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Cystic fibrosis

Andrew Bush and Caroline Elston

ESSENTIALS

Cystic fibrosis (CF) is a recessively inherited disease caused by mutations in the cystic fibrosis gene, located on the long arm of chromosome 7, which codes for a membrane protein—the cystic fibrosis transmembrane regulator protein—that is a chloride channel. More than 2000 CF mutations have been identified, with the ΔF508 mutation being the most common of around 250 mutations that definitely cause disease (70% of CF chromosomes in the European population). Birth incidence varies with country of origin from 1 in 2000 to 1 in 100 000.

Pathophysiology—the most popular hypothesis is that mutant cystic fibrosis transmembrane regulator protein fails to transport chloride ions normally, and there is secondary impairment of sodium, bicarbonate, and water transport. This causes dehydration of pancreatic secretions, eventually leading to pancreatic failure, and in the lungs to increased fluid absorption from the airway lumen and reduction in the depth of the film of airway surface liquid (the 'low volume hypothesis'), with impairment of ciliary function, mucus stasis, and thus chronic infection and inflammation. There is an increasing focus on bicarbonate transport and abnormal airway surface pH as being pathophysiologically important.

Clinical features—most cases of CF are diagnosed in early life by newborn screening, or later with the classical clinical picture of pancreatic insufficiency and suppurative lung disease, but patients with milder genetic mutations may present in late childhood or adulthood. Other pulmonary manifestations include haemoptysis, pneumothorax, allergic bronchopulmonary aspergillosis, and atypical mycobacterial infection. Patients presenting in adult life are often clinically pancreatic sufficient, or they present with other conditions that are also associated with CF gene mutations (e.g. azoospermia, idiopathic pancreatitis).

Diagnosis—this is usually established by the sweat test (pilocarpine iontophoresis or macroduct collection) revealing a high sweat chloride concentration, although increasingly the diagnosis is likely to be made by newborn screening (heel-prick blood samples tested for immunoreactive trypsin and by polymerase chain reaction for common CF mutations). A newborn screening diagnosis is always confirmed with a sweat test.

Prognosis—pulmonary infection and inflammation account for most CF-associated morbidity and mortality. The lungs become transiently infected in early childhood and ultimately chronically infected, typically early on with *Staphylococcus aureus* and *Haemophilus influenzae*, and subsequently with *Pseudomonas aeruginosa* and increasingly commonly with other Gram-negative rods, which are associated with a worse prognosis. Chronic infection and inflammation lead to bronchiectasis, progressive airflow obstruction, and ultimately death from respiratory failure, although outcome has improved dramatically over the past 20 years such that estimated survival for a child born with CF in the late 1990s is to the fifth and sixth decades. This has important implications for the planning of adult health services.

Management of respiratory disease—standard management includes airway clearance with regular physiotherapy. Antibiotic treatment is initially directed at preventing chronic infection. Chronic suppressive antibiotic therapy (colomycin, tobramycin, aztreonam, either nebulized or by dry powder device) is beneficial once patients become chronically infected with *Pseudomonas*. Mucolytic agents are often indicated. Azithromycin, a macrolide antibiotic that appears to modulate inflammation in CF by an ill-understood mechanism, is used increasingly. Ivacaftor is licensed as a specific molecular therapy for the class 3 gating mutations: Orkambi is a combination therapy (ivacaftor and lumacaftor) licensed in Europe for ΔF508 homozygous patients; other specific molecular therapies are in the pipeline.

Management of other features—(1) Pancreatic insufficiency is associated with malabsorption and requires pancreatic enzyme replacement therapy and a high-energy diet in most patients. (2) Distal intestinal obstruction syndrome—severe constipation sometimes leading to bowel obstruction with faecal material in the distal ileum and associated abdominal pain—is relatively common. (3) Diabetes—occurs in up to 30% of patients, with the incidence increasing with age; a high-energy diet should be maintained, with insulin doses adjusted accordingly. (4) Liver function—mild abnormalities are common, with disease progression to cirrhosis in around 5% of patients. (5) Fertility—nearly all men with CF are infertile, but most women with CF can conceive normally. (6) Osteopaenia—low bone mineral density is found in 60% of patients.

Definition

Cystic fibrosis (CF) is a recessively inherited disease caused by mutations in the CF gene, which is located on the long arm of chromosome 7. The classical clinical picture is a combination of pancreatic insufficiency, suppurative lung disease, and high sweat chloride concentration, presenting in early childhood and progressing to early death from respiratory failure. However, genetic analysis has identified many patients with less severe disease, and the clinical spectrum of CF has been expanded by recognition of mutations in association with other conditions, including azoospermia, allergic bronchopulmonary aspergillosis, and idiopathic pancreatitis. Carriers are usually healthy, although they may have an increased prevalence of single organ manifestations like severe sinusitis and bronchiectasis, but although the relative risk is increased, the absolute risk remains very small.

Since the last edition of this book, there has been a paradigm shift in management. Hitherto, treatment has been directed at the early detection of complications such as infection, and treating them very aggressively; improvement with treatment was obvious. Now diagnosis is in well babies, and treatment is increasingly directed at the fundamental molecular defect, and benefit is much harder to demonstrate in a well population.

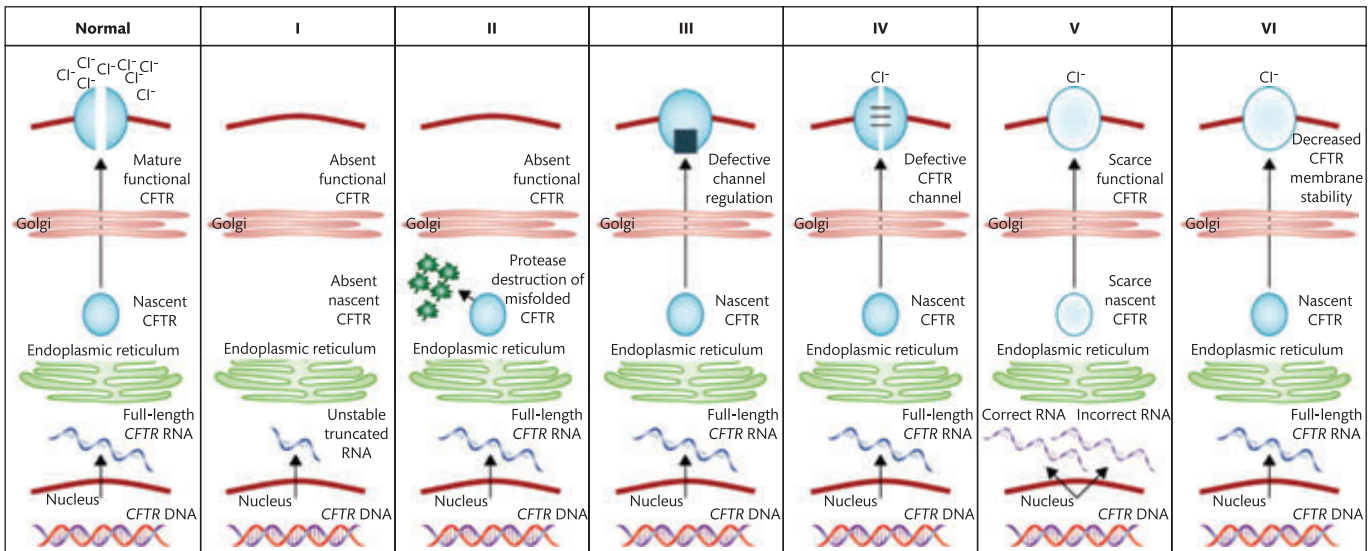
The genetic defect

The CF gene codes for a 168-kDa membrane protein, the CF transmembrane regulator protein (CFTR). CFTR is an ATP-responsive chloride channel, but it also influences other cellular functions such as sodium transport across the respiratory epithelium, cell-surface glycoprotein composition, and normal antibacterial defences, at least 20 functions in all having been described. The protein is expressed in organs involved in CF disease—lungs, pancreas, sweat glands, and so on—but also in some places that do not seem to be affected clinically, such as the choroid plexus, heart, and renal tubules.

More than 2000 related mutations of the CF gene have been described, the nomenclature of which has (somewhat confusingly) been changed recently (see https://www.genet.sickkids.on.ca/cftr/). Around 200 are definitely known to be disease producing, and there is an ongoing project, funded by the US CF Foundation, to differentiate harmless polymorphisms from true disease-producing mutations (see http://www.cftr2.org).

Known disease-producing mutations have been classified according to their impact at a cellular level: class 1, no protein; class 2, disordered trafficking, with intracellular destruction of CFTR; class 3, defective regulation, the so-called gating mutations; class 4, defective channel function; class 5, reduced protein synthesis. A sixth class is reduced half-life of CFTR at the apical cell membrane, due to increased breakdown. The understanding of these abnormalities is valuable as a basis for new generation of actual and potentially corrective treatments, as illustrated in Fig. 18.10.1. Perhaps more important is the distinction between mutations which do not reach the epithelial surface to any degree (classes 1 and 2), and those that have abnormal CFTR at the apical membrane (classes 3–6), because the latter group may be targets for the potentiator ivacaftor.

