiratory technologists according to American Thoracic Society criteria.[24]

Statistical methods:
Polgar (primary reference), Knudson, Asher, Quanjer and Wang reference equations were used to produce percentage of predicted values.[25-28] 'Annual best' 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 gender, 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 predicted. The regional ethical committee determined ethical approval was not required as the data collection was made by regular clinician, retrospectively, anonymously and was not additional to normally collected clinical data.

RESULTS:
Two hundred and nine children were identified (147 with BX, 62 with CF) however 121 were excluded (103 with BX, 18 with CF). Forty five children with BX were excluded for being too young or developmentally delayed for reliable lung function. A further 56 had < 3 calendar years data in the age range: too young (18), too old (17), too newly diagnosed (9), insufficient attendance (10), lobectomy (1) or premature death (1). Finally 2 had spinal muscular atrophy or a non-diagnostic HRCT. Those excluded had been diagnosed more recently (mean difference 2.1 years) and at a younger age (mean difference 1.4 years). They were younger (means 3.5 years difference) and a greater proportion were male (58%). Ethnicity and aetiology were similar. Those excluded with CF were too young to have any or sufficient data. This left 44 children in each group, described in table 1.

		Bronchiectasis	Cystic Fibrosis
Number of individuals		44	44
Spirometry studies, (median per individual)		931 (15)	2066 (45)
Mean Calendar years of data		4.7 years	6.7 years
Lung volume studies, (median per individual)		368 (7)	621 (13)
Mean age at testing (all studies)		10.7 years (5-15)	10.1years (5-15)
Gender: % female		57%	48%
Ethnicity: n(%)	Maori	12 (27%)	2 (5%)
	European	7 (16%)	40 (91%)
	Pacific Peoples	25 (57%)	0 (0%)
	Other	0 (0%)	2 (5%)
BX Aetiology	Unknown	22 (50%)	
	Post Infectious	7 (16%); 6 due adenovirus, 1 to *B. pertussis*	
	Primary Immunodeficiency	6 (14%); 5 humoral, 1 combined deficiencies	
	'Post Oncology Disease/Rx'	6 (14%; 4 leukaemia (2 BMT), 2 lymphoma.	
	Other	3 (7%)	
Asthma diagnosis		17 (39%)	5 (11%)***
B2 Agonist response >12%*,[23]		21 (48%)	31 (70%)
Median CT score (range)		24 (4-65)	
Laterality of disease		89% bilateral	
Median diseased lobes		4 (5% unilobular)	
Chronic *Haemophilus Influenza* infection**,[29]		18 (41%)	
Chronic Pseudomonas infection		0 (0%)	24 (55%)
Median age at diagnosis (initiation of specific therapy)		7.5 years	1 month

Table 1: Study group characteristics: BMT = bone marrow transplant, * ≥1 occasion over study period, ** non typeable, ≥3 positive cultures in 1 year, *** NB 25 (59%) of those with CF were prescribed inhaled corticosteroids.

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 proportion female (BX 57%, CF 48%) were similar, however those with BX had been diagnosed at a significantly older age (mean 7.6 year vs 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% 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, increased when unwell, and antibiotics only for exacerbations (oral or intravenous).[18,30] 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 optimizing the social setting and financial supports, immunizations and encouraging exercise are also promoted.

Lung function*:*
The 'best annual' strategy produced an FEV1 estimate of 68% (CI 63-72%) predicted Polgar at ten years of age, with a slope of -1.9% (CI –0.9 to –2.9%) per annum, (Table 2). FVC was abnormal (79%; CI 74-83%, p<0.0001) but did not change with time (p=0.19). The FEF_{25-75} 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 intercept (p=0.02) but not slope (p=0.69). Those of post-infectious aetiology had the most severe disease and post oncological the least (age ten intercept: 51% and 74% respectively). Gender and ethnicity were not statistically significant determinants of severity or progression. Asthma status predicted slower decline (-2.7 versus –0.6%, p=0.05), (Table 3.)

	Strategy	Intercept at age ten (95% CI)	Slope (95% CI)
FVC (% predicted)	Best annual	79% (74-83)	-0.7% (-1.7 to +0.3)
	All data	74% (70-78)	-0.0% (-1.0 to +1.0)
FEV1 (%predicted)	Best annual	68% (63-72)	-1.9% (-2.9 to –0.9)
	All data	63% (58-68)	-0.9% (-1.6 to –0.1)
FEF25-75 (% predicted)	Best annual	61% (53-68)	-2.6% (-3.9 to –1.4)
	All data	52% (45-59)	-1.1% (-2.1 to 0.0)
FEV1/FVC ratio	Best annual	79% (76-82)	-1.1% (-1.5 to –0.7)
	All data	76% (74-79)	-0.9% (-1.4 to –0.3)

Table 2: Lung function estimates for BX (Polgar reference).

