**An update on the diagnosis and management of cystic fibrosis**

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**Introduction**

Cystic fibrosis (CF) is the most common life-limiting genetic condition in the Western World, with over 10,000 sufferers in the UK alone. (1) It is caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein which regulates ion and water content of epithelial secretions. Defective CFTR results in thick viscid secretions in many different body systems resulting in a truly multi-organ disease which manifests itself most obviously in the lungs where impaired mucociliary clearance results in chronic infection, inflammation and subsequent bronchiectasis with progressive loss of lung function and ultimately respiratory failure. It is inherited as a classic Mendelian autosomal recessive trait and the UK has a relatively high prevalence where 1 in 25 Caucasians are CFTR mutation carriers with a disease incidence of 1 in 2500 live births; ethnic minorities have a lower carrier incidence with correspondingly lower disease rates.

Overall survival has improved dramatically since the millennium such that median life expectancy now extends into the fifth decade. (1)These improvements have been heralded as a success story of modern medicine however with increasing longevity comes a range of co-morbidities, some as complications of the disease itself but some also as a consequence of long-term treatments required to manage CF. Recently, NICE Guidelines for the diagnosis and management of CF have been published and this review aims to provide a CF update in the context of recommendations from the guideline committee.(2)

**Making a diagnosis**

Since 2006 a National Newborn Screening Programme (NBSP) has been in place and most people with CF are now diagnosed shortly after birth via the heel prick test. However the NBSP does not detect less common CF-related mutations such that some children with CF still go undiagnosed and along with those born before 2006 may reach adulthood before diagnosis is contemplated. Furthermore, it is increasingly recognised that NBSP identifies some infants with no clinical features of CF, but who may be at risk of developing the CF syndrome later in life and have been given the designation of Cystic Fibrosis Screen Positive Inconclusive Diagnosis (CFSPID). It is therefore important to maintain vigilance for those whose features suggest CF (see Box 1). In such cases a referral to a local respiratory service is warranted so that further testing and/or referral on to the specialist CF centre can be facilitated. The diagnosis of CF can be made based on clinical presentation alone; however a diagnosis is best supported by genetic screening or an elevated sweat chloride level.

**BOX 1: Clinical features that may support a diagnosis of CF**

**In children**

* Meconium ileus
* Faltering growth
* Malnutrition
* Wet cough
* Symptoms of malabsorption
* Rectal prolapse
* Distal intestinal obstruction syndrome

**In adults**

* Recurrent and chronic pulmonary disease
  + Recurrent infection
  + Bronchiectasis (particularly upper zone distribution)
  + Chronic productive cough
* Pancreatitis
* Sinusitis
* Infertility (male)

**Lung disease**

Reduced clearance of thick mucus results in stasis of respiratory secretions, creating a microenvironment ripe for infection and inflammation. Chronic infection and inflammation eventually cause irreversible bronchiectasis and pulmonary function decline, and 90% of CF deaths are due to progressive respiratory failure. Infection can be detected early in life, commonly with *Haemophilus influenzae* and *Staphylococcus aureus*. With age the prevalence of *Pseudomonas aeruginosa* increases such that by adulthood over 50% are infected. (1) Unfortunately, chronic *P. aeruginosa* infection is associated with increased morbidity and mortality and in order to prevent cross-infection between patients, clinics are segregated based upon microbiology.

**Extra-pulmonary complications**

Defective CFTR is expressed in many organs, resulting in multi-system disease contributing to excessive morbidity (see Box 2).

One of the most common extra-pulmonary manifestations is in the reproductive system where ~98% of males are infertile due to congenital absence of the vas deferens (CBAVD). In women with CF, mucus plugs may act as mechanical barriers to conception but the reproductive tract is otherwise structurally normal. (3)

The pancreas is another commonly affected organ and the term “cystic fibrosis” was coined from its appearance at autopsy. (4) Viscid pancreatic secretions become static with local autolysis, inflammation and fibrosis with subsequent exocrine and endocrine insufficiency. Exocrine abnormalities are characterised by malabsorption of fat and fat-soluble vitamins, whereas dysregulated *Beta-*cells struggle to release insulin adequately and cystic fibrosis related diabetes (CFRD) ensues. (5) CFRD is not only associated with aberrant glycaemia but also accelerated pulmonary function decline and a three-fold increase in mortality. (6)

Elsewhere, stasis of hyperviscous bile can accumulate in the biliary tree causing focal inflammation and fibrosis. In this setting persistent hepatocyte injury can lead to CF related liver disease, the third most common cause of death in children and adolescents with CF. (7) (8) Other common co-morbidities include polyposis and chronic sinusitis in the upper respiratory tract, (9) low bone mineral density, (10) gastro-oesophageal reflux (11) and renal disease. (12)

**Box 2: Complication and co-morbidities associate with CF**

**Upper respiratory tract**

Nasal polyps

Sinusitis

**Lower respiratory tract**

Chronic infection

Bronchiectasis

**Pancreas**

Cystic fibrosis related diabetes

Pancreatitis

**Hepatobiliary**

Cystic fibrosis related liver disease

Gall stones

**Renal**

Kidney stones

Chronic kidney disease

**Gastrointestinal**

Malabsorption

Gastro-oesophageal reflux disease

Distal intestinal obstruction syndrome

**Others:**

Arthropathy

Congenital absence of the vas deferens (Males)

Subfertility (Females)

**Management**

The management of people with CF has evolved dramatically over the last few decades and increasing survival can be attributed to improvements in nutrition, the aggressive treatment of infection, and the recognition of comorbidities, see Box 3.

