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Deaths in childhood from cystic fibrosis: 10-year analysis from two London specialist centres

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ABSTRACT

Introduction Death in childhood from cystic fibrosis (CF) is now an uncommon event in the UK. We wished to assess the circumstances surrounding deaths (and lung transplantation) in the modern era of CF care.

Methods A retrospective review was carried out pooling data from two large paediatric specialist CF units in London for the 10-year period 2000–2009 inclusive.

Results There were 11 deaths and eight children who had a lung transplant out of 1022 children cared for in this period. Median age of death was 14.2 years and transplant 13.0 years, with a female preponderance (82% deaths and 75% transplants). Apart from one child (forced expiratory volume in 1 s (FEV_1) 69%), lung function indicated severe lung disease (median FEV_1 33%, range 12%–69%). Values 5 years prior to death were not predictive (median FEV_1 62%, range 32%–96%), and those 1 year prior were similar to the last recorded levels. Almost all (10/11) died in hospital and 5/11 (45%) were ventilated. Respiratory failure was the commonest mode of death (64%). Only four children (36%) were receiving palliative care, and in six cases (55%) care was withdrawn.

Conclusions The number of deaths in children with CF was small but often unpredictable, so active management was continued until late in the majority, reflected by the fact that almost all were in hospital, and more than half were ventilated. If death from respiratory failure is anticipated following a steady decline, palliative care should be instituted well in advance, with attention to appropriate end of life care.

What is already known on this topic

- Life expectancy continues to increase for those affected with cystic fibrosis.
- Deaths in children with cystic fibrosis are uncommon in the modern era of cystic fibrosis care.

What this study adds

- Death is usually unpredictable so active management is likely to be continued until death becomes inevitable.
- Almost all children died in hospital and often in a paediatric intensive care unit.

INTRODUCTION

Since the first recognition of cystic fibrosis (CF), life expectancy has risen from 6 months to more than 30 years.[1] Consequently, death in childhood has become a rare event and almost all paediatric patients are transitioned into adult care. Data from the UK CF Registry (Cystic Fibrosis Trust 2011) reveal there were 18 deaths in the 4 years 2007–2010 inclusive, for the whole of the UK, which has around 4000 CF children under 16 years old. There has been a fivefold reduction in the UK death rate for CF from 0.66 per 100 000 population in 1968 to 0.12 per 100 000 in 2000.[2] The UK CF survey holds data on all people with CF born after 1968, or born before 1968 and still alive in 1977; the survival of successive cohorts has continued to improve.[3–5] The median predicted survival in the UK is currently estimated to be 41.4 years.[6] This improvement is even seen in those with poor lung function.[7] Similar falls in death rates have been described in France and North America.[8 9] The aim of this study was to look in detail at the circumstances surrounding deaths and those who underwent lung transplantation in the modern era of CF care. Because of the small numbers, we pooled data from two large paediatric specialist CF centres.

METHODS

This was a retrospective review set in the paediatric specialist CF units of the Royal Brompton Hospital and Great Ormond Street Hospital for Children, London. Both units look after patients either on full care basis or shared care with network clinics. Patients are usually transitioned to adult services between their 16th and 17th birthdays (so there is a possibility someone may have died at an adult centre in this age range although we would have known about it). We analysed our CF databases and case notes of children with CF who had either died or received a lung transplant between 1 January 2000 and 31 December 2009 (a 10-year period). Data were collected on CF genotype, gender, microbiology, growth and nutrition, and lung function. In addition circumstances surrounding death were assessed: age, mode and place of death, use of mechanical ventilation, and whether palliative care had been instituted. Anonymised data were recorded on an Excel spreadsheet (Microsoft Office 2000, Seattle, USA) which was transferred into a database using the statistics package, Statistical Package for the Social Sciences (SPSS) for windows V.15.0 (SPSS, Chicago, Illinois, USA). Although this service review of anonymous pooled data did not require ethical approval, the verbal consent of

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parents to review the data of the deceased children was obtained by telephone.