Most mutations are very rare; the commonest in European populations is ΔF508 (now known as p.Phe508del), which is found on



	Normal	I	II	III	IV	V	VI
CFTR defect		No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations		Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples		Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 427insA

Fig. 18.10.1 Classes of *CFTR* mutations.

70% of affected chromosomes, with some variation across Europe. Most genetic laboratories restrict routine testing to the commonest 50 mutations, which together account for over 90% of mutations within a given population. Genotype–phenotype correlations have shown linkage of so-called severe mutations, such as ΔF508, to pancreatic insufficiency and a tendency to more severe lung disease, while mild mutations go with pancreatic sufficiency and a tendency to less severe lung disease. However, in general, the correlation between genotype and the severity of lung disease is poor. Virtually all disease-associated mutations are linked with congenital absence of the vas deferens, resulting in infertility in more than 98% of men with CF, while rarer mutations are linked with isolated male infertility with no other evidence of CF disease.

Targeting the fundamental defect is the new focus of research and treatment. The first licensed compound, which was discovered as a result of high throughput screening, was ivacaftor (VX-770, Kalydeco). Initially studied in the commonest class 3 gating mutation, G551D, but now licensed for all class 3 mutations, the effects are dramatic, with increases in lung function by more than 10%, weight gain, and, dramatically, a halving of sweat chloride. Even more excitingly, some pancreatic insufficient infants have had pancreatic function restored by Ivacaftor, and no longer take pancreatic enzyme replacement therapy. Benefits also extend to young children and patients with mild lung disease. Trials are ongoing in other mutations which reach the cell surface, especially the class 4 mutation R117H. Lumacaftor (VX-809) is designed to correct protein misfolding of class 2 mutations. When given in combination with ivacaftor to patients homozygous (but not heterozygous) for the class 2 mutation ΔF508, the effects on pulmonary function were less dramatic (improvement of FEV_1 by approximately 4%), but pulmonary exacerbations fell by nearly 40%. The current focus is on trials of triple therapy, which apppear at least in Phase II trials to have similar magnitude effects on homozygous and heterozygous ΔF508 patients as does Ivacaftor on Class 3 mutations. A trial of ivacaftor in the class 4 mutation R117H failed to reach its primary endpoint (FEV_1); in adults but not children there were encouraging improvements in some secondary endpoints. Ataluren (PTC_{124}) overrides premature stop codons, and thus are potential therapies for class 1 mutations, as well as other genetic diseases such as Duchenne muscular dystrophy. An initial trial failed to meet the primary endpoint, but work is ongoing. Finally, gene therapy may become available and be applicable to all CF patients. The UK trial showed a statistically significant difference in FEV_1 (stability over one year in the treated group, reduction by 4% in the placebo group). In summary, current studies have led to an explosion of interest in developing new molecules and better vectors. The future challenge will be to reconcile the expectations of the patients with what is in fact a *clinically* useful benefit, in the context of the risk of long-term side effects of a novel therapy administered for decades and the likely enormous fiscal costs (ivacaftor costs around £250 000/patient/year currently).

Pathogenesis

Sweat duct

The primary secretion of the sweat duct is normal in volume and electrolyte concentration. However, as this secretion passes along the sweat duct mutant CFTR fails to absorb chloride ions, which therefore remain in the lumen, with secondary impairment of sodium absorption. The resultant sweat has high concentrations of both sodium and chloride, which is useful for diagnosis and can lead to salt depletion in hot weather.

Pancreas

The synthesis and secretion of pancreatic enzymes in the acinus is normal, but disordered ion transport—primarily of chloride and secondarily of bicarbonate—results in relative dehydration of pancreatic secretions. This in turn leads to low flow and stagnation of secretions in the pancreatic ducts with subsequent autodigestion. The clinical consequences are that low volumes of bicarbonate-depleted pancreatic secretions reach the duodenum, with consequent malabsorption and progressive destruction of the pancreas with cyst formation. Although the islet cells are relatively unaffected at first, they too are progressively destroyed, leading to insulin deficiency.

Biliary tract

Intrahepatic biliary secretions are probably normal in CF, but disordered electrolyte transport across the bile duct results in reduced water movement into the lumen. The bile is therefore concentrated and its volume depleted, leading to plugging and chronic local damage. This eventually causes biliary cirrhosis and associated extrahepatic biliary stenoses. There are secondary changes in bile acids. Other factors may also be important, including human leucocyte antigen haplotype, and the effect of modifier genes.

Gut

Gastric secretions have decreased volume with increased viscosity and sodium concentration. The chloride transport defect similarly leads to altered fluid movement across large and small intestine. These changes are worsened by the addition of dehydrated biliary and pancreatic secretions, as well as by alterations in the osmotic load in the lumen secondary to pancreatic exocrine failure. The resulting deficiency of intraluminal water contributes to meconium ileus in neonates and the distal intestinal obstruction syndrome in adults.

Respiratory tract

The epithelium in the nose, paranasal sinuses, and intrapulmonary conducting airways is disordered in CF, but alveolar function is normal. Defective chloride transport is associated with increased sodium absorption from the lumen. This leads to the net surface electrical charge being altered from a normal of –20 mV to about –40 mV, which can be used for diagnosis. However, the link between the absence or impaired function of CFTR and lung disease is not clear. Perhaps the most likely explanation—the 'low volume hypothesis'—is that uncontrolled sodium and hence water absorption from the lumen leads to a reduction in the depth of the film of airway surface liquid, with impairment of ciliary function, mucus stasis, and thus chronic infection and inflammation. Less plausible is the 'high salt hypothesis', which argues that local antibacterial defences—including lactoferrin, lysozyme, and the cationic antibacterial peptides such as the β-defensins—may be impaired by local changes in salt concentration. Other, not necessarily mutually exclusive explanations include that bacterial adherence to epithelial cells is increased by changes in cell-surface glycoproteins; and that there is reduced binding of microorganisms to CFTR and thus impaired internalization and clearance by the epithelial cells. The net effect is to promote

chronic bacterial infection, and to reduce bacterial clearance, with subsequent inflammatory lung damage. Finally, the role of bicarbonate transport and alteration of airway pH leading to inactivation of components of the innate immune system has recently come to the fore, in part as a result of studies in the CF pig. In summary, although the low volume hypothesis is most popular, there are other possible factors involved, and more work is needed to understand CF airway pathophysiology.

One consequence of chronic bacterial infection of the lower respiratory tract is an exuberant neutrophilic inflammatory response involving especially interleukin-8 (IL-8) and neutrophil elastase. The combination of elastase and other inflammatory mediators, while initially providing a useful antibacterial defence, is thought to contribute to lung damage and speed the progression of bronchiectasis and small airway narrowing. This has led to the seemingly somewhat paradoxical concept of using prednisolone and other anti-inflammatory compounds to reduce inflammation in the setting of chronic bacterial infection.

Heterozygote advantage

The high frequency of the carrier state in European populations (1 in 25) has led to several suggested advantages for the carrier, none of which are proven. These range from reduced susceptibility to infections such as cholera (reduced gut chloride secretion) and typhoid (reduced ingestion of bacteria by gut epithelium) to increased fertility among CF carriers. As yet, no carrier advantage has been proven.

Epidemiology

Genotype

The prevalence and distribution of the disease-related mutations in the CF gene vary with ethnic origin. ΔF508 is commonest in northern European populations, accounting for 82% of CF chromosomes in Denmark but only 32% in Turkey. The W1282X mutation is common in Ashkenazi Jews (48% of CF chromosomes) but rare in other populations. All disease-associated mutations are rare in African and almost unknown in Chinese populations.

Phenotype

Birth incidence varies with country of origin from 1 in 2000 to 1 in 100 000, as listed in Table 18.10.1. Prevalence figures are few and less reliable. CF is likely to be underdiagnosed in the developing world because early childhood malnutrition, diarrhoea, and chest infections are so common in children with no underlying disease. There are at least 10 000 people in the United Kingdom and 30 000 in the United States of America with CF, and these numbers are increasing along with life expectancy. There are now more adults than children with CF in the UK.

Table 18.10.1 Frequency of cystic fibrosis in different populations

Country	Incidence	Calculated carrier frequency
United Kingdom	1:2500	1:25
Turkey	1:3000	1:27
United States of America	1:2000–1:4000	1:22–1:32
Israel	1:5000	1:35
Italy	1:15 000	1:60
African Americans	1:17 000	1:65
Finland	1:40 000	1:100
China	?1:100 000	?1:160

Survival

From 1938 to 1960, most children with CF died before the age of 10. Since 1968, the first-year mortality (chiefly from meconium ileus) has fallen from 18% to virtually zero, and survival curves are linear thereafter, showing progressive improvement over succeeding decades (Fig. 18.10.2). In 1986, the median survival was 25 years and in 1999 about 30 years. Cohort survival analysis shows continuing improvement, and estimated survival for a child born with CF in the late 1990s is 40–50 years. Age-specific mortality rates for females are a little worse than for males, although this difference is narrowing and the world record longevity for both sexes is now over 70 years.

