# Cystic fibrosis in adolescents and adults

MULHERIN D , WARD K, COFFEY M, KEOGAN MT, FITZGERALD M
*Adult Cystic Fibrosis Clinic, University College Dublin, St Vincent's Hospital, Elm Park, Dublin 4*

## Abstract

**A cystic fibrosis (CF) clinic for adults was established in 1977. We have reviewed the data on 164 patients who attended between 1977 and 1989. Twenty four patients had died, 11 being over 20 years of age at the time of death. Of the 140 patients still alive, 61% were male and 53% were aged over 20 years. Only 55% were diagnosed by one year and 88% by ten years.**

**Almost all patients had respiratory symptoms and sputum culture yielded pseudomonas species in 69%. Other respiratory problems included major haemoptysis and pneumothorax, each in 10%. We found a wide range of respiratory impairment among older patients. Among 33 patients aged over 23 years, the mean (±S.D.) percent predicted FEV1 and FVC were 53.3% (±18%) and 71.4 (±20%) respectively. Mean weight in this group was 92.5% (±14) of predicted. Malabsorption occurred in most patients and meconium ileus equivalent occurred in 34%. Other complications were clinical hepatomegaly (16%), diabetes mellitus (9%) and arthropathy (20%).**

**Most patients were taking continuous antibiotics by mouth (89%) and by nebuliser (48%), beta-2 agonists by inhaler (57%) and oral steroids (29%). Almost all were taking multivitamins, pancreatic replacement therapy and multiple nutritional supplements. The number of CF "bed days" grew 12 fold since 1979 and the mean stay in hospital was double the hospital mean. The economic impact was such that over 1/4 of the annual hospital antibiotic budget was expended on CF patients.**

## Introduction

Cystic fibrosis (CF) is an autosomal recessive condition affecting one in 1960 live births in Ireland and characterised by abnormal exocrine secretions and elevated sweat sodium.[1] The life expectancy of those with this condition has improved dramatically since it was first described by Andersen in 1938.[2] Some centres now report a twenty year survival of up to 80% for their patients.[3] As a result, the prevalence of CF among adults is increasing worldwide leading to the development of specialised adult CF centres with experienced multi-disciplinary teams to care for these patients.[4]

In 1977, a CF Clinic was established at this hospital to treat the growing number of adolescent patients being referred from paediatricians. The records of these patients have been computerised and this provided us with the opportunity to review our experience between 1977 and November 1989.

## Method

All patients who attended the CF Clinic between January 1977 and November 1989 were included in the review. Relevant information was stored in our cystic fibrosis database based on the Open Access 2 database (Software Products International Inc., San Diego, California). Some patients were no longer regular attenders at the CF Clinic but, where relevant data on these patients are complete, they have been included in the analysis, *e*

The diagnosis of CF was usually made prior to referral to the CF Clinic. In all cases, it was firmly based, with a compatible history, physical examination and a sweat sodium concentration above 70mmol/L obtained by pilocarpine iontophoresis on at least two occasions.[5] Details of presentation were provided by the referring hospital and confirmed with a parent or guardian, where possible.

A more detailed chart review was carried out on a group of older CF patients to obtain physiological data not available on the database. Records of Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC) and weight (wt) were obtained in these patients. These were expressed as a percentage of the predicted normal for that patient using standardised tables (%FEV1, %FVC, %wt)[6] and were analysed using Student's paired t test.

The data on the number of CF patients admitted and the number of inpatient bed days they required each year were obtained from the annual Hospital Inpatient Enquiry (H.I.P.E.) report augmented by ward records. Data on overall 1988 public inpatient bed days were obtained from the 1988 Report for St. Vincent's Hospital. The estimated average cost of drugs per admission in 1988 was calculated by dividing the total hospital pharmacy expenditure in 1988 by the total number of admissions in that year. The price given for a course of antibiotics is that pertaining in March 1990, inclusive of V.A.T.

## Results

**Structure of population -** In all, 164 patients attended the CF Clinic between 1977 and 1989. Twenty four died during that time. Table 1 gives a breakdown by age and sex of the 140 patients alive at the time of this review. There was a predominance of males with a ratio of males to females of 1.6 tol.