RESULTS

In the 10-year period, there were 11 deaths and eight children who had a lung transplant; and during this time there were a total of 1022 children cared for by both centres (but not necessarily for the full 10 years). There was no temporal trend to deaths over the 10 years. Details of the patients are in table 1.

Table 1 Patient demographics (where applicable, medians and ranges are shown)

	Death	Transplant
Number of patients	11	8
Gender	9F/2M	6F/2M
Genotype		
Δ508/Δ508	4 (36%)	4 (50%)
Δ508/Other	3 (27%)	4 (50%)
Other/Other	4 (36%)	0
Age at CF diagnosis (years)	0.17 (0–1.1)	0.54 (0.04–3)
Age at death (years)	14.2 (3.5–16.5)	–
Age at transplant (years)	–	13.0 (9.2–15.5)
Nutritional status		
Height z score	−1.51 (−4.41 to −0.64)	−1.14 (−2.49 to +0.99)
Weight z score	−1.02 (−6.63 to +0.11)	−1.04 (−2.13 to +0.66)
BMI z score	−0.78 (−3.57 to +1.35)	−0.3 (−2.03–+0.3)
Gastrostomy	7 (73%)	6 (75%)
Lung function (last recorded)	33 (12–69)	24 (22–29)
FEV_1 (% predicted)		
FVC (% predicted)	45 (22–80)	34 (3–44)
Infection status		
Chronic *Pseudomonas aeruginosa*	11 (100%)	8 (100%)
Chronic *Staphylococcus aureus*	7 (64%)	6 (75%)
Chronic *Stenotrophomonas maltophilia*	4 (36%)	3 (38%)
Chronic *Burkholderia cepacia* complex	4 (36%)	0
Chronic *Aspergillus fumigatus*	6 (55%)	2 (25%)
Non-tuberculous mycobacteria	1 (9%)	0
No. IV antibiotic courses in last year	6 (3–10)	5 (3–6)
TIVAD in situ	6 (64%)	7 (88%)
Comorbidities		
CF-related diabetes	1 (9%)	2 (25%)
ABPA	2 (18%)	1 (13%)
CF liver disease	0	0
Gastro-oesophageal reflux	4 (36%)	4 (50%)
Nissen's fundoplication	3 (27%)	3 (38%)
Home respiratory support		
Supplemental oxygen	6 (55%)	8 (100%)
Non-invasive ventilation	0	1 (13%)

Lung function measured in 9/11 children who died.
ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IV, intravenous; TIVAD, totally implantable intravenous device.

The median age of death was 14.2 years and transplant at 13.0 years; unusually one child died at 3.5 years (of multi-organ failure with comorbidity of seizures and severe non-CF enteropathy requiring total parenteral nutrition), and one child at 9 years (with comorbidity of microcephaly and some form of non-CF lung disease that made her oxygen-dependent from birth). The rest were all over 10 years and mostly teenagers. Of note, there was a female preponderance in both those who died (82%) and those transplanted (75%).

Nutritional status was generally poor (table 1) and 68% had a gastrostomy; only 16% had CF-related diabetes. All were chronically infected with *Pseudomonas aeruginosa* and the majority (68%) with *Staphylococcus aureus* (all methicillin-sensitive). Perhaps significantly, 4/11 who died had *Burkholderia cepacia* complex (acquired 1997, 2000, 2001 and 2001). The children had received multiple courses of intravenous antibiotics in the previous year, with a range of 3–10 (median 5), 68% via a total implantable venous access device. As expected, lung function was indicative of severe CF lung disease, although one child had a forced expiratory volume in 1 s (FEV_1) of 69% at annual review shortly before her death. Lung function at 1 and 5 years prior to death or transplant is in table 2 and figures 1 and 2. Objective data on adherence are not available. Only 6 (55%) children who died had home oxygen available, although all those transplanted did. One patient used non-invasive ventilation (NIV) at home prior to transplant. Transcutaneous or arterial CO_2 levels were not routinely collected.

