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Improvements in Clinical Outcomes in Children with Cystic Fibrosis aged Six and 16 years

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Abstract

Aims

Our aim was to assess if outcomes for cystic fibrosis (CF) patients at six & sixteen years of age have improved in the last 17 years looking at FEV_1, BMI and death.

Methods

A retrospective observational study using a prospectively maintained database of CF patients at Cork University Hospital.

Results

84 patients were included in the 16-year-old data and 89 patients were included in the six-year-old data. The mean FEV_1 and BMI (16 years) for the 2002-2007 group was 72.9±21.0% and 18.9±2.53 respectively, 2008-2013 group was 75.4±27.2% and 19.8±2.7 and for the 2014-2018 group was 95.2±16.0% and 22.9±4.1. The percentage of patients (16 years) with chronic pseudomonas status was 37.9% (11/30) in the 2002-2007 group, 51.6 % (16/31) in the 2008-2013 group and 4.2% (1/24) in the 2014-2018 group. The relationship between FEV1 and FVC with BMI remained significant in multivariate analysis (P <0.001). The mean FEV_1 (six years) for the 2002-2007 group was 90.7±16.1%, 2008-2013 group was 99.3±17.9% and for the 2014-2018 group was 100.9±15.8%.

Conclusions

Improvements in FEV_1 and BMI aged six and 16 years are notable as well as a significant decline in the number of patients with chronic pseudomonas.

Introduction

Cystic Fibrosis (CF) is the most common life shortening genetic condition affecting Caucasians[1,2,3]. There is a high prevalence of CF in Europe with a particularly high mean prevalence in Ireland (2.98/10,000) [4,5,6]. Early diagnosis of CF provides opportunities for earlier medical intervention[7]. Lung health is a major indicator of wellbeing in CF which is represented by FEV1 (Forced Expiratory Volume in 1 second)[7]. In 2016, 250 adults (43.9%) and 47 children (8.3%) had chronic pseudomonas aeruginosa infection[7]. Prevalence of CF related diabetes in Ireland is 31.5%[8]. Since 2000, an average of 18 individuals died annually (range: 7-31)[7].

Major recent advances in Ireland include the introduction of new-born screening for CF in Ireland in 2011[8]. Pseudomonas aeruginosa is an early acquired pathogen in CF patients that can lead to chronic infection, more rapid lung function decline and premature death[3,9]. To prevent these poor outcomes, early eradication of pseudomonas protocols have been introduced to aggressively eradicate this organism[,10,11,12]. Patient segregation and isolation to reduce cross infection have become the standard of care[13,14]. The use of Ivacaftor and Lumacaftor /ivacaftor (Orkambi) have been a huge milestone in CF care[15-18]. Ireland subsequently gained access to Lumacaftor/Ivacaftor in 2017 for over 12 years with Delta f 508 homozygous. In February 2018, Lumacaftor/Ivacaftor was extended to the 6-11 year old age group and is now available to children over two years of age[8].

The aim of our project was to assess if outcomes for cystic fibrosis patients have improved in our centre since the introduction of these key measures over the past 17 years. We chose two time points to evaluate patients aged six and sixteen years of age. The timepoint of sixteen years of age was chosen as this is the age for children to be transferred to the adult service in our centre. Six years was also chosen so the impact of of new-born screening in 2011 could be assessed.

Methods

We carried out a retrospective observational study using a prospectively maintained database of cystic fibrosis patients in Cork University Hospital (CUH).

The cystic fibrosis nurse specialists have maintained a record of all cystic fibrosis patients since the early 1980s including all patients who passed away during this time in both the paediatric and adult services.

Approval to access the patient's records was granted by the Cork University Hospital Clinical Governance and Audit Office.

Our inclusion criteria included any child who reached 16 years of age between 1st Jan 2002 and 31st December 2018 under the care of the CUH paediatric cystic fibrosis service were included in the 16 years of age cohort.

Similarly, all children under the care of the CUH paediatric cystic fibrosis service between 1st Jan 2002 to 31st December 2018 who reached six years of age during this time period were included in the six years of age cohort.

