

Introduction



Key points

- Newborn screening for cystic fibrosis leads to a reduction in prevalence, as couples are empowered to make better-informed reproductive choices.
- Adult patients as well as children should be cared for by multidisciplinary teams in specialist cystic fibrosis centres, equipped to understand and manage all aspects of the disease.
- 'CF lung attacks', *i.e.* periods of acute worsening of respiratory symptoms, negatively affect quality of life, accelerate decline in lung function and worsen prognosis.
- Median life expectancy is now in the mid-30s and it is likely this will increase.
- Although most of the morbidity and mortality caused by cystic fibrosis are still due to respiratory disease, complications affecting other bodily systems are becoming more prominent as life expectancy increases.

Cystic fibrosis (CF) is the commonest lethal inherited disease of white races, but it should be noted that in multi-racial Europe, no ethnic group is exempt from the disease, although prevalence varies across the continent. It is usually caused by the absence, dysfunction or reduced numbers of the multifunctional CF transmembrane regulator (CFTR) protein. Mature CFTR is produced after complex post-transcriptional and post-translational processing, which has implications both for prognosis and modern, genotype-specific, therapy. The protein has a key function in regulating the amount of water in the airway surface liquid. If the CFTR protein is not working normally, clearance of bacteria and particles from the lungs is impaired. Either correcting the dysfunction of this protein or dealing with the downstream consequences is key to developing therapies that will modify the natural history of CF.

Epidemiology



The most comprehensive and up-to-date collection of epidemiological data for CF across Europe is the registry maintained by the European Cystic Fibrosis Society (ECFS) (www.ecfs.eu). Data are submitted to the registry by both national CF registries and individual CF centres throughout Europe. The registry collects data from 25 000 CF patients in 21 countries and produces annual summary reports.

“

There is a pressing need to ensure that adult services are established all over Europe, offering the same high standards of multidisciplinary care as paediatric clinics

”

The current report, covering 2008–2009, contains details on 18 999 patients. The 2007 report contains data on 20 204 patients. However, these datasets are likely to suffer from under-reporting. For example, the UK contribution of 4408 patients in the 2007 report (the third-largest in the registry) is likely to be at least 2000 short of the true figure. A high priority must be to resource this database so that data on all CF patients across Europe can be captured.

There are marked age-related changes in resource use, with older patients having more morbidity and requiring more expensive medications and other resources, including noninvasive ventilation. It is important to note that diagnosis by screening is associated with lower healthcare costs.

Prevalence and incidence

Figure 1 shows the prevalence of CF by country within Europe. Table 1 shows the number of patients reported to the ECFS Patient Registry in either the 2008–2009 or 2007 reports, and the age distribution of CF patients. Many countries have at least 90% case ascertainment, but in some countries this figure is much less. A more detailed analysis of the registry data between January 2003 and December 2007 by McCORMICK *et al.*, 2010 (see Further reading), covered 29 025 patients, 25 126 from European Union (EU) countries (as of 2003) and 3809 from non-EU countries. In the EU cohort, 11 742 (47%) were aged over 18 years, emphasising that CF is increasingly becoming a disease of adults. However, only 1205 (5%) were aged over 40 years. There is therefore a pressing need to ensure that adult services are established all over Europe, offering the same high standards of multidisciplinary care as paediatric clinics. There were proportionately more ‘elderly’ CF patients in the 2003 EU countries compared with the non-EU countries (figure 2). This is not due to ascertainment bias (milder phenotypes being diagnosed in the EU): when the analysis was repeated just for CF patients homozygous for the severe mutation $\Delta F508$ (deletion of a phenylalanine residue at position 508 in the protein), the findings were the same. Reasons for the better prognosis and lower mortality could include the lower median age at diagnosis in the EU, and better socioeconomic conditions.

It is intriguing to note that in countries where newborn screening for CF has been introduced, there has been a decline in the prevalence of CF. This may at least in part be due to diagnosis of the first CF child in the family before a second one is conceived, thus giving couples reproductive choices after the birth of a first CF child.

