Personal practice

Cystic fibrosis

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There has been little advance in the understanding of the basic defect of cystic fibrosis in the past 25 years but the life span of patients has increased. This is probably due to a more aggressive approach to treatment or changes in the environment and social conditions, or both. Treatment begins at the time of diagnosis and an important part of management is the development of a good relationship with the parents for what will be a life long commitment to the care of their child. The reliability of the diagnostic sweat test should be in no doubt, especially as, with the introduction of screening tests, some infants will be diagnosed before symptoms develop. Screening must be backed up by reliable sweat testing and, equally important, an organised counselling service. Parents will become anxious while they await the final diagnostic test result and there should be a preliminary discussion with them by a senior member of the paediatric team at the time of this investigation.

The basic management of patients with cystic fibrosis is still based on the objectives and methods first described by Andersen¹—being to ensure optimal nutrition and to prevent or control pulmonary infection. It is difficult to judge which is the most important of these objectives. Recently it has been suggested that improved nutrition may slow the progression of the pulmonary disorder.² The impact of this disorder varies from patient to patient and age to age, therefore basic treatment has to be adapted to the needs of the individual.

Alimentary problems

At least 85% of patients have a deficiency of pancreatic secretions and therefore suffer steatorrhoea. The symptoms of steatorrhoea are more pronounced in the early years of life,^{3 4} suggesting the development of a compensatory mechanism later. The nature of this is unknown but possibly pregastric lipase may compensate for the deficiency of pancreatic lipase.⁵ The duodenal juice is reduced in enzymes and volume, is viscid, and has a reduced

bicarbonate content⁶ which may result in a reduced acidification and dilution of the meal as it passes through the duodenum. Protein and fat are unlikely to be completely digested and it has been suggested that there may also be a reduced water secretion⁷ or excessive absorption, all leading to thickening of chyme which in some older patients results in the syndrome meconium ileus equivalent, more recently named distal intestinal obstruction syndrome,⁸ that is unique to cystic fibrosis. This gives rise to acute or chronic abdominal pain with abdominal distension, alteration of bowel habit, and non-tender palpable masses in the right iliac fossa. The symptoms may progress to acute intestinal obstruction.

Persisting frequent stools or poor weight gain, or both, with adequate doses of pancreatin and a restricted fat diet need an assessment of the degree of gastric acidity and the measurement of the pH in the duodenum. In young patients a supplement of sodium bicarbonate at meal times (15 g/m² per day to a maximum of 15 g/day) may adjust the duodenal pH towards normal. In older patients, 200 to 400 mg cimetidine half an hour before meals to allow absorption and so reduce gastric acid output before the pancreatin is taken, allows more effective enzyme digestion.⁹ Lactose intolerance should also be considered, especially in toddlers, and in an occasional patient evidence of cows' milk protein intolerance or coeliac disease has been found on jejunal biopsy.¹⁰

Meconium ileus equivalent is managed conservatively by intravenous fluids and nasogastric suction if necessary. The mucolytic agent N-acetylcysteine is given in a dosage of 5 to 20 ml of 10% solution three times daily by nasogastric tube, and 30 ml in physiologic saline is given as an enema two to three times in 24 hours.¹¹ Gastrografin (meglumine diatrizoate) by enema may be effective in relieving the obstruction and is useful in allowing radiological definition of the site of the obstruction. The symptoms usually resolve in two to three days.

In the chronic type of meconium ileus equivalent (recurring abdominal pain with relative constipation

and non-tender palpable masses in the right iliac fossa), symptoms usually resolve after a phosphate enema and the judicious use of aperients by mouth (Senokot two to four tablets daily). Occasionally N-acetylcysteine, 5 to 10 ml of a 10% solution three times daily for five to seven days, is necessary (taste should be disguised by blackcurrant syrup). Attempts should be made to improve the control of the steatorrhoea as varying the dose of pancreatin is seldom effective.