TABLE 1 - **Age and Sex Distribution**

| Age | Male | Female | Total | % |
|---|---|---|---|---|
| < 14 years | 6 | 2 | 8 | 6 |
| 14-17 years | 23 | 15 | 38 | 27 |
| 18-20 years | 15 | 5 | 20 | 14 |
| 21-25 years | 28 | 22 | 50 | 36 |
| 26-30 years | 12 | 5 | 17 | 12 |
| 31+years | 2 | 5 | 7 | 5 |
| Total | 86 | 54 | 140 | 100 |

Most patients (79%) were over 14 years old when referred to the CF Clinic. About half (48%) were referred from paediatricians. 15% of the patients were referred by adult physicians and 10% by family doctors. 13% came from Connaught/Ulster, 18% from Munster and 69% from Leinster, with 67% of the latter group from Dublin. The mean duration of follow-up for these patients at the CF Clinic was 4.9 years.

**Presenting Features -** The age at diagnosis is detailed in Table 2 and is correlated with the presenting features. The combination of respiratory symptoms, steatorrhoea and failure to thrive was found in only 13% of our patients at presentation. Only two patients presented as neonates with meconium ileus. Very late diagnosis was associated with more unusual presentations. Among the five patients diagnosed in their twenties, two presented with acute pancreatitis in addition to respiratory problems and one with recurrent pneumothoraces and weight loss.

**Respiratory Infections -** Virtually all patients have had respiratory symptoms at some time. 35% were under one year when these symptoms were first noted but four were over 20

TABLE 2 - **Age at diagnosis and presenting features**

| Age Groups | No. (Cumulative % Diagnosed) | Presenting Features. No.(%) | | |
|---|---|---|---|---|
| | | Respiratory Symptoms | GIT Features | Relative Affected |
| 0 - 6 mths | 73 (45) | 38 (52) | 25 (34) | 31 (42) |
| 6 - 12 mths | 16 (55) | 6 (38) | 10 (63) | 2 (13) |
| 1 - 5 years | 40 (79) | 26 (65) | 31 (78) | 10 (25) |
| 6 - 10 years | 14 (88) | 9 (64) | 5 (36) | 6 (43) |
| 10 - 20 years | 15 (97) | 11 (73) | 4 (27) | 4 (27) |
| 20+ years | 5 (100) | 5 (100) | 2 (40) | 0 |

* Individuals may have more than one presenting feature.

years when they first developed wheeze or cough. Most patients (69%) were chronically colonised by pseudomonas species, 59% by staphylococcus aureus and 38% by haemophilus influenzae. Three cases of mycobacterial infection were identified, including one case of mycobacterium avium - intracellullare infection. These cases were clinically unsuspected until the organisms were isolated in the laboratory.

**Respiratory Complications -** Fifty four (33%) patients have had haemoptysis and 17 have had at least one severe episode (>100ml.). One patient, with advanced pulmonary disease, died during such an episode. All were treated conservatively, at first, but four required transarterial bronchial artery embolisation to control the bleeding.[7] Spontaneous pneumothoraces occurred in 16 patients (10%) and in some cases, were recurrent. The majority resolved following chest tube insertion and simple drainage. Recurrent cases were treated by chemical pleurodesis but in one patient, thoracotomy was required.

**Gastroenterological Complications -** The vast majority of our patients had clinical evidence of exocrine pancreatic insufficiency and required oral pancreatic enzyme supplementation. Meconium ileus equivalent (MIE) occurred in 34% of our patients. Twenty seven patients had palpable hepatomegaly and 37% of those had oesophageal varices. The mean age of diagnosis of varices was 15 years (Range 10-21 years). Injection sclerotherapy has been used in those patients with a history of variceal bleeding. A significant proportion (9%) of patients had established persistent diabetes mellitus. This does not include the many patients who had developed transient glucose intolerance when administered glucocorticoids as treatment during infective exacerbations. The mean age of developing diabetes was 19 years (Range 10-28 years). Ten patients were taking subcutaneous insulin to maintain euglycaemia, three required simple dietary manipulation and two used oral hypoglycaemic agents. Documented cholelithiasis occurred in five cases and surgery was necessary for relief of symptoms in two.

