REVIEW SERIES

The pulmonary physician in critical care • Illustrative case 1: Cystic fibrosis

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The case history of a patient with CF admitted to an ICU is presented and the appropriateness of intensive care management for patients with CF is discussed. Issues relevant to the ICU care of patients with CF are highlighted.

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CASE REPORT

A 26 year old man was admitted to the intensive care unit (ICU) on two occasions. Cystic fibrosis (CF) had been diagnosed at 2 months when he was failing to thrive and he was subsequently found to be homozygous for the $\delta F508$ mutation. At 19 years of age his respiratory tract secretions were colonised by *Burkholderia cepacia*. He had recurrent pneumothoraces requiring two surgical pleurodeses. Immediately before his ICU admissions his forced expiratory volume in 1 second (FEV₁) was 31% predicted. He had pancreatic insufficiency at the time of diagnosis and developed diabetes at the age of 23. He also had CF related liver disease, portal hypertension, and oesophageal varices.

He was admitted to the CF centre with a history of increased breathlessness and sputum production with haemoptysis. Intravenous antibiotics were commenced. *Staphylococcus aureus* and *B. cepacia* were cultured in the sputum. On the night after admission he had a massive haematemesis requiring resuscitation, endotracheal intubation, and transfer to the ICU. An emergency endoscopy identified bleeding oesophageal varices that were banded. Bronchoscopic examination showed aspirated blood throughout the bronchial tree. He was successfully weaned from mechanical ventilation and transferred back to a high dependency area. The subsequent inpatient stay was complicated by decompensation of his liver disease and ascites. He also developed *B. cepacia* septicaemia and was eventually allowed to go home almost 1 month after discharge from the ICU.

Three weeks after discharge from the CF centre he presented to his local hospital with haematemesis. After a further episode of haemorrhage, an endotracheal tube and subsequently a Sengstaken-Blakemore tube were inserted. Endoscopy the following day did not suggest variceal haemorrhage, but a bronchoscopy showed blood predominantly in the right bronchial tree. He required a massive blood transfusion and was transferred back to the ICU at the CF centre. Bronchial angiography demonstrated abnormal bronchial arteries in the right upper lobe and some abnormal vessels in the left lower lobe, which were embolised. After a failed extubation, a percutaneous tracheostomy

was inserted. He continued to have episodes of haemoptysis and developed worsening ascites that compromised diaphragmatic function. The ascites did not improve with conservative management and was drained on two occasions. Hyponatraemia developed probably as a result of a sodium containing elemental feed, intravenous antibiotics, and hyperaldosteronism associated with liver disease. A change to a low sodium non-elemental feed in combination with pancreatic enzymes corrected the hyponatraemia. He subsequently developed *B. cepacia* septicaemia and the intravenous antibiotics were changed based on new sensitivities. Gradual weaning from pressure support ventilation was achieved and he was breathing spontaneously via a tracheostomy 25 days after admission. He was transferred to the respiratory ward on day 28 and discharged home 18 days later. He died suddenly after only 12 days at home following what was thought to be a massive haematemesis.

MANAGEMENT OF CF PATIENTS IN THE ICU

Most critically ill patients with CF have end stage disease and intensive care is not considered; however, when the possibility of intensive care arises for individual patients it is often difficult to determine whether this is appropriate. When a patient with CF is admitted to the ICU a number of specialist issues arise—such as the management of haemoptysis, the treatment of infective exacerbations, and nutritional support—which will be discussed below. Close liaison between the CF and ICU teams is required. Non-invasive ventilation of patients with CF has been found to be highly effective, but does not usually occur in the ICU in the UK and will not be discussed extensively here.

Selecting CF patients for ICU care

The selection of patients with CF who are suitable for admission to the ICU is not easy, partly because there are relatively few published data on which to base the decision. One retrospective multicentre study published in 1978 examined the outcomes of 46 patients who developed respiratory failure between the ages of 1 month and 32 years¹; 21 were aged over 15 years. In 35 episodes (69%) the patients died while receiving mechanical ventilation, and only eight patients (16%) survived for more than 6 weeks after discharge. In this small study age did not appear to influence the probability of survival. Another study examined the outcomes of five mechanically ventilated patients under 1 year of age.² All were successfully weaned from mechanical ventilation and discharged home, and were alive 2–6 years later.

