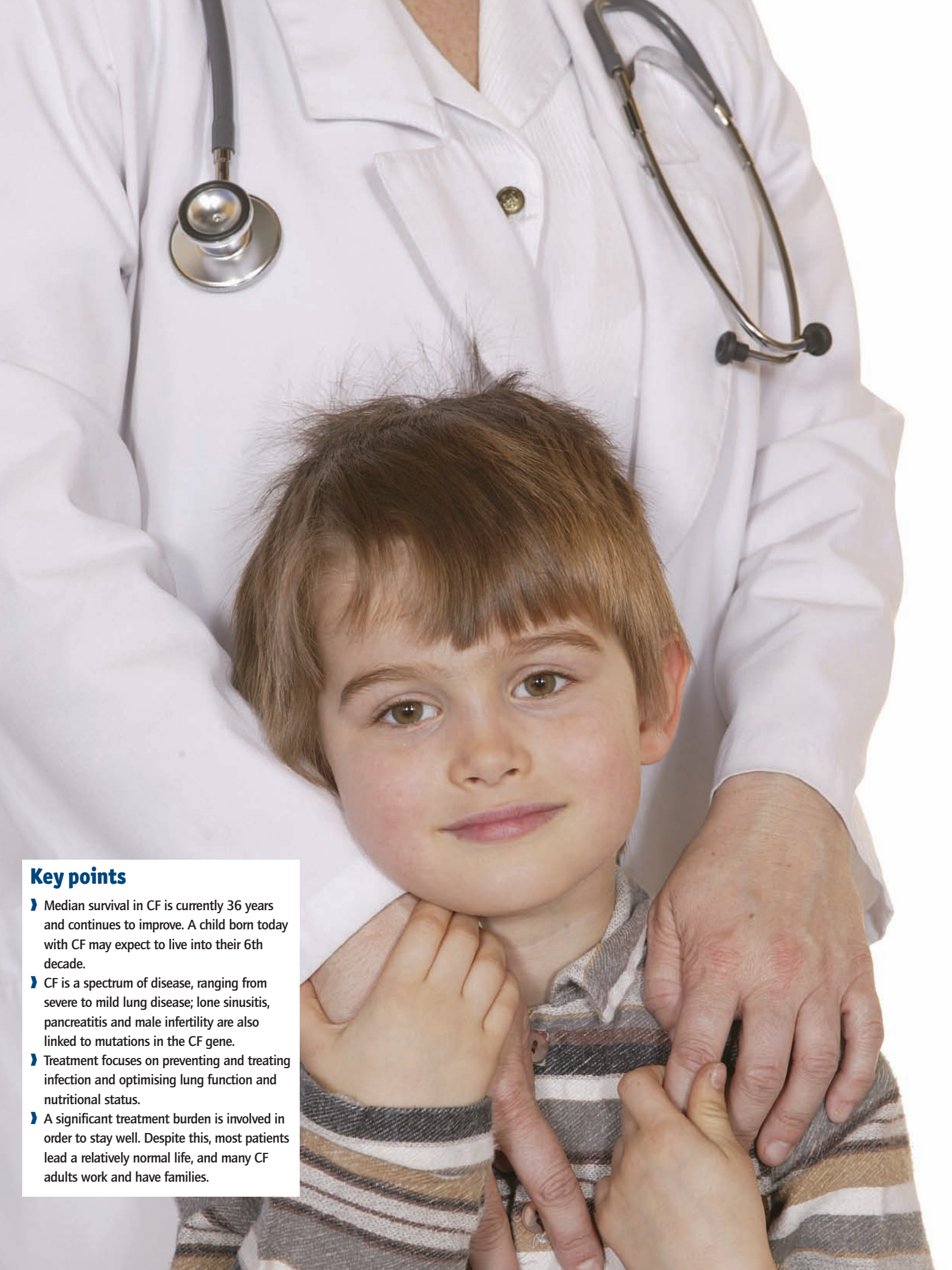

Key points

- Median survival in CF is currently 36 years and continues to improve. A child born today with CF may expect to live into their 6th decade.
- CF is a spectrum of disease, ranging from severe to mild lung disease; lone sinusitis, pancreatitis and male infertility are also linked to mutations in the CF gene.
- Treatment focuses on preventing and treating infection and optimising lung function and nutritional status.
- A significant treatment burden is involved in order to stay well. Despite this, most patients lead a relatively normal life, and many CF adults work and have families.

The ERS designates this educational activity for a maximum of 1 CME credit. For information on how to earn CME credits, see page 99.