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 elevated 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% versus 0% and VC<80%: 46% versus 14%) and were hyper-inflated (RV/TLC>0.3: 47% versus 31%).

Group	% predicted FEV1 10y intercept: Annual best (All data)		% predicted FEV1 Slope: Annual best (All Data)	
Unknown	73% (68%)		-1.4% (-0.7%)	
	p=0.02 (p<0.0001)*			
Post Infectious	51% (49%)		-0.8% (-0.3%)	
				p=0.69 (p=0.18)*
1° immunodeficency	64% (58%)		-2.8% (-1.7%)	
Post Oncology	74% (73%)		-2.4% (+0.7%)	
Female	71% (65%)		-1.9% (-0.6%)	
		p=0.18 (p=0.31)*		p=0.96 (p=0.51)*
Male	63% (60%)		-1.9% (-1.1%)	
Pacific Ethnicity	69% (65%)		-0.9% (-1.0%)	
Maori Ethnicity	63% (59%)	p=0.60 (p=0.76)*	-2.2% (-0.9%)	p=0.45(p=0.70)*
European ethnicity	68% (61%)		-0.9% (-0.0%)	
No chronic organism	73% (68%)		-2.2% (-2.1)	
		p=0.02 (p=0.01)*		p=0.41 (p=0.41)*
Chronic *H.influenzae*	60% (54%)		-1.3% (-0.6)	
Asthma	63% (57%)		-0.6% (-0.0)	
		p=0.16 (p=0.08)*		p=0.05 (p=0.08)*
No Asthma	70% (66%)		-2.7% (-1.4)	

Table 3: Univariate subgroup analysis of BX (Polgar) * between group interactions

Alternative lung function analyses*:*
Using all available data produced an FEV1 estimate for BX of 63% (CI 58-68%) predicted at ten years age and slope of –0.9% (-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 Knudson, 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). Re-analysis with these reference ranges affected the magnitude of gender and ethnicity estimates but not the nominal significance of results.

Comparison with CF*:*
In those with CF, using best annual data, the FVC, FEV1 and $FEF_{25-75\%}$ estimates were 93% (CI 89-98), 85% (CI 80-89) and 79 (CI 82-91) predicted Polgar at ten years of age respectively. The slopes were of –1.7% (CI –0.8 to –2.6), -2.9% (CI –2.0 to –3.8) and –2.5% (CI -1.6 to –3.4) per annum respectively.
When all data was included the estimates had FVC, FEV1 and $FEF_{25-75\%}$ intercepts of 86% (CI 82-91), 77% (CI 73-81) and 68% (61-76). The respective slopes were –1.6% (CI -0.8 to –2.4), –2.5% (CI –1.7 to –3.4) and –1.9% (CI-1.1 to –2.7) per annum. All intercepts were significantly higher in CF than those for BX (all p<0.001). Decline was more rapid in all estimates but only statistically significantly different in the 'all data' analyses of FVC and FEV1 (both p=0.02), (Figure 1.)

DISCUSSION:
These children 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 emphasizes the need for effective and early intervention strategies.