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Two more recent studies, one in the USA³ and one in the UK,⁴ have reached somewhat different conclusions. This is partly related to differences in approach and differences in the definition of "survivors".

The US study³ examined the outcomes of 76 adult patients with CF admitted to an ICU at a CF and transplant centre. The difference between UK and USA practice is exemplified by the observation that, of a total of 136 admissions, only 32 episodes required endotracheal intubation and 30 were admitted for antibiotic desensitisation. Thirty three episodes were precipitated by massive haemoptysis and 11 of these patients (73%) were alive 1 year after discharge from the ICU. The authors did not state whether any of these patients required endotracheal intubation, but this seems unlikely as all of the intubation episodes appear to be accounted for by infective exacerbations. There were a total of 65 admissions for infective exacerbations, 32 of which required endotracheal intubation. A total of 71% of the respiratory failure episodes resulted in survival to ICU discharge. This included 15 episodes that did not require any ventilatory support and 18 episodes that required non-invasive ventilation only. Twenty (62%) of the patients who received endotracheal intubation survived to be discharged from the ICU. Two patients were alive without transplantation 1 year after discharge and 10 had successful transplants. Although 17 subjects who were admitted with respiratory failure received transplants and 14 were alive 1 year later, the proportion of the patients who were transplanted from the ventilator and were alive 1 year later was not stated.

The UK study⁴ examined the outcomes of 31 patients with CF admitted over 8 years to the ICU who required endotracheal intubation. In the UK most patients in the ICU require endotracheal intubation, and restrictions on bed availability mean that other patients are cared for in high dependency units or elsewhere. The patients were divided into two groups. The first group included 12 patients admitted on 13 occasions for respiratory failure, either due to aspiration of blood (three episodes) or infective exacerbations. Five subjects (38%) survived to hospital discharge, a figure similar to the American study described above, but only two patients (16%) survived beyond 6 months. The second group included 16 patients admitted to the ICU after surgical procedures on 18 occasions, 16 of which followed surgical pleurodesis. Fourteen of the subjects survived to hospital discharge and 11 (65%) survived beyond 6 months.

What conclusions can be drawn from these studies? It would appear that the outcome in infants requiring mechanical ventilation because of respiratory failure and in patients requiring ventilation after surgical pleurodesis is good. The outcome in patients admitted to the ICU after massive haemoptysis and haematemesis also appears relatively good. The outcome in the patients in the US study³ also appeared favourable with the majority alive at 1 year, although (as mentioned above) it appears that these subjects did not require endotracheal intubation. Although the outcomes of patients with infective exacerbations in the US study appeared favourable, the population studied was different from that in the UK study in that only a minority required endotracheal intubation. In addition, many of the patients receiving mechanical ventilation subsequently had lung transplants, whereas none of the UK patients who were intubated were transplanted. Both the recent UK and US studies found that FEV₁ was not predictive of survival.

The role of transplantation for endotracheally intubated patients remains controversial. Although one study⁵ has documented a 1 year survival rate of 50% in 10 patients who received mechanical ventilation for up to 42 days, many centres do not consider these patients for transplantation. At the Royal Brompton and Harefield Hospitals⁶ only two of five patients who had been intubated and mechanically ventilated survived transplantation, and both survivors were ventilated for less than 24 hours preoperatively. The poorer outcome of

ventilated patients receiving transplants coupled with severely restricted organ availability discourages transplantation in this group. The different ways in which centres prioritise patients for transplantation will also influence whether organs will become available within a reasonable time scale for ventilated patients. In contrast, non-invasive ventilation is well established as a bridging technique to transplantation.

There are probably many reasons for the poor outcome from invasive ventilation in these patients. They usually have severe pre-existing pulmonary disease and may also have associated liver disease. Even with optimal physiotherapy, sputum clearance will be less effective than in a conscious patient who is able to cough effectively and cooperate with physiotherapy.