Nutritional management. The mainstay of the treatment of the pancreatic malabsorption is the administration of pancreatic supplements with food. Pancreatin is available as powder, granules, capsules, and tablets (Table 1) and is taken just before meals. The dose is adjusted to reduce stool frequency and to improve the quality until no further improvement is achieved. Steatorrhoea is seldom controlled by pancreatin alone and reduction of fat in the diet is necessary. This is achieved by the removal of visible fat from meat, avoidance of food with high fat content, that is fried foods, cream, cheese, pastry, chips etc. A partly skimmed milk is given to infants (Table 2). Skimmed milk is recommended when the infant reaches 7 kg in weight. The reduction of fat requires that extra protein and carbohydrate be given to provide sufficient calories; the aim should be to give one and a quarter to one and a half times the calories required for a normal child of the same size.

Nutritious snacks between meals may be an important source of calories and milk shakes or yoghurt with added glucose polymer and fruit flavouring are usually acceptable. Medium chain triglycerides oil has been added to snacks and used

Table 2 *Low fat formula for infants with cystic fibrosis*

120 ml boiled water
2 level scoops standard infant formula feed (8.4 g)
2 level scoops powdered skimmed milk (5.6 g)
2 level scoops Caloreen or one level scoop castor sugar (8.4 g)
content = 70 Kcal

0.5 g Pancrex V powder should be given with this feed—increasing if stools are unformed or frequent. By the age of 1 year, 1.5–2 g of powder should be taken per meal.

for cooking (but has a relatively low flash point and burns easily). It has a little value as a source of additional energy but has no effect on growth rates.¹² Serum concentrations of essential fatty acids are low in cystic fibrosis patients but clinical symptoms are seldom seen. Supplementation with essential fatty acids should be regarded as experimental at the present time.

Elemental diets to supply all nutritional needs have been devised, but are unpleasant to take and socially inconvenient. The clinical status of patients studied has been changed little and there may be an increased risk of deficiency of essential fatty acids and trace elements.¹³

The fat soluble vitamins A, D, E, and K may be inadequately absorbed. Classic signs of vitamin A deficiency are rare. Rickets is practically unknown but it is common practice to give vitamins A and D in twice the normal daily dosage. Vitamin K deficiency is seen in patients with appreciable liver dysfunction or severe steatorrhoea; a dose of 5 to 10 mg is usually sufficient. Neurological signs associated with low concentrations of vitamin E have been reported in a few patients.¹⁴ The need for routine use of this vitamin is still to be established.

Table 1 *Pancreatin preparations (Constituents per g of powder/granules or per tablet/capsule; BP units)*

Preparation	Dosage*	Lipase	Protease	Comment	Cost/week's treatment†
Cotazym	2–6 capsules per meal	14 000	500	Open capsule and mix with apple sauce. Older children swallow capsule.	3.49
Pancrex V powder	0.5–2 g per meal or feed	25 000	1400	Mix with blackcurrant or apple sauce. Do not sprinkle on food.	1.30
Pancrex enteric coated granules	5–10 g per meal	5000	300	Difficult for infants	7.60
Pancrex V capsules (340)	Adjust to equal powder dose	8000	430	Obtainable as 125 mg. Open capsule and mix as powder.	2.20
Pancrex V tablets	5–15 with meals	1900	110	Suitable for children 3–5 years	3.80
Pancrex V Forte tablets	5–10 with meals	5000	300	Older children and adults	4.16
Nutrizym	2–6 tablets with meals	10 000	560	External sugar coating bromelain shell and enteric coated core of pancreatin	5.15
Pancrease‡	2–5 capsules with meals	4000	400	Microspherules in capsules	17.42

¹/₃–¹/₂ dose should be given with snacks for all preparations.

*Dosage stated as used by the author—may exceed manufacturer's recommendations.

†Therapeutic equivalence not implied—price as at June 1984.

‡Only available in UK on named patient basis.

Cost of one week's supply based on 30 tablets of Pancrex V Forte daily.

Pulmonary problems

Mortality and morbidity in cystic fibrosis are generally determined by the severity of the pulmonary involvement—the rate of deterioration varying greatly from patient to patient. In the past 20 years isolation of bacterial pathogens has become less frequent in the younger patients but respiratory symptoms still occur and it seems probable that a virus infection may cause these. There is evidence to suggest that in the presence of viral infection, adherence of *Pseudomonas aeruginosa* to mucosal cells is increased and may cause the bacteria to be more pathogenic.¹⁵ Signs of deterioration in pulmonary status are a change in the character of cough, onset of night cough, increase and thickening of the sputum, and reduction of exercise tolerance. Abnormal physical signs may be minimal, perhaps some increase in the respiratory rate and evidence of intercostal tug. The chest radiograph may show thickening of the bronchial wall pattern and evidence of peripheral blob shadows. Standard spirometry provides useful information and peak flow measurement is easy to perform. Routine blood counts may be unhelpful and a positive blood culture practically unknown.