	Patients n	Estimated coverage# %	Age years		
			Mean	Median	Range
EU28 countries					
AT	352	39	13.1	11.9	0.2–55.5
BE [¶]	1129	>90	20.4	18.5	0.0–68.5
BG ⁺	95		14.2	13.4	0.2–52.3
CZ [¶]	507	100	17.2	15.8	0.1–55.5
DE [¶]	5048	90	19.9	18.5	0.0–71.5
DK [¶]	451	100	21.8	20.4	0.2–61.3
ES	740	30	17.0	14.9	0.1–57.8
FR [¶]	5640	90	19.1	16.5	0.0–79.6
GR	92	20	16.1	15.9	2.0–41.4
HU [¶]	555	90	15.8	15.4	0.2–60.9
IE ^{¶,§}	1021	90	18.6	18.1	0.4–58.7
IT	539	14	24.6	24.6	0.8–60.4
LV	29	>90	11.6	10.2	1.2–27.0
NL [¶]	1249	97	21.1	18.6	0.1–70.5
PT	117	42%	14.4	12.4	0.0–49.5
SE [¶]	578	85–90	22.5	20.2	0.2–71.1
SI	66	75	13.1	11.9	0.3–54.1
UK ^{¶,+}	4408		19.9	18.7	0.1–75.7
Non-EU28 countries					
BY ⁺	145		12.9	12.7	0.4–33.4
CH	190	24	10.3	10.5	0.2–32.3
IL ^f	533	90	20.2	18.2	0.0–64.5
MD [¶]	41	100	9.6	8.0	0.4–22.7
RS	122	>90	13.0	11.0	1.0–44.4

Table 1 – Cystic fibrosis (CF) in Europe: age distribution, 2009. EU: European Union. #: the estimated percentage of CF patients living in a country who are included in the national registries/national data collections. One individual centre might include almost all patients for some countries (e.g. Latvia and Serbia); [¶]: national CF registry established; ⁺: 2007 data reported for Bulgaria, UK and Belarus; [§]: 2008 data reported for Ireland; ^f: although not officially a national registry, all centres in Israel participate and so considered a registry. Data from the European Cystic Fibrosis Society (ECFS) Patient Registry 2007 and 2008–2009 reports.

Annual mortality

Mortality rate varies with age and is likely to be about 1–2% per year overall. In 2009, there were more than 800 CF patients across Europe living with transplanted lungs. There were 133 CF lung transplants performed in 2009, compared with 108 in 2007. However, it is thought that these numbers are likely to be

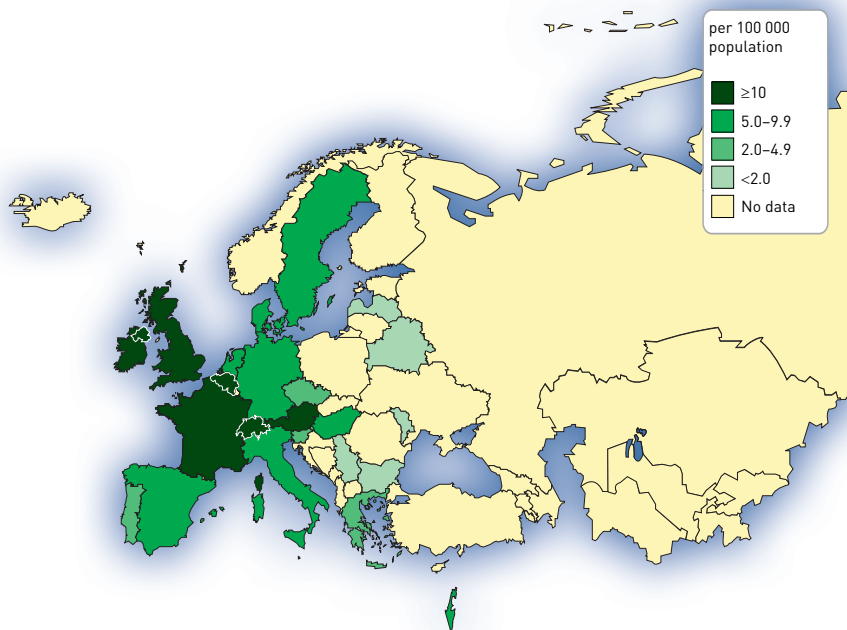


Figure 1 – Estimated prevalence of cystic fibrosis. Data from the 2007 and 2008–2009 reports of the European Cystic Fibrosis Society.

an underestimate as in some countries patients are transferred to a transplant centre and so are not known to their CF registry. Data on liver transplantations performed each year are more difficult to ascertain, but they are performed significantly less often than lung transplants in CF patients – only seven liver transplants were performed in CF patients in 2009, making a total of 93 patients living with transplanted livers in 2009 across Europe.

Causes/pathogenesis

Genetic

CFTR is a widely expressed, multifunctional protein. Its best-known function, that of a chloride channel, is responsible for the abnormal sweat test and is also responsible for some disease manifestations such as electrolyte depletion and heat exhaustion. However, it is naïve to believe that the same functions are responsible for all disease manifestations, and there is increasing evidence that dysregulation of the epithelial sodium channel ENaC is more likely responsible for the pulmonary disease. Recently, the nomenclature of CFTR gene mutations has been revised (www.cdc.gov/dls/genetics/rmmaterials/pdf/HGVSNomenclature.pdf); however, this chapter uses the old nomenclature because it is also used in the ECFS reports. CFTR mutations have been divided into six classes (table 2): classes I–III are severe, associated with pancreatic insufficiency; classes IV–VI are mild and pancreatic sufficient. A combination of a mild and severe mutation predicts a mild (pancreatic sufficient) phenotype. However, there is considerable individual variation within genotypes, which has been related to modifications within the CFTR genetic locus itself, modifier genes elsewhere in the karyotype, and environmental factors; these are the subject of active research. Predicting prognosis in an individual from his or her genotype is not possible.