**Arthropathy and vasculitis -** Many patients (20%) complained of arthropathy characterised by joint pain and swelling that was usually transient but could be persistent. Radiographic examination of the joint was normal in many cases but some had hypertrophic pulmonary osteo-arthropathy. Some had a synovial biopsy performed which had shown non specific inflammation in all except one case where amyloid had been identified in the synovium.[8] Five patients with arthropathy had biopsy proven cutaneous vasculitis which had manifested as a petechial rash or erythema nodosum.

**Fertility -** Seven patients had become pregnant. One had a miscarriage and another sought a termination of pregnancy outside of the country. The remaining five women had full term normal deliveries. The oldest male patient, aged 42, who was diagnosed when he was 29 years old, is the only male who has a child. All other males patients who have requested seminal analysis have been found to be azoospermic.

**Medical Therapy -** Virtually all of our patients were taking daily oral fat soluble vitamin supplementation and also oral pancreatic enzyme replacement therapy. We reviewed the other medical agents used by the 100 patients regularly attending the clinic and excluded from analysis those patients not seen in the previous year. Almost all (89%) used daily oral antibiotics directed against Staphylococcus aureus and / or haemophilus influenzae. Additionally, 48% used twice daily nebulised anti-pseudomonal antibiotics, usually colistin or gentamicin.

Many patients had significant reversible airflow obstruction that required bronchodilator therapy: 57% were taking beta-2 agonists by metered dose inhalers and 36% by nebuliser; 49% were taking oral theophylline preparations and 40% used metered dose inhaled glucocorticoids; finally, 29% were taking oral glucocorticoids, usually 5-lOmg prednisolone daily. Aspergillus fumigatus precipitins, one of the recognised features of allergic bronchopulmonary aspergillosis (ABPA), were found in the serum of 68 of 119 patients tested (57%).

**Adult Group -** Of the 100 regular attenders at the clinic, 33 were aged over 23 years and we reviewed their casenotes in greater detail. Table 3 gives the details of this analysis. The male and female groups were well matched in terms of age and duration of follow-up. The range of pulmonary function and nutritional status in these older patients is very wide. There was no statistically significant difference between males and females for the parameters measured. However at the time of first attendance, mean %FEV1 in males tended to be higher than in females but this trend had disappeared at their last visit after 9.8 years mean follow up.

TABLE 3 - **The older patients (>23 years)**

| | Males | Females |
|---|---|---|
| Number | 20 | 13 |
| Mean Age (Years) | 26.9 | 26.4 |
| Age at diagnosis | | |
| 0- 12 mths | 11 | 5 |
| 1 - 5 years | 4 | 3 |
| 6-15 years | 3 | 3 |
| 15+ years | 2 | 2 |
| Follow up in years | | |
| Mean (S.D.) | 10 (3) | 9.5 (3) |
| Mean %FEV1 (S.D.) | | |
| At first attendance | 70.8 (23) | 60.3 (19) |
| At last attendance | 53.5 (20) | 53.0 (16) |
| Mean Decline | 17.3 (23) | 7.3 (20) |
| Mean %FVC (S.D.) | | |
| At first attendance | 77.9 (19) | 71.8 (20) |
| At last attendance | 74.7 (22) | 66.4 (16) |
| Mean Decline | 3.2 | 5.4 (25) |
| Mean %wt (S.D.) | | |
| At last attendance | 89.7 (15) | 97.0 (11) |

**Morbidity and Resource Implications -** There had been a steady increase in the number of inpatients and outpatients. The total number of inpatient bed days for these patients has increased almost 12 fold between 1979 and 1988. In 1988 alone, these patients, who represent 0.4% of the 18,107 admissions in 1988, accounted for 1% of the total of 124,122 public inpatient bed days in that year. The average length of stay in hospital in CF patients in 1988 was 16.9 days, over double the 7.6 day average for the hospital as a whole. The cost of a typical two week course of intravenous antibiotics for a CF patient with a respiratory infection ranged from IR£360.25 (Ticarcillin/Clavulanic acid and Gentamicin) to IRE 1,342.26 (Ceftazidime and Gentamicin). The cost of antibiotics alone for each patient, therefore, is between five and 20 times the cost of all the drugs used by the average hospital patient in 1988 (IR£62.31) and the total cost of

antibiotics for CF patients represents nearly one third of the total hospital budget for antibiotics. In addition to drug costs, it is difficult to quantify the cost of the labour intensive, highly skilled care which these patients require.