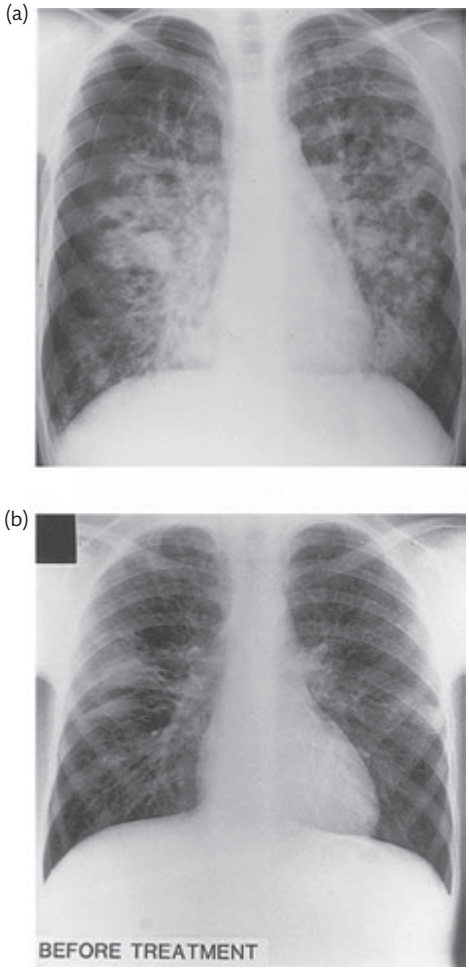


Fig. 18.10.2 (a) The typical chest radiograph appearances of advanced cystic fibrosis lung disease. There is also a right pneumothorax. (b) The chest radiograph in an adolescent boy with cystic fibrosis complicated by allergic bronchopulmonary aspergillosis. Note the wedge-shaped shadow in the right mid zone.

Clinical features

The various age-related problems that can lead to a diagnosis of CF are given in Table 18.10.2. Paediatric presentations are relevant to adult life in that if an adult with atypical respiratory disease turns out to have a family history of a child with CF or an illness shown in Table 18.10.2, then CF should be considered in the adult. The new diagnosis of CF in a younger relative will also prompt cascade screening (see next), usually aiming to discover carriers, but occasionally someone with a clinically mild CF phenotype is discovered. The United States Cystic Fibrosis Foundation Registry data show that as many as 10% of CF patients are not diagnosed until adult life. As in infants, adult physicians may encounter patients with an equivocal diagnosis, for example intermediate sweat chloride with one CF gene. Referral to a specialist centre for ancillary testing such as nasal potential differences should be considered, and whatever diagnostic label is eventually attached, the clinical manifestations of the disease should be treated energetically.

Less than 5% pancreatic function is necessary for normal digestive function, and those presenting with CF in adult life are often clinically pancreatic sufficient. The main presentation is with respiratory problems, usually recurrent lower respiratory infections with chronic sputum production. Some patients have a prior diagnosis of bronchiectasis, atypical asthma, nasal polyposis, acute pancreatitis, nontuberculous mycobacterial infection, or allergic bronchopulmonary aspergillosis. A new CF diagnosis has been described even in adults in their seventh decade. Depletion of sodium chloride and potassium due to excessive sweating, and secondary renal chloride retention, may result in presentation with dehydration and heat exhaustion in an otherwise apparently completely fit adult.

Another important mode of presentation is male infertility due to azoospermia because of congenital bilateral absence of the vas deferens (CABVD). There are different forms of this condition: (1) in association with congenital malformations of the upper urinary tract, in which case there is no increased incidence of CF mutations; (2) as part of classical CF; and (3) as a truly isolated *forme fruste* of CF, with only a single CF mutation and ion transport abnormalities overlapping with, but different from, true CF.

Portal hypertension secondary to macronodular cirrhosis in adult life may also be the first presentation of CF.

There is considerable debate as to the status of adults with single organ manifestations characteristic of, but not confined to, CF (e.g. idiopathic pancreatitis or allergic bronchopulmonary aspergillosis). Some series report a higher than expected incidence of CF mutations, and the occasional unsuspected CF compound heterozygote. In practice, although CF should be excluded as far as possible by appropriate investigations in the patient with a possible single organ disease, most will not have the traditional clinical CF disease as it is currently defined. Such single organ manifestations should be treated on their own merits, whatever the disease is called.

Table 18.10.2 Presentation of cystic fibrosis by age group

Age group	Presenting complaint
Antenatal	Chorionic villus sampling
	Ultrasound diagnosis of bowel perforation [a]
	Fetal hyperechogenic bowel [b]
At or soon after birth	Bowel obstruction (meconium ileus,[a] bowel atresia)
	Haemorrhagic disease of the newborn
	Prolonged jaundice
	Screening (population based or previous affected sibling)
Infancy and childhood	Recurrent respiratory infections
	Diarrhoea and failure to thrive [c]
	Rectal prolapse [d]
	Nasal polyps [e]
	Acute pancreatitis
	Portal hypertension and variceal haemorrhage [f]
	Pseudo-Bartter's syndrome, electrolyte abnormality
	Hypoproteinaemia and oedema
	Screening as a result of cystic fibrosis diagnosis in a sibling/relative
Adolescence and adult life	Recurrent respiratory infections
	Atypical asthma
	Bronchiectasis
	Male infertility (congenital bilateral absence of the vas deferens)
	Electrolyte disturbance/heat exhaustion
	Atypical mycobacterial infection
	Acute pancreatitis
	Screening as a result of diagnosis in affected relative
	Portal hypertension and variceal haemorrhage

[a] Note that meconium ileus may be seen in pancreatic-sufficient infants with CF, as well as rarely in those without the disease.

[b] Most fetuses with hyperechogenic bowel are normal; around 6% have a trisomy, and 4% CF.

[c] Note that up to 15% may be pancreatic sufficient, at least at diagnosis; thriving does not exclude CF.

[d] One in six cases of rectal prolapse is due to CF, if obvious anatomical abnormalities are excluded.

[e] Unlike in adults, where aspirin-sensitive asthma is commonly associated with polyps, children with polyps almost invariably have CF.

[f] Presentation with hepatocellular failure is very rare.

Diagnosis

The vast majority of patients (>98%) with CF can be diagnosed by a sweat test. The occasional patient, particularly with a mutation giving rise to a mild or atypical clinical phenotype, may require more sophisticated testing. However, the major difficulty is usually not in confirming the diagnosis, but in thinking of it in an appropriate context (see next section, and Table 18.10.2). Increasingly, the diagnosis is made by newborn screening. Conversely, false-positive diagnoses are not rare, and a new referral of a patient with CF to the adult clinic should prompt a full review of the diagnosis.

Newborn screening for CF is now standard across the United Kingdom, with babies tested on the heel-prick blood spot taken at age 7–10 days. Measurement of immunoreactive trypsin (iRT) and genetic testing for the four commonest CF genes are performed initially. Equivocal cases have a second heel-prick for iRT and extended genetic testing performed, and a positive screening test should always be confirmed with a sweat test, in case there has been

a laboratory error. This staged protocol leads to the diagnosis being made early in more than 95% of CF babies, hence making a diagnosis of 'typical' CF will become less usual, although CF will still continue to be a diagnostic consideration in many circumstances:

- The infant may have missed out on being screened
- Parents may have refused screening (0.06%)
- There may have been a laboratory error
- The infant may be a true false negative (usually pancreatic sufficient)
- The infant may have been born before screening was introduced
- The infant may have moved from a country where screening is not performed

The newly diagnosed CF infant should be seen early on in a specialist CF clinic so treatment can be commenced.

Sweat testing

The test must only be performed by experienced personnel. Techniques include the classical pilocarpine iontophoresis of Gibson and Cooke, and more recently the macroduct collection. For the diagnosis to be established, tests should be performed in duplicate. The normal concentrations of sweat sodium and chloride increase with age. To diagnose CF in a child, the sweat chloride concentration should be greater than 60 mmol/litre, and the sweat sodium concentration less than that of chloride. In the newborn period, in Europe the upper limit of sweat chloride is considered to be 30 mmol/litre. A sweat chloride of less than 40 mmol/litre is normal in older children and adults, and intermediate concentrations are equivocal. However, there are undoubted cases of CF with normal sweat electrolytes, and the sweat test should always be interpreted in the light of the whole clinical picture. There are a few rare conditions that also cause elevation in sweat electrolyte concentration, but these are rarely a serious diagnostic consideration in practice (Box 18.10.1).

Nasal electrical potential difference

The abnormal potential difference across mucosal surfaces can be measured by passing a soft catheter under the inferior turbinate, referencing it to an electrode placed on abraded skin of the forearm. Normal values are –10 to –30 mV and the CF range is –34 to –60 mV.

