



Improving outcomes in patients with cystic fibrosis

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Dr Geoffrey Warwick
MBChB MD MRCP
Locum Consultant, Respiratory Medicine

Dr Caroline Elston
MBBS FRCP
Consultant in Adult Cystic Fibrosis and Respiratory Medicine
Adult Cystic Fibrosis Unit, King's College Hospital, London



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AUTHORS **Dr Geoffrey Warwick**

MBChB MD MRCP
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Respiratory Medicine

Dr Caroline Elston

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Cystic Fibrosis and
Respiratory Medicine

Adult Cystic Fibrosis Unit,
King's College Hospital,
London



Nebulised therapy is one of the mainstays of cystic fibrosis management



CYSTIC FIBROSIS (CF) IS THE MOST COMMON FATAL INHERITED DISEASE IN CAUCASIAN PEOPLE.

Inheritance follows an autosomal recessive pattern. Recent data indicate that there are more than 9,000 patients with CF in the UK.¹ This would equate to around one or two patients for an average GP practice.

At a cellular level, there is an abnormal CF transmembrane conductance regulator (CFTR), a protein essential for

chloride and sodium homeostasis, caused by a mutation in the CF gene. The most common mutation is $\Delta F508$, although more than 1,500 mutations have been identified. The consequence of this abnormal protein is thick, viscous secretions in the lungs and gastrointestinal tract, which lead to recurrent lung infections and pancreatic insufficiency with intestinal malabsorption.

CF is a multisystem disease and extrapulmonary manifestations are common.

How is cystic fibrosis diagnosed?

What factors affect prognosis?

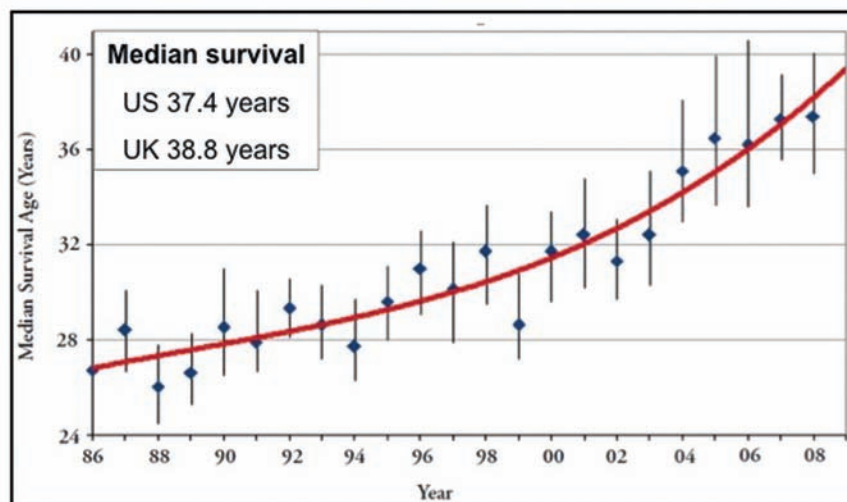
How can exacerbations be prevented?

Most patients present in early childhood with classic or typical CF. They demonstrate one or more of the typical CF phenotypic characteristics (chronic pulmonary disease, gastrointestinal symptoms and malabsorption, nutritional abnormalities, sinus disease), a high sweat chloride concentration and, in the majority, a disease-causing mutation on each CFTR gene. It is not uncommon to identify only one disease-causing CFTR mutation on gene testing, since a



SPECIAL REPORT

CYSTIC FIBROSIS



Source: CFF registry 2008 & UK Annual CF Registry (CF Trust), Data Report 2008

FIGURE 1

Improvement in median survival of patients with cystic fibrosis (1986 to 2008)

screening panel of around fifty mutations is employed. If patients have typical symptoms and a diagnostic sweat test, as is usually the case in classic disease, there is no requirement to look further. If the diagnosis is less certain, e.g. the sweat test is equivocal or symptoms are mild (as may be the case in atypical disease) then extensive mutation screening may be required.

A minority of patients are deemed to have non-classic or atypical CF. They may have only one characteristic feature of CF, a borderline or normal sweat test and either two disease-causing CFTR mutations or an abnormal nasal potential difference measurement.