**Mortality** -Twenty-four of our patients have died since the CF Clinic was established. Respiratory failure was by far the most common cause of death, causing 14 of the 19 deaths (74%) where the cause was clearly established. In addition, one patient died from massive haemoptysis with coexistent end stage lung disease. Three patients died with advanced liver failure and one patient with a suspected brain abscess. The mean age at time of death was 19.4 years (range 14-28) with 11 patients over 20 years when they died.

The average number of siblings in the families of our CF patients was 2.8. Almost half (48%) of the patients had at least one sibling with CF and one third (30%) had a sibling who died from CF.

## Discussion

This is the first detailed analysis of older CF patients in Ireland and is one of the largest series of adult CF patients published to date. Hodson and colleagues published their experience of 316 patients in 1987, but other series have been smaller.[9,10,11]

Analysis of our data confirms the complex multisystem nature of this condition in surviving adults and adolescents. Furthermore, it highlights the profound clinical, psychological and socioeconomic impact of this disease on CF sufferers, their families and the health services. As other series have noted, there is a significant male predominance in our study: this probably reflects the improved survival of males with CF.[9,12] The pattern of diagnosis, both in terms of age and presenting features, reflects previous experience at other centres, with only 55% cases diagnosed by one year and with respiratory symptoms and malabsorption featuring strongly. Some modes of presentation, which carry a poorer prognosis than others, are under-represented in our patients who constitute a "survivor" population.[13] Meconium ileus has been recorded in up to 15% of neonates with CF[14] but only 1% of our patients had presented with it, reflecting the poor survival rate associated with it in the past.

The pattern of sputum colonisation in our patients shows the predominance of pseudomonas species (69%) seen at other centres.[9] Half (48%) of our patients use regular nebulised anti-pseudomonal antibiotics which has been shown to be of benefit to those with troublesome pseudomonal infection.[16,17]

Our case of atypical mycobacterial infection emphasises the importance of this infection in a small number of these patients.[18] A high proportion (57%) have positive serology for aspergillus fumigatus and in previous work, we have identified other markers for atopy.[19]

In older patients with CF and exocrine pancreatic insufficiency, MIE is a well recognised complication.[20] We have established a policy of aggressive treatment usually including oral lactulose and N-acetylcysteine with gastrografin by mouth and by enema. A small number of severe cases require polyethylene glycol solution via a nasogastric tube.[21] Prophylaxis is emphasised in recurrent cases and in addition, drugs are avoided which may facilitate the development of MIE.[22]

The dramatic improvement in the survival of CF patients over the past fifty years has led to an increasing cohort of adult patients who now represent up to 25% of all CF patients.[4] British data suggest that 49.5% survival to 20 years.[3] In many countries, specialised units, such as ours, have developed to treat these adults and it is recognised that these have contributed to improved survival and, in addition, have advanced our understanding of CF through coordinated research.[23,24]

The spectrum of clinical severity found in the older CF patients is enormous, as evidenced by analysis of the status of those patients aged over 23 years. Pulmonary function ranged from normal to severely impaired with a similar pattern in nutritional status. The trend in %FEV1 and %FVC over the 9.8 years of follow-up was towards decline in both, but it was of interest that the rate of decline in females was no greater than in males during this time. It may be that those females that survive the decline noted in teenage years may have a similar prognosis to their male peers.[4,11,25]