Box 18.10.1 Conditions characterized by elevated sweat electrolyte concentrations

In most cases, confusion with cystic fibrosis is very unlikely

- Cystic fibrosis
- Untreated adrenal insufficiency
- Type 1 glycogen storage disease
- Nephrogenic diabetes insipidus
- Malnutrition
- Panhypopituitarism
- Acquired immunodeficiency syndrome
- Artefact (incorrectly performed sweat test, eczema)
- Fucosidosis
- Hypothyroidism
- Ectodermal dysplasia
- Mucopolysaccharidosis

The test is unreliable if the patient has an upper respiratory tract infection. The diagnosis can be further refined by perfusing the nose with solutions of amiloride to block sodium transport, and isoprenaline/low chloride to stimulate CFTR. Nasal potentials require extensive experience if results are to be accurate.

Ion transport can be measured directly from intestinal biopsies in an Ussing chamber, but in most centres this remains a research technique only.

Cystic fibrosis genotype

More than 2000 different mutations causing CF have been reported, of which around 250 are disease producing. Testing for all of them is not currently practical in most centres, although whole exome sequencing of the *CFTR* gene is increasingly performed. It is essential to distinguish disease-producing mutations from harmless polymorphisms. Thus DNA analysis can confirm the diagnosis if two known, disease-causing, mutations are found, but not exclude it. Linkage analysis can be used for antenatal diagnosis if a couple have already had an affected child, even if the actual mutations are not known.

Other investigations

In doubtful cases, evidence of subclinical organ dysfunction may be sought. Pancreatic dysfunction may be manifest by low stool elastase, elevation in 3-day faecal fat excretion, or abnormal results of pancreatic stimulation tests. CT scan of the chest or bronchoscopy may be used to discover minor bronchiectatic changes or infection with typical CF organisms. Azoospermia is strongly supportive of the diagnosis of CF. But note, however, that it is important not to place too much diagnostic weight on clinically minor changes.

Summary

The diagnosis of CF is usually easy to confirm with a properly performed sweat test. There remain a few atypical cases which defy a firm diagnosis. In that event, clinical organ dysfunction should be treated appropriately, and the patient followed up very carefully: often time will clarify the diagnosis.

Screening

Screening tests allow an early diagnosis of CF in populations in order for treatment to be instituted before irreversible organ damage occurs, and to detect CF carriers to allow antenatal diagnosis and the option of termination of affected pregnancies. In both areas there is controversy as to the indications and methods to be used. Universal screening of babies is now offered everywhere in the United Kingdom.

Methods

In the past, crude tests on meconium have been used, but these lacked accuracy and have been superseded by tests carried out on the routine heel-prick blood sample collected from all babies in the first few days of life. These include estimation of immunoreactive trypsin, often combined with polymerase chain reaction (PCR) methods for one or more common abnormal genes, or pancreatitis-related protein. Routine neonatal screening in the United Kingdom is with both immunoreactive trypsin and PCR. Pancreatitis-related

protein screening may perform equally well, and obviates the need for genetic testing, which may be an advantage in some cultures. Across Europe, many different protocols are used, and clearly the genes which should be sought will depend on the frequency in the particular population.

Carrier screening is by PCR for several of the common CF genes on a blood or mouthwash sample. In principle, this sort of screening may be offered to relatives of known CF patients (cascade screening), by written invitation to the general population, or opportunistically at routine antenatal clinic visits or the GP surgery. It is generally considered that carrier testing at birth will not be useful because of the time lag between obtaining and utilizing the information.

Outcome

The evidence for the value of screening for the disease has come from certain retrospective trials, all showing benefit, but with the disadvantage of using historical controls. There has been one prospective randomized trial of neonatal screening from Wisconsin (United States of America) in which 650 341 babies were screened. Of those in whom the diagnosis of CF was made, in 56 the diagnosis was communicated to the parents, and in 40 the diagnosis was suppressed until it emerged on clinical grounds. There were small but clear-cut nutritional benefits in the group in which the screening diagnosis was communicated, persisting to 10 years of age. Furthermore, there were subtle neurocognitive defects detectable in the nonscreened population, who had the lowest fat-soluble vitamin levels at 10 years of age. The nutritional benefits were clearest early in life, at the time when growth is at its most rapid.

In general, carrier screening is poorly taken up when done by invitation, and at antenatal clinics it may be difficult to obtain a sample from the putative father. Cascade screening is generally better utilized, and should be offered at the time of making a new diagnosis.

Summary

Any screening test has false positives, which engender unnecessary anxiety, and false negatives, which may result in complacency. The balance of evidence is clearly in favour of neonatal screening so that early treatment can be given, and antenatal diagnosis offered for future pregnancies. The anxiety about false positives seems transient and deemed by the parents to be an acceptable price for subsequent reassurance. Carrier screening other than by cascade is more difficult, and, unless combined with wider public education, is unlikely to have a major impact. It should be noted that universal screening means it is increasingly rare to make a new diagnosis clinically. However, some mild patients will inevitably be missed on screening and present late; hence it will be important to remember the possibility of a new case of CF, even in a screened population.

Microbiology

People with CF have no detectable immune deficiency and, except for the respiratory tract, have no increased susceptibility to infection. Conventional culture-based microbiology demonstrates that the lungs show evidence of transient infection and inflammation very early in childhood and thereafter become chronically infected, characteristically by *Staphylococcus aureus* and *Haemophilus influenzae*, followed by *Pseudomonas aeruginosa*; infection which is common even in early life. Many other organisms have been implicated, especially in advanced disease, including the different genomovars of *Burkholderia cepacia, Alcaligenes, Achromobacter, Pandoria, Ralstonia, and Stenotrophomonas maltophilia*. Methicillin-resistant *S. aureus* (MRSA) is becoming an increasing problem. With increasing longevity and more aggressive use of antibiotics, the expected bacteria are becoming more antibiotic resistant, and novel microorganisms are emerging, and this pattern is likely to continue. *Aspergillus fumigatus* is frequently isolated, but is more often associated with allergic rather than invasive disease, although this is not a benign organism; other fungi are increasingly detected. Atypical mycobacteria, in particular *Mycobacterium abscessus*, are a major problem, in particular in those with milder disease and *S. aureus* rather than *P. aeruginosa* infection.

Viral, chlamydial, pneumococcal, and other respiratory infections are not more common or severe in CF, but the consequences of these infections may be more important in the damaged and permanently infected CF lung.

The microbiology of the nose and sinuses is the same as for the lung, but the clinical consequences are usually less important.

The advent of molecular based techniques has thrown a whole new light on CF airway infection. There is at least initially much greater bacterial diversity, including anaerobes, in the lower airway. As the disease progresses, diversity is lost. The significance of these molecular findings, including the possibility that some microorganisms are beneficial to the host by inhibiting the growth of pathogens, is still being explored.

Staphylococcus aureus

This is the commonest colonizing organism in childhood, with a prevalence of over 50% in children aged under the age of 9 years. The predilection of *S. aureus* for CF lungs has been ascribed to high electrolyte content of airway surface liquid or enhanced retention in the airways. No phage type predominates and the organism usually remains sensitive to flucloxacillin in spite of prolonged antibiotic treatment. Resistance to tetracycline or erythromycin is relatively common, but multiple antibiotic resistance is rare, although MRSA, both hospital and community acquired, is becoming an increasing problem. The prevalence of staphylococcal colonization falls in adult life when *P. aeruginosa* predominates.

Pseudomonas aeruginosa

This is the commonest infecting organism after the age of 10 years, with reported prevalence varying between 40 and 80%. Enhanced adherence to CF airways promotes infection, but prior antibiotic treatment—in particular if cephalosporin prophylaxis is employed—may play a part. No particular strain predominates, but siblings with CF often carry the same type, and environmental sources have been identified in CF centres, dentistry equipment, hydrotherapy pools, and nebulizers. After some months or years of infection, *P. aeruginosa* produces mucoid alginate as a protective biofilm and the organisms live in mucoid microcolonies. This mucoid variant is associated with a worse prognosis and greater antibiotic resistance. Most infecting strains of *P. aeruginosa* are sensitive to antibiotics at first, but over the years and in association with antibiotic treatment they develop multiple resistance to most antibiotics (except colomycin). There is increasing concern about

epidemic strains of *P. aeruginosa*, which may spread through clinics and carry a worse prognosis. This has resulted in increased emphasis on infection control precautions.

Haemophilus influenzae

Noncapsulated *H. influenzae* is a relatively frequent infecting organism, with prevalence of up to 30%, although it may not be isolated due to overgrowth of *Staphylococcus* or *Pseudomonas*. Antibiotic resistance is seldom a problem.

Burkholderia cepacia complex

There are at least nine different families ('genomovars') of this organism. Genomovar III (*B. cenocepacia*) is the most resistant and virulent organism, but other genomovars are not necessarily benign. The overall prevalence of this organism is low, at 3–5%, but it poses a particular problem due to cross-infection, and some forms can cause rapid deterioration in patients previously only mildly affected. More usual is chronic asymptomatic carriage or progressive deterioration in the late stage of lung disease. Multiple antibiotic resistance is characteristic.

