CLINICAL REVIEW

Cystic fibrosis

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Over 7000 people have cystic fibrosis in the United Kingdom. It is the commonest genetically inherited disease in white populations (1 in 2500 newborns), although it is increasingly recognised as being important in non-white populations. However, most general practitioners have only one or two patients on their list, and as management generally takes place in specialist centres, many general paediatricians will be involved in the care of only a small number of patients.

Progress in our understanding of the disease and the impact of this on management has been rapid over the past 20 years. Cystic fibrosis used to be a digestive and lung disease of young children but more recently has become a complex, multisystem disease extending into adulthood; there will soon be more adults than children with the condition. The predicted median survival for babies born in the 21st century is now more than 50 years.[1] This increased survival—together with changes in standard treatment, the increasing implementation of newborn screening, and the focus on new therapeutic strategies—leads us to consider that an update on this albeit relatively rare disease may be of general interest.

What is the cause of cystic fibrosis?

Cystic fibrosis is an autosomal recessive disease. It is caused by mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene.[2] The commonest mutation is the deletion of phenylalanine at codon 508 (phe508del, until recently known as ΔF508). This occurs in about 70% of patients with cystic fibrosis (www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/cftr.shtml). Over 1600 mutations of the *CFTR* gene have been described. Different mutations in this gene have varying effects on *CFTR* function and can result in different phenotypes of the disease. Some mutations will result in milder forms of the disease, although there is not enough evidence about these rarer mutations to counsel patients about their prognosis. The CFTR protein is expressed in many cells and has several functions, not all of which have been linked with disease. The primary function of the CFTR protein is as an ion channel that regulates liquid volume on epithelial surfaces through chloride secretion and inhibition of sodium absorption.

The commonly accepted explanation for airway disease in cystic fibrosis is the "low volume" hypothesis. A reduced volume of airway surface liquid causes failure of mucociliary clearance, the lungs' innate defence mechanism.[3] The mucociliary dysfunction means that a patient with cystic fibrosis cannot effectively clear inhaled bacteria. In addition, there is an excessive inflammatory response to pathogens. For

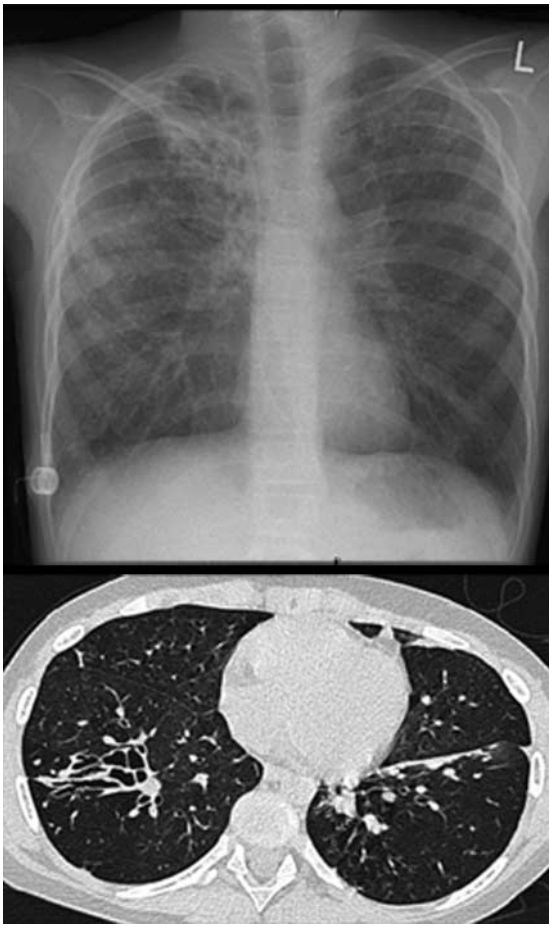

Fig 1 | Severe bronchiectasis in end stage cystic fibrosis shown in chest radiograph (top) and computed tomogram (bottom). For reasons that are not fully understood, the upper lobes are often most severely affected, although the patient has severe bronchiectasis throughout the whole of the right lung. Note presence of indwelling intravenous catheter (a "port-a-cath") on the right lateral chest wall