The future for a child born with cystic fibrosis today

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Educational aims

- To make readers aware of the improved prognosis for patients with CF.
- To recognise that CF is a spectrum of disease.
- To familiarise readers with the management options and the burden of treatment involved.

Summary

Cystic fibrosis (CF) was previously considered to be a childhood disease, with very few patients surviving into adulthood. The past few decades have seen major advances in our knowledge and understanding of this disease. As a result, a child born with CF today can expect a much improved life expectancy and quality of life. This article aims to give an overview of the considerable treatment that is involved and discuss some of the emerging problems associated with this improvement in survival.

CF is a complex, multi-system disease, with a predilection for the lungs and gastrointestinal tract. It is caused by mutations in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. It is the most common fatal inheritable disease in Caucasian populations, and chronic lung infection and inflammation leading to bronchiectasis (figure 1) and ultimately respiratory failure account for most of the morbidity and mortality associated with the disease. Prevalence varies considerably, not just between ethnicities, but also within Caucasian populations. Across Europe, prevalence is as low as 1 in 25,000 in Finland and as high as 1 in 1,800 in the Republic of Ireland [1].

Over the past few decades, there have been considerable advances in CF care and survival has improved dramatically. However, there is still no cure for this devastating disease and, while a child born with CF today can expect a much-improved quality of life and prognosis compared with 20 years ago, this comes at a significant cost to the individual. There is a huge burden of daily treatment, with frequent hospital visits. As patients live longer, new and complex issues are evolving, which pose further challenges for treatment and additional morbidity for the individual.

Evolution of improved life expectancy

In 1938, when CF was first recognised as a specific disease entity, >70% of CF babies died before their 1st birthday. Following the introduction of antibiotics and relatively crude pancreatic extracts in the 1940s (treatments which are still pillars of modern-day management), survival improved. However, the outlook remained poor, with two-thirds of patients failing to reach 7 years of age. Key developments over the following decades significantly advanced the understanding of the disease. The observation that a disproportionately high

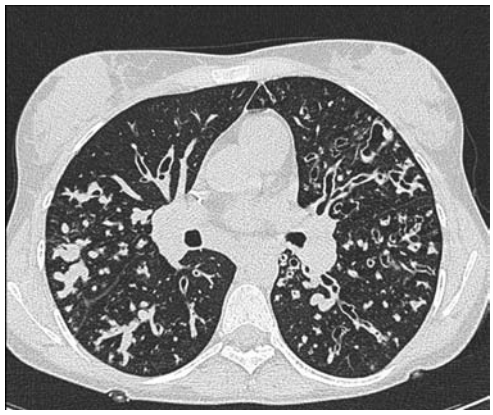


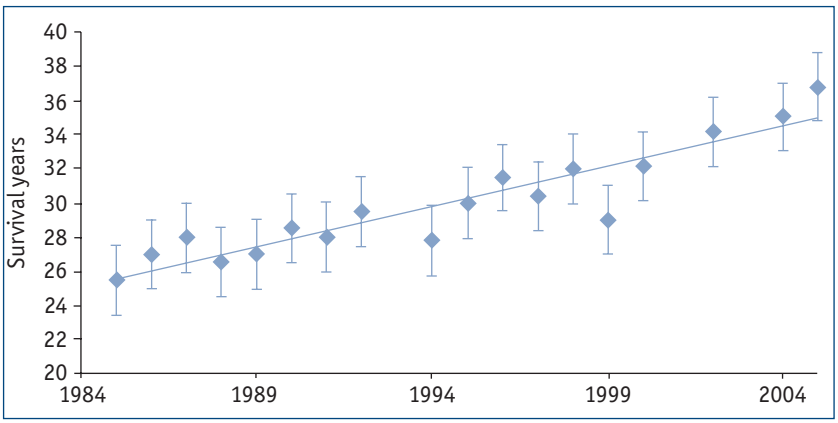
Figure 1
Bronchiectasis in CF. The disease starts to damage the lung from an early age by a process of infection and inflammation, resulting in mucus plugging and significant widespread bronchiectasis.

number of children with CF were presenting to hospital with heat exhaustion during the New York heatwaves in the 1950s led to the discovery of an abnormal sweat composition in CF, with high sodium and chloride levels. Following this came the development of a reliable technique for stimulating and collecting sweat by GIBSON and COOKE [2] in 1959, and hence the introduction of a reliable means of diagnosis. This "sweat test" is still the pivotal diagnostic test used today.