The outcomes to be measured include; patient demographics including date of birth, date of diagnosis, reason for presentation, genotype and initial sweat chloride result at time of diagnosis. Lung function tests: FEV1 and FVC (Forced Vital Capacity) at sixteen years and six years respectively for each cohort. BMI (Body mass index) at sixteen years and six years for each cohort. Pseudomonas status (Leeds Criteria[19]) classified as never (no previous positive pseudomonas sputum or cough swabs), free from (a previous positive pseudomonas sample but none in over the last 12 months prior to transfer), intermittent (<50% of sputum samples positive in the preceding 12 months) and chronic (>50% of sputum samples positive for pseudomonas in the preceding 12 months). Diabetes diagnosis at sixteen or six years of age depending on cohort where insulin was required as part of their care (CF related diabetes defined on the basis of either a two hour oral glucose tolerance test blood glucose of >/= 11.1mmol/L/ fasting blood glucose of >/= 7mmol/L on two or more occasions or fasting blood glucose of >/=7mmol/L plus random blood glucose level of >/=11.1mmol/L or random BG levels of >/= 11.1mmol/L with symptoms of diabetes mellitus on two or more occasions when otherwise clinically well[20]. Also, the use of CFTR modulators and transplant status: Lung transplant undertaken prior to sixteen years.

Statistical analysis using descriptive statistics followed by linear regression analysis for both univariate and multivariable models was carried out using Stata SE Version 13 (Stata Corporation, College Station, TX, USA) for Windows. Features that displayed a P value of less than 0.05 in univariate analyses were included in subsequent multivariable models.

Results

Sixteen-year-old data

In total 85 patients reached 16 years of age between 2002 and 2018; one case file was unfortunately lost to medical records, leaving 84 cases to analyse. The case file lost was a patient in 2002.

We arbitrarily grouped these patients from a 17-year period into 3 groups- two six-year groups and one five-year group to provide greater statistical strength rather than compare each year. Group 1. 2002-2007 (30 patients), Group 2. 2008-2013 (31 patients) and Group 3. 2014-2018 (24 patients).

Table 1. Clinical and Demographic Characteristics of 16-year-old patients with cystic fibrosis, 2002–2018.

Outcome Measured	2002–2007	2008–2013	2014–2018
Mortality (No of Deaths)	5	1	2
No of Living patients who reached 16 years	n=30	n=31	n=24
Age at diagnosis (mean)	2.0 ± 3.9	1.1 ± 2.9	3.6 ± 4.9
BMI, kg/m^2 (mean)	18.9 ± 2.5	19.8 ± 2.7	22.9 ± 4.1
Pseudomonas status:			
Never (%)	6 (20)	2 (6.5)	5 (20.8)
Free From (%)	2 (6.6%)	8 (25.8)	12 (50)
Intermittent (%)	10 (34.5)	5 (16.1)	6 (25.0)
Chronic (%)	11 (37.9)	16 (51.6)	1 (4.2)
Diabetes (%)	1 (3.3)	4 (12.9)	4 (16.7)
Use of CFTR modulators (%)	0 (0)	0 (0)	6 (25.0)
Forced expiratory volume, L (mean)	72.9 ± 21.0	75.4 ± 27.2	95.2 ± 16.0
Forced vital capacity, L (mean)	82.7 ± 18.8	81.7 ± 22.9	103.1 ± 14.9
No. (%) of patients DeltaF508 homozygous	23/30 (76.7)	24/31 (77.4)	14/24 (58.3)

Mortality: No of children who passed away before 16 years of age. Age at diagnosis, BMI, forced expiratory volume and forced vital capacity are shown as a mean ± one standard deviation. Numbers and % are shown for pseudomonas status and use of CFTR modulators.

Table 2. Factors associated with forced expiratory volume levels in 16-year-old patients with cystic fibrosis – linear regression.

	Outcome Measured	Coefficient	Std Error	95% CI	P value
Model 1					
	Age at diagnosis	1.21	0.71	-0.20, 2.62	0.09
	BMI	3.21	0.69	1.85, 4.56	<0.001[2]
	Pseudomonas status (yes)[1]	-15.71	5.07	-25.81, -5.60	0.003[2]
	Diabetes	-7.92	8.51	-24.85, 9.01	0.355
	Use of CFTR modulator	22.78	9.96	2.96, 42.60	0.025[2]
Model 2					
	BMI	2.95	0.65	1.65, 4.25	<0.001[2]
	Pseudomonas status (yes)[1]	-10.77	4.83	-20.38, -1.15	0.029[2]
	Use of CFTR modulator	13.59	9.19	-4.70, 31.89	0.143
Model 3					
	BMI	2.77	0.70	1.37, 4.16	<0.001[2]
	Pseudomonas status (yes)[1]	-9.75	5.04	-19.79, 0.28	0.057
	Use of CFTR modulator	11.51	9.66	-7.12, 30.73	0.237

Features that displayed a P value less than 0.05 in univariate analyses were included in multivariable models.
One subject was excluded from analyses due to missing values (Patient no 85-2002 case).
Model 1: Univariate.
Model 2: Adjusted for each other.
Model 3: Adjusted for each other and year of data collection.
[1]Either intermittent or chronic.
[2]P value significant (<0.05).

