Clinical management of children and adults with cystic fibrosis

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The cystic fibrosis population is increasing by 120-140 patients a year, and by the year 2000 there could be 6000 patients in the United Kingdom, with equal numbers of adult and paediatric patients.¹ It is hoped that better understanding of the underlying defect will be translated into practical treatment such as gene replacement, for at present the median survival for adults is only into the third decade.² The review looks at the current management of cystic fibrosis.

Diagnosis

The modes of presentation are listed (box 1) because some are not well known. Overdiagnosis remains a problem. In some parts of Britain up to 10% of patients referred to regional centres with cystic fibrosis are found to have an alternative diagnosis.³ The total absence of one or more of the major features—malabsorption due to pancreatic insufficiency, chronic suppurative lung disease, and failure to thrive—should lead to caution about the diagnosis. The main reasons for these errors are a disregard of the clinical features or the lack of them, incorrect performance of the sweat test, and faulty interpretation of the results of the test. Some patients (less than 10% seen in the United Kingdom, but up to 38% in one Canadian series), have sufficient pancreatic function for normal digestion, so that even the most sophisticated direct pancreatic function testing can exclude only pancreatic insufficiency and not cystic fibrosis itself. Homozygosity for one of the recognised gene deletions clearly indicates cystic fibrosis. Unfortunately, a cystic fibrosis mutation cannot be detected in about a fifth of patients; thus, negative results in the search for homozygosity of a cystic fibrosis gene does not exclude the diagnosis. In many cases, the final diagnosis still hinges on the accurate performance and correct interpretation of the sweat test.

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Summary points

- Progressive respiratory disease is responsible for much of the morbidity and most deaths in cystic fibrosis
- Improved care has resulted in current survival into the third decade of life
- By the year 2000 there will be 6000 patients with cystic fibrosis in the United Kingdom, with equal numbers of adult and paediatric patients
- Patients should have access to a regional centre, either directly or through some kind of shared care

Chest management

The main reason for improved survival is a meticulous approach to overall care (box 2) and in particular the aggressive treatment of acute and chronic pulmonary infection. The essential components of chest management are the oral, intravenous, and nebulised antibiotics appropriate to infective pathogens cultured from sputum; physiotherapy; and exercise. Maintenance of adequate nutrition and control of diabetes also seem to influence the stability of pulmonary disease.

The main difference in management of the chest and overall care between paediatric and adult patients is the transfer of responsibility for care from the parents to the patient. Compliance with all modalities of care may diminish during adolescence, with the demands on the patient's time, the interference with study and work, and the need to establish independence from parents.

Antibiotics and micro-organisms

It is common practice to give lifelong anti-staphylococcal oral antibiotics (such as flucloxacillin) to treat *Haemophilus influenzae* when this organism is recovered, and to give regular courses of anti-pseudomonas antibiotics to patients who are colonised with *Pseudomonas aeruginosa*. As with most forms of treatment in cystic fibrosis, sound controlled trials showing benefit are lacking. A frequently voiced concern with all aggressive antibiotic regimens in this disease is that they risk the development of antibiotic resistant organisms. The enthusiasm to mount long term, multicentre trials large enough to answer these fundamental questions has not been forthcoming. Consensus guidelines, when they come, will be a poor substitute for hard data.

Progressive lung damage in cystic fibrosis is due to a combination of chronic infection and self damaging host response that persists when patients are free of clinical symptoms with maintained respiratory function and stable body weight.⁴ The dual aim of regular courses of intravenous antibiotics is to treat the

Box 1—Modes of presentation in cystic fibrosis

Well recognised modes of presentation in newborn infants

- Meconium ileus
- Prolonged neonatal jaundice
- Positive screening (for example, immunoreactive trypsin)

Other well recognised modes of presentation

- Recurrent cough or wheeze or respiratory infection
- Offensive loose stools (usually from birth)
- Slow weight gain
- Salty taste when kissed
- Nasal polyposis
- Rectal prolapse
- Heat prostration or dehydration in hot weather

Less well known modes of presentation

- Meconium plug syndrome (most cases do not have cystic fibrosis)
- Failure to thrive with anaemia, hypoalbuminaemia, and dermatitis
- Failure to thrive with metabolic alkalosis and low serum concentration of sodium, potassium, and chloride—pseudo-Bartter's syndrome (such infants often have a normal sweat sodium concentration but a raised sweat potassium concentration)
- Mild suppurative lung disease in adults