There are enormous stresses in the lives of these young patients and their families[26] as they live with an ongoing threat to life. This is heightened by the death of their friends and, for up to a third of our patients, the death of CF siblings. In addition, they require time-consuming therapy on a daily basis, relentlessly reminding them of the significant limitations imposed by their disease and the curtailment of a normal lifestyle.[27] Their struggle to complete their education and achieve their full potential in employment is hampered by repeated hospital admission through illness. Even the most robust of personalities experiences psychological difficulties **at** some time and requires considerable help in coping with their problems. Attempts are been made at many units, including ours, to promote home treatment programmes so that there is as little disruption to a normal lifestyle as possible.[28]

Although paediatric hospitals are accustomed to treating CF, it is a relatively recent development for an adult general hospital. The burden of care for these complex patients, who are chronically ill and require expensive treatment, places a considerable strain on the staff and resources of an acute general hospital. With the increasing number of patients seen at the clinic, the difficulties inherent in caring for them are also increasing. The British Paediatric Association has specified the minimum staffing levels required to run a CF centre[29], which should include a consultant physician supported by junior medical staff, a nurse, two physiotherapists, laboratory technician, parttime dietitian, social worker and secretary per 50 patients. Unfortunately, these standards are rarely met and at this CF Clinic, the patients are cared for within existing staff complements.

Heart-lung transplantation (HLT) offers some hope to CF patients with advanced respiratory disease.[30,31] To date, close to 100 patients with CF have had this operation worldwide and about 60-75% have survived beyond one year at some centres. However, this operation is not without its complications, and, in addition, the small number of units performing this operation has limited the impact of HLT on overall survival in CF. Although Irish patients can undergo HLT in Great Britain, logistical factors such as the distances involved and the scarcity of donor organs make it an uncommon occurrence. For most Irish patients, there is little prospect of HLT until a transplantation programme is established in this country or a firm contractual agreement is entered into by the appropriate Irish authorities and a UK based transplant centre. Currently, it is estimated that about 5% of the 700 or so CF patients in this country are suitable for HLT. This estimate is based on a recent CF Association of Ireland questionnaire survey which asked physicians to identify patients with CF who, in their opinion, were not likely to survive another two years.

In other countries, where prenatal diagnosis and termination of pregnancy are available, there may be a gradual decline in the incidence of CF seen over coming years.[32] However, in the absence of this approach in Ireland, this trend is unlikely to be seen. Therefore, it can be anticipated that the number of Irish adults CF patients will continue to increase. This has major implications for the delivery of future specialised services to this unique cohort of patients.

## Acknowledgements

We wish to thank the Cystic Fibrosis Association of Ireland for their assistance and financial support. We would also like to thank our medical colleagues and staff in St Vincent's Hospital.

## References


1 De Arce M, Mulherin D, McWilliams P, Lawler M, FitzGerald MX, Humphries P. Frequency of deletion 508 among Irish Cystic Fibrosis patients. *Hum Genet* 1990; 85;403-4.

2 Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac diseases. *AmJDis Child* 1938; **56:** 344-99.

3 Phelan P, Hey E. Cystic fibrosis mortality in England and Wales and in Victoria, Australia 1976-80. *Arch Dis Child* 1984; **59**:71-3.

4 British Paediatric Association Working Party on Cystic Fibrosis. Cystic Fibrosis in the United Kingdom 1977-85: an improving picture. *Br Med J* 1988;**297**:1599-602.

5 Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilising pilocarpine by iontophoresis. *Pediatrics* 1959; **23**: 545-9.

6 Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. W.B. Saunders Co., Philadelphia. 1971.

7 Schuster SR, Fellows KE. Management of major hemoptysis in patients with cystic fibrosis. *J Pediatr Surg* 1977; **12**: 889-96.

8 Bourke S, Rooney M, Fitzgerald M, Bresnihan B. Episodic arthropathy in adult cystic fibrosis. *Q J Med* 1987; **224**: 651-9.

9 Penketh ARL, Wise A, Mearns MB, Hodson ME, Batten JC. Cystic fibrosis in adolescents and adults. *Thorax* 1987; **42**: 526-32.

10 Shwachman H, Kowalski N, Kahw KT. Cystic fibrosis, a new outlook. 70 patients above 25 years of age. *Medicine* 1977; **56:** 129-49.

