Liver transplantation for hepatic cirrhosis in cystic fibrosis

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THE HEPATIC LESION IN CYSTIC FIBROSIS

In cystic fibrosis (CF) the primary abnormality in the liver affects the biliary tract cells and results in the production of a reduced quantity of bile with an altered bile acid composition[1,2]. The bile accumulates within intrahepatic ducts causing biliary obstruction, portal tract inflammation and eventually portal tract fribrosis and focal biliary cirrhosis[3]. The quoted prevalence of cirrhosis in CF varies widely from as little as 2% to as much as 25%[4,5]. Most affected children are found within the first 10 years of life to have splenomegaly indicating portal hypertension. The liver, particularly the left lobe, is often also enlarged and firm in texture. Routine liver function tests may be normal or only mildly deranged. Once portal hypertension is established the prognosis is poor: in one large series 20% of the affected children died as a direct result of the liver disease after a mean survival of only 4.5 years[5]. In this and other series there was also an increased risk of death from respiratory failure[4].

TREATMENT

No treatment is yet available which can prevent the development of cirrhosis. In established liver disease the hydrophilic bile salt ursodeoxycholic acid has been shown to improve the liver function tests and nutritional status[6,7], but to date it is not clear whether the progression to cirrhosis is slowed. It has been suggested that children at increased risk for the development of liver disease, such as those presenting with meconium ileus, should receive prophylactic treatment with ursodeoxycholic acid[8].

Other forms of treatment are symptomatic and aim to control the complications resulting from portal hypertension. The following are the most important complications:

Variceal haemorrhage (oesophageal or rectal)
Ascites
Diaphragmatic splinting
Haematological changes of hypersplenism
Malabsorption
Abdominal pain
Portal vein thrombosis
Encephalopathy

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Haemorrhage from varices is the most common, dangerous and frightening of these: the management of acute variceal haemorrhage is reviewed elsewhere[9]. Children with this complication may have to undergo repeated endoscopy and sclerotherapy under general anaesthesia: one of the children we assessed for liver transplantation had monthly sclerotherapy for a year. Variceal bleeding may not be controlled by sclerotherapy and surgical portosystemic shunting may be considered. This procedure may be effective in relieving bleeding but involves a major operation with a significant mortality and morbidity: it also complicates any subsequent attempt at liver transplantation.

Most patients with worsening portal hypertension show progressive decline in pulmonary function. The hepatosplenomegaly and ascites cause diaphragmatic splinting which may result in basal atelectasis and an increased susceptibility to pulmonary infection. The cardiovascular changes of hepatic cirrhosis cause fluid overload and may precipitate heart failure and pulmonary oedema. Rarely, intra-pulmonary shunting may cause cyanosis. Pulmonary function is further compromised by the malnutrition which results from fat malabsorption and increased energy expenditure. An increase in pancreatic supplements is often tried but many children require overnight gastrostomy feeding or even parenteral nutrition. Many patients with severe portal hypertension suffer from abdominal pain. One of many possible causes to be considered is ischaemic gut pain. Reduced or reversed portal venous flow on ultrasound scan is a worrying sign and suggests a risk of portal vein thrombosis. This complication can be devastating and result in intestinal infarction.

LIVER TRANSPLANTATION

Liver transplantation offers the only potentially curative treatment for portal hypertension and its complications. In patients with CF liver transplantation alone was in the past considered unlikely to be successful because there was concern: first, that the lung problems would increase the immediate risk of the operation; and, secondly, that the postoperative need for immunosuppression would result in an increase in pulmonary infection. In addition, there was uncertainty on how to judge the optimum timing of this major procedure: as hepatocellular failure is rare and routine

liver function tests are normal or only mildly deranged, the severity of the liver problem can be underestimated. Some complications which can result from portal hypertension, particularly worsening pulmonary function and nutritional state and episodes of abdominal pain, tend to be attributed to the respiratory and pancreatic dysfunction of CF rather than the hepatic cirrhosis.