The pattern of pulmonary function in BX was similar to that seen in CF, characterized by intrathoracic airway obstruction of the medium to small airways and hyperinflation indicated by elevation of the RV, reduced FEV1 and $FEF_{25-75.}$ The principle outcome was an FEV1 estimate of 68% or 63% predicted (Polgar) at ten years age with a slope of –1.9% or -0.9% per annum depending on strategy ('best' or 'all' data respectively). Other measures of obstructive disease, FEF_{25-75} and FEV1/FVC were also reduced and progressively declined. Lung volume studies demonstrated TLC was normal but RV and RV/TLC ratio elevated. Wide variability in individual severity and progression was evident – not all children with BX had abnormal or deteriorating lung function.
Our results are consistent with adult studies reporting lung function progression and early mortality in established bronchiectasis.[1,2,31,32] In apparent contrast, Karadag et al recently compared lung function (Knudson) at *presentation* with follow up an estimated mean of 4.7 years later in a young Turkish population with bronchiectasis and reported a significant *improvement.*[3] Their population was similar to ours in aetiology, age, gender and principles of treatment but appeared to have milder, more localized disease – (unilobular in 46% vs 5% and bilateral in 47% versus 89%). A much higher proportion received inhaled corticosteroids for bronchodilator responsiveness (78% vs 39%) and 23% had lobectomies for persistent / recurrent symptoms. Differences in methodologies between studies make direct comparison difficult, particularly as our study specifically attempted to exclude the improvement seen following initial therapy by only studying lung function more than six weeks after HRCT diagnosis and by the inclusion of multiple data points. The contrasting improvement in the Turkish population was however substantial – part will be an initial response, part may be the result of population differences (less severe disease) and part possibly due to different management (e.g. higher inhaled corticosteroid use). Long term inhaled steroids or antibiotics have not (as yet) been found to improve lung function.[33-35] In our study, individuals labeled with asthma and prescribed inhaled corticosteroids had a slower decline (borderline statistical significance) but poorer lung function at diagnosis. In addition to therapeutic trials, inter regional comparison, as has occurred in cystic fibrosis through registries, may offer significant insights into the impact of differing aetiologies, severity and management practices.

Sub group analyses in this study are limited by participant numbers, but may generate hypotheses for future study. 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 though 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 bronchiectasis populations including our own with incidence highest in Pacific Peoples, however we did not detect significant differences in severity or progression.[13,29]
The CF group was included because of its well described progressive suppurative lung disease and for a methodological control. Estimates for the CF population demonstrated decline of 2-3% per annum consistent with other studies and reinforces the validity of our analysis strategy.[36] Compared with the BX population, those with CF had milder obstruction but appeared to decline more rapidly (only statistically significant with 'all data' analysis). Pulmonary function may be worse in those with BX due to 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 yet HRCT diagnosis at a median of 8 years.[29] Lack of appropriate early treatment may have contributed to the severity of disease seen.

Pulmonary function is one measure of impairment and has been validated against radiology and quality of life.[2,5-7] However comparing individuals or groups over time is complicated in childhood by lung growth, puberty, gender, ethnicity and the statistical model used. Reference equations based on 'healthy' populations have been developed to predict appropriate volumes and flow rates. As they use different data sources and statistical models they may introduce artifacts that influence estimates. The choice of formulae has been found to significantly affect both intercept and slope.[37-40] Infective exacerbations usually reflect a reversible deterioration and their inclusion may be inappropriate in determining progression. The use of each year'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 and 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.[10,13,28,29,41]
It is however based on compilation of models from 5 different studies with relatively few individuals and takes no account of age, ethnicity or gender for FEV1. The Asher reference is based on an Auckland population (under 14 years of age only) and attempts to account for ethnicity and gender.[42] It is closest to meeting ATS recommendations for reference choice but is only used in our centre and doesn't cover the entire age range.[23] Knudson has wide use in the United States including by the CF Foundation.[43]
Quanjer (Western Europe) and Wang ("US Six Cities Study") are based on large populations and specifically attempt to account for puberty.[44,45] Intercept and slope did vary according to the equation use but our conclusions are robust to formulae choice. This remained true when analyzing the influence of ethnicity and gender. The best annual strategy produced estimates with higher intercepts and more rapid deterioration as has been found in CF studies.[36] This did not affect our conclusions except that the difference in rate of decline was between BX and CF FEV1 was only found to be statistically significant in the 'all data' analysis.

Longitudinal pulmonary function typically has characteristics which traditional statistical methods struggle with 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.[46] Mixed model analysis overcomes these problems and is particularly suited for analyzing continuous, correlated outcomes and provides estimation and hypothesis testing while simultaneously modeling both population and subject specific effects. It has been used previously in longitudinal pulmonary function studies (CF).[46] Using this technique, longitudinal analysis has greater statistical power and is more robust to model selection. Cross sectional data is subject to cohort bias, less efficient and may be less suited to study of disease progression.[37] The main limitations of this study are the relatively small number of individuals and being a retrospective review. Environmental factors such as housing and tobacco smoke exposure were not considered. A previous study estimated 58% of these

households had ≥ 1 smokers.[29] The inclusion and exclusion criteria may introduce a bias and potentially a cohort effect. These children had severe, extensive disease (based on HRCT) and our results reflect their outcome, on treatment, in one center rather than BX natural history.