It was not until the 1980s that a much greater understanding of the basic cellular and genetic defect was realised, with the recognition that the basic defect was CFTR, a protein required for chloride transport on the apical surface of epithelial cells. A seminal publication followed in 1989, with the discovery of the CF gene that encodes for this protein [3]. Since this discovery, >1,300 CF-causing mutations have been identified, with ΔF508 being the most common in the Caucasian population (>70%).

Median life expectancy has continued to improve over the past few decades, from 20 years in the 1970s to 36.8 years in 2005 (most recent estimate from the USA; figure 2). Recent data suggest a child born with CF today has a predicted median survival into their 6th decade of life [4]. A number of factors are thought to have contributed to this improved survival, most notably the development of anti-pseudomonal antibiotics, better nutrition, treatment in specialist centres and early diagnosis.

Figure 2
Median survival of CF patients between 1985–2005. Data from US Cystic Fibrosis Foundation Registry 2006.



CF is a spectrum of disease

The majority of patients with CF are diagnosed in infancy or early childhood with "classic" or "typical" CF. They usually present with one or more of the phenotypic characteristics associated with CF (chronic pulmonary disease, gastrointestinal symptoms and malabsorption, nutritional abnormalities, sinus disease, azoospermia), a high sweat chloride concentration, and in most cases identification of one disease-causing mutation on each CFTR gene. Most (85%) will be pancreatic insufficient. Outcome in CF is influenced by a number of factors. Pancreatic sufficiency and "milder" genotypes are associated with a better long-term prognosis, whereas poor lung function, repeated lung infections, chronic Pseudomonas and *Burkholderia cepacia* infection, and poor nutritional status are all associated with reduced survival. Importantly, there can be quite marked phenotypic variation even in patients with the same genotype: those with classic disease may have a severe course with rapid disease progression or a milder course with very little deterioration over time.

The recognition that some patients may present with only one characteristic feature of CF, with a borderline or normal sweat test, but either a disease-causing mutation on both CFTR genes or an abnormal nasal potential difference measurement has led to the term "non-classic" or "atypical" CF (figure 3) [5]. These patients are usually diagnosed much later, often as adults, are mainly pancreatic sufficient, have milder disease and in general have a better prognosis. Interestingly, the UK CF Trust reported that 12% of new CF diagnoses in 2003 were in patients aged >16 years, and a recent review of patients aged ≥40 years demonstrated that 32% were diagnosed after 16 years of age and 18% were pancreatic sufficient.

With the introduction of newborn screening programmes in many countries, CF will increasingly be diagnosed at birth. Where newborn screening programmes are already in place, studies have demonstrated long-term benefits from early nutritional treatment including improved

growth and, in one study, cognitive development. In addition, early intervention and diagnosis may lead to reduced hospitalisations and ultimately improved survival.

How is a child managed today?

The primary aims of management are to delay the onset of lung infection and to keep the child well nourished and able to enjoy a healthy and happy life. For most, this will involve a daily management regimen; 3-monthly clinic review, with close monitoring of weight, lung function (figure 4) and microbiology; and intermittent hospitalisation. The outcome for patients with CF is improved by care provided by teams of experienced healthcare professionals in specialist centres [6].

Treatment of lung infections

The lungs of CF patients become infected with a surprisingly limited number of pathogens. Initially, *Staphylococcus aureus* and *Haemophilus influenzae* are the major pathogens but ultimately chronic infection with *Pseudomonas aeruginosa* occurs. Recurrent lung infections characterise the disease and most patients will need repeated courses of antibiotics. The most recent respiratory tract cultures should be used to guide the choice of antibiotic, and oral treatment is often sufficient, although prolonged courses (2–4 weeks) are usually required. More severe infections may require *i.v.* antibiotics. These can be given at home but hospitalisation is sometimes necessary with resultant time away from home, school or work.

Chronic *P. aeruginosa* infection is associated with a more rapid decline in lung function and reduction in long-term survival, and preventing or delaying the onset of chronic infection is a crucial part of management. When Pseudomonas is first isolated, a course of treatment to eradicate the organism can delay the onset of chronic infection. A combination of oral ciprofloxacin with nebulised colomycin for 3 months is often used, with clearing of the organism in the majority of cases. Repeated attempts to eradicate the organism when it is cultured intermittently may also be successful and can further delay the inevitable onset of chronic infection [7].

