Cystic fibrosis

J Stuart Elborn

Cystic fibrosis is a common life-limiting autosomal recessive genetic disorder, with highest prevalence in Europe, North America, and Australia. The disease is caused by mutation of a gene that encodes a chloride-conducting transmembrane channel called the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates anion transport and mucociliary clearance in the airways. Functional failure of CFTR results in mucus retention and chronic infection and subsequently in local airway inflammation that is harmful to the lungs. CFTR dysfunction mainly affects epithelial cells, although there is evidence of a role in immune cells. Cystic fibrosis affects several body systems, and morbidity and mortality is mostly caused by bronchiectasis, small airways obstruction, and progressive respiratory impairment. Important comorbidities caused by epithelial cell dysfunction occur in the pancreas (malabsorption), liver (biliary cirrhosis), sweat glands (heat shock), and vas deferens (infertility). The development and delivery of drugs that improve the clearance of mucus from the lungs and treat the consequent infection, in combination with correction of pancreatic insufficiency and undernutrition by multidisciplinary teams, have resulted in remarkable improvements in quality of life and clinical outcomes in patients with cystic fibrosis, with median life expectancy now older than 40 years. Innovative and transformational therapies that target the basic defect in cystic fibrosis have recently been developed and are effective in improving lung function and reducing pulmonary exacerbations. Further small molecule and gene-based therapies are being developed to restore CFTR function; these therapies promise to be disease modifying and to improve the lives of people with cystic fibrosis.

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Introduction

Nearly 80 years ago, cystic fibrosis was identified as a disease by Dorothy Andersen.[1,2] In 1938, she described cystic fibrosis of the pancreas in 49 patients and the disorder was subsequently associated with lung infection and salt loss during a heat wave in New York.[1,2] In the 1950s, median life expectancy for patients with cystic fibrosis was a few months; the main causes of death were meconium ileus and malnutrition subsequent to pancreatic malabsorption.[2] During the past six decades, median age of survival has increased progressively, and is now more than 40 years in developed countries.[3,4] Respiratory failure secondary to progressive lung disease is now the most common cause of death in individuals who do not receive a lung transplant. This improvement in life expectancy has been achieved by understanding the importance of augmenting airway clearance, aggressively treating infection, and correcting nutrition deficits. More recent understanding of how abnormal ion transport in airway epithelial cells results in impaired mucus clearance and infection has underpinned the development of effective mucolytic agents and antipseudomonal antibiotics and the delivery of dedicated multidisciplinary cystic fibrosis care.[5–7] Since the sequencing of the causative cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, laboratory research has focused on developing therapies that correct the underlying basic defect in CFTR function.[7] This approach has started to deliver transformational therapies for patients.[8]

Cystic fibrosis is a classic Mendelian autosomal recessive disorder. It is most common in populations with northern European ancestry where the predominant mutation is Phe508del (also known as F508del).[9,10] People with cystic fibrosis from other regions have a wider range of mutations with the Phe508del mutation being much less prevalent.[11,12] More than 2000 gene variants have been identified, many of which have been associated with disease causation.[10] Mutations have different effects on the manufacture of CFTR protein, its processing function, and its stability at the cell membrane, which opens up the opportunity for different molecular approaches to the different functional consequences of the mutations (figure 1).[8]

CFTR function and dysfunction

The CFTR channel defect is mainly in chloride and bicarbonate transport.[7,8] The interaction of CFTR and other ion channels, particularly the epithelial sodium channel (ENaC), and interactions of CFTR with cellular pathways related to inflammation (inflammasome) might all be important in the pathophysiology of cystic fibrosis.[7] The importance of understanding the pathophysiology of this disease in the first few years of life has been emphasised by recent studies showing that by the age of 3 years, almost a third of children with cystic fibrosis have evidence from CT scan of mucus obstruction, bronchiectasis, and inflammation driven by neutrophils,

Search strategy and selection criteria

I searched MEDLINE using the term "cystic fibrosis" for articles publications between Jan 10, 2008 and Dec 31, 2015. Publications from the past 8 years were the primary source of the review. Review articles and book chapters are cited to provide readers with more details. Consensus statements and guidelines are cited where evidence has been assessed for clinical practice. In the discussions of treatment and prevention, more weight was given to randomised controlled trials and meta-analyses than to evidence of lower quality such as case series.