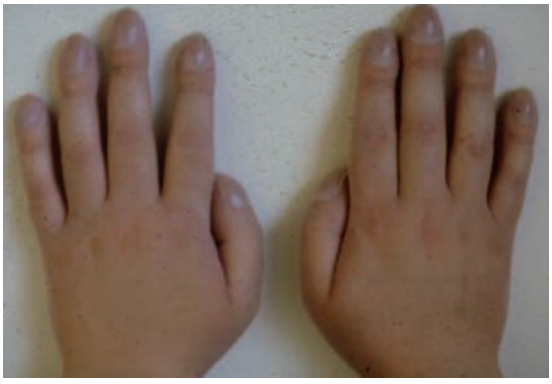

Fig 2 | **Finger clubbing indicates advance suppurative lung disease. It is not characteristic of asthma, with which older patients have sometimes been misdiagnosed**

a given bacterial load, a person with cystic fibrosis will have up to 10 times more inflammation than a person with a lower respiratory tract infection but without the disease. This may also be the case for other insults such as viruses or even for airborne particulate matter and pollutants. The reasons for the excessive inflammatory response to pathogens are not fully understood. The abnormal composition and secretion of mucus may also be important. At birth, the airway is uninfected and probably uninflamed, although some controversy exists in this area,[4] but the end result of the abnormalities described above is irreversible airway damage with bronchiectasis and respiratory failure in most patients (fig 1). Ion and water abnormalities may also cause disease in other epithelia-lined organs (see tables 1, 3, 4)."

What are the clinical features and when should the diagnosis be considered?

Disease manifests in many organs, but most notably the upper and lower airways, pancreas, bowel, and reproductive tracts (table 1).[5] For most patients, lung disease is the most important problem in terms of symptoms and the treatment required and the fact that it is the most likely cause of death. Table 1 outlines the clinical presentation, which varies according to age.

SOURCES AND SELECTION CRITERIA

We searched PubMed for the terms "cystic fibrosis", "therapy", "treatment", "management", "complications", and "diagnosis" in various combinations. We also searched all entries under "cystic fibrosis" in the Cochrane Library. From this search, we selected randomised controlled trials, high quality journal reviews and meta-analyses. We also drew from our own personal archives of references from known leaders in this field.

ONGOING RESEARCH

Research is being conducted into gene therapy that aims at introducing a normal copy of *CFTR* into lung epithelial cells.[21] Achieving expression after repeat administration of viral vectors has been a major problem owing to immune recognition. Because of this, the UK Cystic Fibrosis Gene Therapy Consortium, which has been formed in recent years to develop cystic fibrosis gene therapy for clinical benefit is focusing current efforts on a non-viral approach

New drugs to improve ion transport[22] and osmotic agents[23] to increase airway surface liquid are currently in phase II clinical trials, as are anti-inflammatory agents, mucolytics, and pseudomonas vaccines

New methods for administering current agents, such as the development of dry powder formulations (ease of administration) and of liposomal preparations (enhanced activity) of antibiotics are being developed

How is cystic fibrosis diagnosed?

The optimal diagnostic test for cystic fibrosis is the measurement of sweat electrolyte levels.[6] Patients with the disease have raised concentrations of sodium and chloride (>60 mmol/l, diagnostic; 40-60 mmol/l, intermediate (but more likely to be diagnostic in infants); <40 mmol/l, normal). However, undoubted cases of cystic fibrosis with normal sweat electrolytes have been described. Newer techniques have reduced the amount of sweat needed (fig 3). The test needs to be done by someone trained and experienced. For this reason the diagnosis will usually be made in secondary and tertiary centres, although primary care professionals play a vital role in identifying the patients who need investigation. In the rare cases where the diagnosis remains in doubt, other diagnostic tests are available—for example, measurement of the nasal potential difference to assess altered salt transport is available in a few specialist centres in the UK.[7]

The UK now has a programme for screening all newborns for cystic fibrosis using the Guthrie blood spot test.[8] The initial screen is for raised concentrations of immunoreactive trypsinogen. Positive samples will