Management of the pulmonary disorder. This is based on two objectives, firstly to clear secretions from the lungs and secondly to prevent or control infection.

Physiotherapy is the mainstay for clearing secretions in the tracheobronchial tree. Drainage and manual percussion is begun at diagnosis, the technique being taught to and performed by the parents. The forced expiratory technique¹⁶ can be learnt by patients from 5 years of age, but not until 10 to 11 years of age will they be motivated to perform the treatment adequately, without supervision. This technique enables most older patients to be independent but the more severely affected may not have sufficient muscular strength to carry out the treatment effectively. Two or three 20 minute sessions a day are necessary, preferably before meals. Little benefit is gained by extending the length of a session, the frequency being more important. In hospital, five to six sessions should be given in 24 hours. Mechanical percussors may be useful for patients who refuse to treat themselves or allow others to treat them. Physical exercise should be encouraged in all patients and at all ages.

Mucolytic agents taken orally do not increase the clearance of secretions from the lungs. N-acetylcysteine (20%) administered as an aerosol was shown to improve pulmonary function in some studies¹⁷ but others have failed to confirm this. A

small improvement in function after the inhalation of mistabron (sodium 2-mercaptoethane sulphonate) has been shown,¹⁸ but this needs further assessment. The author has found that an aerosol of isotonic or hypertonic saline (7%) for 10 minutes before physiotherapy sometimes aids the clearing of secretions.

Reversible airflow obstruction may occur and an increased bronchial lability has been shown in cystic fibrosis patients.¹⁹ Pulmonary function improves in some patients after the use of bronchodilators. Salbutamol or terbutaline are given in the usual dosage by mouth. Ventolin solution (0.5%) delivered by nebuliser and given for five to 10 minutes before physiotherapy reduces bronchoconstriction. An improved expiratory flow has been shown after the inhalation of ipratropium bromide²⁰ and this drug should be tried if there is no response to beta₂ adrenoceptor stimulants.

There is agreement that antimicrobial drugs should be used in therapeutic dosage and for adequate periods in the treatment of active infection (Table 3) but there are varying views about their prophylactic use. The drug should be chosen in relation to the throat swab or sputum culture; the antimicrobial sensitivities, intolerance, or hypersensitivity of the patient to the drug; and the policy for the use of antimicrobial drugs in the hospital.

Newly diagnosed patients free of respiratory symptoms, with a clear radiograph, and with no pathogenic bacteria cultured from sputum or cough swab, are not immediately started on prophylactic antibiotics, but at the onset of symptoms or a positive culture erythromycin is prescribed. A

Table 3 *Antimicrobial treatment*

Drug	Child dose (to 10 kg body wt)	Adult dose
<i>Oral treatment</i>		
Erythromycin*	25 mg/kg body wt/per dose	1.0–2.0 g/daily
Flucloxacillin	25 mg/kg body wt/per dose	1.0–2.0 g/daily
Amoxycillin†	25 mg/kg body wt/per dose	1.0–2.0 g/daily
Sodium fusidate	20 mg/kg body wt/per dose	1.5–2.0 g/daily
Chloramphenicol	12.5–25 mg/kg body wt/per dose	2.0 g/daily
Co-trimoxazole	Under 5 years 120 mg twice daily 5–10 years 240 mg twice daily Over 10 years 480 mg twice daily	960 mg twice daily
<i>Intravenous treatment</i>		
Carbenicillin	300–400 mg/kg/day in 5–6 divided doses	
Gentamicin‡	5–7 mg/kg/day in 3 divided doses	
Tobramycin‡	5–7 mg/kg/day in 3 divided doses	

*Erythromycin estolate may cause cholestatic jaundice.

†When organisms produce beta lactamases and these are inhibited by clavulanic acid, augmentin can be used in place of amoxycillin.