The published data on the outcome of liver transplantation in patients with cirrhosis complicating CF is encouraging. Medium-term survival rates for patients with mild to moderate lung disease ranged from 70% to 100%[10–12], and no increase in respiratory infections on immunosuppression was seen, indeed in the majority of patients respiratory function improved.

Heart–lung–liver transplantation should be considered for patients with hepatic cirrhosis and severe, irreversible pulmonary disease. Two adult patients with CF have received triple transplants at Papworth Hospital and one has survived for 6 years (unpublished data). However, the average waiting time for a triple graft is 1 year and patients may wait over 2 years: up to half the patients die while waiting for a suitable graft. One young adult who was initially waiting for triple transplantation finally received a liver graft alone as he was unlikely to survive a wait of several further months. Following liver transplantation his respiratory function improved so dramatically that he is no longer considered a candidate for lung transplantation. For children triple transplantation does not provide a realistic option mainly because of the shortage of suitable organs.

ASSESSMENT FOR LIVER TRANSPLANTATION

Indications for liver transplantation

We have devised a simple scoring system which can be used as a guide to indicate when a child should be referred to a transplant unit for consideration of liver transplantation (Table 1). As all patients with significant portal hypertension have splenomegaly, liver transplantation need not be considered if this finding is absent clinically and ultrasonographically. The scoring system includes indices of the severity of the portal hypertension (frequency and severity of variceal bleeding, ascites), of hepatic synthetic function (albumin value and prothrombin time), of haematological signs of hypersplenism (low white cell count and platelet count) and of nutritional status. A score of 10 or more suggests that the child should be referred for assessment for liver transplantation. In 11 children who were accepted for liver transplantation the scores ranged from 18 to 34 (median 24).

Assessment of hepatic function

The 11 children accepted for transplantation had routine liver function tests that were normal or only mildly deranged (Table 2). Further investigation is therefore needed to define the severity of portal hypertension and the presence of any other complications associated with hepatic cirrhosis (Table 3). Doppler ultrasound of the portal vein may demonstrate a small portal vein diameter with intermittent or reversed blood flow, indicating high portal pressure with a risk of portal vein thrombosis. One of the

Table 1 **Score indicating need for liver transplantation assessment. A score of 10 or more indicates the need for assessment for liver transplantation**

Indication		*Score*	
Portal hypertension	*Splenomegaly* must be present*		
	Varices present	4	Only one is scored!†
	Variceal bleed requiring blood transfusion once or twice	8	
	Variceal bleed > twice or single lifethreatening bleed‡	10	
	Ascites	6	
Hepato-cellular function	Albumin < 30 g/l	2	
	PT > 19s	2	
Hypersplenism	WBC < 4×10^9/l	2	
	Platelets < 100×10^9/l	2	
Nutrition	BMI < 16§	6	
	MAC < 5th%ile¶	6	

*Splenomegaly should be assessed by ultrasound scan if not present clinically
†Patient in shock or requiring transfusion of 20 ml/kg or more
§BMI=body mass index (see Ref 13)
¶MAC=mid-arm-circumference (see Ref 14 which contains the table of 5th and 10th centiles)

Table 2 **Routine liver function tests of 11 children accepted for transplantation were normal or mildly deranged**

	Median	Range	Normal Range
Bilrubin (μmol/l)	21	7–42	2–17
ALP(U/l)	303	110–604	30–135
ALT (U/l)	53	22–105	7–40
Albumin (g/l)	31	17–34	30–51
PT (s)	18.7	15–30	12–16
WBC ($\times 10^9$/l)	3.5	1.8–16.4	4.5–13.5
Plt ($\times 10^9$/l)	60	42–156	150–450

patients we assessed had this worrying sign and in addition had painful arthropathy of the large joints and cyanosis secondary to intra-pulmonary shunting.

Assessment of gastrointestinal function and nutrition

Five of the children accepted for transplantation had meconium ileus at birth. Four of these had required resection of part of the small intestine (in one child one-third of the small bowel was removed) and temporary ileostomies. Abdominal pain, constipation and episodes of distal intestinal obstruction (DIOS) occurred in six of the children and appeared to worsen with progressing portal hypertension. One 16-year-old girl had become opiate dependent because of constant severe abdominal pain for which, despite numerous endoscopic and radiological investigations, no definite cause could be found. The pain resolved completely by 10 weeks following transplantation.

