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**Title:**

Combined liver and pancreas transplantation in two children with cystic fibrosis – first experience in Australia and New Zealand

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**Authors' contributions:**

Sahana Shankar and Rishi Bolia: Drafted the initial manuscript;

Helen Evans and Mark Oliver: Designed the study;

Sahana Shankar, Rishi Bolia, Alexandra Hodgson, Jonathan Bishop and Helen Evans: Collected the data; Alexandra Hodgson, Jonathan Bishop, Helen Evans and Mark Oliver: Reviewed and revised the manuscript;

Mark Oliver: Critically reviewed the manuscript.

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**Abbreviations:**

CF – Cystic fibrosis

CFLD – Cystic fibrosis related liver disease

CFRD- Cystic fibrosis related diabetes mellitus

PERT – Pancreatic enzyme replacement therapy

LFT- Liver function test

AMR – Antibody-mediated rejection

IVIG – Intravenous Immunoglobulins

## Introduction

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The improved survival of patients with cystic fibrosis (CF) has been associated with an increased incidence of clinically significant extrapulmonary complications. Cystic fibrosis–related liver disease (CFLD) is the third-leading cause of mortality in CF. Abnormal CFTR function in the apical membrane of the biliary epithelium leads to decreased bile fluidity and alkalinity, resulting in a sequence of inspissated bile accumulation, inflammation and progressive fibrosis. The spectrum of hepatic involvement ranges from hepatic steatosis (20-60%), to focal biliary cirrhosis (11- 70%) and multi-lobar cirrhosis (5-10%).[1,2] In patients with liver failure or complications of portal hypertension, liver transplantation is the treatment of choice.[3] Majority of patients with CFLD are exocrine pancreatic insufficient and 18 to 20% patients have CF related diabetes mellitus (CFRD) at the time of liver transplantation.[3,4] Simultaneous transplantation of the pancreas in CF patients receiving liver transplantation could potentially improve nutritional status and glycaemic control, thus impacting long-term post-transplant survival. However, combined liver-pancreas transplantation is not routinely performed and only 17 cases of combined liver–pancreas transplantation in CF patients have been reported from 1987 – 2014 according to UNOS data. According to an international survey of pediatric transplant units, eight cases of combined liver-pancreas transplantations have been reported in children with CF from 1995-2011.[5]

We report the first patients with cystic fibrosis from Australia and New Zealand who underwent combined liver and pancreas transplantation.

**Case report**

Patient # 1

An 11-year-old boy presented with a short history of lethargy, abdominal distension, epistaxis and bruising. Clinical examination revealed splenomegaly and subsequent investigations confirmed presence of liver cirrhosis with portal hypertension. Further investigations confirmed the diagnosis of CF (Table 1). The neonatal screening for CF as per the national screening programme had been normal. He was exocrine pancreatic insufficient and was commenced on pancreatic enzyme replacement therapy (PERT). He was euglycemic

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and had preserved lung function at the time of diagnosis (Table 1). Over the subsequent years, he developed worsening portal hypertension with growth faltering and pubertal delay. At the age of 14, he developed CF-related diabetes and was commenced on insulin. He underwent assessment for combined liver pancreas transplant in view of advancing portal hypertension with recurrent epistaxis, poor nutritional status and pubertal delay. The patient underwent a deceased donor whole liver transplant with roux-en-Y anastomosis and heterotopic implantation of pancreatic allograft with enteric exocrine drainage (donor duodenum to recipient proximal jejunum) and systemic venous drainage (portal vein to inferior venacava). He received induction therapy with basiliximab and triple immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil. He required insulin infusion in the immediate post-operative period to ensure normoglycaemia, but this was discontinued on day 5 post-transplant. By day 5, he had achieved a normal stool elastase of > 200 microgram/g of stool having previously had undetectable levels. He had no vascular or biliary complications or episodes of acute cellular rejection. At 2.5 years post-transplant, he has normal liver function tests with resolution of portal hypertension and is independent of insulin and pancreatic enzyme supplementation (Table 1).