Table 1 | **Age related presentations of cystic fibrosis**

Age group	Common presentations	Less common presentations
Antenatal	Chorionic villous sampling or amniocentesis in high risk family; echogenic bowel on ultrasound	Perforated meconium ileus
Neonatal	Diagnosis made on newborn screening; meconium ileus (10% of patients with cystic fibrosis) causing bowel obstruction with or without perforation and peritonitis	Gut atresias; obstructive jaundice; fat soluble vitamin deficiencies (bleeding disorder, vitamin K; haemolytic anaemia, vitamin E; raised intracranial pressure, vitamin A)
Infants and young children	Recurrent respiratory symptoms (cough, wheeze, pneumonias); failure to thrive (exocrine pancreatic insufficiency present in 85-90% of cases leads to steatorrhoea, diarrhoea, and abdominal distension)	Rectal prolapse; dehydration and electrolyte disturbance (pseudo-Bartter's syndrome); anaemia, oedema, and hypoprotenaemia
Older children and adults	Recurrent respiratory symptoms as above (may be labelled asthmatic) with or without finger clubbing (fig 2); nasal polyps or sinusitis; male infertility (congenital bilateral absence of the vas deferens)	Acute pancreatitis; liver disease; malabsorption; dehydration and electrolyte disturbance (pseudo-Bartter's syndrome); pulmonary infection with atypical mycobacteria

be tested for common *CFTR* gene mutations followed by a second screen for immunoreactive trypsinogen if required. Screen positive infants will be referred for sweat testing.

Screening programmes have been in place in some parts of the world for many years, but they may be inappropriate in countries with a low prevalence of *CFTR* gene mutations. The advantages of early diagnosis include nutritional benefits; early access to specialised care; a reduction in the time of diagnostic uncertainty; and the ability to counsel parents for prenatal testing.

Screening programmes have some negative aspects, however. Programmes will identify some healthy heterozygote carriers as potential patients. This may have psychological implications and stress for the family until the diagnosis is excluded. Moreover, some patients, even those with classic cystic fibrosis, will be missed.

Once a diagnosis has been confirmed, other family members may be offered screening. All siblings need to be screened for the disease, which may be presymptomatic or unrecognised. Asymptomatic adult relatives, may wish to be screened for carrier status to enable them to make informed choices about prenatal screening. In our experience, screening and counselling of

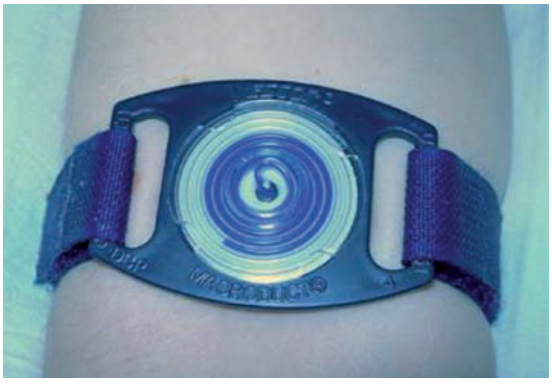

Fig 3 | Child's arm during sweat test with the macroduct system. After pilocarpine iontophoresis to stimulate sweating, the closed capillary collecting system is applied to the skin of the forearm. Sweat can be seen entering the tubing (blue); electrolyte analysis can be reliably performed on as little as 50 µl of sweat

Table 2 | Management of cystic fibrosis lung disease

Disease stage	Pulmonary status	Aim	Management	Comments
Early	Preinfection	Mucus clearance; prevent infection; maintain good lung function	Segregation and cohorting to prevent cross infection*; airway clearance techniques (physiotherapy and adjuncts, mucolytics such as rhDNase,†[10] hypertonic saline†[11]); prophylactic antibiotics (usually against *Sa*†[12]; most commonly flucloxacillin or co-amoxiclav in UK); influenza vaccination usually recommended	Segregation of patients with organisms such as *Bcc* or epidemic strains of *Pa* is common (practice more variable with regard to other strains of *Pa*, *Sm*, or *Hi*); for both rhDNase and hypertonic saline evidence favours short to medium term benefit (no long term or survival data); prophylactic antibiotics decrease incidence of infection with *Sa* (long term benefits not well defined); increase in infection with *Pa* seems limited to trials including broad spectrum cephalosporins
	Intermittent isolation of organisms	Eradication of infection	*Pa* eradication protocols† include both topical (nebulised) and systemic (usually oral ciprofloxacin)	Eradication achieved in 80-90%,[13] but uncertain long term benefit
Intermediate	Chronic infection with usual organisms (*Pa*, *Sa*, *Hi*)	Suppression of bacterial load and thus limitation of inflammatory response	Depends on organism (*Pa*: nebulised tobramycin or colomycin)	*Pa*: medium term benefit,† uncertain effects on survival; new, faster nebuliser devices (such as e-flow and iNeb) available
		Treat infective exacerbations	Oral or intravenous antibiotics appropriate for culture	Elective *v* symptomatic use*
		Reduce inflammation	Ibuprofen*; macrolide antibiotics (azithromycin)†14	Ibuprofen: limited use in much of Europe[15] (used more often in US); azithromycin: good evidence for short/medium term benefit, but mechanism of action uncertain (anti-inflammatory properties thought likely); no evidence supporting a role for corticosteroids except in treating allergic bronchopulmonary aspergillosis
	Infection with less common organisms (*Bcc*, *Sm*, *Ax*)	Eradication if early; suppression of bacterial load most commonly	Treat on an individual basis; seek specialist microbiological advice	Confirm diagnosis in a reference laboratory
	Allergic bronchopulmonary aspergillosis	Reduce allergic response; prevent bronchiectasis	Oral corticosteroids; consider addition of an antifungal agent*	Long course often required
	Non-tuberculous mycobacterial infection	Eradication	Usually prolonged combination treatment: ethambutol, rifampicin, azithromycin, amikacin	Can be difficult to determine whether isolates are contributing to disease manifestations; most would treat if recurrent positive cultures
End stage with complications	Severe haemoptysis	Prevent bleeding, which may be fatal	Bronchial artery embolisation (rarely lobectomy)	
	Pneumothorax		Drainage. Pleurodesis if persistent/recurrent	May affect suitability for transplantation in future
	Respiratory failure		Lung or heart and lung transplantation[16]	