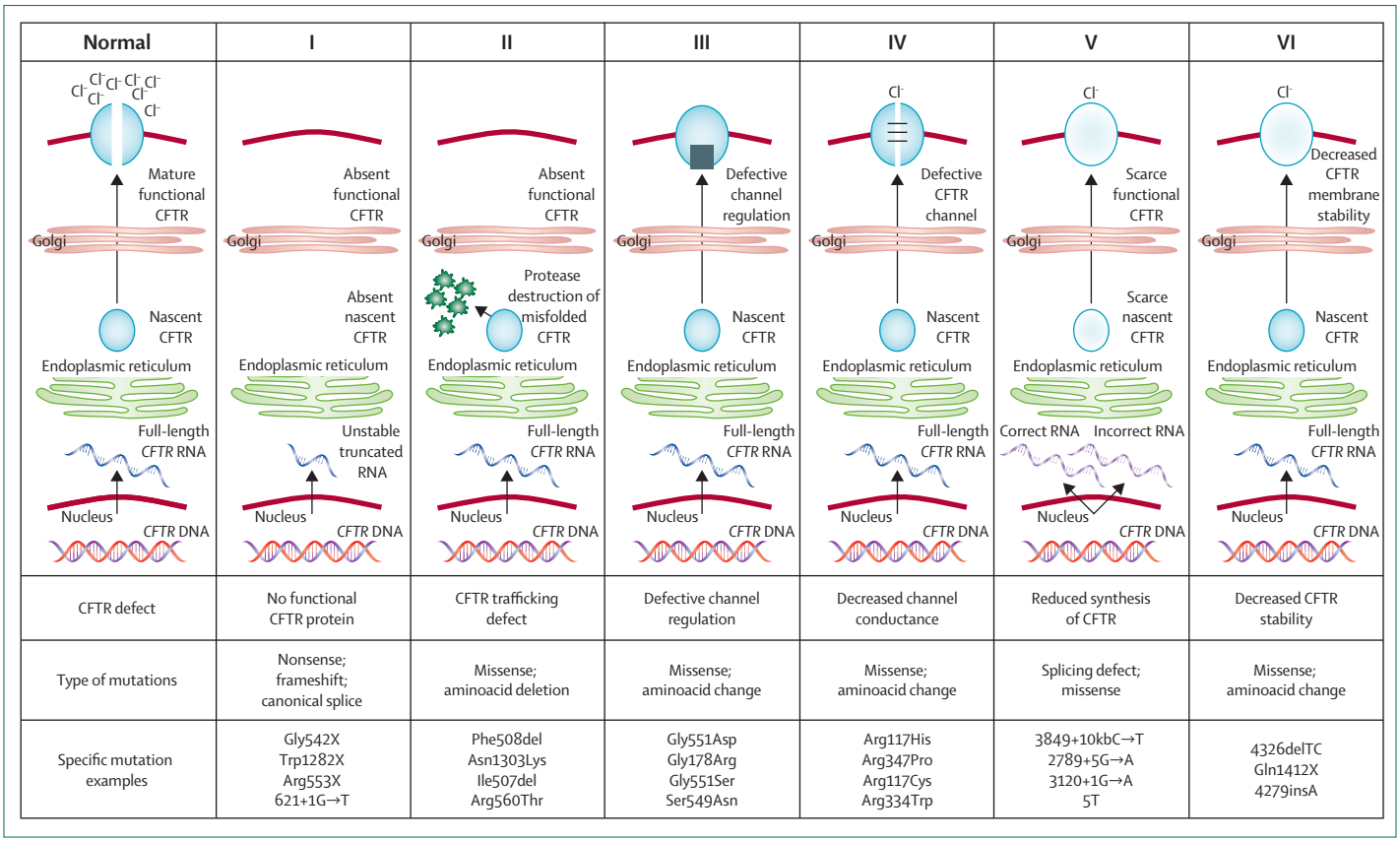


Figure 1: **Classes of *CFTR* mutations**
Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene can be divided into six classes. Class I mutations result in no protein production. Class II mutations (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum, and subsequent degradation in the proteasome. Class III mutations affect channel regulation, impairing channel opening (eg, Gly551Asp). Class IV mutants show reduced conduction—ie, decreased flow of ions (eg, Arg117His). Class V mutations cause substantial reduction in mRNA or protein, or both, Class VI mutations cause substantial plasma membrane instability and include Phe508del when rescued by most correctors (rPhe508del). Reproduced from Boyle and De Boeck.[13]

neutrophil elastase, and recurrent episodes of infection.[14–16] The primary hypothesis to explain these clinical features is that impaired mucociliary clearance caused by abnormal hydration of airway surface liquid is the key underlying defect (figure 2).[7,17–19] This hypothesis has been supported by findings in some animal models but not in others. In some recently developed animal models such as the cystic fibrosis pig and ferret, excessive sodium reabsorption has not been observed.[7] This finding challenges the hypothesis that simple hydration is important in the early impairment of mucociliary clearance.

CFTR also conducts bicarbonate, and dysfunction of the protein changes the pH of airway surface liquid.[17–22] An important series of experiments using airway surface liquid from pig models of cystic fibrosis showed that bacterial killing is highly dependent on pH and therefore a change in pH might result in impaired innate immunity by reducing the function of antimicrobial peptides.[23,24] Airway mucus is also highly dependent on the presence of bicarbonate for normal function and reduced anion concentrations might cause derangements of mucus tethering and detachment, increasing the viscosity of airway mucus.[23] Thus, it is possible that CFTR dysfunction results in multiple consequences to hydration, mucociliary clearance, mucus tethering and function, and impaired innate immunity, and might also predispose to increased intrinsic cellular inflammation. The relative impact of these effects of impaired CFTR function might change with age and disease progression. This heterogeneity of function might also in part explain why there are modest effects from treatments that are directed against one consequence of the basic defect, such as drugs that improve mucociliary clearance or antimicrobial agents.[25]

The cloning of the *CFTR* gene has resulted in a much better understanding of how mucociliary clearance works in health and disease. Understanding how airway hydration and mucociliary clearance is regulated by osmotic forces will benefit a wide range of other lung diseases associated with infection. For example, cigarette smoke impairs CFTR function locally and systemically.[26,27] A better understanding of CFTR biology in health and disease could help to identify factors at work in lung diseases such as chronic obstructive pulmonary disease and bronchiectasis and lead to new treatments.[28,29]

Epidemiology and demographics

The remarkable progress that has been achieved by improving airway mucus clearance and controlling lung infection has changed cystic fibrosis from being predominantly a disease of children to now being predominantly an adult disorder.[3,4,30] The number of adults with cystic fibrosis will continue to increase with almost all deaths occurring in the adult population.[31] Indeed, for the past 5 years, in countries with well funded health-care systems, there have been more adults than children with cystic fibrosis. In developed European countries, the number of adults with cystic fibrosis has been predicted to increase by around 70% by 2025.[4] However, in parts of Europe with less well resourced health-care systems, median life expectancy can be in the second decade of life because of a historical lack of access to treatment.[32] The substantial improvement in life expectancy in developed countries has resulted from delivery of care in well organised, multidisciplinary cystic fibrosis centres and use of effective drugs to treat infection and improve mucociliary clearance.[33–35]

Cystic fibrosis affects many systems in the body and the phenotypic effects change with age (table 1). This progression requires multidisciplinary care and, increasingly, age-specific expertise. The capacity of health-care systems to deal with an increasing number of adult patients has been identified as a potential challenge because there is currently an inadequate provision of adult services in many countries, and in several countries adults with cystic fibrosis are still looked after in paediatric services.[4]