Almost all of the children died in hospital, with only 1/11 dying at home. A significant proportion of 5/11 (45%) was ventilated in the paediatric intensive care unit (PICU) in their final illness (table 3). Three children were intubated and ventilated at other hospitals before transfer to the PICU at the CF centres; two children were never extubated after procedures (one had a lung transplant, one had a bronchial artery embolisation). One child received NIV on the ward for symptomatic relief prior to death. Only four children (36%) had been instituted on a palliative care pathway prior to their final illness, with the remainder being actively treated to this point. Severe respiratory compromise with respiratory failure was the commonest mode of death (64%), while two children (18%) died postlung transplantation

Table 2 Potential predictors of death or the need for transplantation (where applicable, medians and ranges are shown)

	Death	Transplant
Number of patients	11	8
FEV_1 last recorded	33 (12–69)	24 (22–29)
FEV_1 1 year prior	32 (6–64)	34 (19–44)
FEV_1 5 years prior	62 (30–96)	30 (20–54)
Absolute fall/year in FEV_1 over 5 years	8.9 (6.1–12.5)	10.7 (4.7–16.5)
FVC last recorded	45 (22–80)	52 (38–69)
FVC 1 year prior	45 (21–83)	44 (30–57)
FVC 5 years prior	66 (34–104)	61 (39–82)
Absolute fall/year in FVC over 5 years	4.3 (0.5–8.5)	7.7 (1.5–18)
Exercise tolerance*		
Desaturation ($SpO_2 \geq 4\%$)	1 (25%)	6 (86%)
No desaturation	3 (75%)	1 (14%)
Not tested	7	1
Wheelchair use	3 (27%)	3 (38%)

Lung function shown as % predicted (2/11 children who died were unable to perform spirometry).
*Exercise testing was either modified shuttle test or 3-min step test.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

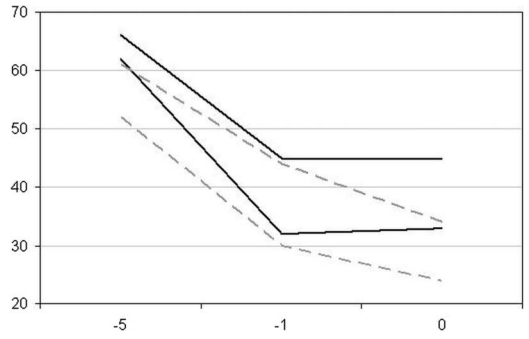

Figure 1 Change in lung function (median FEV_1 and FVC % predicted) over 5-year period prior to death (n=9, 'D' solid lines) or transplant (n=8, 'Tx' dashed lines). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

(one at 2 weeks post-transplant, one 6 years later from obliterative bronchiolitis). One child died of multi-organ failure felt not to be related to the underlying CF, and one child died after cerebral infarction following bronchial artery embolisation for haemoptysis with an unexpected anomalous arterial circulation. In about half the cases (55%), a decision to withdraw care was made prior to death. None of the children who died were on a waiting list for lung transplantation for the following reasons: unexpected rapid deterioration (n=5), contraindication due to comorbidity (n=2), previous lung transplant (n=2), and family and patient did not want to consider it (n=2).