“ Although many young people and adults with cystic fibrosis are in full-time education or employment, progression of the disease may curtail these activities ”

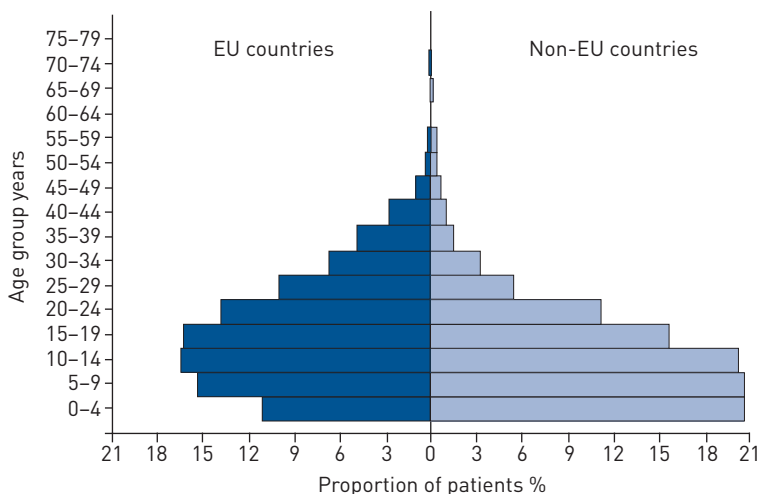


Figure 2 – Population pyramid of mean age of patients with cystic fibrosis in European Union (EU) and non-EU countries (2003 EU classification). Bulgaria, Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Romania, Slovakia and Slovenia are included in non-EU countries in this figure. Reproduced from McCORMICK *et al.*, 2010, with permission from the publisher.

Mutation class has implications for treatment development. Whereas current therapy is aimed at the downstream consequences of CFTR dysfunction, such as bronchial infection and pancreatic destruction, treatment will in future be aimed at correcting the underlying molecular abnormality. Treatment will be either independent of mutation class (gene therapy, the efficacy of which is thought unlikely to vary with underlying CF genotype) or specific to mutation class. Examples of the latter include the orally active compound PTC124, which overrides premature but not physiological stop codons (class I mutations); molecular chaperones (‘correctors’) to prevent intracellular

Class	Description	Example mutation
Class I	No CFTR synthesis (mutation inserts premature stop codon)	G542X
Class II	CFTR processed incorrectly and does not reach apical cell membrane	ΔF508
Class III	CFTR reaches apical membrane but channel regulation is abnormal	G551D
Class IV	CFTR reaches apical membrane but channel open time is reduced	R334W
Class V	Reduced CFTR synthesis	R117H
Class VI	CFTR reaches apical cell membrane but has a shortened half-life due to more rapid turnover	1811+1.6kbA>G

Table 2 – Classes of cystic fibrosis transmembrane regulator (CFTR) mutation.

degradation of abnormal CFTR (class II mutations); and potentiators, to increase the activity of CFTR at the cell surface (class III mutations, but may also need to be applied to class II mutations in combination with molecular chaperones). Some of these strategies are likely to be applicable to other genetic diseases.

There are regional variations in gene frequency across Europe. In summary, homogeneity is greatest in central, western and north-eastern Europe, where 10 mutations account for more than 80% of CF chromosomes; it is much less in, for instance, Spain, Bulgaria, Turkey and Greece, where 25 mutations must be determined in order to detect 85% of CF chromosomes. This is important for a number of reasons. Firstly, if newborn screening is to be implemented, using PCR for gene detection, the panel of genes that is most useful will vary across Europe. Secondly, if a diagnostic genetics laboratory is set up, then their routine screening panel will be different in different parts of Europe. Thirdly, comparisons of survival must take account of genetic variation: countries with a higher prevalence of mild mutations (classes IV–VI) might be expected to have better survival curves than those with more severe mutations. Comparisons between countries can be facilitated by studying groups from each with the same homogeneous genotype, usually homozygous $\Delta F508$. Finally, it should be noted that of about 1900 mutations so far identified, fewer than 50 are definitely disease producing. The ongoing CFTR-2 project should help to elucidate this, and the project website gives useful information about unusual mutations (www.cftr2.org).

Environmental

Adverse environmental circumstances, particularly passive and active exposure to tobacco smoke, may worsen CF, but there are no known environmental causes of the disease. However, it is estimated that environmental circumstances contribute at least as much to the prognosis as CFTR gene class and modifier genes.