Newborn screening

Newborn screening for cystic fibrosis is now implemented in most countries with a high prevalence of the disease (figure 3).[36] Newborn screening programmes reduce disease severity, burden of care, and costs of care. They also prevent delayed and missed diagnoses.[37,38] Several methods are used, including immunoreactive trypsinogen (IRT) testing combined with DNA mutation analysis, double IRT testing, and pancreatitis-associated protein (PAP) testing.[39] The methodology used depends on geographical, ethnic, and economic issues, and countries should make an independent analysis as to the most effective protocol that meets local needs. In most programmes, IRT testing is followed by testing for a panel of common cystic fibrosis mutations. Blood samples are taken soon after birth by heel prick. A sweat test should be done as the final diagnostic test. Appropriate support for parents of newly diagnosed infants and referral to a cystic fibrosis care centre are essential in such programmes.[37]

Screening has identified some children with an uncertain diagnosis associated with a positive IRT test, one or no identified mutations, and intermediate concentration of sweat chloride of 30–60 mmol/L. These children should be assessed very carefully and followed up because although they are asymptomatic in early years, some will develop a cystic fibrosis phenotype as they get older.[39] These individuals usually have mutations associated with residual function of the CFTR protein. In the USA, this diagnosis has been called cystic fibrosis metabolic syndrome.[40]

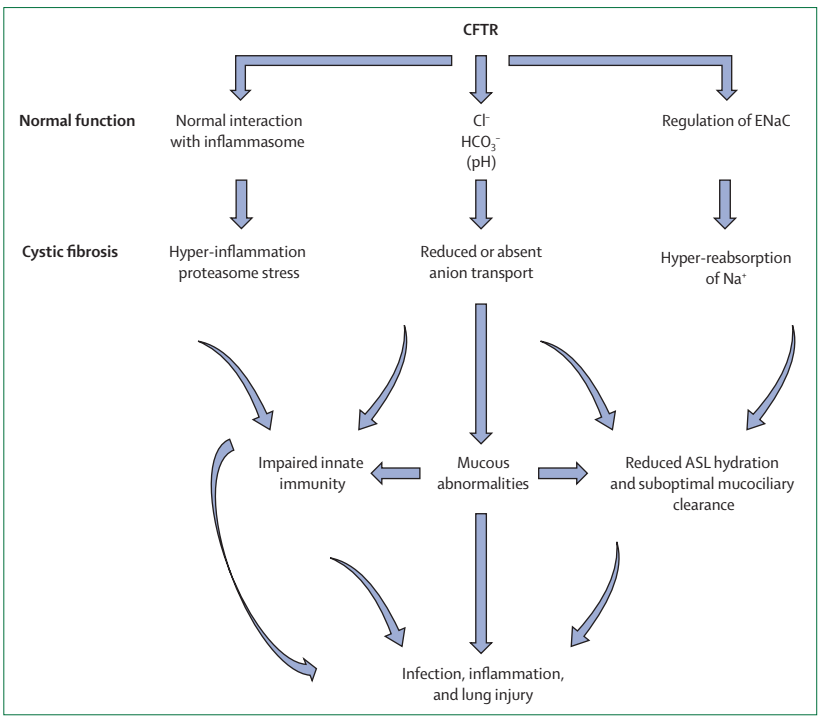


Figure 2: **Effects of CFTR dysfunction**
ASL=airway surface liquid. CFTR=cystic fibrosis transmembrane conductance regulator. ENaC=epithelial sodium channel.

CFTR mutations

Most mutations of the *CFTR* gene are missense alterations, but frameshifts, splicing, nonsense mutations, and inframe deletions and insertions have been described.[8] About 15% of identified genetic variants are not associated with disease. *CFTR* mutations can be divided into six classes according to their effects on protein function (figure 1).[19,41] This approach is helpful because it relates to the molecular and cellular processes in gene translation and protein processing and has some useful clinical correlates (figure 4). Class I, II, and III mutations are associated with no residual CFTR function and patients with these mutations on average have a severe phenotype, whereas individuals with class IV, V, and VI mutations have some residual function of CFTR protein and have a mild lung phenotype and pancreatic sufficiency.[41] As with any system of classification, there are several over-simplifications. For example, although the most common northern European mutation, Phe508del, is predominantly a class II trafficking mutation, around 3% of protein is trafficked to the cell membrane where it is not functional and has properties of a class III gating mutation and a class VI mutation.[11,19,41]

	0–10 years	10–20 years	20–35 years	>35 years
Airways	Early mucinous plugging and bronchiectasis	Established bronchiectasis	Established bronchiectasis with haemoptysis/pneumothorax	Progressive respiratory failure/lung transplant
Predominant infection	*Staphylococcus aureus*	*S aureus*/intermittent *Pseudomonas aeruginosa*	*P aeruginosa* and other non-fermenting Gram-negative bacteria, ABPA	..
Pancreas	Pancreatic exocrine insufficiency	..	Cystic fibrosis-related diabetes mellitus	..
Liver	Abnormal liver function test results	Cirrhosis	Portal hypertension (5–10%)	Liver transplant
Gut	Meconium ileus	..	Distal intestinal obstruction syndrome	..
Reproductive system	Absence of vas deferens	..	..	..
Other	..	..	Arthropathy, cystic fibrosis-related bone disease (osteoporosis)	..

ABPA=allergic bronchopulmonary aspergillosis.