All the children who were listed for transplantation were undernourished (Table 4). In the presence of gross organomegaly and ascites the weight is not an accurate measure of nutrition. The weights in the 11 children ranged from well below the third to the 75th centile (median eighth centile), but the mid-arm-circumference (MAC) was less than the fifth centile in all (Table 5)[13]. Fat malabsorption was present in six of the children and four received high strength enzyme preparations with a daily intake of lipase (average 33.427 units lipase/ kg/day) higher than recommended[15] (Table 4). The child with the highest daily lipase intake (Patient 5) developed a haemorrhagic colitis probably as a direct result of the enzyme dose. In children with CF related cirrhosis steatorrhoea is only in part due to pancreatic insufficiency and may not be improved by an increase in pancreatic enzyme intake. Five children required supplemental feeds, two were given overnight gastrostomy feeds and three who were awaiting transplantation urgently were started on total parenteral nutrition (TPN) because of recurrent vomiting.

Table 3 **Indices of portal hypertension and hepatic function in the 11 children accepted for transplantation**

Varices present	11
Variceal bleeding	7*
Ascites	10
PV diameter < 6mm	3
Reversed PV flow	1

*Two children had bled eight times each. PV=Portal vein

Table 4 **Indices of nutritional status**

Patient	Sex	Age	Weight (%)	Height (%)	MAC (%)	Lipase U/kg/day
1	F	14.3	≪3	3	<5	7385
2	M	11.5	75	75	<5	7385
3	M	14.0	50	70	<5	4900
4	F	8.4	60	97	<5	22727*
5	M	5.8	10	25	<5	73765*
6	F	16.4	≪3	3	<5	19286*
7	M	19.0	10	5	<5	17931*
8	F	12.9	3	≪3	<5	5000*
9	F	13.4	20	50	<5	5263*
10	F	15.8	8	25	<5	8000
11	F	13.0	<3	3	<5	6824

*Patients with fat malabsorption
MAC=Mid-arm circumference

ASSESSMENT OF RESPIRATORY FUNCTION

Hepatic cirrhosis has adverse effects on respiratory function. These may include intrapulmonary shunting, pulmonary oedema, pulmonary hypertension from fluid overload and diaphragmatic splinting from organomegaly and ascites. In children with CF respiratory function is likely to be particularly badly affected as the diaphragmatic splinting impairs effective coughing and chest physiotherapy and thus predisposes to mucous plugging and infection. In five of the children accepted for transplantation respiratory function had deteriorated over the previous 6 months (Table 6) with more and thicker sputum and increasing breathlessness. In three of the children the standard respiratory function tests had dropped by 30% to 50% over the past year and from one to six courses of intravenous antibiotics had been given for exacerbations of pulmonary infection. One child had become cyanosed due to an intra-pulmonary shunt of 35%. Two children had been assessed elsewhere but considered unsuitable for liver transplantation, and one child was receiving palliative terminal care in a local hospice.

After the good outcome of transplantation in the first five children transplanted for hepatic cirrhosis we assessed and

Table 5 **Fifth and tenth centile of upper arm circumference (mm) for boys and girls (see Ref 14)**

	Boys		Girls	
Age (years)	5 centile	10 centile	5 centile	10 centile
1–1.9	142	146	138	142
2–2.9	141	145	142	145
3–3.9	150	153	143	150
4–4.9	149	154	149	154
5–5.9	153	160	153	157
6–6.9	155	159	156	162
7–7.9	162	167	164	167
8–8.9	162	170	168	172
9–9.9	175	178	178	182
10–10.9	181	184	174	182
11–11.9	186	190	185	194
12–12.9	193	200	194	203
13–13.9	194	211	202	211
14–14.9	220	226	214	223
15–15.9	222	229	208	221
16–16.9	244	248	218	224
17–17.9	216	253	220	227
18–18.9	245	260	222	227
19–24.9	262	272	221	230