Occupational

Low socioeconomic status is associated with an adverse outcome at all ages. In the USA, CF patients always reliant on Medicaid (a health programme for families and individuals with a low household income) had a three-fold greater risk of dying at every age than those who never relied on Medicaid, underscoring the adverse effects of poor socioeconomic conditions.

Others


Exceptionally rare cases of phenotypic CF with apparently completely normal CFTR gene sequences have been described. It is possible that these cases relate to mutations in one of the many genes encoding proteins with which CFTR interacts during processing, or that interact functionally with mature CFTR. Mutations in the sodium channel ENaC, which is downregulated by CFTR, have been associated with a CF-like disease.

Clinical manifestations and consequences



Diagnosis of CF

Diagnosis is increasingly by newborn screening, measuring immunoreactive trypsin (IRT) and one or more ethnically appropriate genes on the routine heel-prick sample



taken from the baby at 7–10 days of life. Diagnosis should always be confirmed with a sweat test. In patients with suspicious symptoms, diagnosis can almost always be made by a sweat test performed in an experienced centre (> 98% of cases), and the sweat test should be the first-line investigation. It should be noted that false-positive and false-negative tests will invariably occur at inexperienced centres. There are rare cases of genuine CF with equivocal or even normal sweat electrolytes. In these cases, ancillary diagnostic methods are needed, including genetic testing and measurement of transepithelial potential differences (*in vivo* in the nose, the usual method; in the lower airway; or *in vitro* on a rectal biopsy). These tests are only available in very few centres. Diagnostic algorithms have been published in Europe and the USA; they are very similar (see Further reading).

A further diagnostic issue is the spectrum of 'CFTR-related' disorders, and their relationship with CF. It is known that patients with idiopathic bronchiectasis, congenital bilateral absence of the vas deferens, idiopathic (non-alcoholic) pancreatitis, and severe sinusitis (all conditions seen in established CF) have a higher prevalence of CF mutations than would be expected; and indeed, in some adults, these are actually the first presentation of true CF. Most usually, the patient has a single CF mutation, a normal sweat test, and a single-organ manifestation such as bronchiectasis. In time, in some subjects, a second disease-producing mutation may be discovered, confirming the diagnosis of CF. The remainder are classed as having a CFTR-related disorder; in practice, the treatment of the single organ manifestation is driven by the nature of the disease, not by the diagnostic label.

Manifestations of CF

The basic details of the disease are described in standard books and monographs. When first described, CF was considered a pulmonary and digestive disease; now, it is known to affect most body systems. The important manifestations of CF, especially in longer-surviving patients, are shown in table 3.

Most of the morbidity and mortality of CF is still due to respiratory disease. The lungs are essentially normal at birth, but soon become chronically infected and inflamed. The conventional view is that the initial pathogens are usually *Staphylococcus aureus* and *Haemophilus influenzae*. Subsequently, chronic infection with *Pseudomonas aeruginosa* becomes established in most patients, although the prevalence of chronic infection is being reduced by attention to prevention of cross-infection in hospitals, and aggressive eradication regimes at the time of first isolation. This conventional view is having to be widened. Firstly,

Lower airway	Chronic infection, especially with <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> and, in particular, <i>Pseudomonas aeruginosa</i> , together with a widening range of other Gram-negative rods; acute exacerbations; atypical mycobacterial infection; bronchiectasis; haemoptysis; pneumothorax; allergic bronchopulmonary aspergillosis
Upper airway	Nasal polyps, sinusitis, rarely mucocoele
Liver	Biliary cirrhosis, portal hypertension, gall stones, bile duct stricture
Gastrointestinal comorbidity and complications	Severe constipation, distal intestinal obstruction syndrome, Crohn's disease, coeliac disease, giardiasis, cow's milk protein intolerance, increased incidence of malignancy
Endocrine pancreatic failure	Insulin deficiency, which adversely impacts on clinical state before frank diabetes mellitus develops
Bone disease	Related to: CF itself (CFTR is expressed in bone), malabsorption of vitamin D and vitamin K, immobility, poor calcium intake, pubertal delay, gonadal failure, and the systemic effects of pro-inflammatory cytokines
Genito-urinary	Infertility due to bilateral absence of the vas deferens, stress incontinence, vaginal candidiasis
Sweat gland	Electrolyte depletion in the sweat (pseudo-Bartter's syndrome)

Table 3 – Multi-organ complications of cystic fibrosis (CF). CFTR: CF transmembrane regulator.

the aggressive use of antibiotics has led to the emergence of other Gram-negative bacilli, including the *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans* and *Pandoria apiospermum*. Secondly, the use of anaerobic cultures has shown that lower airway flora contain at least as many anaerobes as *P. aeruginosa*. Finally, molecular microbiology (16s rRNA, for example) has shown a far more diverse bacterial and fungal flora in the lower airways of CF patients than was previously suspected. It is unclear whether the CF airway is intrinsically pro-inflammatory in the absence of infection, or whether there is an exaggerated response to infection or some other dysregulation of the control and resolution of infection. What is clear is that the intense inflammatory response is itself harmful, and, combined with chronic infection, leads to bronchiectasis, cor pulmonale and death from respiratory failure unless the patient receives a lung transplant.

