Liver transplant

Liver transplantation is the only potentially curative treatment available for liver cirrhosis. In spite of early concerns about the outcome of the procedure in patients with CF, and the effects of immunosuppression on respiratory infections, successful liver transplantation has been consistently reported. Current indications for isolated liver transplantation include progressive liver failure or intractable variceal bleeding with mild pulmonary involvement (Debray et al, 1999; Lamireau et al, 2006).

The difficult problem of choosing the optimal time for liver transplantation in CF has been the subject of considerable debate (Jonas et al, 2005). Evaluation should not be delayed until signs of hepatic decompensation occur (Noble-Jamieson et al, 1996; Bond et al, 2000; Genyk et al, 2001). Transplantation before severe decompensation is the strategy at most centres. Some authors have suggested a scoring system that might be useful to help decide the timing for liver transplantation (Noble-Jamieson et al, 1996). The system is heavily weighted towards variceal bleeding as a positive indication. Gooding et al examined the need for transplantation in a group of patients with variceal haemorrhage (Gooding et al, 2005). Their cohort of 18 patients, managed with sclerotherapy, banding and/or shunts, had virtually the same survival as sex and age-matched CF controls without liver disease. The authors suggested that liver transplantation should be limited to those patients with true evidence of hepatocellular dysfunction and failure, and not simply for the management of portal hypertension.

A recent poll among European centres (Melzi et al, 2006) reported information obtained on 57 patients transplanted between 1990 and 2001. Median age at time of liver transplantation was 12.2 years, with a greater prevalence of males (74%). It is interesting that the mean age of liver transplant did not change significantly between 1990 and 2001. In the same report the first indication for transplant was liver failure (64%), followed by hypersplenism (16%), gastrointestinal bleeding (12%) and malnutrition (8%).

An FEV₁ in the vicinity of 70% has been suggested as indicating satisfactory lung function in a transplant candidate (Genyk et al, 2001). Some authors have reported successful isolated liver transplantation in patients with an FEV₁ as low as 35% predicted and a 10-25% sustained improvement in lung function following transplantation (Noble-Jamieson et al, 1996). Mortality, however, is significantly higher in patients with a six month pre-transplant FEV₁ <40% predicted (Melzi et al, 2006).

Improved survival statistics with a long term survival of 75% and better suggest that isolated liver transplantation is a viable treatment option (Mack et al, 1995; Noble-Jamieson et al, 1996; Bond et al, 1999; McClean et al, 2003). The most recent review reported a one and five year survival of 91.6% and 75% respectively in 12 patients with a mean age at transplant of 10.3 years (Fridell et al, 2003).

Patient and graft survival in CF is comparable to that of liver transplants performed for other indications without associated lung disease (Fridell et al, 2003). Late mortality is generally related to progression of pulmonary disease. Improved survival of paediatric compared to adult patients has been reported and probably reflects the natural history of CF (Bond et al, 1999; Bond et al, 2000).

An improvement in nutritional status and pulmonary function following liver transplantation has been uniformly reported (Mieles et al, 1989; Noble-Jamieson et al 1994; Mack et al, 1995; Urgelles et al, 2001; Milkiewicz et al, 2002; Colombo et al, 2005). In the latter study a significant improvement in BMI, fat-free mass and bone mass was observed in patients following liver transplantation. Several factors account for the improvement in lung function seen post transplant; improved diaphragm function with removal of organomegaly and ascites, reversal of intrapulmonary shunting, better nutrition and post-operative immunosuppression inhibiting the inflammatory process in the airways.

One of our adult patients remains well 16 years following isolated liver transplantation.
Liver and lung transplantation

Combined transplantation of the lungs and liver is an infrequently performed operation in patients with CF. It is indicated for end-stage lung and liver disease when single organ transplantation is precluded by severe disease in the other organ system. It is estimated that 3% of patients requiring consideration for lung or heart-lung transplantation for end-stage lung disease will have impaired synthetic liver function and portal hypertension severe enough to preclude isolated thoracic organ transplantation. No single centre has accumulated significant experience of performing this complex operation.