Table 1 describes the initial results of our patients who reached 16 years of age. Overall, there was a significant increase in FEV_1 from 95.2±16.0% in the 2014-2018 group when compared with 72.9±21.0% from the 2002-2007 group. Similarly, BMI improved over the time frame of our study from 18.9±2.53 back in 2002-2007 to 22.9±4.1 in 2014-2018.

From a pseudomonas viewpoint the number of patients with chronic pseudomonas infection fell significantly from 37.9%in 2002-2007 to 4.2% in 2014-2018. Only one cohort demonstrated the effect of CFTR modulators- the 2014-2018 cohort. 10 patient years of ivacaftor exposure and two patient years of Lumacaftor/Ivacaftor exposure in total.

There has been only one bilateral lung transplant (performed in UK) in a patient attending our centre in this time period- An 11-year old male in 2015 who subsequently passed away at 13 years of age.

Table 2 demonstrates that BMI (FEV 1: P <0.001, FVC: P<000.1), pseudomonas status (FEV1: P 0.003, FVC: P 0.017) and use of CFTR modulators (FEV 1: p 0.025, FVC 0.027) were all significantly related to forced expiratory volume in univariate models. Similar results were found for forced vital capacity data. Subsequent multivariable analysis revealed the relationship between FEV1 and pseudomonas status remained borderline significant (P 0.029 in Model and 0.057 in Model 3). The relationship for CFTR modulators and FEV1 trended to an insignificant relationship (P 0.143 in Model 2 and 0.237 in Model 3). The relationship between FEV1 and FVC with BMI remained significant in multivariable analysis adjusted for each other and year of data collection (P <0.001).

Six-year-old data

Table three demonstrates our results for all patients who reached six years of age between 2002 and 2018. We arbitrarily grouped these patients once again: Group 1. 2002-2007 (29 patients), Group 2. 2008-2013 (30 patients) and Group 3. 2014-2018 (30 patients).

The mean FEV_1 rose from 90.7±16.1 in the 2002-2007 group to 100.9±15.8 in the 2014-2018 group. The mean BMI for the 2014-2018 group was 15.5±1.0, 2008-2013 group was 16.1±1.8 and the 2002-2007 group was 16.1±2.0. Chronic pseudomonas rates fell once from 10.3% in 2002-2007 to 0% in 2014-2018. Only four patients (13.3%) in the 2014-2018 group and two patients (6.7%) in the 2008-2013 group received CFTR modulators.

Table 3. Clinical and Demographic Characteristics of six-year-old patients with cystic fibrosis, 2002–2018.

Outcome Measured	2002–2007	2008–2013	2014–2018
Mortality (N)	2	2	0
No of living patients who reached six years	n=29	n=30	n=30
Time to diagnosis:			
Before or at birth (%)	7 (25.0)	10 (33.3)	13 (48.1)
Before 1 year (%)	10 (35.7)	13 (43.3)	8 (29.6)
Between 1–2 years (%)	6 (21.4)	4 (13.3)	1 (3.7)
>2 years (%)	5 (17.9)	3 (10.0)	5 (18.5)
No (%) of patients DeltaF508 homozygous	19/29 (65.5)	16/30 (53.3)	20/30 (66.7)
BMI, kg/m^2 (mean)	16.1 ± 2.0	16.1 ± 1.8	15.5 ± 1.0
Pseudomonas status:			
Never (%)	17 (58.6)	10 (33.3)	13 (43.3)
Intermittent (%)	6 (20.7)	11 (36.7)	2 (6.7)
Free from (%)	3 (10.3)	8 (26.7)	15 (50)
Chronic (%)	3 (10.3)	1 (3.3)	0 (0)
Diabetes (%)	0 (0)	0 (0)	0 (0)
Use of CFTR modulator (%)	0 (0)	2 (6.7)	4 (13.3)
Forced expiratory volume, L (mean)	90.7 ± 16.1	99.3 ± 17.9	100.9 ± 15.8
Forced vital capacity, L (mean)	94.1 ± 14.6	101.7 ± 15.2	102.8 ± 16.7

Mortality: No of children who passed away before 6yrs of age. BMI, forced expiratory volume and forced vital capacity are shown a mean ± one standard deviation. Numbers and % are shown for time to diagnosis, pseudomonas status and use of CFTR modulators.