Respiratory management

Most of the morbidity and mortality of CF is due to respiratory disease. Much of the treatment effort is therefore devoted to preventing chronic infection and inflammation, which lead to bronchiectasis, progressive airflow obstruction, cor pulmonale, and ultimately death.

Typical physical findings are cough with purulent sputum, together with crackles and occasional wheezes, chiefly in the upper lobes and occasionally finger clubbing. There are scoring systems such as the comprehensive Schwachman and simpler Taussig scores, but the use of these in clinical practice is limited.

The chest radiograph is often normal but may show thickened bronchial walls and small areas of consolidation which start in the upper lobes, and may progress to involve the whole lung (**Fig. 18.10.2a**). A variety of radiographic scoring systems have been proposed (e.g. Crispin–Norman, Brasfield, Northern, and Brody scores). However, chest radiographs are relatively insensitive, especially to early CF lung disease, and the early and repeated use of high-resolution CT (HRCT) scanning, both as a monitoring tool in clinical practice and an endpoint in randomized controlled trials, is increasingly advocated. There is no doubt HRCT detects early disease, but that outcomes are improved is not clear, and there are concerns about lifetime cumulative radiation exposure. Magnetic resonance imaging is getting better at detecting lung disease, and may replace HRCT in the future.

Lung function tests show obstruction with relatively well-preserved gas transfer. The forced expiratory volume in 1 s (FEV_1) is conventionally used to assess the extent and progression of lung disease; however, this is an insensitive test, and increasingly more subtle indices of gas mixing derived from multibreath washout tests, such as lung clearance index, are being used both clinically and as an endpoint in randomized controlled trials. Exercise tolerance and arterial blood gases are well maintained until there is extensive lung damage, when hypoxaemic respiratory failure supervenes. CO_2 retention occurs late.

Basic respiratory care is mandatory for all CF patients, including avoidance of active and passive tobacco exposure, avoidance where possible of pollution, regular exercise and full immunization, including influenza annually. More specific treatments are discussed next.

Antimicrobials

Oral antibiotics

The use of prophylactic antistaphylococcal antibiotics is controversial, and is currently the subject of a large multicentre trial (http://www.cfstart.org.uk/) most would use continuous twice-daily oral flucloxacillin if there is evidence of chronic infection. Minor exacerbations of respiratory symptoms in the patient not infected with *P. aeruginosa* should be treated with a 1-month course of a high-dose antibiotic that will cover *S. aureus* and *H. influenza*, with changes made depending on culture results.

Ciprofloxacin is used at the time of first isolation of *P. aeruginosa*, combined with nebulized antibiotics (see next) to try to prevent chronic infection: the duration of therapy is controversial. Ciprofloxacin is also used to cover milder exacerbations of symptoms in the patient chronically infected with *P. aeruginosa*, but ciprofloxacin resistance soon becomes common.

Nebulized antibiotics

Nebulized colomycin combined with oral ciprofloxacin is indicated at the time of first isolation of *P. aeruginosa*. Increasingly, a one-month course of nebulized tobramycin is being used instead; there is no advantage to adding a second month. This approach has been shown in a randomized trial to delay chronic infection. However, the combination of oral, intravenous, and nebulized antibiotics that is most effective in preventing the progression from first isolation to chronic infection has not been established.

Once *P. aeruginosa* infection is established, randomized controlled trials have shown benefit from long-term nebulized antibiotics. In Europe, colomycin is the drug most often used. In the United States of America, nebulized tobramycin is preferred. No medium-term comparison of the two has been reported. Occasional patients bronchoconstrict with nebulized antibiotics: a test dose should therefore be given, with spirometry measured before and afterwards, and if necessary pretreatment with a bronchodilator prescribed. Colomycin and tobramycin can both now be given through dry powder devices; a bronchoconstrictor trial should be done even if the nebulized preparation has been tolerated. Nebulized aztreonam is another therapeutic option. There are ongoing trials of newer antibiotics, and also studies to determine the best protocols.

Intravenous antibiotics

Infective exacerbations not responding to oral antibiotics, particularly those of *P. aeruginosa*, are usually treated with a combination of an intravenous aminoglycoside and a semisynthetic antipseudomonal penicillin or cephalosporin. These are frequently given at home. A large randomized controlled trial has established that once-daily tobramycin is equally efficacious and at least as safe as three times daily treatment. Drug metabolism in the CF patient is very different from normals and other patient groups. Although some centres recommend 3-monthly courses of intravenous antibiotics, irrespective of symptoms, for all CF patients chronically infected with *P. aeruginosa,* this approach is rarely if ever used in UK adult centres. However, the threshold for giving intravenous

antibiotics has become low, with very few clinicians waiting until the patient has developed several new symptoms.

It is increasingly being realized that CF pulmonary exacerbations are not benign. Around a quarter of patients never regain their baseline spirometry, and frequent exacerbations are associated with an accelerated decline in lung function and a greater likelihood of death or lung transplantation. Hence, reduction in the frequency of exacerbations is increasingly being used as an endpoint in randomized controlled trials of treatment.

Particular issues related to infection

Cross-infection

Fear of nosocomial acquisition of resistant organisms is widespread in the CF community. The apparent increase in prevalence of *P. aeruginosa* in specialized clinics probably reflects more assiduous bacterial culture techniques. However, most centres advocate separate clinics for CF patients with and without *P. aeruginosa*. Ideally, patients on arrival should be allocated their own room where they remain for the duration of the visit, with the professionals coming to the room, rather than the conventional model. The use of masks, gloves, and gowns by professionals is controversial, and not widely practised in the United Kingdom. Strict cohorting has also been advocated with regard to more resistant organisms, in particular *B. cenocepacia* and *Mycobacterium abscessus*.

Sensible guidelines should be applied to all CF patients: these include diligent handwashing, no sharing of physiotherapy equipment, and the use of single cubicles ideally for all inpatients, but mandatory for those with difficult organisms. Communal physiotherapy and keep-fit sessions should be discouraged, and there is no doubt that conferences for CF patients can result in transmission of infection. Careful microbiological surveillance is essential, and special measures may be needed if there is a true epidemic strain within a particular clinic.

Viral infections

Viral infections, trivial in themselves, have been implicated in causing transient reduction in airway defences and an increased risk of *P. aeruginosa* acquisition. Most physicians would at least give oral antibiotics (as already mentioned in this chapter) to cover viral exacerbations. Annual influenza immunization is advisable.

Nontuberculous mycobacteria

These organisms may be harmless commensals. Unlike *M. tuberculosis*, evidence of tissue invasion is generally held to be required to diagnose infection, but this evidence cannot often be sought in CF and decisions as to whether to treat are difficult. Evidence from autopsy studies suggests that atypical *mycobacteria* should be treated only if they are repeatedly found in sputum. CT scanning may be helpful in reaching a decision as to whether to treat, with indications for treatment being deterioration in clinical state and CT appearances in a patient with repeated positive isolates. *M. abscessus* seems to carry a particularly poor prognosis and there should be a low threshold for its treatment.

The prevalence of nontuberculous mycobacteria has increased over the past 10 years. Particular concern has focused on the emerging predominance of *Mycobacterium abscessus*, with studies reporting infection rates of between 3 and 10% in the United States and Europe. It is now recognized as a major respiratory pathogen in CF, leading to accelerated decline in lung function, and infection with it is considered a contraindication to lung transplantation in most UK centres, although infected patients should at least be discussed with a transplant centre. Treatment is challenging and requires extended therapy with a combination of antibiotics that are often poorly tolerated, and treatment failure is not uncommon. Typical regimen include an intravenous induction phase followed by consolidation for many months with combinations of oral and nebulized therapies.

A recent publication of evidence using whole genome sequencing is a significant concern. This demonstrated between patient transmission of *Mycobacterium abscessus* in a UK CF centre despite conventional cross-infection measures, although the exact route of transmission remains to be established. There are now published US/European guidelines for the diagnosis and management of nontuberculous mycobacteria in CF.

Aspergillus, including allergic bronchopulmonary aspergillosis

Evidence of exposure to *A. fumigatus* is common in CF (e.g. positive skin prick test, RAST, IgG precipitins, and sputum culture). It is becoming clearer that this organism, even in the absence of allergic bronchopulmonary aspergillosis (ABPA, see Chapter 18.14.2), may not be as benign as was once thought.

The prevalence of ABPA is disputed, but probably around 10%, although the major diagnostic criteria for this condition are also common features of otherwise uncomplicated CF. Sophisticated immunological testing has been used to try to refine the diagnosis, but an abrupt fourfold rise in total IgE, often in association with IgG precipitins to aspergillus, is the simplest and most reliable investigation. By contrast to typical infective exacerbations of CF, large fleeting radiographic shadows are typical (Fig. 18.10.2b). Treatment is with oral corticosteroids or pulsed methyl prednisolone; the roles of itraconazole and voriconazole are controversial, but they are increasingly used.

Scedosporium and other fungi are also coming to the fore as causing similar complications in CF.