accepted children with poorer lung function (FVC (forced vital capacity) and FEV_1 (forced expiratory volume in 1s) 30%–50% predicted). Routine lung function tests are effort dependent and so reflect poorly the extent of pulmonary disease in children with diaphragmatic splinting and malnutrition. The aim of the assessment is to establish whether reduced respiratory function is caused by irreversible parenchymal lung disease or whether it is secondary to the effects of portal hypertension, and thus potentially reversible following successful transplantation. In addition to routine lung function tests further investigation is used to indicate irreversible lung damage such as extensive fibrosis or severe pulmonary hypertension. Useful investigations include blood gas measurement, chest radiography and computed tomography[16], electro and echocardiography, intrapulmonary shunt measurement by isotopic lung perfusion scan[17] and repeated bacterial, fungal and viral cultures of sputum. If these investigations suggest that liver transplantation alone is contraindicated, a heart-lung liver transplant offers the only prospect for survival. The following are the contraindications to liver transplantation without heart-lung transplantation:

1 Longstanding history of severely compromised lung function with frequent exacerbations of pulmonary infection
2 Colonization with *Pseudomonas cepacia* or other multi-resistant organisms
3 Raised resting arterial pCO_2
4 Extensive fibrosis on chest computer tomography
5 Evidence of severe pulmonary hypertension with right ventricular dysfunction

The medium-term results for heart–lung transplantation are less good than for liver transplantation alone[18–20] and triple transplantation has seldom been attempted because of the technical problems and the difficulty finding suitable donor organs.

PREOPERATIVE CARE

Pulmonary function and nutrition should be improved as much as possible. Chest physiotherapy should be intensified and active pulmonary infection treated aggressively with intravenous antibiotics. Children with sticky pulmonary secretions benefit from nebulized DNase[21] which eases bronchial lavage. Most children are poorly nourished and

Table 6 **Indices of respiratory function at assessment in the 11 children accepted for transplantation**

	Range	Median
FVC % predicted	40–102	73
FEV_1 % predicted	30–90	63.5
O2 saturation (%) in air	82–98	94.5
pC02	3.5–4.9	4.5
Sputum cultures		
Pseudomonas aeruginosa	8	
Staphylococcus aureus	6	
MRSA	1	
Aspergillus	3	

FVC=forced vital capacity; FEV_1=forced expiratory volume in 1s; MRSA=methicillin-resistant *Staphylococcus aureus*

Table 7 **Peri-operative details of the nine transplanted children**

	Median	Range
Waiting time (days)	52.5	2–90
Duration of surgery (hours)	6	4–8
Blood loss (ml/kg)	86	12–223
In children with previous surgery (*n*=5)	159	86–223
In children without previous surgery (*n*=4)	44	12–58
Operative problems		
Splenectomy necessary in one child		
Dense adhesions (children with previous surgery) in two children		
Small portal vein size (4, 5, 6 mm) in three children		

require supplemental feeding; some develop recurrent vomiting and require TPN.

There is a chance that a greatly enlarged spleen may have to be removed at operation so we recommended that children are vaccinated with Hib and Pneumovax vaccine before acceptance for transplantation.

OPERATIVE PROBLEMS

The waiting time for a suitable organ is unpredictable (Table 7) but in our programme high priority patients generally wait for less than 3 months. As most children are in the older age group, organ shortage is less of a problem than in infancy and there is a good chance that a size matched organ will be offered in time.

From the surgical point of view, children with CF belong to a relatively low risk operative group. Many children have not had previous abdominal surgery and removal of the diseased liver is therefore rarely complicated by the presence of dense adhesions. An important practical point is that the biliary anastomosis should be fashioned between the donor common bile duct and a Roux loop, thus removing the recipient's biliary tree entirely. A high incidence of biliary strictures and leaks occurred in patients in whom a duct to duct anastomosis was used. It is possible that the collagen deposition around bile ducts and ductules and biliary cell necrosis as described by Lindblad[22] is responsible for poor healing at the biliary anastomotic site.