Linear regression analysis was subsequently carried out on this dataset also. BMI is a strong determinant with regard to FEV1 (P 0.024) and FVC (P 0.031) levels in 6-year-olds although BMI levels haven't changed to a statistically significant level between the 2002-2007 and 2014-2018 cohorts. None of the other variables displayed a convincing

relationship with FEV1 and FVC. Time to diagnosis was not statistically significant under univariate analysis (FEV1: P 0.507 and FVC: P 0.575). Neither was pseudomonas status (FEV1: P 0.381, FVC: P 0.437), diabetes diagnosis (FEV1 P 0.08, FVC P 0.068) or use of CFTR modulators (FEV 1 P 0.197 , FVC P 0.115) amongst our six year old patients.

Discussion

The group of patients born before the introduction of newborn screening showed no difference in the age of diagnosis between the different cohorts. The most likely reasons for this are that prior to newborn screening the diagnosis of cystic fibrosis was on the basis of characteristic clinical findings and laboratory values, and in the past the diagnosis was often not clear cut on an initial consultation[21]. Equally the age of onset of symptoms is highly variable from antenatal evidence of echogenic bowel to adolescent onset respiratory symptoms. A similar experience was found in the US in 1996 where only two states had introduced newborn screening by that time. The earlier diagnoses provided by newborn screening have not demonstrated an improvement in outcomes for our six-year old patients as of yet as only a very small minority of patients in our 2014-2018 cohort benefitted from screening. Significant Improvements in FEV_1 and BMI are noted over the past 17 years at both six & sixteen years of age. In the past five years, our sixteen year old patients have reached the European Cystic Fibrosis Society (ECFS) recommendation of a BMI >20kg/m2 in adults with CF and matches national figures of an average BMI of 22.3 in 2016[8,22]. BMI, pseudomonas status and use of Ivacaftor/Orkambi medications were all significantly related to forced expiratory volume and forced vital capacity levels in univariate models at sixteen years. The relationship between pseudomonas status remained significant (or borderline significant) in multivariable models at sixteen years, while the relationship for medication use trended to insignificant – but the numbers were low for this variable. A limitation to this study is that we did not collect data on imaging e.g. CT thorax in these patients.

There is a huge decline in the number of patients with chronic pseudomonas at 16 years of age although the rate of acquiring pseudomonas infection has not changed. This may be related to changes in antibiotic prescribing including use of inhaled therapy leading to pseudomonas eradication. Our low chronic pseudomonas rates are in keeping with national figures of 8.3% from the national CF registry in 2016[8]. Shidhani et al report that they have detected a decline in the overall prevalence of pseudomonas infection in their CF population which we have not detected[23]. The likely reason for this is that both studies were carried out at single centre sites which have different catchment areas in Ireland- we cover Munster while Children's Health Ireland at Crumlin covers Leinster so geography may play a role. However, they describe a similar change in the pattern of severity of pseudomonas infection to our study with a fall in chronic pseudomonas rates[23]. We did not assess in this study whether the prevalence of multidrug resistant bacteria had increased during the same time frame. A further limitation to our study is its retrospective nature. Internationally, our chronic pseudomonas rates as per the Leeds Criteria are lower than the US at 40% in adolescents as of 2015[24].

In conclusion, the real driver behind the more favourable FEV_1 and FVC outcomes we are seeing in recent years are the more optimal BMI levels that we are observing in our patients as demonstrated by our multivariable analysis (Table two). It is hoped that improvements in FEV_1 and BMI will translate into an improvement in the quality of life and longevity in this population as they enter adulthood which we hope would be a finding relevant internationally.
This would suggest that for us to continue to see improving FEV1 and FVC levels at six years of age, a goal would be to increase dietetic support and nutritional supplementation during these initial formative years.

Continued improvement in the outcomes aged 16 years will be accrued when the group diagnosed by newborn screening are assessed (aged 16 in 2027). We look forward to seeing the outcomes in teenagers and young adults in those receiving CF modifiers from early infancy and early childhood and expanding the number of patients who receive modifier therapy.

Continued investment by the Health Service Executive in the maintenance of multidisciplinary teams in designated CF centres as advocated in the National Model of Care for Cystic Fibrosis will be vital to provide state of the art care to children, teenagers and adults with cystic fibrosis.

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Declaration of Conflicts of Interest:
The authors of this paper declare that we do not have any conflicts of interest.