Box 2—Management routines

Regional cystic fibrosis centre

- Confirmation of the diagnosis
- Offer of referral to geneticist
- Regular review by cystic fibrosis team (six monthly visit to district general hospital by members of team or 12 monthly review at cystic fibrosis centre)

District or regional centre

- Open access
- Regular review by physiotherapist
- Regular review by dietitian
- Regular review by paediatrician or adult physician
- Ensure involvement of general practitioner

Periodic monitoring and investigation (important)

- Collection of sputum or cough swab for bacteriology
- Measurement of weight (and in children, height)
- Radiography of the chest
- Monitoring of lung function
- Monitoring of adherence to treatment

Periodic monitoring and investigation (optional)

- Ultrasound examination of liver, spleen, and gall bladder
- Three day estimation of faecal fat loss
- Screening for diabetes mellitus

pulmonary infection and limit the persisting host response. Intravenous antibiotics are empirically given for two weeks three to four times a year for patients infected with *P aeruginosa*.

In children there is some evidence that chronic colonisation with *P aeruginosa* may be delayed for 18 months by introducing nebulised colistin and ciprofloxacin on first isolation of *P aeruginosa*.⁵ For adult patients who are chronically colonised with *P aeruginosa* the indications for giving nebulised antibiotics are less clear. Some units introduce them when regular courses of intravenous antibiotics fail to maintain clinical stability—that is, when increasing sputum weight is associated with both a decline in body weight and pulmonary function.

The emergence in adult and paediatric clinics of *P cepacia* is a huge problem for patients and doctors alike. Some strains of this organism seem to be non-pathogenic in cystic fibrosis. However, the so called epidemic strain is effectively resistant to all currently available antibiotics and can be associated with accelerated lung disease. These two facts, coupled with the definite but poorly defined mode of cross infection,⁶ have had a massive impact. Segregation of patients to prevent cross infection has resulted in social isolation and has led many units to reorganise clinic and inpatient arrangements. Present evidence points to the importance of close rather than casual contact in promoting cross infection. Fear of acquiring *P cepacia* is beginning to deter patients from attending social gatherings, holiday camps, and hospitals. There is an urgent need to learn more about how the organism is passed between patients. For example, it is clear that in siblings with cystic fibrosis there is a high risk that the organism will pass from one to the other, but we have no information about how to prevent this. An extreme position would be to advise one sibling to move out of the home altogether. Few, if any, would give such drastic advice, and yet we have to face the possibility that this may be the only really effective strategy.

Physiotherapy, exercise, and clearance of secretions

Efforts to clear pulmonary secretions are a challenge to the patient, parents, and physiotherapist. Physiotherapy uses a wide variety of techniques, the choice of which depends on the severity of the disease, the age and independence of the patient, and the preference of the physiotherapist. The basic techniques are

controlled breathing, thoracic expansion exercises, the forced expiration technique, postural drainage, in selected cases a positive end expiratory pressure mask, and for younger patients percussion.⁷ In addition to teaching the appropriate physiotherapy techniques to patients and relatives, the physiotherapist also measures lung function, checks the patient's suitability for bronchodilators, assesses fitness and devises home exercise programmes, and monitors adherence to treatment (physiotherapy, exercises, and respiratory drugs).

The long term benefits of the role of exercise are unproved. Nevertheless, in the few patients who are inclined to engage in regular and really vigorous exercise (cycling, running, or swimming), the prevention of expected long term deterioration in lung function and the improved fitness and overall well-being can be striking. Even in these patients, however, physiotherapy cannot be replaced by exercise, and the two should have complementary roles.⁸ Fitter patients have a better survival⁹ but this may reflect milder disease progression rather than the benefit of regular daily exercise programmes.

Many patients have reversible airways obstruction, and a home record of the peak expiratory flow is useful in determining whether to treat with bronchodilators or inhaled steroids. Early trials suggest that the inhalation of DNase can produce remarkable short term improvement in lung function in patients who produce moderate quantities of purulent sputum.¹⁰ This product is likely to be marketed shortly, but further studies are required to identify those patients in whom the anticipated high cost of this drug can be justified by reduced infection and improved lung function and survival.

Nutrition

Faecal nutrient losses, poor appetite, respiratory infection, and increased energy expenditure explain why patients require above average energy intakes.¹¹ Diets high in fat, protein, and carbohydrate are recommended. The new pH sensitive, enteric coated microsphere preparations of pancreatic enzymes have achieved substantially improved fat absorption, accompanied by diminution in abdominal distension, stool odour, and number of bowel actions. Where enzyme supplements fail to abolish abnormal fat loss in the stool, this can sometimes be achieved with the addition of H₂ receptor antagonists or omeprazole. Bile acids can dissolve cholesterol gall stones and increase the flow of biliary sludge, which are sometimes associated with intermittent jaundice. The results are awaited of long term trials using ursodeoxycholic acid to prevent or delay irreversible hepatic fibrosis.