Nasal potential difference is an investigation carried out in only a few specialist centres. The electrical response of the nasal epithelium to the instillation of various fluids is measured by means of an electrode. In CF patients, this response differs from normal patients in a characteristic pattern and is a marker of CFTR dysfunction.

Patients with atypical CF tend to present at an older age, often in adulthood, are mainly pancreatic sufficient, have milder disease and a better prognosis. Clinicians must, therefore, have a high index of suspicion in cases where suggestive symptoms are present and non-typical CF may be a possibility.

Recognising the symptoms and signs that may point to a diagnosis of CF is important so that appropriate referral and investigations can be organised.

Symptoms suggestive of CF in the first two years of life include failure to

thrive, steatorrhoea, recurrent chest infections, meconium ileus, rectal prolapse and prolonged neonatal jaundice. In older children, additional suggestive symptoms include 'asthma'-like symptoms, clubbing and idiopathic bronchiectasis, nasal polyps and sinusitis, and heat exhaustion with hyponatraemia.

Suggestive symptoms in patients who present in adulthood, who are more likely to have atypical CF, include azoospermia, bronchiectasis, chronic sinusitis, acute or chronic pancreatitis, allergic bronchopulmonary aspergillosis, focal biliary cirrhosis, abnormal glucose tolerance, portal hypertension and cholestasis/gallstones.

PROGNOSIS

A number of factors affect prognosis in CF patients. Survival is closely related to lung function^{2–4} and great efforts are therefore made to minimise loss of FEV₁. Colonisation of the lower airways with certain bacteria can confer a worse prognosis, in particular, *Pseudomonas aeruginosa*⁵ and *Burkholderia cepacia*.⁶ Consequently, attempts are made to eradicate *Pseudomonas* when it is first isolated (see below). More frequent pulmonary exacerbations are associated with an accelerated decline in FEV₁,⁷ underpinning the importance of prompt and effective management of infections.

Other factors associated with a worse prognosis are diabetes⁸ and poor nutritional status.⁹ A better prognosis is seen in patients who are pancreatic-sufficient¹⁰ although this is the minority.

When CF was first described, the

outlook was poor; most babies died in infancy. It was with the introduction of antibiotics and pancreatic enzyme replacement, treatments which remain pillars of modern-day management, that life expectancy began to improve. In the past few decades, with continual advances in management, the prognosis for CF patients has improved significantly (see figure 1, above). The current median survival for CF patients in the UK is 38.8 years¹¹ and a patient born today with CF can expect to live to the age of 50 or beyond.¹²

DIAGNOSIS

When CF is suspected the diagnosis can be confirmed by measuring the sweat chloride concentration and by looking for CFTR mutations. Late diagnosis of CF leads to worse outcomes.¹³ A newborn screening programme was introduced in the UK in 2007. Immunoreactive trypsinogen is measured in blood taken from a heel prick in all neonates, and is a marker of pancreatic injury consistent with (but not specific for) CF. Newborn screening leads to improved nutritional outcomes which may lead to improved pulmonary function in later life.^{14,15}

CARE SETTING

It has been shown that clinical outcomes are better for CF patients managed in dedicated paediatric and adult CF centres.¹⁶ CF care in the UK is provided by regional specialist centres, operating to nationally approved standards.¹⁷ Care is provided by a dedicated multidisciplinary team which includes

key points

SELECTED BY

Dr Peter Saul

GP, Wrexham and associate GP Dean for North Wales

Cystic fibrosis (CF) is the most common fatal inherited disease in Caucasian people. Inheritance follows an autosomal recessive pattern. At a cellular level there is an abnormal CF transmembrane conductance regulator (CFTR), a protein essential for chloride and sodium homeostasis, caused by a mutation in the CF gene. The consequence of this abnormal protein is thick, viscous secretions in the lungs and GI tract, which lead to recurrent lung infections and pancreatic insufficiency with intestinal malabsorption.