Other methods of treatment

Airway clearance

Chest physiotherapy should be performed twice-daily as a routine, increasing at times of infective exacerbation. Different groups advocate different techniques (e.g. active cycle of breathing, autogenic drainage, and mechanical devices, such as the positive expiratory pressure mask, flutter, and external oscillation jacket). External oscillation has been shown to be less good than conventional airway clearance, and the equipment is much more expensive. There are otherwise no good comparisons between these approaches, and none has emerged as best. It is probably best to offer a choice of techniques to the patient. Physical exercise such as swimming supplements but should not replace formal airway clearance sessions. See Chapter 18.9 for further discussion.

Alteration in mucus properties

Human recombinant DNase *in vitro* reduces sputum viscosity. In the then largest randomized controlled trial in the CF literature,

once-daily nebulized human recombinant DNase resulted in small but sustained improvement in lung function and reduction in pulmonary exacerbations. However, individual responses are very variable, and the treatment is expensive. A carefully monitored $n = 1$ trial is recommended before starting long-term therapy.

Two trials of hypertonic saline have shown minimal improvement in lung function, but the second trial, which was the only one powered for this purpose, showed a significant reduction in infective exacerbations. The burden of two extra nebulized treatments must be considered if this is to be prescribed.

Dry powder mannitol is also available as an aid to airway clearance. It is thought to act by rehydrating the airway surface. The expense and inconvenience (multiple capsules have to be inhaled at each treatment) mean that mannitol is only recommended when other treatments are not working, but some patients find this a very effective treatment and the aforementioned considerations should not be a deterrent.

Oxygen and other respiratory support

By analogy with the Medical Research Council and Nocturnal Oxygen Treatment Trial (NOTT) trials of oxygen in chronic obstructive pulmonary disease (see Chapters 18.8 and 18.15), one would anticipate that long-term oxygen would be beneficial to the chronically hypoxic CF patient. The only trial of this approach was underpowered and thus inconclusive. Oxygen is usually prescribed for symptoms, and for patients with chronic hypoxia irrespective of symptoms. Nasal ventilation may used during acute deteriorations, and as a useful short-term expedient while transplantation is awaited. It may usefully palliate symptoms during terminal care.

Bronchodilatation

Bronchial hyperreactivity is common. Troublesome wheeze may need treatment with short-acting bronchodilators. However, β_2-agonists may cause paradoxical bronchoconstriction, and should be used cautiously. Long-acting β_2-agonists should only be given if there is clear-cut evidence of benefit. Persistent recurrent wheeze, particularly in the atopic CF patient, may be treated with inhaled or oral corticosteroids (ICS). However, it should be noted that ICS use in other contexts is associated with an increased prevalence of pneumonia, tuberculosis, and atypical mycobacterial infection, so they should only be used if there is clear evidence of benefit, particularly in view of the expense, the already considerable treatment burden, and the worrying evidence that ICS may in fact prolong neutrophil survival in the airway.

Anti-inflammatory therapy

The pathogenesis of CF lung disease includes an exuberant neutrophil-mediated inflammatory response which, via the release of neutrophil elastase and other mediators, may cause much of the tissue damage in the airways. Early in the course of the disease it is unclear whether infection is a prerequisite for inflammation, or if CF is intrinsically proinflammatory. However, in established CF airway disease, both are present. This has led to the seemingly paradoxical proposal that patients with chronic bronchopulmonary sepsis should be iatrogenically immunosuppressed. Various approaches have been tried, although none is in wide clinical use.

Oral corticosteroids

Usage in severe airway obstruction and allergic bronchopulmonary aspergillosis is discussed earlier. Long-term routine use was assessed in a multicentre, double-blind trial comparing prednisolone 2 mg/kg on alternate days, 1 mg/kg on alternate days, and placebo. This showed: (1) no benefit, except in patients infected with *P. aeruginosa*; (2) sustained improvement in lung function in colonized patients; (3) unacceptable side effects (growth failure, cataract, glucose intolerance), necessitating stopping the higher dose after 2 years and the lower dose after 4 years. Although regular alternate-day steroids may be considered for up to 2 years in some patients, their routine use cannot be justified.

Inhaled corticosteroids

Since oral steroids are beneficial, but at the cost of unacceptable side effects, it would seem logical to use long-term ICS. However, a recent study showed no detrimental effects if inhaled corticosteroids were withdrawn from a large group of CF patients. Although an observational database review suggested some benefit, most would consider that they should not be a routine part of treatment. If they are used, consideration should be given to stepping down the dose at every clinic visit, analogous to the treatment of asthma.

Ibuprofen

A multicentre, double-blind, placebo-controlled trial of ibuprofen showed a slowing of the rate of decline of lung function, particularly in young patients. However, ibuprofen is not widely used. A second, underpowered study showed better forced vital capacity (FVC) but not FEV_1, on ibuprofen. This may be because: (1) not all age groups benefited; (2) there are theoretical reasons for believing that lower doses may actually be harmful, meaning that ibuprofen levels need to be measured and a high dose given; and (3) if intravenous aminoglycosides have to be administered for an acute exacerbation of chest disease, there is a significant risk of nephrotoxicity.

Macrolide antibiotics

These are included in this section because modulation of inflammation is their likeliest mode of action. They were first used in a CF-like illness, diffuse panbronchiolitis, prevalent in middle-aged people in East Asia. Diffuse panbronchiolitis is characterized by chronic airway infection with mucoid strains of *P. aeruginosa*, the hallmark of CF. It was shown serendipitously that treatment with low-dose erythromycin reduced the 10-year mortality from 90% to less than 10%. Subsequently, randomized controlled trials have demonstrated benefit of azithromycin in CF, and this treatment is used increasingly. Macrolides have multiple actions on the immune system and growth factors *in vitro*, but their precise mechanism of action in CF has not been determined. A Cochrane review reported that evidence for treatment benefit beyond six months is limited.

Other anti-inflammatory approaches

Although anti-inflammatory defences are normal in CF, they are overwhelmed by the burden of neutrophil elastase. Boosting the natural defences (α_1-antitrypsin, secretory leukoprotease inhibitor) by nebulizer has been the subject of small and inconclusive trials; α_1-antitrypsin therapy has been shown to be ineffective in a large trial; a trial of a leukotriene B_4 receptor antagonist was halted because

of increased infective exacerbations in the active treatment arm, underscoring the fact that immune modulation may not always be beneficial.

There are anecdotal reports of the successful use of methotrexate, ciclosporin, and intravenous immunoglobulin in CF, particularly in those with severe, nonbronchiectatic airflow obstruction. There are no large trials of these approaches.

Particular respiratory complications

Haemoptysis

Blood streaking of sputum is common in CF and requires no special treatment. Massive haemoptysis is variously defined, usually as the expectoration of more than 250 ml of blood in 24 h, and is an acute emergency which requires active management. It is often, but by no means always a complication of severe lung disease, and the source is from hypertrophied bronchial arteries. The patient should be admitted, given antipseudomonal intravenous antibiotics, and any clotting abnormalities corrected. Careful chest physiotherapy should be continued. Tranexamic acid and terlipressin are sometimes used to try to control haemorrhage. If bleeding does not settle, or recurs, then bronchial artery embolism should be considered. All sizeable bronchial arteries should be occluded. Preoperative bronchoscopy does not influence management, and often fails to define the side of bleeding. The major risk of embolization is inadvertent occlusion of a major spinal artery, resulting in paraplegia. Lobectomy is rarely necessary, and carries a high risk in these patients, who are often very compromised.

Pneumothorax

This is usually a complication of late-stage lung disease. Small pneumothoraces may require no special measures; moderate or large pneumothoraces are initially treated with tube drainage. HRCT scanning may be necessary to define optimal placement of drainage tubes in complex pneumothoraces. Careful physiotherapy must be continued, and intravenous antibiotics given. If there is a continued air leak, pleurodesis should be undertaken. However, it is important to consult with the local transplant service before doing this, because aggressive pleurectomy is seen by some to be a contraindication to subsequent transplantation.

Upper airway disease

Nasal polyps are seen in up to 50% of adults with CF. Treatment is with nasal steroids in the first instance. If medical management fails, surgical polypectomy is indicated, but 50% will require a second procedure within 2 years. Abnormal sinus radiographs are universal, but symptomatic sinusitis relatively rare. If present, sinusitis should be treated medically with prolonged antibiotics, nasal steroids, and possibly decongestants in the first instance; surgery may be required although symptoms often return after a couple of years. Rarely, surgery is needed for mucocele of the frontal sinuses.

Gastrointestinal management

Pancreatic insufficiency needs to be treated in 85% of cases; meconium ileus or distal intestinal obstruction syndrome affects up to 30%; symptomatic liver disease occurs in about 5%, but in general the gastrointestinal manifestations of CF are less important than the lung disease. For a few patients, however, they are the dominant problem.