Reversible factors need to be identified before deciding to intubate and ventilate a patient with CF, and those with end stage disease should not normally receive this form of support. The relative lack of published evidence makes it difficult to make decisions for individual patients and, where possible, both the patient and the family need to be involved in the decision making process. It is only rarely appropriate to ventilate patients with CF who develop respiratory failure, and this is well illustrated by the experience at the Royal Brompton Hospital where only 16 such episodes have occurred over an 8 year period.⁴

Management of massive haemoptysis

Guidelines have been published for the management of massive haemoptysis (>240 ml/day).^{7,8} Medical treatment includes the correction of coagulation defects with vitamin K and fresh frozen plasma. An infective exacerbation is often a precipitant and intravenous antibiotics should be commenced. The affected lung should be kept dependent in an attempt to avoid contamination of the other lung. There is case report evidence for the use of tranexamic acid.⁹ An attempt should be made to localise the site of bleeding. This can be achieved in a number of ways. Many patients experience a sensation of gurgling in a particular part of the chest^{8,10,11} and a recent study has shown that this is a reliable guide.⁸ The chest radiograph may also show unilateral air space shadowing. If doubt remains, bronchoscopy should be performed. Bronchial embolisation is effective⁸ and carries a low risk of complications that include chest pain, dysphagia, bronchial necrosis, bowel ischaemia, and, very rarely, paraplegia.^{10,12,13}

Management of infective exacerbations

Antibiotics should be selected based on the most recent sputum culture. *Pseudomonas aeruginosa* is usually treated with an aminoglycoside in combination with another antipseudomonal antibiotic. Combination therapy is thought to reduce the risk of emergence of resistance. Although a recent study has suggested that monotherapy with tobramycin is effective,¹⁴ it cannot be recommended in the ICU setting. The choice of antipseudomonal antibiotic includes carbapenems such as meropenem, carboxypenicillins such as ticarcillin, ureidopenicillins such as azlocillin, or third generation cephalosporins such as ceftazidime. Piperacillin appears to be associated with febrile reactions in patients with CF¹⁵ and should be avoided. Once daily tobramycin does appear to be effective in patients with CF,¹⁶ but this conclusion is based on a small study and confirmation is required. *Burkholderia cepacia* is usually multiresistant but may be sensitive to chloramphenicol, cotrimoxazole, ceftazidime, temocillin, or meropenem.¹⁷ If the pulmonary pathogen is unknown, antipseudomonal antibiotics should always be given in conjunction with an antistaphylococcal antibiotic such as flucloxacillin. Aminoglycosides have a higher volume of distribution in CF patients than in non-CF individuals so a higher dose is usually required. Monitoring of aminoglycoside drug levels is essential.

Regular physiotherapy is crucial in these patients as they are unable to clear their secretions spontaneously. Whether toilet

Table 1 Common cystic fibrosis related pathologies, complications and principal elements of management in intensive care (for details see text)

CF related pathology	Complication	Management
Lung disease		
Bacterial colonisation of airways	Infective exacerbations	<ul style="list-style-type: none"> • Antibiotics • Physiotherapy • DNase
	Multiresistant pathogens	<ul style="list-style-type: none"> • Antibiotics selected according to sensitivities
	Sputum plugging	<ul style="list-style-type: none"> • Endobronchial suction • Bronchoscopy • DNase
Obstructive lung disease	Difficult ventilation	<ul style="list-style-type: none"> • Bronchodilators
	Prolonged weaning	<ul style="list-style-type: none"> • Tracheostomy • NIV
Other	Haemoptysis	<ul style="list-style-type: none"> • Tranexamic acid • Bronchial artery embolisation
Gastrointestinal disease		
	Pancreatic insufficiency	<ul style="list-style-type: none"> • Pancreatic enzymes • Elemental feed
	Distal intestinal obstruction syndrome	<ul style="list-style-type: none"> • Maintain good hydration • Lactulose • N-acetyl cysteine • Gastrografin enema
Liver disease		
	Coagulopathy	<ul style="list-style-type: none"> • Vitamin K • Fresh frozen plasma
	Thrombocytopenia	<ul style="list-style-type: none"> • Platelet transfusion
	Altered drug metabolism	<ul style="list-style-type: none"> • Careful drug prescribing practice
	Variceal haemorrhage	<ul style="list-style-type: none"> • Variceal banding
Diabetes	Hyperglycaemia	<ul style="list-style-type: none"> • Intravenous insulin
Other		
CF upper airway disease	Sinusitis	<ul style="list-style-type: none"> • Avoid nasal intubation • Antibiotics