In addition to chronic infection, there are periods of acute deterioration of respiratory symptoms, termed 'pulmonary exacerbations', or better, 'CF lung attacks'. There is no agreed definition of a pulmonary exacerbation, despite the fact that reduction in frequency is commonly used as an end-point in clinical trials. They are common, and effects include: 1) a marked adverse effect on quality of life; 2) failure to recover baseline lung function in up to one-third of exacerbations; 3) an association with accelerated deterioration in lung function; and 4) an adverse impact on prognosis. Other important respiratory complications include allergic bronchopulmonary aspergillosis, pneumothorax (which carries a bad prognosis because of associated severe lung disease), massive haemoptysis, and lung or lobar collapse.

Many patients have malabsorption of nutrients caused by pancreatic insufficiency from diagnosis; ultimately, 85% of patients become pancreatic insufficient. Malabsorption



should not be assumed to be due to pancreatic disease: coeliac disease, inflammatory bowel disease and the complications of neonatal surgery may all lead to steatorrhea (an excess of fat in the faeces). A relatively common intestinal complication is distal intestinal obstruction syndrome (DIOS), caused by accumulation of thick tenacious secretions and malabsorbed fat in the terminal ileum. This must be distinguished from constipation, to which CF patients are also prone. Another more unusual gastrointestinal complication is biliary cirrhosis leading to portal hypertension.

As patients survive longer, systemic complications become more prominent. These include: CF-related diabetes, which eventually affects nearly half the pancreatic-insufficient CF population; bone disease leading to pathological fractures; and, particularly in women, stress incontinence.

Finally, although standard advice is that CF carriers are as healthy as the general population, there is a higher prevalence of CFTR mutations (*i.e.* more carriers) in groups of patients with single organ, CF-like disease.

Impact of CF on the individual

The diagnosis of CF, whether in the patient him/herself or a family member, may have a considerable economic impact. In particular, a woman who has become the mother of a CF child may refocus her career intentions, and opt to remain at home caring for the CF child rather than pursuing a career. Although many young people and adults with CF are in full-time education or employment, progression of the disease may curtail these activities. A spouse or parent may need to give up work, and rely on social security payments, as the patient becomes sicker. The other main fiscal costs for adults are time off work, community support and, for the rare really ill child, home tutoring. In the UK, adults will attain an employment rate that is 80% of that seen in a control population matched for age and sex. Half of CF adults are in paid employment, and around a quarter are in full-time education (www.cfstudy.com). However, calculating the costs of CF to society should also take account of loss of productive working years in individuals with CF and their carers.

Costs of CF treatments: impact on health services and society

The costs of care vary with the stage of the illness, being highest in the year following diagnosis, and again rising later as the disease worsens. The vast majority (90%) of patients will use pancreatic enzyme replacement supplements, and many will use rhDNAse and nebulised antibiotics

(tobramycin or colomycin), each costing several thousand euros per patient per year. These antibiotics are also now available in dry powder delivery devices, but this has not brought down the cost. Newer treatments are likely to be even more expensive. The emerging issue of the costs of genotype-specific treatments will be discussed in detail later.

It should also be noted that there are marked regional differences in the use of expensive treatments, suggesting that cost may be a factor in what patients receive. rhDNase was used in between 2% (Hungary) and 87% (Belgium) of patients in 2007, and nebulised antibiotics in 5% (Hungary) to nearly 50% (UK, Belgium, Germany). Chronic oral macrolide use ranges 0–35%.

The costs of treatment escalate as the patient becomes sicker. Treatment of lung disease is likely to involve repeated courses of expensive intravenous antibiotics. Patients being treated for atypical *Mycobacteria* are prescribed particularly expensive medications. As respiratory disease worsens, home oxygen and noninvasive ventilation may be required, and eventually very prolonged hospital stays are likely. Maintenance of good nutrition may require placement of a gastrostomy for supplemental enteral feeds. Treatment of CF-related diabetes, liver disease and bone disease adds to the rising costs, and these may culminate in the costs of lung transplantation.