Table 1: **Onset of cystic fibrosis disease by approximate age**

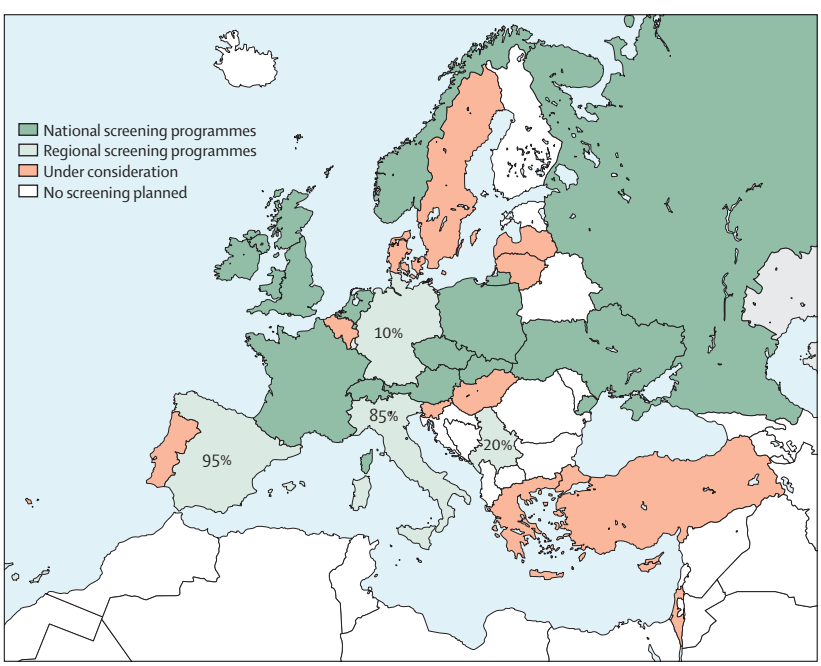


Figure 3: **Newborn screening programmes in Europe, 2014**
Figure source: Dr Kevin Southern.

The potential role of other genes, which might affect other important pathways in the pathophysiology of cystic fibrosis, is of interest. Several large studies using a genome-wide association approach have identified genes that are particularly associated with non-pulmonary complications.[42–44] So far, this strategy has not yielded any specific therapeutic targets.

To help patients, family members, health-care providers, and scientists to understand some of the complexities and clinical implications of the wide range of identified *CFTR* mutations, a website has been developed by a group at Johns Hopkins University (Baltimore, MD, USA) to provide information about specific cystic fibrosis mutations.[45] The CFTR2 website includes information about the most common 160 mutations worldwide from 39 696 people with cystic fibrosis. By analysing registry and functional data from cell studies, the researchers have been able to provide useful information about genotype–phenotype relations. This information is particularly helpful in individuals who have residual function mutations and less severe phenotypes.[46]

For the **CFTR2 website** see http://www.cftr2.org/

Late diagnosis

Cystic fibrosis is usually identified following newborn screening or during the first few years of life.[40] People who are diagnosed after 20 years of age usually have a mutation associated with residual CFTR function such as Arg117His (also known as R117H; figure 4).[40,47] These individuals might have mild respiratory symptoms in childhood but develop bronchiectasis, pancreatitis, or present with infertility later in life. The diagnosis is made by a sweat test and DNA analysis.[48,49] Individuals with a late diagnosis have good survival, reflecting the higher prevalence of mutations associated with residual function and a less severe phenotype.[48,49]

Lung disease in cystic fibrosis

The dominant pathology in the lung is inflammation generated primarily by failure to clear microorganisms and the generation of a toxic pro-inflammatory local microenvironment.[50,51] Lung disease starts early in life with CT scan evidence of bronchiectasis in about a third of patients within the first few months.[20,21] Bronchiectasis is associated with raised concentrations of neutrophil elastase, which further disrupts innate immunity, increases mucus production, damages peptides and proteins in the airway, and digests the extracellular matrix.[15,16,52] Neutrophil elastase and other neutrophil-derived proteases such as cathepsin S and matrix metalloproteinases are the main driving force of injury and the development of bronchiectasis.[52–55]

In children with cystic fibrosis, repeated respiratory tract infection with viruses and bacteria such as *Haemophilus influenzae* and *Staphylococcus aureus*

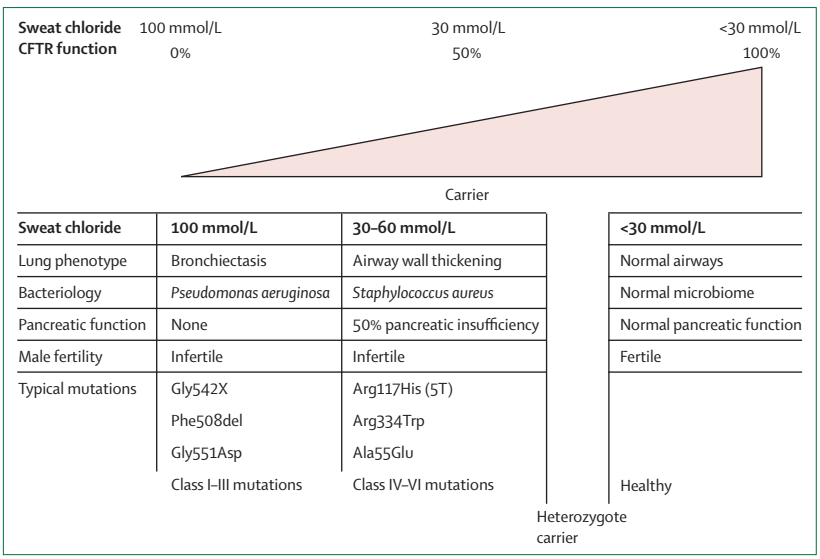
results in direct and indirect damage from the inflammatory response to airway infection.[56] As the disease progresses, bronchiectasis develops and people with cystic fibrosis become susceptible to a range of Gram-negative bacteria. These microorganisms are most commonly found in the environment and are only associated with human infection in situations where the host is immunocompromised or the integrity of the host epithelium is compromised.[51,57] *Pseudomonas aeruginosa* is the most predominant lung infection in cystic fibrosis. A range of other Gram-negative, non-fermenting bacteria are becoming more prevalent in patients with cystic fibrosis, such as *Stenotrophomonas maltophilia* and *Achromobacter* spp. These organisms have in common constitutive and acquired resistance to antibiotics with Gram-negative activity and when exacerbations of symptoms occur, patients usually require intravenous therapy.[58,59]