Specialist services have also evolved over time and people with CF should be managed in regional CF centres. In paediatrics a shared-care approach can be adopted between specialist centres and local services to minimise disruption to schooling and family life. The CF centre model of care revolves around a specialist multi-disciplinary team (MDT) with close links to other medical and surgical specialities. The core CF MDT consists of respiratory physicians, specialist nurses, specialist physiotherapists, clinical psychologist, dieticians and pharmacists. CF centres should be organisationally and structurally designed to minimise the risk of cross-infection between patients.

**BOX3 3: Principles of optimal CF care**

1. Aggressive treatment of infection
2. Airway clearance
3. Optimisation of nutritional status
4. Close monitoring of complications and co-morbidities

**Treatment of infection**

Regular surveillance for lung infection is warranted from an early age, ideally with regular sputum sampling. Antibiotic strategies are targeted towards chronic suppression of the classical CF pathogens *S.aureus* and *P. aeruginosa*. In younger age-groups *S. aureus* is more prevalent and the recent NICE guidelines suggest chronic prophylaxis with flucloxacillin may be appropriate**.** In those with a first or new growth of *P. aeruginosa,* initiation of eradication treatment has been shown to be successful. Eradication strategies should include nebulised antibiotics in addition to a short course of oral or intravenous antibiotics. Despite eradication being initially successful, infection often returns and treatments targeted toward chronic *P. aeruginosa* infection include long-term nebulised antibiotics such as colistimethate, tobramycin and aztreonam. In the last decade dry powder formulations of some nebulised antibiotics have become available which are quicker and easier to take but can be associated with increased cough. **(13-15)**

Chronic pulmonary infection is punctuated by exacerbations characterised by acute deterioration in symptoms and lung function. Although milder exacerbations can be successfully treated with oral antibiotics, many require admission to hospital for intravenous antibiotics, glucocorticoids, optimisation of nutritional status and input from chest physiotherapists for intensive airway clearance. Exacerbations carry an associated risk of mortality and hence chronic inhaled antibiotics are targeted towards the suppression of infection to prevent exacerbations. In addition, chronic macrolide therapy e.g. azithromycin has been shown to effectively reduce pulmonary inflammation and exacerbation rate in both adults and children.

**Airway clearance**

Historically, physiotherapy for people with CF was focussed solely on manual chest clearance techniques to help mobilise respiratory secretions. However, modern physiotherapy includes a combination of chest clearance techniques, exercise and inhaled mucolytic therapies. Physiotherapists work with patients and families to tailor an individualised regimen that is effective and as efficient as possible. Mucolytic therapies include recombinant human DNA cleaving enzymes such as dornase alfa (nebulised to break down viscid human and bacterial DNA material in CF sputum) and mucus hydrators such as nebulised hypertonic saline and inhaled mannitol.

**Nutritional status**

Malnutrition has strong associations with poorer clinical outcomes in CF and hence close attention to nutritional status is important. (16) Increased daily energy demands due to progressive lung disease require increased oral calorie intake including enteral tube feeding if oral supplementation is insufficient. Exocrine pancreatic insufficiency is present in 85% of the CF population where oral pancreatic enzyme replacement therapy (PERT) is given with fat and protein containing meals, snacks and drinks. (17) Additionally, supplementation of the fat-soluble vitamins A, D, E & K is needed to optimise nutritional status. Poor nutritional status, pulmonary disease and glucocorticoid use can all have detrimental impact on bone health and low bone mineral density is present in ~20% of people with CF. (1) Monitoring of vitamin D levels and dual energy X-ray absorptiometry (DEXA) are therefore routinely performed in at-risk patients.

**Close monitoring of complications**

CF MDTs should offer a comprehensive annual review of all people with CF in order to optimise current management, assess pulmonary and nutritional status and screen for other complications. CFRD is a distinct form of diabetes and is associated with more rapid lung function decline and increased morbidity at lower levels of dysglycaemia than type 1 and 2 diabetes: CF MDTs are therefore recommended to perform annual screening for the disease preferably involving continuous glucose monitoring. An assessment of mental wellbeing and other psychosocial indicators, liver disease and exercise capacity are also recommended.

**Disease modifiers**

Recently, drugs targeting the defective CFTR protein have been developed and are licensed for some genotypes. NICE has approved ivacaftor for use in people with certain “gating” mutations (which account for ~5% of the UK CF population) under the proviso they can only be prescribed by specialist CF centres. (18) In those with responsive genotypes, ivacaftor is associated with dramatic improvements in lung function, nutritional status, exacerbation rate and rate of pulmonary function decline. (19) In the UK, no products are currently routinely available for people with the common F508del mutation although trials are ongoing.

**How can GPs help support patients and their families?**

The specialist CF MDT should provide timely information so that GPs can provide appropriate support to people with CF and their families. The NICE Guideline Committee have suggested ways in which this support may be provided, see Box 4. Particularly close support may be required in end of life setting, in partnership with the CF centre or local homecare teams, or at the time of transition from paediatric to adult services.

**Box 4: How can primary care support people with CF and their families?**

Prescribing medications in batches of 1 month for routine medicines and longer if advised by the specialist team

Providing routine annual immunisation for people with CF and their families

Managing health problems not related to CF

Supporting family members or carers

Certification of illnesses

Working in partnership with CF specialist team at the end of life.

**Resources**

* [**https://www.cysticfibrosis.org.uk/**](https://www.cysticfibrosis.org.uk/)
* [**http://www.nhs.uk/conditions/Cystic-fibrosis/Pages/Introduction.aspx**](http://www.nhs.uk/conditions/Cystic-fibrosis/Pages/Introduction.aspx)

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