Pancreatic insufficiency

This is usually present from birth, with low levels of bicarbonate and lipolytic and proteolytic enzymes in pancreatic secretions. Those with clinical pancreatic sufficiency secrete low but adequate levels of enzymes. Some develop pancreatic insufficiency later in life. The usual presentations are neonatal meconium ileus (which is occasionally seen in pancreatic-sufficient CF patients and normal babies) or failure to thrive with associated steatorrhoea and malnutrition. Consequences can include anaemia, vitamin deficiency, and occasionally oedema; complications include rectal prolapse, intussusception, volvulus, and distal intestinal obstruction syndrome.

The diagnosis is confirmed by estimation of human faecal elastase (which can be used even if the patient has been started on pancreatic enzymes), demonstration of unsplit fat globules in the stool, or increased faecal fat on a 2- or 3-day stool collection. Formal testing of pancreatic function is seldom required.

Treatment with pancreatic enzyme and vitamin supplementation is usually straightforward and successful. Enteric-coated enzyme preparations are taken before meals and the quantity adjusted to achieve normal stools. The commonest cause of failure is poor compliance, although occasionally lactose intolerance, inflammatory bowel disease, coeliac disease, or bowel infection/infestation may coexist. Hence a gastrointestinal review should be instituted rather than uncritical dose escalation of pancreatin in nonresponding patients. A few patients need to take H_2 blockers, proton pump inhibitors, or antacids to achieve better control of symptoms. Large-bowel strictures have developed in some patients (usually children) taking high-strength enzyme preparations, probably as a toxic effect of the coating rather than the enzymes themselves.

Nutrition

Vitamin supplementation should be given to all patients to cover fat-soluble vitamin deficiency. Most multivitamin tablets contain vitamins A and D, but vitamin E needs to be given separately to maintain adequate intake. Vitamin K supplementation is prescribed for its effects on bone health. The diet should otherwise be normal, with a high calorie intake, usually 130% of recommended daily allowance. However, a recent study suggested that oral high-calorie supplements are often ineffective, and patients unable to maintain weight in spite of optimal dietary advice can be helped by enteral feeding, which is better tolerated by gastrostomy than by a nasogastric tube in the long term.

Distal intestinal obstruction syndrome

Constipation and a loaded colon are relatively common in CF and usually respond to modification of the diet, pancreatic supplements, and a high fluid and roughage intake; occasionally lactulose and/or a macrogol laxative (e.g. Movicol) is helpful. Severe constipation merges into the distal intestinal obstruction syndrome with pain, palpable faecal masses, and complete obstruction with faecal material in the distal ileum or ascending colon. The cause is multifactorial with imbalance of pancreatic enzymes and diet, disturbed fluid and electrolyte transport, faecal dehydration, and abnormal intestinal mobility all playing a part.

Patients present with chronic intermittent pain or episodes of complete obstruction. Although the differential diagnosis is wide and includes common conditions such as appendicitis, most patients improve with medical treatment and surgery should be avoided unless there is clear evidence of another diagnosis. Treatment with a balanced intestinal lavage solution, 500–1000 ml/h by nasogastric tube, usually moves the faecal blockage within 4–6 h. Alternatives are gastrografin by mouth or enema, or oral *N*-acetylcysteine. Occasionally, removal of inspissated faeces at colonoscopy is needed.

Other gastrointestinal complications

Pancreatitis is rare but should be excluded in cases of abdominal pain. It usually affects those who are clinically pancreatic sufficient. Treatment is conventional, with special attention to pulmonary infections, because the pain of pancreatitis may interfere with physiotherapy.

Gastro-oesophageal reflux is common, in particular in severe CF lung disease, sometimes with overt vomiting, and may be associated with coughing, physiotherapy, and bronchodilators which may relax the oesophageal sphincter. Aspiration of stomach contents is seldom a clinical problem. Although peptic ulcer disease might be expected in view of the low pancreatic bicarbonate secretion, there is only one report of an increased frequency of ulceration. *Helicobacter pylori* infection is uncommon, perhaps because of antibiotic treatment.

Lactose intolerance, coeliac disease, and inflammatory bowel disease occur with slightly increased frequency in the CF population, but symptoms may be misattributed to CF and diagnosis therefore delayed. Both giardiasis and *Clostridium difficile* gut infection have been reported as being more frequent in CF, but these are not common clinical problems.

As adults survive longer, it is clear that there is an increased risk of colon cancer, and possibly other malignancies. Whether CF adults should undergo screening with faecal occult bloods, and if so, how frequently, is not known.

Liver disease

Liver disease causes problems in 5% and death in 2% of people with CF, but abnormal liver function tests are very common and up to 50% have biliary cirrhosis demonstrable at autopsy. With increasing survival, liver disease may become more important.

Although liver enlargement and jaundice occasionally occur in early childhood, liver disease is usually signalled by hepatosplenomegaly or abnormal liver function on routine testing. Decompensation with jaundice, ascites, or encephalopathy is rare and occurs late. Variceal bleeding only occurs in a minority of those with established chronic liver disease, but may be the presenting symptom of CF itself, or of liver disease in a patient known to have CF. Minor or modest elevations of aminotransferase, γ-glutamyl transpeptidase, or alkaline phosphatase levels are very common but do not correlate with established liver disease unless the enzyme levels are greater than four times normal. Routine ultrasonography detects fatty change or multilobular cirrhosis: the finding of portal vein dilatation, splenomegaly, or collateral vessels indicating portal hypertension. Cholangiography is occasionally needed for diagnosis of gallstones: this may reveal irregularities of the intrahepatic ducts, suggesting chronic liver disease, and significant strictures of the common bile duct may also be seen. Liver biopsy is seldom needed.

No treatment has been shown to modify the course of chronic liver disease in CF, although clinical and biochemical improvements have been shown following treatment with ursodeoxycholic acid. This bile acid stimulates bile flow, may protect the hepatocyte from toxicity of bile acids, and is helpful in primary biliary cirrhosis. Many hepatologists therefore recommend its use in CF.

Jaundice must be investigated to exclude drug hepatotoxicity or treatable obstructive cause, but is otherwise a late event with poor prognosis. Variceal bleeding is treated with injection sclerotherapy or banding ligation, and in the short-term balloon tamponade or vasoconstrictor drugs may buy a little time. Surgical treatment is hazardous due to lung disease and in a few patients the insertion of a transjugular intrahepatic portal systemic shunt may be an alternative. Prophylactic treatment of varices has not been shown to help and may be detrimental. Ascites and encephalopathy are rare and are usually preterminal events to be managed conventionally.

In most cases of complicated chronic liver disease, management is made more difficult by the presence of lung infection that must be aggressively treated. Respiratory failure may develop concurrently. When this occurs, intubation and ventilation are seldom successful.

Diabetes

Glucose intolerance in CF increases with age, being rare under 10 years, affecting 14% by 15 years, and over 65% at 25 years. By this age 32% are frankly diabetic. Even when glucose tolerance is normal, reduced insulin secretion is frequent, and should be sought in a patient who is deteriorating on conventional treatment. This is caused by gradual and progressive loss of β cell mass in line with pancreatic fibrosis. Peripheral insulin sensitivity is usually normal and autoimmune factors are not involved.

Diagnosis is based on conventional World Health Organization (WHO) recommendations. Many recommend annual oral glucose tolerance tests, but screening for diabetes in a CF clinic is sometimes done by measurement of HbA1c (not thought by most to be a useful screening tool), together with random or fasting blood sugar levels. Increasingly, continuous glucose monitoring is used for diagnosis. Diabetes is usually diagnosed at such screening, but a few patients present with weight loss and increased frequency and severity of chest infections, although polyuria and polydipsia occasionally develop first. It has been suggested that the onset of diabetes is a marker of general deterioration, but many patients return to their previous level of health when diabetes is controlled. Interestingly, improved insulin secretion has been reported in young patients with class 3 mutations treated with Ivacaftor (above). Oral hypoglycaemic agents should not be used outside the context of a randomized controlled trial; the treatment of insulin deficiency is insulin replacement. Control of blood sugar is relatively simple, with flexible use of short- and long-acting insulins. The usual dietary recommendation is to maintain an energy intake of 150% of normal with frequent balanced meals, with adjustment of insulin to suit. Ketoacidosis and insulin resistance are almost unknown.

Early microangiopathy has been shown in CF patients with diabetes, but retinopathy, neuropathy, and nephropathy are rare. This may be in part due to the mildness of the diabetes, but is likely to become more common as survival improves. Nevertheless, CF patients

(in particular women) with diabetes tend to have excess morbidity and slightly increased rate of decline in weight and lung function, but this is being improved by early detection and treatment of insulin deficiency.

Other organ systems

Reproductive

Almost all men with CF have obstructive azoospermia with otherwise normal sexual function. This is due to absence of the vas deferens, and although there are no sperm in the ejaculate (which is usually of reduced volume) there is normal spermatogenesis and Leydig cell function. Counselling about infertility should be done well before the time of puberty, and certainly before permanent relationships develop. Most men opt to confirm the azoospermia by a sperm count. *In vitro* fertilization using aspirated sperm has been successful and there are now many CF fathers.