Bacteria from the *Burkholderia cepacia* complex, particularly *Burkholderia cenocepacia*, have been major pathogens in cystic fibrosis and are associated with increased mortality.[57] Careful infection control has reduced patient-to-patient transmission of *B cenocepacia* with a reduction in prevalence in the cystic fibrosis population. In addition to Gram-negative bacteria, environmental non-tuberculous mycobacteria, particularly *Mycobacterium abscessus* and *Mycobacterium avium-intracellulare*, are increasing in prevalence in patients with cystic fibrosis and are difficult to treat because they are constitutively resistant to antibiotics.[59–61]

Recent studies, using next-generation sequencing techniques, have identified a much greater range of other bacteria in the airway, including obligate anaerobes.[62,63] These bacteria can be detected in the airways of healthy individuals. It is not yet clear whether some of these other species are pathogenic, but some studies in patients with cystic fibrosis have suggested that diversity of the bacterial ecology in the lower airway is associated with better lung function compared with a very high relative abundance of one organism such as *P aeruginosa*.[64–66] These data raise important questions about the use of antibiotics in cystic fibrosis and might explain why some studies in which prophylactic antibiotic treatment was given to newly diagnosed and young children with cystic fibrosis reported an increased prevalence of *P aeruginosa* as a consequence.

Infection control

The high level of transmissibility of many important microorganisms that cause infection in the cystic fibrosis lung has been a troubling issue during the past three decades.[67,68] There is strong evidence that *B cepacia* complex organisms, *P aeruginosa*, meticillin-resistant *S aureus*, and *M abscessus* can be transmitted from patient to patient.[68,69] All of these organisms are associated with poor clinical outcomes and substantial effort is now made in cystic fibrosis centres to reduce cross-infection and nosocomial spread.[70] Many centres now implement hygiene practices to ensure no patient-to-patient contact and strict isolation policies in clinic and inpatient environments.[67,68] This strategy has reduced the cross-infection caused by *B cenocepacia*, although there is less robust evidence for *P aeruginosa*.[71] The negative side of such segregation is a loss of peer support between patients and the restrictions associated with having meetings with only one person with cystic fibrosis in attendance. This challenge has been mitigated by use of online chat rooms, webcasts, and other uses of social media.



Sweat chloride	100 mmol/L	30–60 mmol/L	<30 mmol/L
Lung phenotype	Bronchiectasis	Airway wall thickening	Normal airways
Bacteriology	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Normal microbiome
Pancreatic function	None	50% pancreatic insufficiency	Normal pancreatic function
Male fertility	Infertile	Infertile	Fertile
Typical mutations	Gly542X	Arg117His (5T)	
	Phe508del	Arg334Trp	
	Gly551Asp	Ala55Glu	
	Class I–III mutations	Class IV–VI mutations	Healthy

Figure 4: **Relation between phenotype, genotype, and CFTR function in patients with cystic fibrosis, carriers, and healthy individuals**
CFTR=cystic fibrosis transmembrane conductance regulator.

Inflammation in the cystic fibrosis lung

The cystic fibrosis lung is an inflammatory microenvironment.[6,51,72] There are some data to support the hypothesis that mutations in *CFTR* make epithelial cells intrinsically more pro-inflammatory compared with healthy cells.[7,72,73] How important this characteristic is in the initiation of inflammation in the cystic fibrosis lung is still debated. It is possible that it has a role in early life and as infection becomes a regular and subsequently chronic contributor to the airway microenvironment, inflammation is driven predominantly by bacteria, fungi, and viruses. Understanding how this microenvironment operates is likely to provide important leads to the development of effective anti-inflammatory therapies. Studies of antiproteases, corticosteroids, and non-steroidal anti-inflammatory agents have only identified high-dose ibuprofen as an effective agent, mainly in teenagers, although this treatment is not widely used. Current programmes are investigating compounds that promote resolution of infections (such as lipoxins, resolvins, and protectins) or that protect against protease damage.[51,73,74]

Treatment of lung disease in cystic fibrosis

The treatment of lung disease in cystic fibrosis is central to clinical management.[35,75–77] Airway clearance is almost universally taught to parents of newborn infants dignosed with cystic fibrosis and is encouraged throughout the rest of the individual's life.[76,78] There are good theoretical principles for use of airway clearance and the range of techniques increase sputum production. However, there are few appropriately powered randomised controlled trials to support the use of airway clearance.[78] In a recent study comparing the conventional active cycle of breathing technique, which is routinely practised in many countries, versus a vibrating vest, the active cycle technique was superior to the vest and associated with fewer pulmonary exacerbations.[79] These findings suggest that airway clearance techniques are not equally effective and that further studies are required in this area of therapy.[79]

Oral antibiotics are used prophylactically in some countries to prevent *S aureus* infection, despite the concerns of an increased risk *of P aeruginosa* infection.[77] Some small studies have suggested that use of prophylactic antibiotics results in fewer hospital admissions, but this outcome in itself is not sufficient to justify their use. In children, repeated infections are treated with oral antibiotics aimed at *S aureus* and *H influenzae*.[39] At the time of first culture of *P aeruginosa* or other Gram-negative organisms, most physicians will prescribe antibiotic treatment with the aim of eradication.[77] A regimen of oral ciprofloxacin and inhaled colistin for 3 months was introduced on the basis of evidence from a prospective treatment study that used historical control data.[80] Studies with inhaled tobramycin have been more robust and treatment with this drug for 1 month eradicates *P aeruginosa* in around 70–80% of cases and this is of equal efficacy to the ciprofloxacin plus colistin combination.[81–83] Both regimens are recommended for antibiotic eradication therapy. Ensuring eradication of *P aeruginosa* is an important priority in cystic fibrosis care and many paediatric centres now report a prevalence of chronic *P aeruginosa* of less than 10% in their clinics.[84]