Most patients present in early childhood with classic or typical CF. They demonstrate one or more of the typical CF phenotypic characteristics (chronic pulmonary disease, GI symptoms and malabsorption, nutritional abnormalities and sinus disease). A minority of patients have non-classic or atypical CF. They tend to present at an older age, often in adulthood, are mainly pancreatic sufficient, have milder disease and a better prognosis.

Survival is closely related to lung function and great efforts are therefore made to minimise loss of FEV₁. Colonisation of the lower airways with certain bacteria can confer a worse prognosis, in particular, *Pseudomonas aeruginosa* and *Burkholderia cepacia*. Consequently, attempts are made to eradicate *Pseudomonas* when it is first isolated. Other factors associated with a worse prognosis are diabetes and poor nutritional status.

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When CF is suspected the diagnosis can be confirmed by measuring the sweat chloride concentration and by looking for CFTR mutations. Immunoreactive trypsinogen is measured in blood taken from a heel prick in all neonates, and is a marker of pancreatic injury consistent with (but not specific for) CF.

CF is characterised by chronic bacterial infection of the lower airways with intermittent pulmonary exacerbations, when patients have increased respiratory symptoms, particularly cough and increased volume and purulence of sputum. Clinical outcomes are better for patients managed in dedicated paediatric and adult CF centres.

Courses of antibiotics are typically longer and at higher doses in CF. Oral antibiotics can be used for minor exacerbations, but IV antibiotics are more often required. Chronic *Pseudomonas* infection is associated with a more rapid decline in lung function and a reduction in long-term survival. Prevention or delay of the onset of chronic infection is a priority. Nebulised antibiotics are prescribed for patients chronically colonised with *Pseudomonas*, leading to less frequent use of IV antibiotics, fewer admissions and better preservation of lung function.

doctors, specialist nurses, physiotherapists and dietitians, with access to other hospital specialists who can deal with the CF complications, e.g. diabetologists and gastroenterologists. Patients receive regular monitoring and are reviewed at least three monthly.

Many centres offer homecare services. Intravenous antibiotics may be administered by patients at home, which has been shown to be a safe, practical and acceptable alternative to hospital treatment and, if patients are appropriately selected, outcomes are similar.^{18,19} However, treatment must be closely monitored by the hospital team.

GPs have an important role in communication and ongoing support of patients with CF and their families. It is important that GPs maintain close communication with their local specialist centre so that optimal treatment can be delivered.

The GP is responsible for ongoing prescription of much of the routine treatment recommended by the specialist CF centre. It is essential that CF centres keep GPs adequately informed about the medication recommended, some of which may be unfamiliar and may be off licence.

In between hospital visits patients may present to their GP with minor pulmonary exacerbations, and may request courses of oral antibiotics which should be of an appropriate length (typically two weeks) and guided by previous sputum cultures. If patients fail to respond they should be encouraged to attend their specialist centre for further review. GPs should ensure patients are fully immunised, including arranging for a yearly influenza vaccination. In some instances, practice nurses are involved in the care of patients, e.g. in the regular flushing of portacaths.

Towards the end of a patient's life, the GP practice may have an important role in terminal care and later bereavement counselling.

TREATMENT OF LUNG INFECTIONS

CF is characterised by chronic bacterial infection of the lower airways with intermittent pulmonary exacerbations, when patients have increased respiratory symptoms, particularly cough and increased volume and purulence of sputum.

Antibiotic therapy has been the mainstay of CF therapy for decades. Courses of antibiotics are typically longer and at higher doses than for other patients owing to enhanced

clearance of many drugs in CF.²⁰ Oral antibiotics can be used for minor exacerbations, but intravenous antibiotics are more often required. The choice of antibiotics is guided by respiratory tract cultures. Patients may have long lines or indwelling ports inserted, facilitating intravenous access.

Chronic *Pseudomonas* infection is associated with a more rapid decline in lung function and a reduction in long-term survival.⁵ Prevention or delay of the onset of chronic infection is, therefore, a management priority. On first isolation, an eradication course is instituted that typically comprises a combination of oral ciprofloxacin with nebulised colistin for three months, which clears the organism in the majority of cases. Repeated attempts at eradication, when it is intermittently cultured, may also be successful in delaying the inevitable long-term colonisation.²¹

PREVENTING EXACERBATIONS

An essential part of the management of CF is maintenance therapy, which decreases the frequency of exacerbations, improves lung function and stabilises disease.