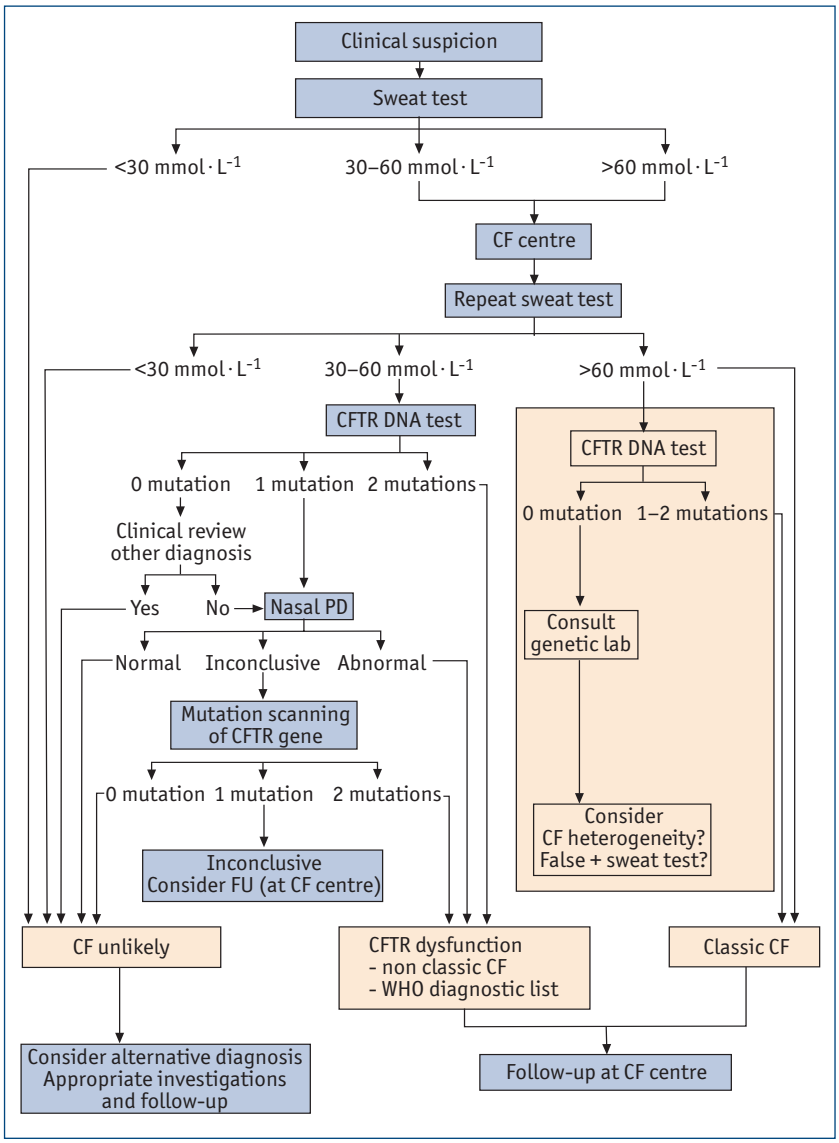


Figure 3
The diagnostic algorithm for CF. Often diagnosis is straightforward, but with non-classic disease an extensive work-up may be required. Reproduced from [5], with permission from the publisher. PD: potential difference; FU: follow-up.

Figure 4
Lung-function measurement in a CF clinic.