People with cystic fibrosis have recurrent exacerbations of disease. Pulmonary exacerbations are episodes in which there is an increase in symptoms of chronic lung infection, particularly cough and sputum production.[85] They are associated with increased breathlessness, fatigue, reduced exercise tolerance, and systemic symptoms associated with an acute phase inflammatory response.[85,86] There is a small increase in bacterial load and often a reduction in forced expiratory volume in 1 second (FEV_1) and other measures of lung function, increased inflammation with raised C-reactive protein concentration and leucocyte count, and an increase in inflammatory biomarkers such as sputum neutrophil elastase.[87] The understanding of the natural history of pulmonary exacerbations, and their identification, treatment, and follow-up is a high priority in cystic fibrosis care. Exacerbations are usually diagnosed on the basis of clinical symptoms, signs, and measurements of lung function and oxygen saturation.[86] There are accepted, reliable biomarkers that allow us to define, monitor, and predict pulmonary exacerbations, although symptoms, pulmonary physiology, and some measurements such as C-reactive protein and calprotectin might have some use.[87]

A range of therapies reduce the frequency of pulmonary exacerbations. Dornase alfa was the first treatment shown to reduce exacerbations in a controlled trial; subsequently, inhaled antibiotics, tobramycin, colistin and aztreonam, inhaled levofloxacin, hypertonic saline, mannitol, and oral azithromycin have also been shown to reduce exacerbations. These therapies are either licensed or included in guidelines across the world.[77,84] These therapies generally result in a modest 3–5% improvement in FEV_1 and a substantial reduction in the frequency of pulmonary exacerbations. However, it is not clear whether these treatments used in combination are additive.

Episodes of pulmonary exacerbation usually develop over several days and are treated with antibiotics and increased airway clearance. For *S aureus* and *H influenzae* infection, oral antibiotics are usually given.[76,77] In patients chronically infected with *P aeruginosa* or other Gram-negative bacteria, these episodes usually require treatment with intravenous antibiotics. This treatment usually consists of an extended action penicillin, third-generation cephalosporin, or carbapenem in combination with an aminoglycoside or polymyxin.[77,88] Treatment is recommended for 14 days, although there is no strong evidence base to support this length of treatment.[77] Some individuals become very unwell during these episodes and require support with nutrition, and supplementary oxygen, and can on some occasions require non-invasive ventilatory support. Effective treatment of exacerbations is important, because around 25% of exacerbations do not resolve and increased frequency of exacerbations is associated with greater decline in lung function, reduced quality of life, and poor overall survival.[86,89,90]

Pancreatic and biliary disease in cystic fibrosis

Epithelial cells in the pancreatic and biliary ducts are also affected by CFTR dysfunction.[91] Mucus obstruction occurs early in utero and most individuals with severe mutations have pancreatic insufficiency at birth and soon after.[92–94] This is caused by a chronic obstructive pancreatitis. By contrast, individuals with class IV, V, or VI mutations are often pancreatic sufficient at birth, although some develop pancreatic insufficiency later in life.[93,94]

Pancreatic insufficiency can be treated with pancreatic enzyme replacement therapy.[91,95] Careful titration of dose with matched energy intake is important in the dietary

management of pancreatic insufficiency. All cystic fibrosis multidisciplinary teams should have specialist dietetic support to manage the nutritional consequences of pancreatic insufficiency and increased metabolic rate.[39] The increased metabolic rate is caused by a combination of factors including the underlying gene mutation, increased work of breathing, and the metabolic consequences of chronic infection.[96] Optimum management of nutrition requires an increased energy intake with matched support from pancreatic enzyme replacement therapy.[97] Cystic fibrosis is also associated with biliary cirrhosis, although this occurs in less than 10% of patients.[94] More commonly, people with cystic fibrosis have variably abnormal liver function tests. A small proportion of such patients develop cirrhosis or portal hypertension and when this occurs should be considered for liver transplantation.

Metabolic consequences of cystic fibrosis

The development of cystic fibrosis-related diabetes mellitus is an increasing problem, occurring in up to 40% of adults, and is associated with poorer survival, particularly in female patients.[98] This disorder is caused by insulin deficiency resulting from the destructive pancreatic disease that ultimately destroys islet cell function.[99,100] Management of cystic fibrosis-related diabetes requires expertise from a cystic fibrosis dietician and input from a specialist diabetes team who understand the differences between cystic fibrosis-related diabetes and conventional diabetes mellitus.[101] Treatment is usually insulin replacement and the maintenance of a high energy diet.[100] Complications of cystic fibrosis-related diabetes are now becoming apparent with evidence of macrovascular and microvascular disease.[100] The combination of intravenous aminoglycoside use and diabetes is a major contributor to renal dysfunction in people with cystic fibrosis.

Osteopenia is common in cystic fibrosis. Patients with cystic fibrosis have a lower bone mineral density than healthy controls because of pubertal delay, and the consequences of the *CFTR* mutation, chronic inflammation, and inactivity all contribute to osteopenia.[102] The risk of osteopenia should be considered in dietary and lifestyle advice, which should encourage good calcium intake and exercise with appropriate vitamin D supplementation.[103] If osteoporosis develops, there is an increased risk of fracture and bisphosphonate therapy is recommended.[104]

Renal dysfunction is an increasing problem in patients with cystic fibrosis and is commonly caused by the use of intravenous aminoglycosides; in particular, gentamicin has been associated with acute and chronic renal failure. These drugs should be monitored carefully and once-daily regimens are recommended because they have similar efficacy to multiple-dose regimens and there are strong indications that there is less nephrotoxicity with once-daily dosing.[105]

Management of end-stage disease in cystic fibrosis

The progressive effects of infection and inflammation of the airways lead to extensive bronchiectasis and bronchiolitis obliterans, which inevitably result in respiratory failure. All patients with cystic fibrosis who develop respiratory failure should be offered the option of lung transplantation when they are on a trajectory of declining lung function, frequent exacerbations, and an FEV_1 of less than 30% predicted.[106,107] This presentation now occurs very infrequently in children in high-income countries and is predominantly an issue for adults. Lung transplantation is increasingly successful with 60–70% survival at 5 years.[108] Unfortunately, in countries where the availability of organs is lower than the number of potential recipients, patients can die while waiting for a transplant. In other countries with an efficient infrastructure to maximise organ retrieval, few patients with cystic fibrosis die without the opportunity of transplantation.