In infants with cystic fibrosis, breast milk is usually suitable. For the formula fed infant, maximal intake of nutrients with a minimal need for pancreatic supplements can be achieved either with a casein hydrolysate milk formula to which is added a fat emulsion and additional carbohydrate or by adding these items to a conventional cows' milk formula. For the older patient who stops gaining weight and has a poor appetite, weight gain can sometimes be achieved with nutritional supplements based on skimmed milk powders, carbohydrate sources, medium chain triglyceride fat emulsions, or flavoured food supplements. Short or long term nocturnal enteric feeding is increasingly used, though as with many other types of treatment in cystic fibrosis there is a dearth of evidence of benefit from controlled trials. Where long term enteral feeding is used feeding by gastrostomy may make the treatment more acceptable.¹² Gastrostomy feeding is also used to improve nutrition in those requiring transplantation.

It is common practice to give multivitamin supple-

ments to prevent deficiency of fat soluble vitamins. Vitamin E deficiency, which causes haemolytic anaemia and only partly reversible spinocerebellar degeneration and peripheral neuropathy, is a rare complication of cystic fibrosis. Most cases occur in patients with liver disease of ileal resection. The risk of vitamin E deficiency merits the routine use of vitamin E supplement. Malabsorption of another fat soluble vitamin, vitamin A, can rarely lead to reversible night blindness. The optimum doses of these vitamins, and the role for monitoring their serum concentrations, have yet to be established in controlled studies.

Common complications

Pneumothorax is associated with severe lung disease and carries a poor prognosis. Small pneumothoraces in the patient with borderline respiratory failure present a difficult management problem. The patient should always be given intravenous antibiotics. If the pneumothorax fails to resolve a week after either needle aspiration or the insertion of a drainage tube (under radiological control) then prompt consideration should be given to apical stapling with videothoracoscopy by an experienced surgeon. Pleurodesis should not be used as it may prejudice future transplantation.

Haemoptyses—usually small—are common, cause concern to the patient, and are due to erosion of the bronchial mucosa by infection. Moderate sized haemoptyses require hospitalisation and intravenous antibiotics. If haemoptysis is large and persistent, temporary relief can be provided with infusion of vasopressin. Permanent relief requires bronchial artery embolisation.¹³

Glucose intolerance increases with age. A quarter of our adult patients have insulin dependent diabetes. The development of diabetes may be associated with a decline in overall clinical state.¹⁴ Poor control of diabetes results in increased weight loss in underweight patients and deteriorating pulmonary function and thickened sputum. Conversely, good control of diabetes may stabilise or improve clinical state.¹⁵ The treatment of diabetes in cystic fibrosis differs from that in normal patients. All diabetic patients with cystic fibrosis should receive insulin; ketoacidosis is rare and there should be no dietary restriction, although the correct timing of meals and snacks is important.

Box 3—Complications of cystic fibrosis

Respiratory

- Respiratory infection
- Pneumothorax
- Haemoptysis
- Allergic bronchopulmonary aspergillosis
- Nasal polyposis
- Deterioration during and after pregnancy

Cardiovascular

- Cor pulmonale

Gastrointestinal

- Rectal prolapse
- Distal ileal obstruction syndrome (meconium ileus equivalent)
- Cirrhosis, hypersplenism, portal hypertension
- Gall stones, cholecystitis
- Biliary stricture
- Intussusception

Other

- Salt loss (in acute illness or hot climate)
- Psychological problems
- Diabetes mellitus
- Male subfertility
- Vasculitis, purpura
- Hypertrophic pulmonary osteoarthropathy
- Cystic fibrosis arthropathy

A few children with cystic fibrosis develop cirrhosis with portal hypertension and oesophageal varices, but hepatobiliary disease presents more commonly in adults as cholecystitis, abdominal pain or fluctuating jaundice from biliary strictures, and bleeding from gastric or oesophageal varices. Asymptomatic gall stones are sometimes found during routine abdominal ultrasound.

Informing a male adolescent about subfertility (fertility is theoretically possible by in vitro fertilisation using spermatozoa aspirated from the epididymis) or telling a married couple that they cannot have children, can be devastating for the patient. Women with cystic fibrosis, even those with severe disease, are fertile. Eight women at our adult unit have produced 10 normal infants, but two of these mothers have subsequently died from severe lung disease and a third has required a double lung transplant. Pregnancy in patients with severe disease may increase the requirement for intravenous antibiotics and exacerbate diabetes. During pregnancy the use of aminoglycosides is contraindicated, and some antibiotics (ciprofloxacin and monobactams, for example) are not recommended for use in pregnancy. After pregnancy lost pulmonary function may not recover.