Early reports of reduced fertility in women with CF have not been confirmed and most can conceive normally. The child by definition carries one mutation from the mother: the risk of CF in the baby is therefore 1 in 50 in white populations, with a carrier frequency of 1 in 25. Counselling and paternal genotyping allows reassurance for most CF pregnancies and identifies a 1 in 2 risk when the father is a carrier. Successful pregnancies have been completed by many hundreds of CF women, but women with severe lung disease may not be able to complete a pregnancy safely, the risks rising with impaired lung function and especially when the FEV_1 is less than 30% predicted. Children born have been healthy, without an increased frequency of birth defects despite the mothers' extensive drug treatment. Lactation is normal.

Vaginal candidiasis secondary to antibiotic treatment is relatively common in CF. Stress incontinence is particularly distressing in both sexes, and may interfere with coughing, physiotherapy, and normal sexual relationships. Sexual behaviour in both genders may be inhibited by low weight, delayed puberty, cough, sputum, haemoptysis, breathlessness, and indwelling catheters, but most people adapt well and persistent problems are few.

Skin and joints

Clubbing is almost universal in those with significant lung disease., and regresses after successful lung transplantation. Hypertrophic osteoarthropathy is rare. Episodic arthritis, predominantly affecting the large joints, is quite common and associated with chest infections. Erosive arthritis is rare. Pain responds to nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids or immunosuppression are seldom needed. Systemic vasculitis has occasionally been reported but is surprisingly rare considering the extent of immune activation, the frequency of circulating immune complexes, and the number of drugs taken.

Kidneys

Glomerulonephritis has been reported but is probably no more frequent than in the normal population. Acute tubular necrosis is rare and usually associated with higher than recommended aminoglycoside levels or the additional prescription of NSAIDs. Very large numbers of aminoglycoside treatments and CF-related diabetes are associated with progressive decrements in renal function. Renal stones are common in CF, probably due to excess oxalate absorption secondary to altered bowel bacterial flora. Systemic amyloidosis has occasionally been reported secondary to prolonged pulmonary infection.

Central nervous system

Acute ototoxicity occasionally results from aminoglycoside treatment but is not seen when serum levels are well controlled, but there does seem to be a cumulative effect from repeated aminoglycoside courses. Cerebral abscess rarely complicates lung sepsis. Vitamin E deficiency leads to a cerebellar syndrome combined with peripheral neuropathy.

CF-related bone disease

Reduced bone mineral density is common in CF, with prevalence among adults of up to 60%, and onset in children has been described. This is partly due to general malnutrition as well as vitamin D malabsorption, but relative immobility is sometimes a factor. Other factors may include delayed puberty and hypogonadism, the effect of the systemic inflammatory response, immobility, inhaled and oral steroid therapy, and vitamin K deficiency. However, CFTR is expressed in bone and CF bone disease may be seen in otherwise well patients, including children. An increased rate of fractures has been reported, and rib fractures from coughing can interfere with adequate physiotherapy. Vertebral compression fractures are fortunately rare.

Regular bone mineral density measurements are recommended, with extra vitamin D and calcium supplementation when low. Bisphosphonates can cause bone pain when given intravenously. Oral preparations can be used, and trials are ongoing to determine the optimal timing of treatment. Prevention is by encouraging a high dairy intake, weight-bearing exercise, and supplementation with vitamin K.

Management of respiratory failure

Recurrent and persistent chest infection leads to progressive decline in lung function with eventual respiratory failure in most patients, although in about 2% the liver fails first. At this stage, the issues of transplantation should be addressed. If a patient wishes to explore the possibility of transplantation, then preoperative work-up, counselling, surgical assessment, and placement on the waiting list should take place 2 years before the predicted date of death. Others may opt for palliative care.

Lung transplantation

Selection criteria are listed in Table 18.10.3. Prediction of prognosis is difficult; whereas in the 1990s patients with an FEV_1 less than 30% had a median survival of two years, now the figure is more than five years. The timing of assessment is judged on the level and rate of decline of lung function, arterial blood gases, and the frequency and severity of chest infections.

Patients on the waiting list must be managed optimally to maintain lung function and nutrition, often with gastrostomy feeding. Noninvasive ventilatory support can provide a bridge to transplantation for patients with progressive respiratory failure, but intubation and conventional ventilation are not recommended.

Table 18.10.3 Selection criteria for lung transplantation

Indications	Severe respiratory failure in spite of optimal treatment
	Severely impaired quality of life
	Patient positively wants a transplant
Strong contraindications	Active aspergillus or mycobacterial infection
	Noncompliance with treatment
	Other end-organ failure
	Gross malnutrition
Relative contraindications	Preoperative ventilation
	Previous thoracic surgery
	Chemical pleurodesis

Donor organs are scarce and at least 50% of listed CF patients never receive a transplant. The results for lung transplantation are the same as for other lung diseases, with a survival of 70% at 1 year and 50% at 3 years. See Chapter 18.16 for further discussion. Recently, living donor lobar transplantation has been offered to CF patients, with comparable results.

Liver transplantation is appropriate for the occasional patient dying of liver failure with relatively good lung function: survival at 5 years is 85%.

Terminal care

The timing of the decision to switch to palliative care is difficult and should be made in conjunction with the patient and relatives. The most distressing symptoms are cough, sputum retention, breathlessness, and exhaustion. Small doses of morphine are usually well tolerated and only seldom worsen respiratory failure.

The CF team

As with many chronic diseases, the purely medical care of CF is relatively straightforward. Proper holistic care requires a team approach, and without such a team, care will be second rate. Typically, the core of the team is formed by a specialist nurse, a physiotherapist, a dietitian, a psychologist, and a social worker, together with a specialist doctor. It is unrealistic to expect every hospital to provide this, and hence close contact with a tertiary centre is advisable. Many of the physical issues (airway clearance, nutritional management) have been discussed here already. Equally important are many of the psychological problems springing from the presence of a chronic disease.

The normal process of adolescence includes rebelling and breaking free of parental care. In those with CF this may never have been achieved, because the parents have wanted to keep control of treatment regimens, and have been reluctant to allow independence. Although paediatric clinics should have established a pattern of the adolescent coming into the consulting room alone, frequently this does not happen, and the adult physician is often confronted with parents who resent the idea that their now grown-up child should be seen on their own. Conversely, the consequences of a full-blown adolescent revolt (nonacceptance of treatment, abuse of cigarettes, alcohol, soft and hard drugs, and high-risk sexual behaviour) may be particularly catastrophic in the patient with CF. The authors still know of no easy answer to adolescence and its aftermath.

Knowledge of fertility issues is notoriously poor among adult men with CF: these may need to be tackled tactfully. The issues surrounding pregnancy in the woman with CF, who may herself be severely breathless, but desperately wishing for a child, also require sensitive handling (see earlier).

Further education and employment are also difficult issues in the setting of chronic physical disability, but skilled help may allow patients with CF to maximize their potential. A fuller account of the many and complex psychosocial issues surrounding care can be found elsewhere, but appreciation of these issues is just as important as knowing the correct management of the physical problems of CF.

Future prospects

The first CF animal model was the mouse, generated more than 20 years ago by using molecular techniques to disrupt *CFTR*. Although clearly this was a major step in CF research, mice did not recapitulate many important features of human CF disease. They developed intestinal disease but were not pancreatic insufficient, and they did not have spontaneous CF lower airway disease. This may relate to species differences in the extent of expression of CFTR and other ion channels. However the mouse nose has similar bioelectric properties to the human CF nose, and has been used for early phase CF treatment studies. Somatic cell nuclear transfer, the technique used to create Dolly the sheep, has now also been used to create CF pigs and ferrets. CF pigs develop intestinal disease, but are exocrine and endocrine pancreatic insufficient and have a lung phenotype similar to human CF. Neonatal CF ferrets have intestinal disease and pancreatic disease as well as early lung infection. The CF ferret does not universally develop meconium ileus, and endocrine pancreatic function is better preserved than in the CF pig, making it possibly an even better model of human disease. However, caution is necessary in extrapolating findings from animals to man; there is no doubt that they are a significant advance, but animals are not humans.

The growth in basic scientific understanding of CF will lead to further new treatments directed at the mutant CFTR gene or protein. The ultimate aim must be to have specific molecular therapies for everyone with CF, irrespective of genotype. CFTR undergoes complex folding, both during and after translation, and it may be that more than one compound will be needed to correct this. Ivacaftor will increasingly be explored in all class 3–6 mutations to increase CFTR function, and also in combination with therapies for classes 1 and 2, and also gene therapy, to amplify the effects of getting CFTR to the cell surface.

Research is ongoing into correction of the disordered electrophysiology with sodium channel blockers, promoters of chloride transport via alternative channels, is already well advanced. Inhaled bicarbonate is being considered, to correct airway surface pH. There is, therefore, a real prospect that new fundamental treatments will prevent the development of CF disease and lead to improved health, prolonged survival, and reduction in lifelong supportive therapy not merely in the class 3 mutations, but in all CF patients. The two main challenges to be overcome are (a) how to show benefit in an increasingly well patient group; and (b) how to fund these medications—ivacaftor costs $330 000 per patient per year.

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