Costs of emerging treatments: a new challenge

The cost of illness is likely to increase greatly with the advent of novel, expensive medications. Ivacaftor (VX-770) is a class III channel-opening small molecule, which has been tested in CF patients carrying at least one copy of the G551D mutation in a recent double-blind, placebo-controlled, 24-week trial. Patients receiving the active compound saw an increase of more than 10% in forced expiratory volume in 1 second (FEV₁) (a key measurement of lung function), were half as likely to have a pulmonary exacerbation, gained on average 2.7 kg in weight, and, almost incredibly, halved their sweat chloride concentrations. This medication is licensed in the USA, where it costs \$294 000 (about €220 000) per patient per year. The impact will depend initially on the country prevalence of CF, and the percentage of patients who carry the G551D mutation (Ireland has the highest prevalence, with 7.6% of its total CF population carrying G551D). In the UK, if all of the 5% of the CF population who carry at least one copy of G551D were prescribed the medication, the cost would be €75 million per year, raising the cost of CF care by about 50%. It is likely that VX-770 will be useful in other class III mutations, and possibly in some more common mutations in combination with a corrector such as VX-809, which facilitates the trafficking of misfolded class II mutations such as ΔF508 to the apical cell membrane. Strategies will be needed to decide who will benefit from these novel small molecule therapies, and how they will be financed.

Prevention



Complete prevention would only be possible if universal carrier screening were possible and acceptable to the public. Screening would have to be genetic, but there would always be the likelihood of missing rare variants. Experience is that in any case, take-up of carrier screening offered in an antenatal clinic is low, in the absence of a family history. Newborn screening should facilitate a reduction in prevalence. In the first instance, there is an opportunity for the couple to test future pregnancies for CF;

and secondly, genetic testing (targeted at the genes found in the affected baby) can uncover other at-risk couples in the extended family, also enabling antenatal diagnosis.

Management



Management of CF

The bedrock of pulmonary management is: 1) the aggressive use of oral, intravenous and nebulised antibiotics to prevent and treat infection; 2) airway clearance, including exercise and the choice of a number of physiotherapy techniques; 3) avoidance of active and passive smoking; and 4) full immunisation, including influenza annually. Mucoactive agents employed include rhDNAse, hypertonic saline and mannitol. Macrolide antibiotics have been shown to be beneficial, although the exact mechanism has not been determined. Other anti-inflammatory drugs are more controversial. Pancreatic insufficiency is treated with pancreatic enzyme replacement therapy, sometimes supplemented by gastric acid-lowering strategies such as H₂ receptor antagonists and proton pump inhibitors; DIOS may require gastrograffin orally or by enema, or intestinal lavage with Klean-Prep (Helsinn). CF-related diabetes is treated with insulin. The reader is referred to standard texts for more detailed discussions of treatment options for the less usual complications.

Patterns of care

Care in a specialist CF centre is essential. Definitions of what constitutes a 'centre' are neither evidence based nor uniformly agreed. The definition will be modified according to local needs; what is feasible in a densely populated urban area will be impracticable in a country with a very dispersed population. In such cases, core expertise may need to be collected in a central location, supporting more distant centres with clinic visits, telemedicine, and the implementation of agreed treatment protocols. The ideal CF centre should include the following:

- A critical mass of patients sufficient to maintain expertise; ideally a minimum of 100 paediatric or adult patients, though this may not be possible in many parts of Europe.
- A core multidisciplinary team (MDT) of CF specialist health professionals, or, in satellite centres, professionals who among their other commitments will ensure that they maintain competence in CF, with particular attention to continuing professional development. This group will comprise: at least two appropriately trained specialist paediatricians or adult physicians; clinical

“

It is estimated that environmental circumstances contribute at least as much to the prognosis as gene class transmembrane regulator gene class and modifier genes

”

nurse specialists; physiotherapist; dieticians; a social worker; a psychologist; a pharmacist; and administrative support.

- Enough personnel for cross cover during periods of annual and study leave.
- Other medical and paramedical staff with experience of CF; for example, ward nurses who understand the requirements of the condition.
- Expertise throughout the MDT in the complications of CF and the specialised procedures required by people with CF, or at least access to a major centre in the country that is able to manage these.
- Support of staff from other specialist services with experience in management of the related issues that arise in patients with CF, such as ear, nose and throat specialist expertise, endocrinology, obstetrics and surgery.
- Access to diagnostic and specialist laboratory facilities, particularly microbiology. Some services (genetics, for example) may be provided off-site at a national referral centre.
- Facilities for inpatient and outpatient treatment, including an appropriate number of beds for people with CF.
- Regular audit of practice.

Guidelines for management have been published, and the reader is referred to the websites of the ECFS (www.ecfs.eu), the UK CF Trust (www.cfrust.org.uk) and the North American CF Foundation (www.cff.org); all these organisations have published useful consensus and standards of care documents.