Antibiotics

Nebulised antibiotics are prescribed for patients chronically colonised with *Pseudomonas*, leading to less frequent use of intravenous antibiotics, fewer admissions and better preservation of lung function.²² Newer nebuliser devices allow faster treatment times and greater portability. Colistin, tobramycin and aztreonam are established nebulised antibiotics in the UK, although there are several other antibiotics in development, e.g. amikacin.

In addition to their antibiotic properties, macrolide antibiotics have been shown to have an anti-inflammatory, immunomodulatory effect. Azithromycin, given three days a week, has been shown to produce a modest improvement in lung function and weight gain and a reduction in the number of pulmonary exacerbations in patients chronically infected with *Pseudomonas*.²³

Mucolytics

The sputum of patients with CF contains large amounts of DNA, released from degenerating neutrophils, and this contributes to sputum viscosity. Recombinant human DNase (rhDNase) reduces sputum viscosity and has been shown to increase lung function and weight, and reduces the frequency of pulmonary exacerbations.²⁴ Recent

SPECIAL REPORT

CYSTIC FIBROSIS

epidemiological data suggests that the use of mucolytic therapy has contributed to improved survival in the most severe cases.²⁵ Additionally, regular use of nebulised hypertonic saline leads to an increase in lung function, less frequent exacerbations and better quality of life.²⁶

PHYSIOTHERAPY

Physiotherapy has long been a central component of CF care. Older techniques for airway clearance such as postural drainage and percussion (tip and tap) have given way to newer forced expiratory techniques, such as the active cycle of breathing and autogenic drainage.

There is no evidence that any one technique is superior to another and therapy is, therefore, tailored to suit the individual patient's preferences and requirements.

Adjuncts to physiotherapy are available such as the positive expiratory pressure (PEP) and flutter devices, intermittent positive pressure breathing (the Bird ventilator), and non-invasive ventilation may be used to improve clearance of secretions.

A PEP mask contains a valve through which patients blow during physiotherapy. This generates positive pressure in the airways, keeping them open and allowing air flow to reach beyond areas of mucous obstruction and move the mucus towards the larger airways, where it can be coughed up. A flutter, or oscillating PEP, contains a steel ball that oscillates during expiration. These oscillations are transmitted to the airways where they loosen and mobilise secretions.

NUTRITION

The majority of CF patients are pancreatic insufficient. The diagnosis of pancreatic insufficiency can be confirmed by the measurement of faecal pancreatic elastase. The resulting malabsorption, coupled with typically increased energy requirements, can lead to malnutrition and this significantly impacts on prognosis.⁹

Close involvement of the dietitian is essential to maintain body weight and optimise absorption of fat soluble vitamins. Patients take oral pancreatic enzyme replacement with meals and learn to adjust their dose according to the fat content of their meals.

In some cases, in order to maintain nutritional requirements, supplemental overnight feeding may be required and patients may have a feeding tube (PEG) inserted.

FUTURE DIRECTIONS

Gene therapy has been the subject of research for many years. The search for an effective vector to insert normally functioning DNA into affected cells has progressed slowly but candidate agents are in development.²⁷ Trials of gene therapy are ongoing, coordinated by the UK Cystic Fibrosis Gene Therapy Consortium. An alternative approach is provided by drugs that modulate CFTR, targeted at specific defects in CFTR transcription, processing or functioning. Of a number of agents currently in development, the most promising is VX-770, a CFTR potentiator, and initial data from phase III trials have been encouraging. Results from larger studies are awaited. Other agents currently in development include drugs to restore airway surface liquid, anti-inflammatory agents and new anti-infective agents.²⁸

CONCLUSIONS

The outlook for patients with CF has improved significantly in the past few decades. Provision of care by multidisciplinary teams in dedicated specialist centres, aggressive treatment of infections and newer, evidence-based therapies have all contributed to this improved survival. With ongoing research into novel therapies, continued improvement can be expected in the prospects for patients with CF.