bronchoscopy is better than blind endobronchial suction is unknown, but inspection of the bronchi and suction is used when ventilatory problems arise and sputum plugging is suspected.

The role of recombinant human deoxyribonuclease (DNase) is uncertain in ventilated patients. In patients with CF it reduces the frequency of infective exacerbations^{18,19} and has been shown to be safe and effective in those with severe disease.²⁰ However, efficacy is thought to be dependent upon effective sputum clearance which is more difficult in the ventilated patient. The effect of DNase on sputum clearance in ventilated patients has not been studied directly but, when a patient has been receiving DNase before admission to the ICU, it is generally continued.

Tracheostomies and weaning

Weaning patients with CF from mechanical ventilation is frequently prolonged and tracheostomies are often used to facilitate this process. A percutaneous rather than a surgical technique may be preferred for convenience and a lower incidence of complications.²¹ There is limited experience in the use of percutaneous tracheostomies in patients with CF, and it is unknown whether the infected bronchial secretions in these patients predispose to a higher incidence of postoperative infections.

Non-invasive ventilation

As described above, invasive ventilation is associated with poor outcomes. Non-invasive ventilation has therefore been investigated as an alternative and has been shown to be effective in selected cases.^{22,23} It may also be used to facilitate weaning from mechanical ventilation.

Gastrointestinal pathology and liver disease

Early nutritional support should be commenced. An elemental feed may be used or, alternatively, a standard feed with pancreatic enzyme supplementation. In those with liver disease a feed with a low sodium content should be used to avoid hypernatraemia.

Patients with CF who are acutely unwell, especially after surgery,²⁴ are at risk of developing the distal intestinal obstruction syndrome (DIOS); fever, dehydration,²⁵ and opioid analgesia may all contribute. Preventative strategies include the avoidance of dehydration, continuation of pancreatic enzyme supplementation, use of lactulose, and a carefully considered approach to the use of opioids. Treatment options include nasogastric or rectal N-acetyl cysteine, Gastrografin enemas, and intestinal lavage with a balanced electrolyte solution containing polyethylene glycol. Surgery can usually be avoided.

The incidence of liver disease in patients with CF depends on how it is defined, but it may occur in 25% of subjects²⁶ and symptomatic liver disease occurs in less than 5% of cases. Many patients with CF have a small increase in the liver isoenzyme of alkaline phosphatase and γ -glutamyl-transpeptidase but, if these enzymes are raised to more than four times normal, then liver disease is usually present. The presence of liver disease undoubtedly increases the risk of complications occurring during an ICU admission because of an increased risk of bleeding due to thrombocytopenia and coagulopathy. Oesophageal varices may be present. Care should be taken with the use of drugs that are metabolised by the liver or excreted in the bile. Ascites may cause diaphragmatic splinting and may need to be drained to facilitate ventilation.

Diabetes

A significant proportion of patients have CF related diabetes (CFRD). The prevalence appears to increase with age and one study has reported a prevalence of about 15%.²⁷ Tight control of blood glucose levels is associated with improved survival in critically ill non-CF patients.²⁸

CONCLUSIONS

Intensive care is only appropriate for a small number of patents with CF with reversible complications of their disease. Limited evidence is available to help in deciding which patients should be selected for support of organ failures in the ICU and how such patients should be managed. There is a need for more research in this area. A summary of some of the problems that may be experienced is given in table 1. Where possible, severely ill CF patients should be transferred to their CF specialist centre and this will facilitate optimal treatment of their multisystem disease. It is also easier for decisions about continuation of treatment to be made where pre-existing trusting relationships have developed between patients, their relatives, and their clinicians.

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