There are some contraindications to transplantation; many centres do not perform the procedure in patients with *B cenocepacia* and some do not perform transplantations in patients with chronic *M abscesses* because of poor outcomes.[109] For patients with predominant hypoxic respiratory failure, non-invasive ventilation can be a useful symptomatic treatment and can provide a bridge to transplantation. In individuals with hypercapnia, extracorporeal membrane oxygenation can be used as a bridge to transplantation. Selection of patients for transplantation and management in the pretransplant phase require careful communication between cystic fibrosis and transplant teams. After transplantation, there is often progressive handover of care from the transplant team to the referring cystic fibrosis team. It is important that good communication continues in this phase of care.

The palliative management of end-stage cystic fibrosis lung disease or end-stage bronchiolitis obliterans syndrome after transplantation should usually be done by the cystic fibrosis team that has built up a long-standing relationship with the patient with the assistance of specialists in palliative care.[109] Management of the end stage of disease is very important for the individual and for family and friends. Where possible, appropriate family or partners should be involved in decision making about how the last period of life is managed.[110] Most young adults with cystic fibrosis wish to have a high level of autonomy in decision making, and where possible, discussions should be sensitively and explicitly handled around the time of first transplant discussions and continued regularly through end-stage care.

Psychosocial consequences of cystic fibrosis

Chronic disorders can have substantial psychosocial effects on the wellbeing of affected individuals and their families.[111] During childhood, the disease affects the person with cystic fibrosis, their parents, caregivers, and siblings,

	Class	Drug	Effect on sweat chloride	Clinical response		Reference
				FEV_1	Pulmonary exacerbations	
Gly551Asp	III	Ivacaftor	50% decrease	10% increase	40% decrease	118–122
Gly551Ser, Gly178Arg, Gly1244Glu, Gly1349Asp, Ser549Asn, Ser549Arg, Ser1251Asn, Ser1255Pro	III	Ivacaftor	50% decrease	10% increase	NK	123
Arg117His	IV	Ivacaftor	25% decrease	3% increase (>18 years)	NK	124
Stop mutations (eg, Gly542X)	I	Ataluren	No change	No change	No effect	125, 126
Phe508del	II	Ivacaftor plus lumacaftor	8% decrease	3% increase	30% decrease	127, 128

FEV_1=forced expiratory volume in 1 s. NK=not known.

***Table 2*: Summary of clinical trial results of precision medicine-based treatments of CFTR dystinction by small molecules in people with cystic fibrosis, by mutation**

and often the wider family. The effects of having a life-limiting disease, progressively increasing symptoms including exacerbations, and a very high burden of care can affect behaviour and result in psychological distress.[18,112] In general, psychological distress is related to a negative outcome in disease, affecting adherence to treatment and hospital attendance, more frequent exacerbations and hospital admissions, and poor quality of life measures.[113,114] People with cystic fibrosis and their families have to deal with growing up, adolescence, and the challenges of adulthood while maintaining complex treatment programmes, which can take up to 4 h per day to deliver. Support from the cystic fibrosis care teams including social workers, nurses, and other professionals is crucial in helping families to navigate through life events while maintaining the best possible health and quality of life.

Recent studies have shown a high prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers.[114] Such psychological distress should be sought and dealt with appropriately using support mechanisms, cognitive therapies, or pharmacological interventions as appropriate.[112] Recent guidelines from the US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society provide a structure for prevention and treatment of anxiety and depression.[112] Interventions to prevent psychological distress, and treatment when appropriate, should be available to all patients with cystic fibrosis and their families.[112,114]

Innovative therapies

The recent development of drugs that correct the basic defect in CFTR function has substantially improved the prospect of effective disease-modifying treatment for cystic fibrosis.[8] The prevention of lung disease with effective therapies that correct CFTR function is a clear objective and might be particularly effective if they can be started close to the time of diagnosis by newborn screening.

Two approaches have attempted to deliver effective disease-modifying therapies. The first approach is the use of small molecules to modulate the CFTR protein and restore functional ion transport. The second approach is the use of molecular or gene therapy approaches to correct the mutation, at RNA or DNA level, and produce a normal CFTR protein that corrects mutated CFTR dysfunction by bypassing it.

Small molecule therapy

The first small molecule that has demonstrated efficacy is ivacaftor.[115–117] This drug was identified through high-throughput screening and subsequently modified to optimise its therapeutic effect.[116] Preclinical studies have shown that ivacaftor corrects CFTR-mediated chloride transport in most class III mutations, class IV mutations, and some other residual function mutations in human bronchial epithelial cell cultures,[117,118] and restores mucociliary function. A subsequent series of clinical trials has shown that ivacaftor has a high level of efficacy in class III mutations, particularly in patients with the Gly551Asp mutation (also known as G551D) or eight other related gating defects (table 2).[118–123] Compared with placebo, treatment with ivacaftor improved lung function (FEV_1) by around 10%, reduced sweat chloride concentration by around 60 mmol/L, improved quality of life, and reduced the frequency of pulmonary exacerbations.[119] This drug has also been tested in patients with class IV mutations, particularly those with the Arg117His mutation.[124] In this study, there was no significant effect on lung function, although ivacaftor did reduce sweat chloride concentration by around 25 mmol/L. In individuals older than 18 years and in those with a polythymidine tract variant of 5T, the improvement in FEV_1 was significant.[124] Further studies are underway to explore the use of ivacaftor in other partially functioning mutations.