Bcc=Burkholderia cepacia complex; Pa=Pseudomonas aeruginosa;Sa=Staphylococcus aureus; Hi=Haemophilus influenzae; Sm=Stenotrophomonas maltophilia; Ax=Alcaligenes xylosoxidans.
*Strategies for which consensus is lacking.
†Strategies based on randomised controlled trials or meta-analyses.

Table 3 | Gastrointestinal problems and their management

Organ	Manifestation	Management	Comments
Pancreas	Exocrine insufficiency (85-90% of newborns): malabsorption, steatorrhoea, poor growth	Supplementation with pancreatic enzymes† and fat soluble vitamins	May be aided by alkaline environment (H_2 blockers or proton pump inhibitors)*
	Pancreatitis	As for other causes; Pancrex powder	Uncommon; occurs only in patients with pancreatic excocrine sufficiency
Oesophagus	Gastro-oesophageal reflux	Prokinetic plus antacid; surgery if recalcitrant	Probably common; reported incidence variable
Small bowel	Meconium ileus	Gastrograffin enemas; surgery (with or without resection)	About 10% of newborns with cystic fibrosis
	Distal intestinal obstruction syndrome	Bowel cleaning agents such as Gastrograffin or kleanprep	Review dose of and adherence to enzymes
	Coeliac disease; malabsorption despite adequate enzymes	Gluten-free diet	Incidence seems to be increased in cystic fibrosis
	Crohn's disease	Usual treatment	Incidence seems to be increased in cystic fibrosis
Colon	Constipation	Dietary advice, laxatives	Check no malabsorption, if present, check use of pancreatic enzyme replacement therapy carefully
Rectum	Rectal prolapse	Usually resolves with pancreatic enzymes; rarely surgery required	
Liver[17]	Fatty liver (usually not symptomatic); cirrhosis (variceal bleeding, hypersplenism)	Ursodeoxycholic acid, taurine*; severe cases may need transplantation	Liver disease in up to 30% of patients by adulthood; liver cell failure late, with ominous prognosis

* Treatments for which consensus is lacking.
† Treatments based on randomised controlled trials or meta-analyses.

other family membersis most readily facilitated through primary care but requires coordination between genetic laboratories to ensure rapid and cost efficient testing.

Management

Most patients in the UK and Europe receive care coordinated by a tertiary cystic fibrosis centre, which improves outcomes. However, patients benefit greatly from links with and access to local care, in many cases having formalised "shared care" with local clinics. Primary care teams can provide valuable help with surveillance and early treatment of infection; dietary and nutritional support; and social and psychological support for patients and families. Primary care also provides continuity during the difficult transition from paediatric to adult care; an informative patient's perspective of the issues encountered during this period has recently been published.[9]

Much of the current clinical practice has evolved over decades without being subjected to high quality randomised controlled trials. Tables 2-4 outline the various treatments and indicate those that are based on randomised controlled trials, meta-analyses, or systematic review and those that are treatments for which we consider consensus is lacking.