Prognosis



The steady improvement in prognosis over several decades is related temporally to various advances in management strategies (figure 3). Undoubtedly these innovations have contributed to improving survival, but the less spectacular progress made by CF multidisciplinary teams making incremental gains by better application of basic treatments has also contributed greatly. Currently median survival is to the mid-30s, but a recent paper has predicted median survival into the mid-50s for men and into the

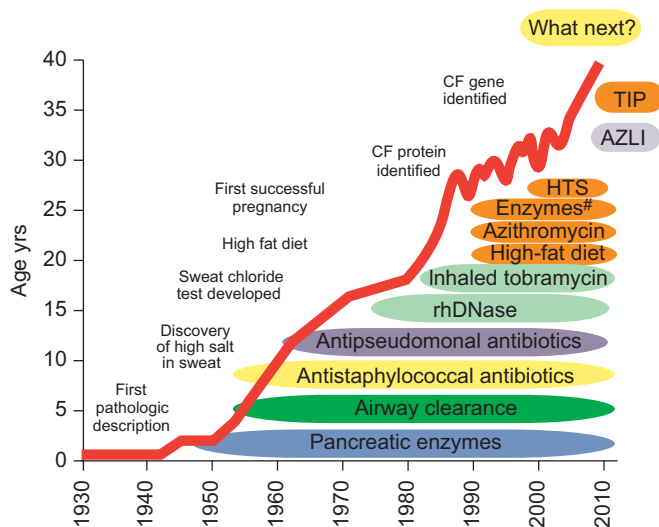


Figure 3 – Schematic illustration of how the introduction of novel cystic fibrosis (CF) therapies influenced patient survival over the decades. HTS: high throughput screening; AZLI: aztreonam for inhalation solution; TIP: tobramycin inhalation solution. #: enteric-coated pancreatic enzymes. Reproduced and modified from ELBORN, 2013.

mid-40s for women. The discrepancy in mortality between men and women has been described before. The gap begins after childhood and may be related to a greater mortality rate in CF women developing diabetes compared with nondiabetic women and all CF men. This gap is closing, probably due to the earlier and more aggressive use of insulin. The underlying mechanisms of the interactions between sex and insulin deficiency are not known.

A number of factors are leading to an improved prognosis, to which early detection and improved treatments contribute. Increasingly mild clinical CF phenotypes are being detected and incorporated into survival curves, thus prolonging apparent life expectancy. Nonetheless, it is anticipated that life expectancy for all patients with CF will increase over time.

Future developments



Immediate needs

There are a number of basic standards of diagnosis and care that need to be implemented across Europe.

- We must ensure that CF is diagnosed early throughout Europe, preferably by newborn screening; and that everyone in Europe has access to appropriate diagnostic testing, performed by experienced personnel.
- We must ensure that every CF patient is genotyped, in order to determine eligibility for novel small molecule therapies.
- Having been diagnosed, it is essential that from diagnosis, every CF patient in Europe has access to CF specialist centre care by the full MDT and all necessary medications. This last is an ambitious goal because CF medications are expensive and currently many European countries cannot afford them.
- On reaching adulthood, it is essential that patients are treated in a CF unit experienced in CF care. This is a pressing need: adult CF clinic development has lagged behind paediatrics in many parts of Europe.

Medium-term needs

It is clear that the predictions in the previous edition of this book have not all been fulfilled! We should aim to achieve the following:

- Universal newborn screening in Europe.
- Evidence-based care for newborn-screened babies,

driven by the performance of randomised controlled trials with appropriate end-points. There is currently only one (a negative trial of hypertonic saline) that is of a satisfactory standard. This aim is in the mainstream of the European Union drive for medicines for children.

- Access to all evidence-based CF medications across Europe, eliminating regional inequalities.
- All European CF patients being seen regularly at a fully staffed, fully equipped CF centre; this is particularly necessary, and particularly far from being achieved, in adult patients. There is clear evidence that specialist centre care is beneficial.
- Increased use of care in the community and telemedicine to minimise hospital contacts.
- A fully funded, comprehensive registry which captures data on all European patients.

Recent trends will necessitate changes in the provision of care:

- Increased longevity will mean a radical rethink about the burden of care. A well adult who happens to have CF with minimal impact is not likely to want to take many therapies or perform as much airway clearance as the sick CF patient.
- Increased longevity will also mean we need to detect and deal with new emerging infections and new iatrogenic complications, such as antibiotic allergy and subtle long-term medication side-effects.
- New treatments will increase the financial costs of care: new products will build on old concepts, such as novel inhaled antibiotics and mucolytics; more therapies will address the basic defect (gene therapy, for example) and PTC124 for class I mutations.
- More attention must be paid to extrapulmonary complications. There will be pressure on diabetic and endocrine clinics, and obstetric services for pregnant women with CF.
- There will be increased demands for lung transplant services, which will mean optimising the donor supply, novel techniques to salvage donor lungs previously thought to be untransplantable, living related donation, and ultimately a transgenic large mammalian source.

