

# Cystic fibrosis

## What is cystic fibrosis?

Cystic fibrosis (CF) is a multi-organ disease best managed in a multidisciplinary setting in conjunction with a specialist centre for CF, with treatment tailored to the individual.

Conventional treatment has improved greatly over the past few decades. Newer approaches such as gene and small molecule-based treatments may have more potential to halt disease progression.

## Genetics

CF is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, on chromosome 7. [1] There are at least 2,000 mutations in the CFTR gene. Different mutations result in different phenotypes. Some mutations result in milder forms of the disease. One study identified some mutations which appeared to have no pathological effect at all. [2] The most common mutation in the white population is the delta-F508 (DF508).

CFTR is an ATP-responsive chloride channel that also affects other cellular activities, such as sodium transport across the respiratory epithelium, composition of cell surface glycoprotein and antibacterial defences.

## How common is cystic fibrosis? (Epidemiology)

CF is the most common autosomal recessive genetic disease in white populations, [3] although it can affect people from any ethnic group. [4]

- Prevalence in the white population is 1 in 3,000–4,000 newborn infants, [3] with calculated carrier frequency of 1 in 25. [5] 11,319 people were recorded as having CF in the 2023 UK CF Registry. [6]
- The only risk factor is a family history of the condition.

# Pathogenesis

The abnormality in the CFTR gene explains the pathology of CF.

## High sodium sweat

Primary secretion of sweat duct is normal but CFTR does not absorb chloride ions, which remain in the lumen and prevent sodium absorption.

## Pancreatic insufficiency

Production of pancreatic enzymes is normal but defects in ion transport produce relative dehydration of pancreatic secretions, causing their stagnation in the pancreatic ducts.

## Biliary disease

Defective ion transfer across the bile duct causes reduced movement of water in the lumen so that bile becomes concentrated, causing plugging and local damage.

## Gastrointestinal disease

Low-volume secretions of increased viscosity, changes in fluid movement across both the small and large intestine and dehydrated biliary and pancreatic secretions cause intraluminal water deficiency.

## Respiratory disease

Dehydration of the airway surfaces reduces mucociliary clearance and favours bacterial colonisation; local bacterial defences are impaired by local salt concentrations and bacterial adherence is increased by changes in cell surface glycoproteins.

Increased bacterial colonisation and reduced clearance produce inflammatory lung damage due to an exuberant neutrophilic response involving mediators such as IL-8 and neutrophil elastase.

# Symptoms of cystic fibrosis (presentation)

- As normal digestive function is possible with <5% pancreatic function, CF can present at any age.
- The most common presentation is with respiratory problems – usually recurrent lower respiratory tract infection (LRTI) with chronic sputum production.

However, immunoreactive trypsinogen (IRT) is now measured on a dried blood spot obtained on the Guthrie card at day six of life. Samples with abnormally raised IRT levels will undergo CFTR mutation screening. This was introduced in 2007. This therefore means that clinical presentation of CF will become rarer. However, screening failures do sometimes occur. Presentation of CF varies with age.

## **Presentation and diagnosis**<sup>[7]</sup>

Antenatal	Amniocentesis/chorionic villus sampling (CVS). Ultrasound demonstration of bowel perforation/hyperechogenic bowel (4% cases due to CF).
Perinatal	Screening. Bowel obstruction with meconium ileus (bowel atresia). Haemorrhagic disease of the newborn. Prolonged jaundice.
Infancy and childhood	Family history. Recurrent respiratory infections. Chronic pulmonary disease. Diarrhoea. Failure to thrive (thriving does not exclude diagnosis). Rectal prolapse. Nasal polyps (in children, nearly always due to CF). Acute pancreatitis. Portal hypertension and variceal haemorrhage. Pseudo-Bartter's syndrome, electrolyte abnormality. Hypoproteinaemia and oedema.
Adolescence/adulthood	Screening. Family history. Recurrent respiratory infections. Atypical asthma. Bronchiectasis. Chronic pulmonary disease. Chronic sinus disease. Male infertility with congenital bilateral absence of the vas deferens. Heat exhaustion/electrolyte disturbance. Portal hypertension and variceal haemorrhage.

## Signs

These may include:

- Finger clubbing.
- Cough with purulent sputum.
- Crackles.
- Wheezes (mainly in the upper lobes).
- Forced expiratory volume in one second (FEV1) showing obstruction.