11 Di Sant'Agnese PA, Davies PB. Cystic fibrosis in adults. 75 cases and a review of 232 cases in the literature. *Am J Med* 1979; **66:** 121-132.

12 Michalsen H. Cystic fibrosis in Norway. *Scand J Gastroenterol* [Suppl 143] 1988;**23**:31-33.

13 Wilmott RW, Tyson SL, Dinwiddie R, Matthew DJ. Survival rates in cystic fibrosis. *Arch Dis Child* 1983; **58**: 835-6.

14 Sturgess JM, Czegledy-Nagy E, Corey M, Thompson MW. Cystic fibrosis in Ontario. *Am J Med Genet* 1985; **22**: 383-93.

15 Friend PA, Pulmonary infection in cystic fibrosis. *J Inf* 1986:**13:** 55-72.

16 Hodson ME, Penketh AR, Batten JC. Aerosol carbenicillin and gentamicin treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis. *Lancet* 1981; **2**: 1137-9.

17 MacLusky I, Levison H, Gold R, McLaughlin FJ. Inhaled antibiotics in cystic fibrosis: is there a therapeutic effect? *J Pediatric* 1986; **108:** 861-5.

18 Mulherin D, Coffey MJ, O'Halloran D, Keogan MT, FitzGerald MX. Skin reactivity to atypical mycobacteria in cystic fibrosis. *Resp Med* 1990; **84:** 273-6.

19 Ward K, Coffey M, FitzGerald MX. Atopy: a prognostic indicator of mortality and morbidity in adult cystic fibrosis? *Am Rev Resp Dis* 1988; **137:**304.

20 Hanly JG, FitzGerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *Br Med J* 1983; **286:** 1411-3.

21 Davidson AC, Harrison K, Steinfort CL, Geddes DM. Distal intestinal obstruction syndrome in cystic fibrosis treated by oral intestinal lavage, and a case of recurrent obstruction despite normal pancreatic function. *Thorax* 1987; **42**: 528-41.

22 Mulherin D, Fitzgerald M. Meconium ileus equivalent in association with nebulised ipratropium bromide in cystic fibrosis. *Lancet* 1990; **335**: 552.

23 David TJ. The case for cystic fibrosis centres. *J Roy S Med* 1987 [suppl 15]; **80**; 51-4.

24 Anonymous. Survival in cystic fibrosis. *Lancet* 1984; **I:** 663-4.

25 Huang NN, Schidlow DV, Szatrowski TH, et al. Clinical features, survival rate and prognostic factors in young adults with cystic fibrosis. *Am J Med* 1987;**82**: 871-9.

26 Miller MS. Role of the mental health professional in cystic fibrosis. 10th International Cystic Fibrosis Congress, Sydney, Australia. 1988 Excerpta Medica, Hong Kong 124-9.

27 Webber BA. Is postural drainage necessary? 10th International Cystic Fibrosis Congress, Sydney, Australia. 1988 Excerpta medica. Hong Kong 29-35.

28 Stead RJ, Davidson TI, Duncan FR, Hodson ME, Batten JC. Use of a totally implantable system for venous in cystic fibrosis. *Thorax* 1987; **42**:149-50.

29 Jackson ADM. Working party on cystic fibrosis. *Arch Dis Child* 1986; **61**:724. Dark J, Corns PA. The current state of lung transplantation. *Thorax* 1989; **44:**689-92.

30 Tsang V, Khagani A, FitzGerald M, Banner M, Hodson ME, Yacoub M, Heart and lung tranplantation for cystic fibrosis. Proceedings of the 16th Annual Meeting of the European Working Group for Cystic Fibrosis. Prague, 1989; 172.

31 Whitehead B, Helms P, Goodwin M et al. Heart-lung transplantation for children with cystic fibrosis. *Thorax* 1990; **45:** 316P.

32 Dodge JA. Implications of the new genetics for screening for cystic fibrosis. *Lancet* 1988; **ii:** 672-4.



Correspondence: Professor MX FitzGerald, Medical Professorial Unit, St Vincent's Hospital, Elm Park, Dublin 4.