We conclude that the pulmonary function of this group of children with BX declines significantly over time, despite therapy. This finding was replicated no matter which reference equation (Asher, Knudson, Polgar, Quanjer or Wang) or analysis method ('all data' or 'best annual') was used. Aetiology had a significant impact on severity which may indicate an opportunity to target screening and therapies. The abnormalities seen show a similar pattern to CF with evidence of intrathoracic airway obstruction and hyperinflation. Peers with CF had less severe lung function but may decline more rapidly. Overall we found the majority of 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.[47-49] 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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Figure Legends:

Figure 1: Linear mixed model estimates for the FEV1 of children with bronchiectasis (BX) and cystic fibrosis (CF) using the Polgar reference. 'Annual best' strategy involves using only the highest FEV1 for each calendar year while 'All data' uses all available data.

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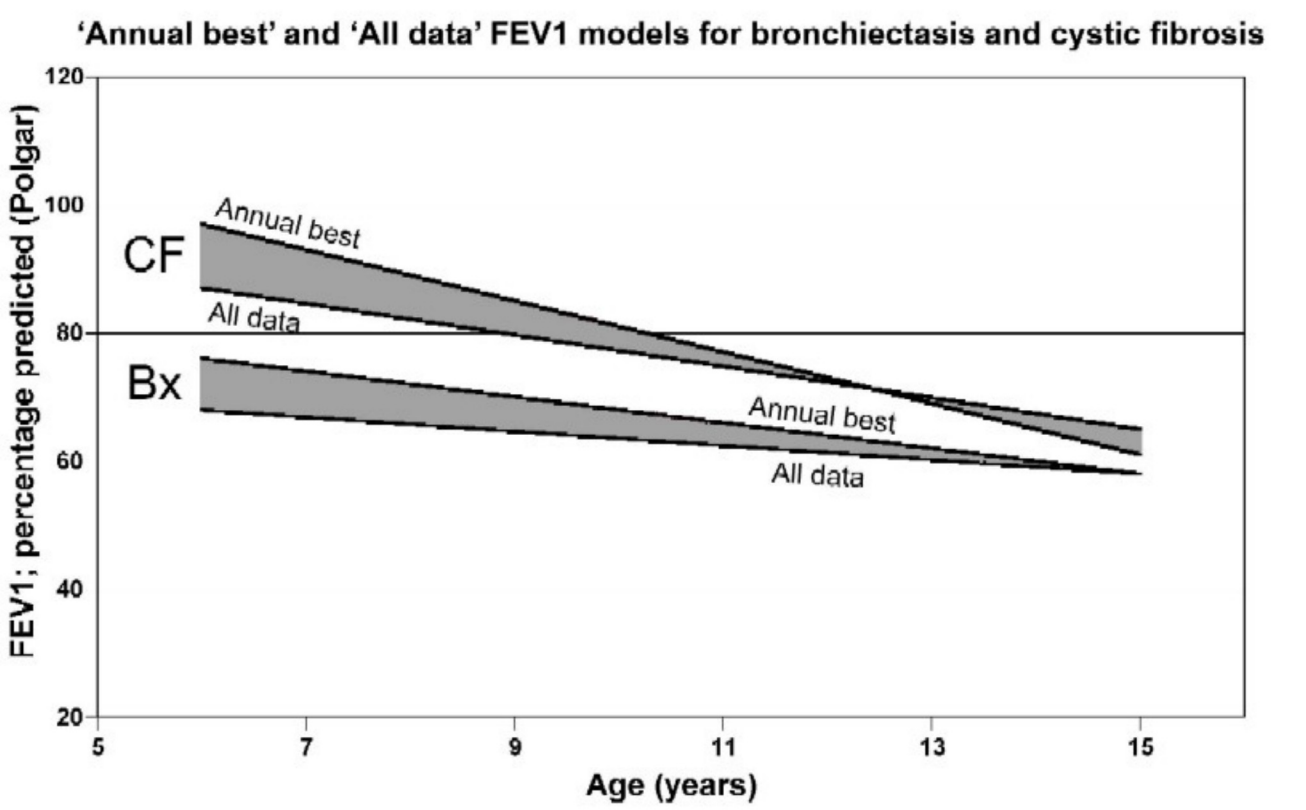
'Annual best' and 'All data' FEV1 models for bronchiectasis and cystic fibrosis
FEV1; percentage predicted (Polgar)
120
100
80
60
40
20
CF
Annual best
All data
Bx
Annual best
All data
5
7
9
11
13
15
Age (years)