Babies diagnosed with CF will usually have no signs or symptoms.

## Diagnosing cystic fibrosis (investigations)

- Sweat testing confirms the diagnosis and is 98% sensitive. Chloride concentration  $>60$  mmol/L with sodium concentration lower than that of chloride on two separate occasions.
- Molecular genetic testing for CFTR gene.
- Sinus X-ray or CT scan - opacification of the sinuses is present in almost all patients with CF.
- CXR or CT of thorax.
- Lung function testing - spirometry is unreliable before 6 years.
- Sputum microbiology - common pathogens include *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Escherichia coli* and *Klebsiella pneumoniae*.
- Various blood tests including FBC, U&Es, fasting glucose, LFTs and vitamin A, D and E levels are usually performed.
- Semen analysis if appropriate.

## Managing cystic fibrosis<sup>[8]</sup>

Most patients' care is co-ordinated by a CF tertiary centre.<sup>[9]</sup> However, an Australian study found no difference in care between that provided in specialist centres and that provided by outreach services. This may be more relevant in remote areas.<sup>[10]</sup> A German study reported that CF patients most valued healthcare staff who were friendly, approachable and communicative.<sup>[11]</sup>

## Respiratory problems

Most of the morbidity and mortality associated with CF is caused by respiratory disease where chronic infection and inflammation lead to [bronchiectasis](#), progressive airflow obstruction, [cor pulmonale](#) and finally death.

Probably as a result of more successful treatment of classic bacterial infections in CF, there are now increasing problems with multi-resistant isolates of *P. aeruginosa* and innately resistant organisms such as *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans* and non-tuberculous mycobacteria. Meticillin-resistant *S. aureus* (MRSA) is a growing problem.

The following interventions are commonly used to prevent and treat respiratory problems:

- In the early, pre-infected stages, mucus clearance, preventing infection and maintaining good lung function are the main aims.
- Chest physiotherapy should be given twice-daily and this is increased with infective exacerbations.
- Additional physical exercise is also beneficial and should be encouraged.
- Regular sputum samples are sent for bacterial culture.
- Prophylactic antibiotics are used to reduce *S. aureus* in children and also to prevent secondary bacterial infections when a patient has a presumed acute viral respiratory infection.
- Antibiotic choice for infective exacerbations will depend on the organism.
- Infection with less common organisms requires specialist microbiological advice.

- Patients with *P. aeruginosa* have a 2- to 3-fold increased risk of death over eight years. This is eradicated by various combinations of oral, inhaled and intravenous antibiotics. Pre-colonisation pseudomonal eradication protocols usually include both topical (nebulised) and systemic antibiotics.
  - A Cochrane review examining various combinations of oral antibiotics (ciprofloxacin and azithromycin), inhaled therapies (tobramycin, aztreonam, and colistin) and intravenous therapies (ceftazidime and tobramycin) found that there was insufficient evidence to support any particular antibiotic regimen over others, but that intravenous therapy does not appear to be superior to oral antibiotics.<sup>[12]</sup>
  - Intravenous home treatment using tobramycin or amikacin is sometimes used where suitably trained staff are available.<sup>[13]</sup>
- The National Institute for Health and Care Excellence (NICE) recommends treatment of chronic *P. aeruginosa* with nebulised aztreonam, colistimethate sodium or tobramycin.<sup>[7]</sup> For patients who cannot take the nebulised form, NICE has recommended dry powder inhalation formulations of colistimethate sodium and tobramycin.<sup>[14]</sup>
- A Cochrane review found insufficient evidence to suggest a significant beneficial effect on FEV1 by long-acting inhaled bronchodilators and recommended further research into spirometric changes from baseline, quality of life and adverse effects.<sup>[15]</sup>
- Similarly, a later review found very low certainty evidence about the effects of short-acting inhaled bronchodilators.<sup>[16]</sup>
- Dornase alfa is a recombinant form of human deoxyribonuclease and is given by nebuliser. It cleaves neutrophil-derived DNA in sputum to reduce viscosity and therefore aid sputum removal. It has been shown to be associated with improvement in lung function and possibly a reduction in respiratory exacerbations. Cochrane looked at the timing of administration before and after airway clearance and found no difference in adults. The results in children suggested that inhalation prior to airway clearance may be more beneficial for small airway function than inhalation after, but with considerable uncertainty in the evidence.<sup>[17]</sup>