Patient # 2

Patient 2 was diagnosed with CF (Table 1) and pancreatic insufficiency at 2 years of age when he was investigated for recurrent pneumonias and failure to thrive. He had had a normal newborn screening for CF. At around 6 years of age, he was diagnosed with CFLD when noted to have hepatomegaly with mildly deranged liver function tests (LFT) and a coarse, heterogeneous liver on ultrasound. He was commenced on insulin at 10 years of age after being diagnosed with CFRD. The liver disease progressed to significant portal hypertension by the age of 11 years requiring prophylactic variceal banding. At the age of 14, he was started on the novel drug Ivacaftor. A year later, he had an acute decompensation with development of diuretic-refractory ascites requiring regular paracentesis and albumin infusions. Labile glycaemic control, contributed partly by poor compliance, prompted initiation of an insulin pump. He was listed for combined liver-pancreas transplantation due to worsening portal hypertension, poor nutrition and brittle diabetes. He had renal dysfunction and poor lung function, however renal and lung

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transplantation were not indicated (Table1). He underwent a deceased donor whole liver transplantation with duct-to-duct anastomosis and heterotopic implantation of pancreatic allograft in the pelvis with systemic venous drainage (portal vein to Inferior venacava) and proximal enteric exocrine drainage (side to side anastomosis of the donor duodenum to recipient jejunum). He received basiliximab for induction and tacrolimus, mycophenolate mofetil and prednisolone for maintenance. His immediate post-operative course was complicated by possible antibody-mediated rejection (AMR) of the pancreas on day 5 which was treated with plasmapheresis, hemofiltration and intravenous immunoglobulin (IVIG) infusion. Although a pancreatic biopsy was not obtained, it was presumed to be AMR due to the presence of high titres of donor-specific antibodies pre-transplantation. He received monthly IVIG infusions for 6 months following transplantation. He had a prolonged hospital stay due to multi-drug resistant gram-negative sepsis and renal dysfunction with hyperkalemia requiring a period of hemofiltration. He had normal exocrine and endocrine function at the time of discharge 5 weeks after transplantation. At 12 months post-transplant, he remains euglycemic and pancreatic sufficient with resolution of portal hypertension and improvement in lung function (Table 1).

**Discussion**

Exocrine and endocrine pancreatic insufficiency is common in patients with severe CFLD. Exocrine pancreatic insufficiency has a direct impact on nutrition, thus affecting liver transplant outcomes. Analysis of UNOS data revealed long term outcomes in CF liver transplant recipients to be inferior to those undergoing transplantation for other etiologies.[3] Adverse outcomes are noted to be higher in those with exocrine pancreatic insufficiency and poor nutritional status.[6] Development of CFRD results in up to six-fold increase in risk of mortality, due to decline in pulmonary function.[7] CFLD is recognised as an independent predictor of development of CFRD. Notably, the incidence of new onset diabetes post-liver transplant is significantly higher at 57.7% in CF patients compared with 9% in non-CF patients.[8] This is likely related to progressive beta cell destruction associated with CF and superimposed toxicity of immunosuppressants. Clearly, the role of the pancreas in nutrition and glycaemic control makes combined liver-pancreas transplantation in CF patients an attractive option. In a survey of pediatric liver transplantation centres across North America,

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Europe and Oceania, 94% of respondents indicated that they would consider a simultaneous liver-pancreas transplant in a patient with CF.[5] Given the results of this survey, it is surprising that there are few published cases (Table 2). We report our experience to add to the limited existing literature, with the intention that this leads to increased consideration of liver-pancreas transplantation in this population.

Both our patients were listed for liver transplantation due to complications of long-standing portal hypertension secondary to CFLD. Both had FEV1 more than 40% at the time of listing thus not warranting consideration for additional lung transplantation. Both were pancreatic insufficient and insulin-dependent at the time of listing. Indications for pancreas transplantation in CF are not clearly established. Of the cases reported so far (Table 2), 70% of patients had CFRD and all the patients were pancreatic insufficient except for 17 patients for whom data regarding exocrine function was not available.[4,5] A survey of pediatric transplant units observed that in addition to abnormal oral glucose tolerance test, some respondents considered exocrine pancreatic insufficiency alone in the absence of overt diabetes as an indication for pancreas transplantation in CFLD.[5] The high rates of post-transplant diabetes mellitus and its detrimental effects on lung function and survival provides rationale to offer simultaneous pancreas transplantation to those with overt diabetes or impaired glucose tolerance. However, isolated exocrine insufficiency as an indication for transplantation is debatable particularly in the setting of organ scarcity coupled with waitlist mortality rates as high as 6.8 per 100-patient years in those waiting for a simultaneous kidney-pancreas transplant.[9]

The pancreatic graft can be implanted either en-bloc or separate.[10] Although, en-bloc transplantation of both liver and pancreas has the advantages of being technically easier as it involves fewer anastomoses and is more physiological in achieving proximal enteric drainage and portal venous drainage, there is an argument that en-bloc transplantation carries a risk of adverse outcome to both the organs if one organ is affected.[11] One case series reported higher rates of vascular complications in en-bloc transplants.[5] However, it would be premature to draw conclusions about the superiority of one technique to another given the limited available information (Table 2). Both of our patients had separate implantation of pancreas grafts with proximal enteric drainage and

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systemic venous drainage due to surgical preference. The first patient had a choledocho-jejunal biliary anastomosis whereas the second patient had a choledocho-choledochal anastomosis. Duct-to-duct biliary anastomosis is reported to be associated with higher rates of biliary complications in CF population and most authors advocate roux-en-Y biliary anastomosis in CF patients.[12] Neither of our patients has experienced biliary or vascular or other surgical complications thus far.