DISCUSSION

We have described 11 children with CF who died over a 10-year period, with some comparative data for eight children from the same two centres who received a lung transplant. Death in childhood from CF is a relatively rare event nowadays; in the UK only three children under 16 years died in 2009, and four in 2010.[6] It is hoped it will become even rarer since the introduction in 2007 of newborn screening throughout the UK. Nevertheless, it is important that parents with a newly diagnosed child realise that it can still happen. This paper highlights the factors associated with childhood mortality in CF. Clearly comorbidity can be a critical issue and the two younger children who died (aged 3 and 9 years) had significant non-CF-related medical conditions. Gender also seems to be an issue, as in our series 79% of those who died or had a transplant were female

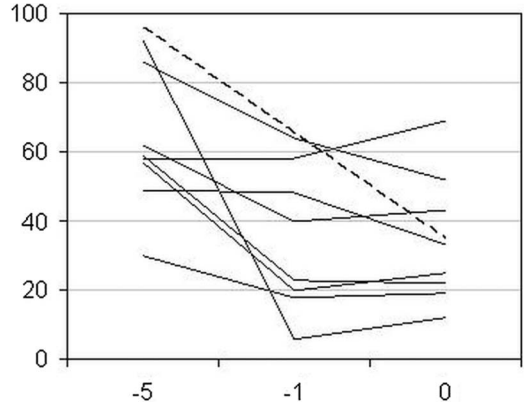

Figure 2 Change in FEV_1% predicted over 5-year period prior to death in individual patients (n=9). Dashed line is extrapolation as 1-year data missing for that patient. FEV_1, forced expiratory volume in 1 s.

Table 3 Characteristics of death (patient number with %)

Number of patients	11 (100%)
Place of death	
Home	1 (9%)
Local hospital	3 (27%)
Tertiary centre	7 (64%)
Cause of death	
Respiratory failure	7 (64%)
Postlung transplant	2 (18%)
Multi-organ failure	1 (9%)
Other	1 (9%)
Care pathway	
Active care	7 (64%)
Palliative care	4 (36%)
Mechanically ventilation	
Yes	5 (45%)
No	6 (55%)
Non-invasive ventilation	
Yes	1 (9%)
No	10 (91%)
Withdrawal of care	
Yes	6 (55%)
No	5 (45%)

subjects. Previous publications have reported significantly higher mortality in female subjects,[10 11] although interestingly work from one of our centres (Brompton) analysing data from 1993–2002 failed to show any gender differences in lung function or mortality.[12] It is known that lung function, as a marker of severity of CF lung disease, serves as a predictor of mortality, yet recent work (albeit in adults) has shown that median survival at significantly low levels of lung function (FEV_1<30% predicted) has increased from 1.2 years in 1991 to 5.3 years in 2003.[7] This illustrated the fact that spirometry alone will not necessarily predict mortality, and it is likely the rate of decline is more important.[13] In our series, lung function 5 years prior to death was certainly not predictive (median FEV_1 62% with a wide range of 32%–96%), and the lung function values 1 year prior were similar to the last recorded levels. Looking at the individual values did not reveal a particular pattern and indeed one of the children had an FEV_1 of 69% predicted a month before her death. Fitness levels as assessed by maximal oxygen uptake during exercise are known to predict mortality in CF,[13 14] but in our series exercise testing was only regularly recorded in patients undergoing transplant assessment. Other factors identified in the literature that are known to influence mortality are genotype,[15] nutritional status,[16] chronic infections with certain bacteria[17 18] and socioeconomic status.[19 20]

Only one child died at home, the rest were in hospital, and the majority (n=7) in their specialist CF centre while the other three were in a hospital closer to home. This was partly because children tend to be managed actively until death is inevitable, at which point withdrawal of care took place in 6/11 (55%) children. Death was not expected in all the children reflected by the fact only 4/11 (36%) were receiving palliative care. As Robinson *et al* stated 'the short term prognosis may be uncertain even if the final outcome is clear',[21] which means that active management is often continued until quite late in the course of the terminal illness. It is now not uncommon for active and palliative management to proceed at the same time,[22] and there seems to be a more clinically aggressive approach taken to end of life care