‡Peak concentration 15 minutes after iv injection should be 8–10 µg/ml and the trough value less than 2 µg/ml.

change to flucloxacillin or admission to hospital may be necessary if there is a poor response. Antimicrobials are not given for less than two weeks and are continued until symptoms have cleared.

Patients diagnosed because of respiratory symptoms, or later at time of severe exacerbation of symptoms, are treated as inpatients. *Staphylococcus aureus* is the pathogen most commonly isolated from patients with mild to moderate pulmonary damage, but occasionally it is *Haemophilus influenzae*. The choice of antimicrobial is flucloxacillin (amoxycillin or co-trimoxazole added if *H influenzae* is present). Poor clinical response to this regimen indicates the addition of sodium fusidate. In some patients the addition of antibiotics delivered by nebuliser may be helpful in reducing secretions and chloramphenicol may be very effective in the severely ill.

P aeruginosa is very frequently present in the tracheobronchial secretions of patients with severe pulmonary damage, sometimes in association with *Staph aureus* or *H influenzae*, or both. Intravenous aminoglycosides and anti-pseudomonas penicillins are given intravenously for 10 to 14 days, occasionally for up to three weeks. It is usual to use paired agents. These intravenous antimicrobials have effect on staphylococcus and *H influenzae*; oral antibiotics are not usually indicated during this treatment. The third generation cephalosporins and ureido penicillins all need evaluation in relation to cystic fibrosis.

Total clearing of the sputum and cough is unlikely in patients with more than minimal lung damage. After hospital discharge, antimicrobials are continued for six to eight weeks, longer during the winter months. Increase in cough, sputum, and breathlessness and a loss of weight are indications for the reintroduction of treatment.

Aerosol antibiotics were introduced nearly 40 years ago by Andersen¹ in the management of infants and young children with established infection with staphylococcus and later as a prophylaxis. The late Dr Winifred Young was convinced of the benefit of this treatment in young children but was not able to prove this scientifically. A double blind cross over trial at the Brompton Hospital²¹ showed subjective and objective benefit in young adult patients with chronic pseudomonas infection. The debate continues on the value of this treatment, but indications for use are the following:

(1) Infants aged under 1 year admitted to hospital with lower respiratory infection should be given aerosol treatment while in hospital. If there is a relapse shortly after discharge, aerosol treatment should be started at home and continued for two to three weeks and the situation should then be reviewed. This treatment is recommended even if the cough swabs are negative.

(2) Patients who develop radiological change on a previously clear radiograph, who have *Staph aureus* on throat swab or in sputum, and who do not respond to anti-staphylococcal drugs. The treatment should be given for two to three weeks at home. Inpatient treatment may be avoided.

(3) Patients with moderately severe pulmonary involvement with a positive culture for pseudomonas: after intravenous treatment they should be discharged home and aerosol treatment given for two to three weeks after which time the situation should be reviewed.

(4) Patients who need frequent admissions with a culture positive for pseudomonas may be given aerosol treatment for two to three weeks with the hope that hospital admission may be delayed.

The antimicrobial most commonly used is gentamicin (Table 4). Carbenicillin is a sticky solution and causes furniture in the room to become tacky. This treatment is time consuming and expensive. It is, therefore, important to review the response and to stop treatment from time to time to determine whether the patient can maintain status quo.

Other respiratory complications. Asthma can occur in cystic fibrosis patients and should be treated in the usual way, although cromoglycate and inhaled steroids may not be effective in the presence of appreciable sputum output. Corticosteroids given orally may be very helpful in a difficult situation.

A few patients develop a mould allergy particularly to *A fumigatus*. This may present with paroxysmal cough, wheeze, and fever. Radiographs show dense homogenous shadows. The peripheral blood has a noticeable eosinophilia and skin testing gives an immediate and delayed reaction to the mould.²² Corticosteroid treatment (prednisolone 1 mg/kg/day) is given for six weeks and then gradually withdrawn. This is combined with intensive physiotherapy and antibiotics.

Haemoptysis is rare in infancy and childhood and in most patients is trivial. Reassurance is necessary and the vitamin K status should be assessed.