From the anaesthetic point of view the extent of pulmonary disease is of concern. A session of chest physiotherapy and bronchial lavage in the intubated patient before surgery can be beneficial. The extent by which abdominal distension impairs pulmonary function often becomes obvious when the abdomen is opened: in some patients a dramatic improvement in oxygenation and CO_2 exchange occurs once the diaphragmatic splinting is relieved.

POSTOPERATIVE CARE

The postoperative care of children transplanted for CF is in most respects similar to that of children transplanted for primary hepatic indications but extra attention needs to be paid to pain relief, the chest, bowel function and nutrition. It is clearly most important to prevent serious pulmonary infection during the early postoperative phase. Intravenous antibiotics, chosen to cover the child's current pulmonary organisms, are given until the child is out of bed and mobile. Children with positive aspergillus serology or aspergillus on culture are also given intravenous amphotericin in a dose of 1 mg/kg or oral itraconazole. Vigorous physiotherapy and inhalation of DNase are restarted immediately postoperatively. Effective chest physiotherapy following major surgery may be too painful to be tolerated and two children have had epidural catheters with good pain relief. We would use this technique more frequently if there was not concern over the risk of bleeding complications.

Table 8 **Early postoperative complications in the nine patients**

Pneumonia	6
Biliary stricture ± leak	4
Acute rejection	1
Prolonged ascites	2
CMV hepatitis (reactivation)	1
DIOS	1
Tacolimus toxicity	2

CMV=Cytomegalovirus; DIOS=distal intestinal obstruction

Postoperative ileus is universal following liver transplantation but usually resolves after 2 to 3 days. Children with a tendency to DIOS must be observed carefully for intestinal obstruction and it is our practice to give enteral acetylcysteine or small volumes of gastrografin as soon as bowel sounds return. It is important to restart enteral feeding as soon as possible with sufficient enzyme supplements. During the process of adjusting the amount of pancreatic enzyme, poor absorption of oral cyclosporin, which is fat soluble, may result in low or unstable levels. Large daily doses (up to 30 mg/kg/day) may be needed to achieve therapeutic levels. We now prefer to use Neoral, which is a recently licensed micro-emulsion of cyclosporin, or the other newly licensed immunosuppressant, tacrolimus, which is very well absorbed.

POSTOPERATIVE COMPLICATIONS

In comparison with children transplanted for other indications we have seen an increased incidence of postoperative pneumonia and biliary complications in children with CF (Table 8). Six of the nine children developed symptoms and radiographic changes of pneumonia, requiring treatment with intravenous antibiotics, and two children had to be reventilated. One girl was ventilated for 42 days and required a tracheostomy. However, the median duration of ventilation, only 2 days, did not differ from children transplanted for other reasons.

Of the nine children transplanted, biliary problems occurred in four, all of whom had a duct to duct biliary anastomosis. Two children developed strictures at the site of the anastomosis and the other two had biliary leaks as well as a stricture. In two children the biliary tract was revised to a duct to Roux loop. The third patient had a successful percutaneous balloon dilatation and the fourth had a stent inserted endoscopically. We hope that most biliary problems will be avoided in the future by using a duct to Roux biliary anastomosis in all children with CF receiving transplants. The other complications that occurred were all typical early

postoperative problems (Table 8). The hospital stay ranged from 15 to 62 days with a median of only 27 days.

OUTCOME

All nine transplanted children were alive from 4 to 55 months (median 30 months) following transplantation. Since the preparation of this manuscript two further children with CF have received liver grafts and were doing well 3 weeks postoperatively. With good graft function portal hypertension is relieved and malabsorption, nutrition and respiratory function all improve rapidly.

Liver function remained normal in eight children but one boy required retransplantation 14 months later for chronic cholestasis and a giant cell hepatitis of unknown cause. Unfortunately, his second graft also shows evidence of a chronic hepatitis. In all the children the spleen regressed in size and none has suffered variceal bleeding since transplantation.

Gastrointestinal function and nutritional status improved in the majority. The symptom of recurrent abdominal pain, which had been present in six children, also largely resolved. The girl who had become opiate dependent because of constant severe abdominal pain was able to be weaned from systemic and oral opiate medication. Fat malabsorption improved rapidly and it was possible to reduce the daily intake of pancreatic enzyme by an average of 60%.