The second small molecule strategy has been to target patients who are homozygous for the Phe508del mutation with a combination of a corrector drug to restore trafficking of CFTR and a potentiator to make it functional.[129] Two phase 3 clinical trials of the corrector lumacaftor in combination with ivacaftor have recently

been reported (table 2).[127] Compared with placebo, combination lumacaftor and ivacaftor improved FEV_1 and reduced the frequency of pulmonary exacerbations.[128] Additionally, there was a non-significant increase towards increased weight and a modest improvement in quality of life scores in patients treated with the combination. Around 10% of patients reported chest tightness with some associated bronchoconstriction. However, this effect seemed to settle after a few weeks of treatment and only resulted in withdrawal from the study in five patients. The improvement in FEV_1 after combination treatment with lumacaftor and ivacaftor was lower than that seen after treatment with ivacaftor in patients with the Gly551Asp mutation (3% *vs* 10%); however, the effect on frequency of pulmonary exacerbations was similar (30% reduction *vs* 40% reduction). In the phase 2 study, sweat chloride concentrations were measured and showed a modest reduction of 9 mmol/L after combination treatment with lumacaftor and ivacaftor, compared with 60 mmol/L in the Gly551Asp studies. Overall, these studies suggest that CFTR function is tractable with small molecules, but further studies are required to increase the efficiency of CFTR correction and potentiation.

Two studies have reported the effects of chronic coadministration of lumacaftor and ivacaftor in cell lines and showed that combination therapy reduces the functional rescue of Phe508del-CFTR in human bronchial epithelial cell cultures exposed to the drugs for 48 h.[130,131] Ivacaftor interferes with the pharmacological correction of Phe508del-CFTR by lumacaftor. There is also a finding in one of the studies that ivacaftor treatment decreases wildtype CFTR function in human bronchial epithelial cells.[130,131] The mechanism of this interaction seems to be a reduction in the stability of corrected Phe508del-CFTR by ivacaftor, which does not occur in Gly551Asp-CFTR. This interaction in part might explain the modest effect of combination therapy on sweat chloride concentration shown in two large clinical trials.[130,131] Other correcting drugs such as VX-661 (Vertex Pharmaceuticals, Boston) are also made unstable by ivacaftor, thus reducing the functional effects on CFTR. These studies highlight the importance of considering drug–drug and drug–protein interactions in the further development of small molecule combination therapy in cystic fibrosis.

A further small molecule approach has been developed for class I stop mutations. Ataluren allows ribosomal readthrough of premature stop codons.[125] This drug has also been studied in muscular dystrophies. In phase 2 studies, this drug showed some promise with electrophysiological correction of CFTR function and some improvement in FEV_1.[126] These findings were not substantiated by a phase 3 study, which only reported a very small effect on FEV_1 in patients not receiving aminoglycosides.[132] Aminoglycosides also have an effect on ribosomal readthrough and might account for the finding that patients not receiving inhaled aminoglycosides had a greater effect on stabilisation of FEV_1 compared with those receiving aminoglycosides. Further studies with ataluren are currently underway.

Gene and molecular therapies

Since the cloning of the *CFTR* gene, the potential for gene and molecular therapies has generated a great deal of excitement and anticipation. Some studies have shown that CFTR function can be restored in the nose of people with cystic fibrosis. The first major study of lung delivery has recently been reported and has shown some effects on important clinical parameters of FEV_1 and some measures on CT scan.[132] This study is a further milestone in the development of disease-modifying therapies for people with cystic fibrosis and suggests that substantially more efficient vectors and delivery systems are required to achieve sufficient expression of CFTR to result in a clinical benefit.

Some other compounds are currently being developed with corrector and potentiator effects, and these are likely to enter clinical trials this year. An oligonucleotide drug, PQR-010 (QR-010, ProQR, Leiden, Netherlands), has been developed that repairs the genetic defect in RNA, and is currently in phase 1 clinical trials.

Clinical trials in cystic fibrosis

With the improving quality of life and outcomes for cystic fibrosis, selecting endpoints for clinical trials has become more difficult.[133] Absolute change in FEV_1, time to next exacerbation, or frequency of exacerbations have been acceptable endpoints for licensing authorities. However, decline in lung function and frequency of exacerbations are decreasing with improved treatment and these endpoints could become too insensitive for use in clinical trials. New biomarkers are being developed that might be more sensitive overall and more specific for precision medicine interventions. For example, the measurement of lung clearance index by multiple breath washout is more sensitive than FEV_1 and can allow studies to be done with smaller numbers of patients.[134] For precision medicine approaches with corrector and potentiator therapy, organoids and rectal biopsies might be useful to determine whether a particular rare mutation is responsive to a particular corrector or potentiator, and might also allow modelling to select the correct doses of combination drugs in individual patients.[135]

Cystic fibrosis care

Delivery of clinical care in patients with cystic fibrosis depends upon specialist multidisciplinary teams with an appropriate discipline and skill mix to ensure that all aspects of cystic fibrosis disease are managed effectively.[136] This process has been helped by national and international standards of care and guidelines that offer cystic fibrosis centres standards to benchmark high performance, which has driven high quality improvement culture. Most

countries have a cystic fibrosis registry that allows year-to-year comparison, as well as the opportunity to compare centres with similar resources and geography. These registries allow centres, regions, and countries to look at real outcomes and differences in practice and provide a quality improvement framework by which cystic fibrosis care can be progressively enhanced.[137] Continuing to improve care by managing performance against real outcomes and including patients, carers, and national cystic fibrosis organisations in this process is a pioneering model and is crucially important in the management of new therapies targeted at the basic defect in cystic fibrosis.

Contributors

I am sole author and contributor.

Declaration of interests

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