- High-dose ibuprofen may slow progression of lung disease, especially in children.<sup>[18]</sup>
- Azithromycin has also been shown to reduce inflammation and improve respiratory function in CF. However, benefits beyond six months and the issue of emerging resistance require further research.<sup>[19]</sup>
- Hypertonic saline by a nebuliser is often given for its osmotic action. Other osmotic agents are being developed. A Cochrane review found low-certainty evidence that hypertonic saline was an effective adjunct to physiotherapy during acute exacerbations in adults, and generally poor evidence to determine its effect in other situations. It recommends that future research focuses on the role of nebulised hypertonic saline in conjunction with CFTR modulator therapy.<sup>[20]</sup>
- Mannitol dry powder for inhalation is recommended by NICE as an option for treating cystic fibrosis in adults:<sup>[21]</sup>
  - Who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase; **and**
  - Whose lung function is rapidly declining (FEV1 decline greater than 2% annually); **and**
  - For whom other osmotic agents are not considered appropriate.
- A Cochrane review could not obtain sufficient high-quality evidence to conclude whether inhaled corticosteroids were beneficial in cystic fibrosis.<sup>[22]</sup>
- CFTR modulator therapies are the first targeted therapy for CF. They correct defective CFTR proteins by improving function, increasing production, or improving intracellular processing of the gene products. They are targeted at specific CFTR mutations, meaning patients must have a particular genotype to benefit. A 2023 Cochrane review found evidence that triple therapy (with three CFTR modulator agents) produces improvements in important outcomes, including quality of life and FEV1. Dual therapies are less effective, and monotherapy did not have sufficient evidence of an effect on clinically-important endpoints.<sup>[23]</sup> At the time of writing, three different formulations of CFTR modulator therapy were funded by NHS England, subject to certain criteria.<sup>[24]</sup>



- In the end stage, management focuses on the common complications, which include haemoptysis, pneumothorax and respiratory failure.
- Lung or heart and lung transplantation listing should be considered where there is respiratory failure. Due to scarcity of donor organs, approximately a third of CF patients on the list die before receiving a donor lung.<sup>[25]</sup>

### **Nasal polyps**

50% of adults with CF have [nasal polyps](#). Treat with nasal steroids initially; if this fails, polypectomy is usually performed (50% require repeat within two years).

### **Pancreatic insufficiency**

At least 85% of patients with CF have pancreatic insufficiency. This usually presents with neonatal meconium ileus or failure to thrive, steatorrhoea and malnutrition which can cause anaemia, vitamin deficiency and sometimes oedema. It can cause rectal prolapse, intussusception, volvulus and obstruction.

Pancreatic insufficiency should be confirmed with stool elastase; presence of unsplit fat globules in stool or 2-3 days' stool collection for faecal fat.

Pancreatic enzymes are traditionally prescribed. However, a Cochrane review has found that there is no evidence regarding the risks and benefits of long-term treatment, nor on the timing of doses.<sup>[26]</sup>

### **Maintaining adequate weight**

Patients should be weighed regularly. They will have high energy needs, especially those with recurrent chest infections or those who lose a lot of fat in their stools. Protein intake needs to be at least twice the normal recommended amounts.

- Despite the issues evident in the Cochrane review above, the British National Formulary recommends taking enteric-coated enzyme preparations with, immediately before or just after food to achieve optimal concentration in the duodenum. The dose is adjusted to achieve normal stools. Drugs may be needed to reduce acid secretion, as well as vitamin supplements for the fat-soluble vitamins A, D and E.

- High intake of calories (130% normal) is usually required.<sup>[27]</sup>
  - Comparing actual resting energy expenditure (REE) to predicted REE is an objective indicator of disease severity and progression as well as energy requirements. There is evidence of a recent trend for patients to exceed their energy requirements and develop obesity. The REE approach is helpful in understanding this phenomenon.<sup>[28]</sup>
  - Research supports the use of high-calorie diets in underweight patients but further work needs to be done on the most efficacious route of delivery.
  - If the patient is unable to maintain weight, enteral feeding via gastrostomy may be required.
  - There is no evidence that oral calorie supplements are beneficial for children with CF. Short-term protein supplements may be of benefit in adults but further research is required.<sup>[29]</sup>

### **Liver disease**<sup>[30]</sup>

Liver disease is seen in up to 30% of patients by adulthood. Liver cell failure usually occurs late, with ominous prognosis. It is fatal in 2-4% of CF cases and is the third most common cause of death in CF patients.