in CF.[23] Continuing active management will have reflected the wishes of the patient and family who may find comfort (both physical and psychological) in the continuation of what has been lifelong treatment, such as chest physiotherapy or antibiotics. There are few downsides to these CF therapies (unlike, for example, chemotherapy in a terminal cancer patient), and there may even be symptomatic benefit, especially from physiotherapy and sometimes oxygen. In one published series, 75% received intravenous antibiotics and 36% chest physiotherapy within 12 h of their death (72% even received oral vitamins).[21] Until death is inevitable, it is understandable that most of our patients and their families elect to stay in hospital, and most choose a hospital death. The majority have built up close relationships over many years with the CF team and ward staff, who can give them great support, which continues after death. The wishes of the child and family should remain paramount in all these decisions. There are not many large studies of circumstances surrounding deaths from CF, and hardly any data available on children. A study of all CF deaths in Canada during 1996 (n=45) showed that 82% died in hospital with 16% being ventilated on the intensive care unit.[24] A study from Boston Children's Hospital, USA, covering 44 deaths (1984–1993) that included nine patients aged <20 years found 98% (43/44) died in hospital.[21] In a series of adults from Newcastle, UK, of the 35 dying of progressive lung disease, 89% (31/35) died in hospital, with one patient ventilated.[25]

In our series, 5/11 (45%) children died while intubated and ventilated. Two of the children died after procedures requiring general anaesthesia and were never extubated. One child was intubated as an emergency in a local hospital before transfer to the PICU in his CF centre where he died within 24 h. Although some might argue he should not have been intubated, it was a better process for the family who all had time to gather round the bedside and say goodbye, rather than have him dying suddenly in their local Accident & Emergency Department. One child was intubated locally and again transferred to the CF centre having suddenly deteriorated significantly after a few weeks of inpatient treatment for a chest exacerbation. Finally, one child was intubated in her local hospital having deteriorated suddenly over a few days, and this was certainly unanticipated as her FEV_1 was 69% only a month prior to her death. The issue of ventilating patients with CF has been debated, and aside from the non-controversial issues of intubation for procedures or reversible CF complications (eg, pneumothorax, massive haemoptysis), the picture is changing.[26 27] This is because the outlook after ventilation for respiratory failure has improved and death is no longer inevitable, especially in younger children.[28] However, we would certainly aim to avoid intubation at the stage when death is inevitable and end of life care is more appropriate. In the UK, this will usually include those waiting for transplant (although this is not necessarily the case in the USA). There can be an issue with patients dying on the waiting list, as the desire to keep going with active management in case organs become available at the last moment can mean death is not handled properly, and appropriate end of life care not instituted.[22 25 29] In our series none of the children were on the transplant waiting list, although two had previously received transplants.

Only 55% children who died were having long term oxygen therapy at home prior to their final illness; this figure seems somewhat low and for some was explained by the suddenness of their deterioration. There is surprisingly little evidence for its use in CF, however,[30] and in fact many patients adhere poorly to home oxygen, especially if it makes no difference to their symptoms. Only one child had used NIV prior to death for symptomatic relief of dyspnoea. There were concerns before initiating the NIV that it might complicate her end of life care, and prolong her suffering, but this did not turn out to be the case. Historically, concerns existed that mucus plugging in CF may be worsened by NIV, though this has been refuted with the use of positive pressure as an everyday adjunct to physiotherapy for many children. A randomised, crossover study in adults with CF suggested improved daytime functioning following the use of nocturnal NIV.[31] In spite of this, however, NIV use in paediatric CF is low, with around 0.4% of the UK and Australasian childhood CF population in receipt of therapeutic NIV, with use during acute exacerbations and also as a bridge to transplant.[32]

In conclusion, the number of deaths in children with CF is small. With the advent of new therapies, for example, small molecule cystic fibrosis transmembrane conductance regulator correctors and potentiators, it is hoped (and anticipated) that childhood deaths will become even rarer. Since death was not always predictable, active management was continued until quite late for the majority. This was reflected by the fact that almost all children in this series were in hospital, and more than half were ventilated at the time of death. If death from respiratory failure follows a steady decline, as is more often the case in adults, palliative care should be instituted well in advance, and be followed by appropriate end of life care.

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Notes