Lung disease

The aims of treating the lungs at different stages of disease vary; table 2 outlines the conventional management at each of these stages. Many of the treatment options have been discussed in systematic reviews. Respiratory treatments represent the greatest challenge to patients and families: doing physiotherapy and taking inhaled drugs such as antibiotics often takes up a lot of time—more than an hour a day during periods of good health and much longer during a respiratory exacerbation.

Table 4 | Management of other common complications of cystic fibrosis

Organ	Manifestation of cystic fibrosis	Treatment	Comments
Upper airway	Polyps[18]	Topical steroids; antibiotics; surgery if medical management fails	Surgery may have medium term benefit, but recurrence common
	Sinusitis	Topical steroids; antibiotics; surgery if medical management fails	Most cases are asymptomatic (changes seen on x ray films or computed tomograms almost universal): no treatment required
Endocrine pancreas[19]	Insulin deficiency; frank diabetes	Insulin; continue high fat diet; oral hypoglycaemic agents rarely useful	Deleterious impact on respiratory health and nutrition even before diabetes diagnosed
Bones	Osteopenia; pathological fracture	Prevention: weight bearing exercise, high dairy intake, vitamin D and K therapy* (bisphosphonates if severe*)	
	Cystic fibrosis arthropathy	Anti-inflammatory agents	
Sweat gland	Electrolyte depletion leading to failure to thrive, acute collapse	Sodium and potassium chloride supplementation	
Male reproductive tract	Bilateral absence of vas deferens	Sperm aspiration, and assisted fertilisation techniques	
Female reproductive tract	Vaginal candidiasis; stress incontinence	Topical antifungal agents	Seek gynaecological advice

*Treatments for which consensus is lacking.

SUMMARY POINTS

Cystic fibrosis is the commonest inherited disease in white populations, with an incidence of 1 in 2500 newborns; over 7000 people in the United Kingdom currently have the disease

Until recently, the diagnosis has been largely clinical, although the widespread implementation of a screening programme for newborns is now complete in the UK

Cystic fibrosis is a multiorgan disease best managed in a multidisciplinary setting in conjunction with a specialist centre for cystic fibrosis, with treatment tailored to the individual

The cornerstones of management are proactive treatment of airway infection and encouragement of good nutrition and an active lifestyle

Conventional treatment has improved greatly over the past few decades; however, current treatments at best slow the decline in lung function. Newer approaches such as gene and small molecule based treatments may have more potential to halt disease progression

Extrapulmonary disease

Patients with cystic fibrosis often have gastrointestinal problems; table 3 outlines the nature and management of these (management should be in close collaboration with a specialist dietician). Table 4 lists other complications of the disease, plus their management strategies.

Psychological issues

Cystic fibrosis clearly poses a huge burden to patients and families in terms of the life shortening nature of the disease, the time consuming treatments prescribed, and the ongoing morbidity. Times of particular stress include diagnosis, adolescence (when adherence to treatment can often be poor), and end of life. Support and coping strategies from clinical psychologists with experience of the disease are often invaluable.[20]

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ADDITIONAL EDUCATIONAL RESOURCES

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Bush A, Alton E, Davies JC, Griesenbach U, Jaffe A. *Cystic fibrosis in the 21st century (progress in respiratory research)*. Basel: Karger, 2005.

Cystic Fibrosis Trust, 11 London Road, Bromley BR1 1BY (www.cftrust.org.uk/)—Charity whose work includes research into the disease and support to patients and their families

Cystic Fibrosis Foundation (www.cff.org/)—US non-profit organisation whose work includes research into the disease and support to patients and their families

Genetics Home Reference (http://ghr.nlm.nih.gov/condition=cysticfibrosis)—US government website supplying general scientific information on the disease

Association of Clinical Biochemistry. *Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK*. 2003. http://acb.org.uk/docs/sweat.pdf

Cystic Fibrosis Mutation Database (www.genet.sickkids.on.ca/cftr/)—Aims to provide researchers and other professionals with up to date information about individual mutations in the *CFTR* gene and phenotypic data

Information on the UK newborn screening programme (www.ich.ucl.ac.uk/newborn/cf/index.htm)

Breathing Room (www.thebreathingroom.org/cg)—Illustrations of many issues affecting patients and their carers

UK Cystic Fibrosis Gene Therapy Consortium (www.cfgenetherapy.org.uk)—The research programme of three leading gene therapy groups in the UK