Research needs and unanswered questions



The paradigm shift from treating the downstream consequences of CFTR dysfunction, such as infection with antibiotics, to addressing the fundamental consequences of the molecular defect, is likely to gather momentum, and more designer molecules to treat other classes of mutations are urgently needed.

Currently, the UK CF Gene Therapy consortium (www.cfgenetherapy.org.uk) is carrying out the first therapeutic gene therapy trial (*i.e.* 'Does it help the patient?' rather than 'Can we get the gene to be expressed in the human airway?'). It seems likely that the results will stimulate further refinements in this area, leading to further big trials.

A huge research need is to find meaningful surrogate end-points for clinical trials. Thankfully, in CF the annual mortality is low and the average decline of spirometric

indices is slow, but this implies that neither of these conventional end-points is useful. Other possibilities include: more sophisticated lung function tests, such as lung clearance index; markers of inflammation in blood, induced sputum or breath condensate; expression of CFTR mRNA and protein; and electrophysiological tests. The choice will vary depending on the clinical trial question. Validating these biomarkers is an ongoing and important research task.

Further reading



Data sources

- Olesen HV, Zolin A, Viviani L, *et al.* European Cystic Fibrosis Society Patient Register Annual Report 2007. Karup, European Cystic Fibrosis Society, 2010. www.ecfs.eu/projects/ecfs-patient-registry/annual-reports
- Viviani L, Zolin A, Olesen HV, *et al.* European Cystic Fibrosis Society Patient Register Annual Report 2008–2009. Karup, European Cystic Fibrosis Society, 2012. www.ecfs.eu/projects/ecfs-patient-registry/annual-reports

General

- Allen J, Panitch H, Rubenstein R. Cystic Fibrosis. Lung Biology in Health and Disease. Vol 242. New York, Informa Healthcare USA, 2010.
- Hodson M, Geddes D, Bush A, eds. Hodson and Geddes's Cystic Fibrosis. 4th Edn. London, Hodder Arnold, 2013.
- Mogayzel PJ, Naureckas ET, Robinson KA, *et al.* Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2013; 187: 680–689.

Diagnosis of CF

- De Boeck K, Wilschanski M, Castellani C, *et al.* Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006; 61: 627–635.
- Farrell PM, Rosenstein BJ, White TB, *et al.* Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr* 2008; 153: S4–S14.
- Ooi CY, Dupuis A, Ellis L, *et al.* Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language? *Thorax* 2012; 67: 618–624.
- Simmonds NJ, Bush A. Diagnosing cystic fibrosis: what are we sweating about? *Thorax* 2012; 67: 571–573.

Microbiology

- Nagano Y, Elborn JS, Millar BC, *et al.* Development of a novel PCR assay for the identification of the black yeast, *Exophiala (Wangiella)* dermatitidis from adult patients with cystic fibrosis (CF). *J Cyst Fibros* 2008; 7: 576–580.
- Rogers GB, Daniels TW, Tuck A, *et al.* Studying bacteria in respiratory specimens by using conventional and molecular microbiological approaches. *BMC Pulm Med* 2009; 9: 14.
- Tunney MM, Field TR, Moriarty TF, *et al.* Detection of anaerobic bacteria in high numbers in sputum from patients with cystic fibrosis. *Am J Respir Crit Care Med* 2008; 177: 995–1001.

Epidemiology

- Bobadilla JL, Macek M, Fine JP, *et al.* Cystic fibrosis: a worldwide analysis of CFTR mutations – correlation with incidence data and applicability to screening. *Hum Mutat* 2002; 19: 575–606.
- Dodge JA, Lewis PA, Stanton M, *et al.* Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007; 29: 522–526.
- McCormick J, Mehta G, Olesen HV, *et al.* Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. *Lancet* 2010; 375: 1007–1013.
- Sims EJ, Mugford M, Clark A, *et al.* Economic implications of newborn screening for cystic fibrosis: a cost of illness retrospective cohort study. *Lancet* 2007; 369: 1187–1195.
- Verma N, Bush A, Buchdahl R. Is there still a gender gap in cystic fibrosis? *Chest* 2005; 128: 2824–2834.

CF-related diabetes

- Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 2005; 28: 2141–2144.
- Moran A, Dunitz J, Nathan B, *et al.* Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009; 32: 1626–1631.

Novel therapies

- Bush A, Simmonds NJ. Hot off the breath: 'I've a cost for' – the 64 million dollar question. *Thorax* 2012; 67: 382–384.
- Clancy JP, Rowe SM, Accurso FJ, *et al.* Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation. *Thorax* 2012; 67: 12–18.
- Elborn JS. Personalised medicine for cystic fibrosis: treating the basic defect. *Eur Respir Rev* 2013; 22: 3–5.
- Ramsey BW, Davies J, McElvaney NG, *et al.* A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011; 365: 1663–1672.
- Rosenfeld M, Ratjen F, Brumback L, *et al.* Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA* 2012; 307: 2269–2277.