- Commonly, LFTs are abnormal and should be treated with caution. They can be a reflection of CF without liver disease, CF-related liver disease or the side-effects of medication.<sup>[31]</sup>
- Usually seen as hepatosplenomegaly.
- Ultrasound is a useful confirmatory investigation. Other imaging modes - eg, scintigraphy - may be required.
- Ursodeoxycholic acid improves bile flow and produces some improvement but does not alter the course of chronic liver disease.

Liver transplantation should be offered to CF patients with progressive liver failure and/or with life-threatening sequelae of portal hypertension. They should also have relatively good lung function, to support long-term survival.

### **Diabetes and glucose intolerance**

A 2014 Danish study reported an incidence of CF-related diabetes among 11- to 16-year-old children of 12–14%, This incidence remained unchanged over the previous two decades.<sup>[32]</sup>

- Screening for diabetes is performed at regular intervals.
- Insulin replacement is usually required with the dose adjusted to match high dietary intake. Early insulin therapy may be beneficial but further research is required.<sup>[33]</sup>
- A Cochrane review found no significant conclusive evidence that long-acting insulins, short-acting insulins or oral hypoglycaemic agents had a distinct advantage over one another in controlling hyperglycaemia or clinical outcomes associated with CF-related diabetes.<sup>[34]</sup>

### **Reproductive health and fertility**

Nearly all males with CF have obstructive azoospermia with sexual function that is otherwise normal; there is normal spermatogenesis but no vas deferens. Early counselling should be offered about infertility and sperm count. In vitro fertilisation with aspirated sperm has been used successfully.

Women are generally of normal fertility but need genetic counselling. There is an inherent risk to pregnancy with severe lung disease (FEV1 <30% predicted).

Offspring of patients with CF will be carriers of cystic fibrosis.

### **Psychological problems**

CF is a huge burden to patients and families. This is because of:

- The life-shortening nature of the disease.
- The time-consuming treatments prescribed.
- The ongoing morbidity.

Insufficient evidence exists on psychological interventions or approaches to support people with CF and their caregivers and multicentre studies are needed.<sup>[35]</sup>

### **Osteoporosis<sup>[36]</sup>**

There is an increased risk of osteoporosis in patients with CF. Around one third of adults with CF have [osteoporosis](#).

Patients should be recommended to take calcium, vitamin D and bisphosphonates as appropriate. Patients usually have regular dual-energy X-ray absorptiometry (DXA) scans.

### **Follow-up of patients** <sup>[8]</sup>

Patients have regular follow-up by their specialist.

UK standards recommend that:

- Patients should be seen twice a year by a multidisciplinary team working in a specialist centre.
- GPs should provide shared care in conjunction with specialists.
- Children should be transferred to adult services by the age of 18 at the latest.

In general, the following investigations are performed at regular intervals:

- Pulmonary function tests.
- CXR.
- DXA scan.
- Blood glucose.
- Respiratory cultures.
- Ultrasound scan of the liver.
- Vitamin D levels.

Varicella antibodies are usually checked for and the varicella vaccine is usually offered to those children who need it.

All patients should receive the annual influenza vaccination. They should also receive the pneumococcal vaccine.

## Prognosis

The pronounced improvement in life expectancy over the period of two decades is largely the result of centralisation of care at CF centres and aggressive treatment of symptoms.

- Median survival in 1999 was 30 years. Projected life expectancy for patients increased from 31 years to 37 years over the period of a decade.<sup>[37]</sup>
- A UK longitudinal study reported an estimated survival of 45–57 in males (depending on age of diagnosis) and 40 in females.<sup>[38]</sup>
- Females and those people of lower socio-economic status have a worse prognosis.<sup>[39]</sup>
- The use of rDNase has been shown to lead to a marked improvement in survival of patients with a low FEV1.<sup>[40]</sup>

## The future

The great hope for the future is that therapies that treat the basic defect will normalise life expectancy for those born with CFTR mutations. Gene therapies are under development, although not yet available for clinical use.<sup>[41]</sup>

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## Further reading

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