We were initially surprised to find that respiratory function remained stable or improved. All patients reported subjective improvement as indicated by decreased cough and sputum production and less breathlessness with physical activities. The need for intravenous antibiotics to treat chest infections was reduced and lung function scores for FVC and FEV_1 improved or remained stable in eight of the children: only one 19-year-old girl showed a 20% reduction 4.5 years following transplantation (Figures 1 and 2). The child who had been cyanosed at assessment due to intrapulmonary shunting gradually improved and was pink in air 6 weeks following transplantation.

POSSIBLE REASONS FOR THE IMPROVEMENT IN RESPIRATORY FUNCTION

When a cirrhotic liver is replaced the adverse effects on lung function, such as diaphragmatic splinting, pulmonary oedema and intrapulmonary shunting, are corrected. In addition immunosuppressive therapy may have a specific beneficial rather than a detrimental effect on lung inflammation. At the European Cystic Fibrosis Conference in Madrid in 1993 a patient was presented whose pulmonary function scores rose markedly following renal transplantation and immunosuppression with cyclosporin. A number of studies have recently highlighted the beneficial effects of steroidal and non-steroidal antiinflammatory drugs on pulmonary function[23,24].

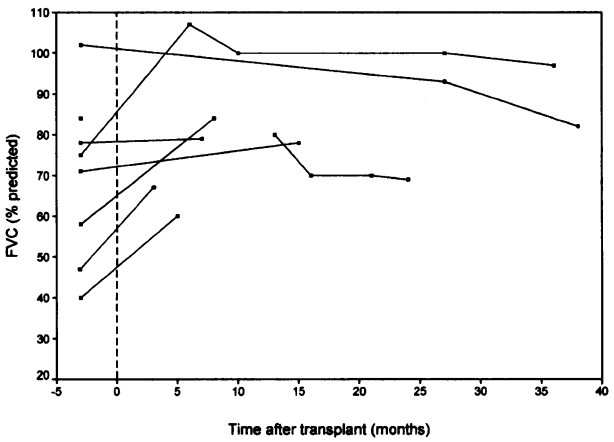

Figure 1 **Graph showing forced vital capacity (FVC; percentage predicted) before and after transplantation**

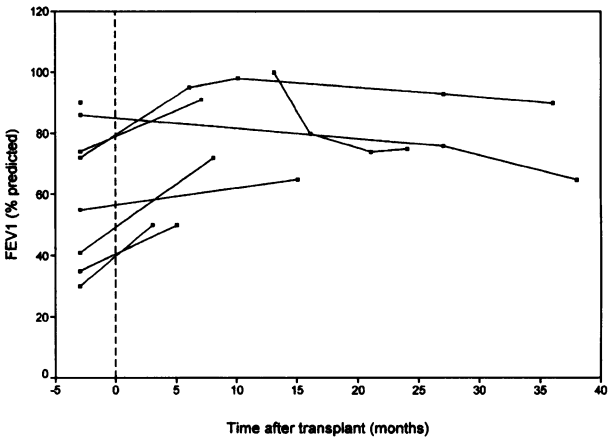

Figure 2 **Graph showing forced expiratory volume in 1s (FEV_1; percentage predicted) before and after transplantation**

SUMMARY

About 10% of children with CF develop hepatic cirrhosis and progressive portal hypertension. As the portal hypertension worsens these children are likely to develop serious variceal bleeding and other complications including malnutrition and a decline in respiratory function. Indices of lung function may fall as much as 50% in a year and chest infections may require frequent admissions to hospital. The respiratory symptoms are often attributed to CF related lung disease and affected children may therefore be considered unsuitable for liver transplantation. We propose a simple scoring system which can help to select patients who should be referred for assessment of liver transplantation.

After careful assessment and preparation children with lung function indices as low as 30% predicted can have a successful outcome after liver transplantation. With good

graft function portal hypertension is relieved and absorption, nutrition and respiratory function all improve. The improved quality of life of these children is remarkable.

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