References:
1. Salvatore D, Buzzetti R, Baldo E, Forneris MP, Lucidi V, Manunza D et al. An overview of international literature from cystic fibrosis registries. Part 3. Disease incidence, genotype/phenotype correlation, microbiology, pregnancy, clinical complications, lung transplantation and miscellanea. 2011. Journal of Cystic fibrosis: Official journal of the European Cystic Fibrosis Society 10(2):71-85.
2. Blanchard AC, Horton E, Stanojevic S, Taylor L, Waters V, Ratjen F. Effectiveness of a stepwise Pseudomonas aeruginosa eradication protocol in children with cystic fibrosis. 2016. Journal of Cystic Fibrosis. 16(2017):395-400.
3. Pamukcu A, Bush A, Buchdahl R. Effects of Pseudomonas aeruginosa colonization on lung function and anthropometric variables in children with cystic fibrosis. Pediatric Pulmonology. 1995;19(1):10-15
4. Farrell PM. The Prevalence of cystic fibrosis in the European Union. Journal of Cystic Fibrosis. 2008 Sep;7(5):450-453.
5. Farrell P, Joffe S, Foley L, Canny GJ, Mayne P, Rosenburg M. Diagnosis of cystic fibrosis in the Republic of Ireland: epidemiology and costs. Irish Medical Journal. 2008;100(8):557-560.
6. Lowton K and Gabe G. Life is a slippery slope: perceptions of health in adults with cystic fibrosis. Sociology of health and illness. 2003. 25(4):289-319
7. The Cystic Fibrosis Registry of Ireland (CFRI). 2016 Annual Report.
8. Cystic Fibrosis Ireland. Cystic Fibrosis Ireland Annual Report 2017.
9. Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. American Journal of Respiratory Critical Care Medicine. 2003;167(6):841-849.
10. Ratjen F, Doring G, Nikolaizak WH. Effect of inhaled tobramycin on early pseudomonas aeruginosa colonisation in patients with cystic fibrosis. Lancet. 2001;358(9286):983-984.
11. Treggiari MM, Retsch-Bogart G, Mayer-Hemblett N, Khan U, Kulich M, Kronmal R et al. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. Archives of paediatric and adolescent medicine, 2011;165(9):847-856.
12. Barry PJ, Donalson AL, Jones AM. Ivacaftor for cystic fibrosis. BMJ. 2018;361:k1783.
13. Saiman L, Siegel JD, Lipuma JJ, Brown RF, Bryson EA, Chambers MJ et al. Infection Prevention and Control Guideline for Cystic Fibrosis: 2013 Update, Infect Control Hosp Epidemiol. 2014 Aug;35 Suppl 1@S1-S67
14. Saiman L and Siegel J (2004). Infection Control in Cystic Fibrosis. Clinical Microbiology Reviews: 17 (1); 57-71.
15. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation, New England Journal of Medicine. 2011;365:166301672.
16. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A et al. Efficacy and safety of ivacaftor in patients aged 6-11 years with cystic fibrosis with a G551D mutation. American Journal of Respiratory Critical Care Medicine. 2013;187:1219-1225
17. Davies JC, Cunningham S, Harriet WT, Lapey A, Regelmann WE, Sawicki GS et al. Safety, Pharmacokinetics and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single arm study. Lancet Respiratory Medicine. 2016;4:107-115.
18. Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D et al. Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis. Am J Respir Crit Care Med. 2014 Jul 15; 190(2): 175–184.
19. Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginoasa infection in cystic fibrosis patients. J Cyst Fibros 2:29-34
20. Waugh N, Royle P, Craigie I, V Ho, L Pandit, P Ewings et al. Screening for Cystic Fibrosis-Related Diabetes: A Systematic Review. 2. Defining cystic fibrosis-related diabetes Southampton (UK): NIHR Journals Library May 2012
21. Farrell PM, Beryl J. Rosenstein BJ, White TB, Accurso FJ, Castellani C et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report J Pediatr. 2008 August ; 153(2): S4–S14.
22. Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Bryon M et al. ECFS Standards of Care: Best Practice guidelines. Journal of CF 2014 4:13,S23-42.
23. Al Shidhani K, O'Reilly R, Javadpour S, O'Sullivan N, McNally P, Cox DW. The Prevalence of Pseudomonas Aeruginosa Infection Over a Ten-Year Period in Children with Cystic Fibrosis. Irish Medical Journal. June 2019. Vol 112(6):946
24. Cystic Fibrosis Foundation Patient Registry 2015 Annual Data Report Bethesda, Maryland ©2016 Cystic Fibrosis Foundation