Preterminal disease

The management of preterminal disease has been considerably changed in the past five years by the limited availability of organs for transplantation. Preterminal disease does not indicate that the patient is necessarily going to die. Prediction of death within two years can be made for 50% of patients whose forced expiratory volume in one second is less than 30%.¹⁶ On the basis of this principle the necessity for referral for transplantation can be anticipated about a year in advance of death. After the patient has been accepted for a transplantation, the aim is to sustain life by aggressive treatment with enteral feeding, nocturnal oxygen, respiratory stimulants, continuous intravenous antibiotics, and nasal intermittent positive pressure ventilation.¹⁷ Unfortunately, limited organ supply sometimes defeats these heroic efforts, and a proportion of patients supported by this type of technology die deprived of the final comforts of actively managed terminal care.

Conclusion

Current scientific breakthroughs herald a better future for the management of cystic fibrosis. Until radically new treatments are available, the management of cystic fibrosis requires meticulous attention to detail by patient and doctor. The management of cystic fibrosis has become increasingly specialised and complex, and there is a case that all patients should have access to the facilities available at a regional cystic fibrosis centre.¹

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Lesson of the Week

Unsuspected *Pneumocystis carinii* pneumonia and vertically acquired HIV infection in infants requiring intensive care

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Infants with *Pneumocystis carinii* pneumonia may be the first family members to be diagnosed as having HIV infection, particularly as some mothers are unaware of their own infection

The condition of infants with acute respiratory distress may deteriorate to the point of needing assisted mechanical ventilation, particularly during seasonal outbreaks of respiratory syncytial virus infection. In some of these children the course of their illness may have been complicated by secondary bacterial infection or aspiration of gastric contents. Alternatively, the underlying infection may have been particularly virulent or the host unusually susceptible—for example, infants with some degree of chronic lung disease of prematurity or an underlying congenital heart disease. In practice, having excluded respiratory syncytial virus, most physicians choose antimicrobial treatment to cover the common community acquired respiratory pathogens in the age group. We describe three such cases in infants aged 8 weeks, 4 months, and 5 months in whom the aetiological agent and underlying disease—*Pneumocystis carinii* pneumonia and vertically acquired HIV infection—were unsuspected as their condition deteriorated.

Case reports

CASE 1

An 8 week old black girl was admitted to a general paediatric ward with a brief history of irritability and vomiting after feeding. When aged 4 weeks she had been admitted and treated with antibiotics for seven days. On this occasion she was tachypnoeic with a respiratory rate up to 80 breaths/minute. She was later noted to be hypoxic breathing room air and was treated with supplemental oxygen. Throughout her initial stay in hospital she received intravenous cefuroxime. The working diagnosis was an acute respiratory illness

complicated by aspiration of gastric contents. On general examination her length and weight were just above the 10th centile for age and her head circumference was between the 50th and 90th centile. She had a palpable spleen tip.

One week after admission her breathing deteriorated to the point of needing endotracheal intubation and mechanical ventilation. After initial management and stabilisation in a general intensive care unit she was transferred to this paediatric intensive care unit by the transport team. Results from blood tests showed consistently low lymphocyte counts (around $1.89 \times 10^9/l$) and a series of chest x ray films showed a progressive diffuse interstitial lung process (figure). *P. carinii* pneumonia was confirmed by bronchoalveolar lavage and HIV positivity by serum testing.

CASE 2

A 5 month old white girl was admitted to a general paediatric ward with a brief history of low grade fever, cough, and difficulty in feeding. She had been admitted previously with an apparent infection. On this occasion she was noted to be tachycardiac and tachypnoeic (respiratory rate 50-60 breaths/minute), with an audible expiratory grunt. On general examination her length and weight were just above the 10th centile for age and her head circumference was on the 50th centile. She had a palpable spleen tip and her liver was 2 cm below the costal margin. As in case 1, her condition deteriorated until she required endotracheal intubation and mechanical ventilation. Nasopharyngeal aspirate was tested to exclude respiratory syncytial virus and she was treated with intravenous flucloxacillin and ampicillin. Results of blood tests showed consistently

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Case 1: Radiographs showing initial diffuse interstitial lung disease (left), which progressed to bilateral "white outs" with visible air bronchograms