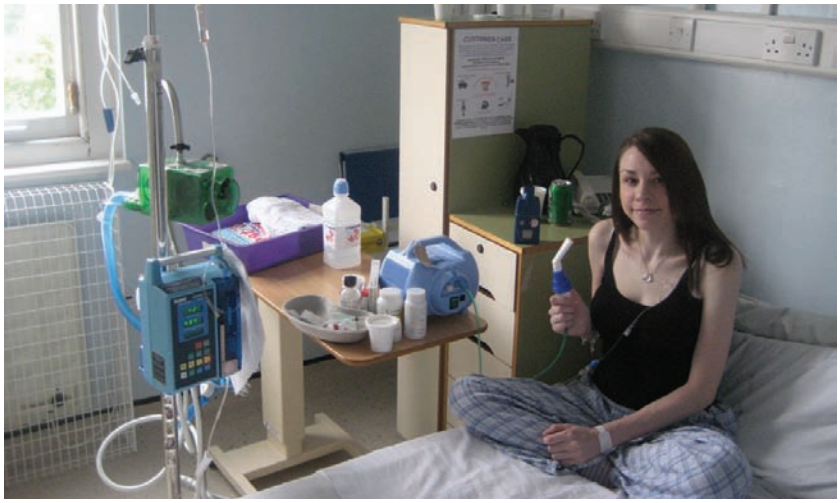
Preventing exacerbations

Much of the treatment for CF is aimed at preventing exacerbations and maintaining lung function, because repeated infections and poor lung function are associated with reduced survival. Nebulised antipseudomonal antibiotics, nebulised human recombinant DNase, nebulised hypertonic saline, and oral azithromycin have all been shown to decrease the frequency of exacerbations and maintain lung function. There is considerable debate about the ideal time to introduce each of these therapies. In general, nebulised antibiotics are introduced once a patient has become infected with Pseudomonas. The macrolide antibiotic azithromycin seems to act primarily as an anti-inflammatory agent and has been associated with improved lung function and reduced frequency of pulmonary exacerbations even before infection with Pseudomonas has occurred [8]. DNase (which reduces sputum viscosity) aids airway clearance, although not all patients respond and a trial of treatment is usually recommended before long-term therapy is commenced [9]. Hypertonic saline again aids airway clearance and is often used as an additional therapy to DNase [10]. It may also have a role in those patients who do not respond to DNase.

Physiotherapy

For those patients with respiratory symptoms, daily physiotherapy is an integral part of treatment. A number of techniques are available, although none have been shown to be superior to any other. These include active cycle of breathing, autogenic drainage and mechanical devices, such as the positive expiratory pressure mask, flutter and external oscillation jacket. Physical exercise is actively encouraged as an adjunct to formal airway clearance sessions.

Figure 5
An in-patient undergoing regular treatment.



Nutrition

There is a strong relationship between nutritional status, severity of lung disease and prognosis [11]. As most patients with CF have pancreatic insufficiency, they require pancreatic enzyme replacement with meals and snacks to prevent malabsorption and optimise nutritional status. Fat-soluble vitamins are poorly absorbed and vitamin supplements are usually necessary. Patients are advised to eat a high-fat, high-energy diet as their energy requirements are generally increased to 120–150% when compared with healthy individuals of the same age and sex. Those who struggle to maintain their weight within the normal range may require supplemental feeding, and some will require nasogastric feeding or gastrostomy.

Compliance

The average patient with CF may need to take >40 tablets per day, in addition to their nebulised treatments and twice-daily physiotherapy, just to stay well (figure 5). Both nebulised therapies and physiotherapy are time consuming, and understandably compliance is often an issue, particularly as many of these preventative treatments provide no immediate benefit.

Complications

As patients get older, a number of other disease-related complications may develop, often requiring yet more treatment. Low bone mineral density occurs in 15–25% of adults and leads to an increased risk of fragility fractures [12]. CF-related diabetes (CFRD) affects up to 50% of patients by the age of 40 years and is associated with an accelerated decline in lung function, weight loss and reduced life expectancy by up to 10 years. Most patients with CFRD require treatment with insulin and, unlike other forms of diabetes, dietary restriction is not advised. Long-term diabetic complications have been reported and are likely to occur more frequently as CF patients live longer with diabetes [13].

Constipation is a relatively common occurrence in CF, but usually responds to a modification of diet, pancreatic enzyme dose and laxative therapy. At the more severe end of this spectrum is distal intestinal obstruction syndrome, which occurs almost exclusively in those who are pancreatic insufficient and affects ~20% of patients. Treatment with repeated doses of laxative agents, such as gastrografin or a balanced intestinal lavage solution are usually successful [14]. Liver disease develops predominantly in childhood and is the cause of death in ~2% of patients. Although biliary cirrhosis is a relatively common finding in CF, only ~5 % of patients progress to clinically significant disease and portal hypertension. Patients with evidence of liver disease are usually prescribed ursodeoxycholic acid, although its long-term efficacy in preventing the progression of liver disease in CF remains unproven [15].

Pneumothorax and haemoptyis both occur with increasing frequency as the disease progresses, adding to disease morbidity in affected individuals. Allergic bronchopulmonary aspergillosis occurs in ~10% of patients and for some can be a recurrent problem requiring repeated courses of steroids. The incidence of nontuberculous mycobacterial infection seems to be increasing and while this does not always require treatment, some of these organisms can be associated with clinical decline and can be very difficult to treat. Ultimately, most patients will progress to respiratory failure and when this occurs noninvasive ventilation is often used, either to provide symptom relief or as a bridge to lung transplantation. Lung transplantation should be considered for all patients with end-stage lung disease. Sadly, many patients will die on the transplant waiting list because of a shortage of donor organs.