Further reading

Mogayzel PJ Jr, Flume PA. Update in Cystic Fibrosis 2009. *Am J Respir Crit Care Med* 2010; 181(6):539–44

REFERENCES

- 1 Final UK Cystic Fibrosis Registry Report 2009 www.cftrust.org.uk/aboutcf/publications/cfregistryreports/Final_UK_Cystic_Fibrosis_Registry_Report_2009.pdf
- 2 Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada, 1970–1989. *Am J Epidemiol* 1996;143(10):1007–17
- 3 Hayllar KM, Williams SG, Wise AE et al. A prognostic model for the prediction of survival in cystic fibrosis. *Thorax* 1997; 52(4):313–7
- 4 Kerem E, Reisman J, Corey M et al. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326(18):1187–91
- 5 Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol* 1992;12(3):158–61
- 6 Muhdi K, Edenborough FP, Gumery L et al. Outcome for patients colonised with *Burkholderia cepacia* in a Birmingham adult cystic fibrosis clinic and the end of an epidemic. *Thorax* 1996;51(4):374–7
- 7 Konstan MW, Morgan WJ, Butler SM et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatrics* 2007;151(2):134–9.e1
- 8 Moran A, Dunitz J, Nathan B et al. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32(9):1626–31
- 9 Corey M, McLaughlin FJ, Williams M et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41(6):583–91
- 10 Correlation between genotype and phenotype in patients with cystic fibrosis. The Cystic Fibrosis Genotype-Phenotype Consortium. *N Engl J Med* 1993;329(18):1308–13
- 11 UK CF Registry Annual Data Report 2008. From www.cftrust.org.uk/aboutcf/publications/cfregistryreports/

- 12 Dodge JA, Lewis PA, Stanton M et al. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Europ Resp J* 2007;29(3):522–6
- 13 Sims EJ, Clark A, McCormick J et al. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics* 2007;119(1):19–28
- 14 Farrell PM, Kosorok MR, Laxova A et al. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med* 1997;337(14):963–9
- 15 McKay KO, Waters DL, Gaskin KJ. The influence of newborn screening for cystic fibrosis on pulmonary outcomes in New South Wales. *J Pediatrics* 2005;147(3, Supplement 1):S47–S50
- 16 Mahadeva R, Webb K, Westerbeek RC et al. Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study. *BMJ* 1998; 316(7147):1771–5
- 17 CF Trust 2001. Standards for the clinical care of children and adults with cystic fibrosis in the UK. www.cftrust.org.uk/aboutcf/publications/consensusdoc/
- 18 Pond M, Newport M, Joanes D et al. Home versus hospital intravenous antibiotic therapy in the treatment of young adults with cystic fibrosis. *Europ Resp J* 1994;7(9):1640–4
- 19 Riethmueller J, Busch A, Damm V et al. Home and hospital antibiotic treatment prove similarly effective in cystic fibrosis. *Infection* 2002;30(6):387–91
- 20 de Groot R, Smith AL. Antibiotic pharmacokinetics in cystic fibrosis. Differences and clinical significance. *Clin Pharmacokinet* 1987;13(4):228–53
- 21 Smyth A. Update on treatment of pulmonary exacerbations in cystic fibrosis. *Curr Opin Pulm Med* 2006;12(6):440–4
- 22 Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest* 2001;120(3 suppl):107S–13S
- 23 Saiman L, Marshall BC, Mayer-Hamblett N et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*. *JAMA* 2003;290(13):1749–56
- 24 Fuchs HJ, Borowitz DS, Christiansen DH et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331(10):637–42
- 25 George PM, Banya W, Pareek N et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. *BMJ* 2011; 342: d1008
- 26 Elkins MR, Robinson M, Rose BR et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354(3):229–40
- 27 Davies JC, Alton EFWF. Gene therapy for cystic fibrosis. *Proc Am Thorac Soc* 2010;7(6):408–14
- 28 Anderson P. Emerging therapies in cystic fibrosis. *Ther Adv Respir Dis* 2010;4(3):177–85

Useful information

The Cystic Fibrosis Trust is a national charity in the UK which funds research into the disease and provides information and support to patients and families www.cftrust.org.uk

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