Table 4 Nebulised antibiotics

Drug	Dosage*	Frequency of administration
Gentamicin	40–80 mg	Twice daily
Tobramycin	40–80 mg	Twice daily
Colistin sulphomethate sodium	125 000 u to 1 mu	Twice daily
Carbenicillin	0.5–1 g	Twice daily

*These antibiotics are usually dissolved in 2–3 ml water; 2 ml will be nebulised in about 20 minutes; the lower dosage is used in infants; treatment is given after physiotherapy to allow better penetration into the bronchial tree.

Spontaneous pneumothorax is rare in children but if symptomatic intercostal drainage is necessary, air leaks persist for more than a week, or when a second pneumothorax occurs, should be treated by abrasion pleurodesis or pleurectomy.

Other problems

Diabetes. Diabetes is rare before 10 years of age, usually presenting with loss of weight and frequency of micturition. Coma and ketoacidosis are rare. Carbohydrate cannot be severely restricted, and all patients eventually need insulin.

Liver dysfunction. Liver dysfunction causing clinical problems rarely occurs in early childhood and is managed conservatively if possible but surgical intervention may very occasionally be necessary.

Immunisation

At the appropriate age, immunisation against diphtheria, pertussis, tetanus, poliomyelitis, and measles (the usual exceptions and precautions apply) should be given. Before measles vaccination a patient in contact with measles should be given protective immunoglobulin.

Follow up

Regular review in outpatients is very important, most patients being seen at two monthly intervals. This enables patients to recall symptoms and problems accurately and to discuss new anxieties. A short physiotherapy session enables a fresh sputum or throat swab to be sent for culture and the therapist can reinstruct the patient and parents from time to time. The change in character or frequency of cough is important as examination of the chest may show no added sounds, although the volume of sputum has increased. The weight should be plotted and reasons for any deviation sought. Abdominal distension may indicate a change in bowel habit or dietary indiscretions. Determination of peak flow is helpful to monitor early signs of airway obstruction. Radiographs should be taken for assessment every six months.

The attitude of the team treating the patient must be positive without being over optimistic. With parents' groups and various publications, there is a much greater awareness of the complications that can occur and this knowledge may cause stress to some parents: time must therefore be given to allow discussion.

The aim is to enable the child to grow and develop and to have a positive outlook towards the future, even though it is known that the child will eventually die. It is important that the parents are helped to develop a day to day philosophy, not worrying about what is going to happen in a few years and so missing out on the present. The medical team must also be aware that it is easy in this disorder to extend a life into a living death.

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Fifty years ago

Atelectatic or compensatory bronchiectasis

LEONARD FINDLAY (*London*)—*Arch Dis Child* 1935;**10**:61–84

‘... the so-called triangular shadow in the skiagram occupying one or other diaphragmatico-vertebral angle is shown to be caused by encysted effusions, fibrosis of the lung and thickened pleura, pneumonic consolidation, and collapse of the lung. Stress is laid on the re-inflatability of the lung as essential for a diagnosis of pulmonary collapse.’

‘In three personal cases with an accompanying triangular shadow, the bronchie(c)tatic lesion was situated at the right base, was of mild degree, and was completely recovered from. In one the shadow was certainly due to collapse of the lung and it is concluded that this was the cause of the bronchiectasis. In one other case collapse was the probable cause, and in the third case pneumonic consolidation appeared to be the more likely aetiological factor.’

(Leonard Findlay was a noted Glaswegian who early in his medical career worked in Sir Robert Muir’s University Department of Pathology where rickets became his chief interest. After postgraduate work in Germany he started his paediatric career at the Royal Hospital for Sick Children, Glasgow. He was to become the first holder of the Samson Gemmell chair in Medical Paediatrics (later Child Health) there, and was renowned for his powers of clinical observation. He resigned his chair in 1930, and this paper was written while he was working as a physician to the Princess Elizabeth of York Hospital for Children, London.

I seemed to spend a lot of time doing bronchograms in the 1950s. All too many children had gross saccular lesions. Although the pathogenesis of bronchiectasis is now known to include conditions in which the lung’s natural defence mechanisms may be impaired, the prompt treatment of pneumonia with antimicrobial drugs, the decline in pertussis, and in primary tuberculosis in young children with its aftermath of bronchial damage, have all led to a dramatic fall in its prevalence. PAMELA A DAVIES.)