Survival at a cost?

Unfortunately, many of the treatments aimed at preventing or delaying disease progression in CF may in themselves cause side-effects or long-term complications. Repeated courses of antibiotics, for instance, can lead to the development of multiple drug allergies, thus limiting treatment options, as well as the emergence of drug-resistant organisms that are more difficult to treat. Most clinicians would advocate the use of an aminoglycoside antibiotic in combination with another antipseudomonal antibiotic when giving *i.v.* therapy, but repeated courses of aminoglycosides can cause significant hearing loss, vestibular damage and renal failure, even when drug levels are therapeutic. Prolonged use of azithromycin as an anti-inflammatory agent may predispose to antibiotic resistance, particularly in nontuberculous mycobacteria which are inherently difficult to treat, and reports of resistance in *S. aureus* and *H. influenzae* following long-term azithromycin use are emerging. As patients live longer and are exposed to more treatment, it is increasingly important to assess the impact of treatments so that the potential benefits outweigh the risks of developing these and possibly other long-term complications. In addition, there is a significant financial cost to consider as many of the drugs used to treat CF are expensive.

Living with a chronic illness can pose other challenges for the individual. Life events that most of us take for granted, such as seeking employment, obtaining insurance, securing a mortgage, forming long-term relationships and having families may not be straightforward. Having a chronic illness can also be very isolating, and unfortunately because of the potential for cross-infection between individuals with CF, patients are now advised to avoid contact with each other. For many this will take away an important support network.

Future developments

Considerable efforts to increase our knowledge and understanding of the basic genetic defect and to develop new therapies aimed at improving long-term survival and ultimately finding a cure are ongoing. Understanding of the effect of modifier genes may help to explain the variable clinical course seen in CF even when controlling for genotype. New therapeutic approaches are being developed to address all stages of the disease. Gene therapy, which aims to use a normal gene as a drug to override the faulty version, is now a real possibility and the UK CF gene consortium will be begin a large gene therapy trial in 2008–2009. A number of potential therapies designed to correct the function of the defective CFTR protein produced by the CF gene and to correct disordered ion transport are being evaluated. With these therapies, there is the real prospect of preventing the development of disease in individuals with CF, further improving survival and decreasing the need for arduous daily therapy. In addition to treatments that target the underlying defect, further treatments are being

Useful weblinks

UK CF Trust
www.cftrust.org.uk

US CF Foundation
www.cff.org

Cystic Fibrosis mutation database
www.genet.sickkids.on.ca/cftr/

Figure 6.
A CF grandmother. This patient, with non-classic CF, was labelled a "difficult asthmatic" for many years.

developed and evaluated to treat and prevent the progression of established disease. Clinical trials of new inhaled antibiotics are taking place and a number of anti-inflammatory agents are being assessed to see if they can reduce inflammation in the CF lung. The introduction of newborn screening will also provide an opportunity to assess early intervention strategies.

Conclusion

There have been considerable advances in CF care and management since the disease was first recognised in 1938, with a dramatic improvement in life expectancy. A child born with CF today can now expect to live into their 6th decade (figure 6), but we should not forget that this improvement in survival comes with a significant burden of treatment. As patients live longer, new challenges are emerging both as a consequence of getting older with CF but also as a result of the treatments that have led to this improved survival. Ongoing research efforts continue to search for treatments that will prevent the development or progression of the disease and ultimately produce a cure.

Educational questions

1. Which of the following statement(s) is/are true?
a) The prevalence of CF is the same in all Caucasian populations.
b) A child born with CF today would be expected to live into their 50s.
c) All patients with CF present in early childhood.
d) CF is always associated with pancreatic insufficiency.
2. Which of the following factors are associated with a worse prognosis in cystic fibrosis?
a) A diagnosis of non-classic CF.
b) Chronic infection with Pseudomonas.
c) Pancreatic sufficiency.
d) Repeated lung infections.
e) Poor nutritional status.
3. Which of the following is/are true with regards to treatment?
a) Eradicating Pseudomonas from the lungs can delay the onset of chronic infection.
b) All infections should be treated with *i.v.* antibiotics.
c) Nebulised antibiotics are prescribed from the age of diagnosis.
d) Side-effects of long-term treatment are uncommon.
4. Which of the following complications are more likely to occur as patients get older?
a) Liver disease.
b) CF-related diabetes.
c) Infection with *Staphylococcus aureus*.
d) Pneumothorax.

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Suggested answers

1. b
2. b, d and e
3. a
4. b and d