Survival data for combined liver-lung transplantation is now very encouraging. In a case series of nine patients with CF from Cambridge actuarial survival at one and five years was 55.6% and 44.4% respectively (Praseedom et al, 2001). Couetil and colleagues achieved one and five year actuarial survival rates of 85.7% and 64.2% respectively (Couetil et al, 1997). The United States experience of combined lung and liver transplantation (Barshes et al, 2005) reports eleven patients who underwent combined transplantation between 1987 and 2004. Median age at the time of transplantation was 15 years (range 12-30 yrs), and pre-operative FEV1 30% predicted (range 18-38%). Survival analysis demonstrated a one and five year survival of 79% and 63% respectively, which is comparable to survival data for isolated liver transplantation (83% and 71% respectively) and isolated lung transplantation (78% and 59% respectively) in the United States.

It has been suggested that combined liver-lung transplantation may offer an immunological advantage with a lower incidence of acute lung rejection compared to isolated lung transplantation (Praseedom et al, 2001; Kotru et al, 2006; Faro et al, 2007). In the study by Kotru lung rejection rates of 0.2/patient/year in patients receiving lung-liver transplants were significantly lower than 0.8/patient/year for isolated lung transplant (p=0.001). In addition, no cases of bronchiolitis obliterans were reported for lung-liver recipients in the 36-104 month follow-up. These findings were confirmed in the study by Faro et al who demonstrated a lower incidence of both acute rejection (p=0.025) and bronchiolitis obliterans (p=0.02) post lung-liver transplantation (Faro et al, 2007) compared to isolated liver transplantation.

Long waiting times are a problem for combined lung-liver transplant candidates with mean waiting times for isolated liver and lung-liver recipients of four and 13 months respectively reported (Kotru et al, 2006).

There is a need for additional studies to better identify the specific indications for combined lung-liver transplantation, although current survival data is very promising.

Liver and pancreas transplantation

At least 85% of patients with CF have pancreatic exocrine insufficiency and at least 34% develop CFRD (Costa et al, 2005). Cystic fibrosis related diabetes leads to pulmonary decline (Koch et al, 2001) and a six-fold increase in mortality (Moran et al, 2001). In addition, 15% of recipients of isolated liver transplantation develop diabetes due to the immunosuppressive regimens used (Marchetti et al, 2005). Patients with CF and pancreatic insufficiency are thus at increased risk of developing diabetes post transplant, and those who already have CFRD may have worsening of their glycaemic control and increased mortality.

There have been several case reports of successful combined liver-pancreas transplants for children with CF, including four patients who received en bloc liver-pancreas transplants (Stern et al, 1994; Fridell et al, 2005; Young et al, 2005; Mekeel et al, 2007). The en bloc technique is a simpler operation and does not require any biliary anastomoses, reducing the risk of biliary complications. In addition to an improvement in liver function and resolution of portal hypertension, no patient has required insulin or pancreatic enzyme supplementation post surgery. Patient and graft survival is equivalent to that of isolated liver transplantation, with no increase in complications. In a recent series of three patients with CF who received combined liver-pancreas transplantation, one and five year survival was 100% (Mekeel et al, 2007).

There are no case reports that describe a downside to combined liver-pancreas transplants, but this may represent a reporting bias.

Liver and small intestine transplantation
There is one case report in the literature of a successful combined liver and small intestine transplant in a child with CF (Fridell et al, 2003). The seven month old boy presented with short-gut syndrome after multiple bowel resections for meconium ileus and progressive liver failure from intravenous hyperalimentation. Post-operatively the child has not had any episodes of rejection. He requires pancreatic enzyme supplementation but has not developed diabetes.

**Key points**

• Current indications for liver transplantation include progressive liver failure or intractable variceal bleeding with mild pulmonary involvement

• Increased surveillance is required in patients with CFLD

**References**


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