Cystic fibrosis

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Abstract

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive condition in Caucasians. It is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Early detection of CF, improvements in management, multidisciplinary care in specialist CF centres and new treatments have seen survival rates improve in recent decades. CF is a multisystem disease with a predilection for the lungs and digestive tract. Chronic lung infection and airway inflammation lead to bronchiectasis, progressive airflow obstruction and ultimately death from respiratory failure in the majority of patients. Treatment of acute and chronic lung infection, optimization of nutritional status and management of CF-related complications such as diabetes form the basis of disease management. New therapies known as CFTR modulators that target specific mutations of the CF gene are now available. Ivacaftor, the first drug licensed for individuals with class 3 mutations, is associated with improvements in lung function and weight, and a reduction in frequency of exacerbations. More recently, the combination therapy ivacaftor–lumacaftor for patients homozygous for the Phe508del mutation has been given approval in the USA. A number of other therapies that target both the underlying genetic defect and established disease are in the pipeline.

Keywords CFTR; cystic fibrosis; gene therapy; ivacaftor; lung function; *Pseudomonas*; respiratory tract infection

Key points

- Care delivered in specialist CF centres by an experienced multidisciplinary team is associated with improved outcomes. Regular monitoring of respiratory function, nutritional status and sputum microbiology at least every 3 months and annual screening for CF-related complications is routine
- Treatment of acute and chronic lung infection, optimization of nutritional status and management of CF-related complications such as diabetes form the basis of disease management
- The challenge of adherence to therapy associated with increasing treatment complexity and burden of care in CF is increasingly recognized. Strategies aimed at ensuring high levels of adherence to complex treatment routines is an evolving area of interest
- A new era of therapy is emerging following the discovery of treatments which target the underlying genetic defect. Kalydeco (Ivacaftor), a cystic fibrosis transmembrane conductance regulator (CFTR) modulator for use in patients with class 3 gene mutations (around 5%) is the first to be licenced. Orkambi (Lumacaftor–Ivacaftor) for individuals homozygous for the Phe508del mutation received Food and Drug Administration approval in July 2015 but is not yet available in the UK

Prevalence and prognosis

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive condition in Caucasians. The prevalence varies with country of origin from 1 in 2000 to 1 in 100,000 and is highest in Caucasian populations. In the UK, the incidence is 1 in 2415 live births, and there are >10,500 people with CF.

CF is a complex, multisystem disease, and while the majority of morbidity and mortality is associated with respiratory disease, other organs affected include the pancreas, liver, intestine, sinuses, bones and male reproductive tract. Early detection and improvements in management have seen survival rates improve. The current median survival in the UK is now 41 years.

Pathogenesis

CF is caused by a mutation in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is located on the long arm of chromosome 7. The CFTR protein is a chloride channel expressed in the apical membrane of epithelial cells. It primarily regulates the movement of chloride, but is also involved in sodium, bicarbonate and water transport. Mutations in both copies of the gene result in clinical disease.[1]

Although 2001 CFTR gene mutations are identified in the Cystic Fibrosis Mutation Database, less than 200 are associated with disease. The most common mutation, Phe508del, is found in approximately 70% of the Caucasian population. CFTR mutations can be grouped into six classes according to their impact at a cellular level (Table 1).

In the lungs, dehydration of the respiratory epithelium and defective mucous clearance result in viscous secretions that are predisposed to bacterial colonization. Over time, chronic infection and airway inflammation lead to bronchiectasis, progressive airflow obstruction and ultimately death from respiratory failure. In early life, *Staphylococcus aureus* and *Haemophilus influenzae* are the predominant organisms, but by adulthood around 60% of CF patients are infected with *Pseudomonas aeruginosa*; this is associated with a more rapid decline in lung function and reduction in long-term survival. Other less common pathogens such as *Burkholderia cepacia*, methicillin-resistant *S. aureus*,

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Class mutations

Class of CFTR mutation	Defect	Mutation examples	Drug therapy
I	Defective protein production	Nonsense mutations e.g Gly542X, Trp1282X	Ataluren — PTC124[a]
II	Defective protein processing	Phe508del — 70% Caucasians	Lumacaftor/ivacaftor (Orkambi®) VX-661/ivacaftor[a]
III	Defective channel regulation	Gly551Asp — 4%	Ivacaftor (Kalydeco®)
IV	Defective conduction	Arg117His Arg347Pro	Ivacaftor[a]
V	Reduced functional CFTR protein	3849 + 10kbC 2789 + 5G	Ivacaftor[a]
VI	Decreased CFTR stability	4326delTC	

[a] Current trials.

Table 1

Achromobacter and non-tuberculosis mycobacteria can also be associated with adverse respiratory outcomes.

Diagnosis

Most cases of CF are diagnosed in early life by newborn screening, which is now standard across the UK. Immunoreactive trypsinogen is measured in blood taken from a heel prick in all neonates and is a marker of pancreatic injury consistent with CF. If concentrations are found to be high, genetic testing and a sweat test (pilocarpine iontophoresis), which is an assessment of CFTR dysfunction, are performed; these will confirm the diagnosis in >95% of babies with CF.

Despite the introduction of newborn screening, individuals can present clinically with one or more of the phenotypic characteristics associated with CF (Table 2). Clinicians must therefore have a high index of suspicion in cases where suggestive symptoms are present. A high sweat chloride (>60 mmol/litre) and identification of two CFTR mutations confirm the diagnosis in most individuals. Some individuals, however, present with only one characteristic feature of CF and a borderline (30–60 mmol/litre) or normal (<30 mmol/litre) sweat test. Further evaluation of CFTR dysfunction by nasal potential difference testing may then be indicated. Diagnosis in adulthood is increasingly seen and is often associated with milder disease and, in general, a better prognosis.

Disease management

Centrally coordinated CF care delivered in specialist centres by a multidisciplinary team including clinicians, nurse specialists, physiotherapists, dieticians and psychologists is recognized worldwide to result in the most favourable outcomes. Regular review should take place at least every 3 months, with monitoring of respiratory function, weight and sputum microbiology. Annual screening for complications such as diabetes mellitus, allergic bronchopulmonary aspergillosis, liver and bone disease can also guide therapy. Person-to-person transmission of infection is reported in CF, and microbiological cohort segregation is now a recommended standard of care.

Respiratory disease

Assessment: respiratory function is assessed by forced expiratory volume in 1 second (FEV_1) and is an important predictor of survival. The lung clearance index is more sensitive in identifying early small airways disease, although it is not yet routinely available in clinical practice. Computed tomography can be helpful in identifying complications or the extent of structural lung damage, although its use in routine monitoring is limited by the risks of radiation (Figure 1).

Treatment: management of respiratory disease aims to prevent or delay the onset of chronic infection, maintain lung function and prevent pulmonary exacerbations (Table 3). Regular nebulized antipseudomonal antibiotics, nebulized mucolytic or osmotic agents to aid airway clearance and oral azithromycin have

Clinical manifestations of cystic fibrosis

Infants and children

- Meconium ileus
- Recurrent respiratory infections
- Failure to thrive or low body mass index
- Diarrhoea
- Nasal polyps
- Acute pancreatitis

Adults

- Recurrent respiratory infections
- Bronchiectasis[a]
- Atypical asthma
- Sinus disease
- Pancreatic insufficiency
- Hepatobiliary disease
- Pancreatitis[a]
- Malnutrition
- Male infertility[a]

[a] Atypical CF associated with single-organ disease and later presentation.

Table 2