Another important consideration whilst contemplating multi-visceral transplantation in CF is burden of care. The multi-system nature of the disease entails significant treatment burden. Every CF patient is expected to use 3-5 non–respiratory therapies daily.**Error! Bookmark not defined.** With increased treatment complexity comes the cost of poor adherence. This is particularly true in adolescents and young adults who must maintain increasingly difficult and time-consuming therapeutic regimens every day without an apparent immediate benefit. Combined liver-pancreas transplantation, in principle, alleviates treatment burden and offers adolescents a tangible benefit i.e., preserving the transplanted organ, achievable through adherence to therapy. Compliance to anti-rejection medications in both our patients has been good as evidenced by therapeutic drug monitoring but adherence to pulmonary therapies has been challenging. Quality of life in both our patients has improved significantly although this has not been assessed objectively.

The infective complications resulting from the burden of additional immunosuppression in lieu of the pancreas in a heavily colonised cohort such as CF needs careful consideration. Mekeel et al reported no difference in infectious complications between liver only and combined liver-pancreas transplant groups in a small study. Our practice is to devise an antibiotic protocol in coordination with the infectious diseases team based on the patient's organisms and antibiotic sensitivities. The magnitude of infection risk needs further evaluation in larger studies.

The addition of pancreas does not seem to affect patient survival. Two-year survival rates in CF liver transplant recipients with and without simultaneous pancreatic grafts were similar (87.5% vs 84.4%). Poor graft outcomes in pancreas are related mainly to technical

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failure or graft rejection.[13] With improvement in surgical techniques, five-year graft outcomes now exceed 70% in most centres. Although, pancreatic graft rejection continues to pose a problem, simultaneous transplantation of the liver offers the additional immunological benefit of inducing tolerance to the pancreatic graft.[14] In all the cases reported so far, patient and graft survival rates have been encouraging (Table 2). Apart from possible pancreatic rejection in the early post-transplant period experienced by patient #2, both patients at a follow up of 30 and 12 months respectively, have normal liver graft function with no episodes of rejection, remain off PERT and insulin therapy with improvement in growth and lung function (Table 1).

Given the evident interest and apparent benefits, but relative rarity of combined liver-pancreas transplantation in CF, we speculate that the barriers to combined transplantation include scant evidence base, technical difficulty combined with limited surgical experience and expertise, unclear indications and limited organ availability for patients with CF.

Based on our preliminary experience, combined liver-pancreas transplantation should be considered in patients with CFLD with overt diabetes. Simultaneous pancreas transplantation improves the overall nutritional status and pulmonary function in liver transplant recipients with CF in the short term. It is necessary to undertake objective evaluation of the impact of liver-pancreas transplantation on quality of life and burden of care in CF. Long term data on safety and post-transplant outcomes are required before more definitive recommendations can be made.

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Table 1. Baseline, pre-transplant and post-transplant characteristics of patients

| | **Patient 1** | | **Patient 2** | |
|---|---|---|---|---|
| Age at diagnosis | 11y | | 2y | |
| Gender | Male | | Male | |
| CF genotype | Delta F508 homozygote | | Delta F508 homozygote<br>G551D mutation | |
| Exocrine pancreatic insufficiency | Yes | | Yes | |
| CFRD | Yes | | Yes | |
| Alpa1 Antitrypsin Pi type | PiMM | | PiMM | |
| | **Pre-transplant** | **24 months Post-transplant** | **Pre-transplant** | **12 months Post-transplant** |
| BMI (kg/m$^2$)<br>BMI Z score<br>Height cms (Z score)<br>Weight kgs (Z score) | 18.6<br>-0.92<br>171.4(-0.39)<br>54.7 (-0.82) | 21.6<br>-0.29<br>172 (-0.65)<br>64.1 (-0.5) | 19.73<br>-0.36<br>152 (- 2.33)<br>48.7 (- 1.64) | 22.39<br>- 0.32<br>155.2 (- 2.31)<br>50.9 (- 1.29) |
| FEV1<br>FEV1/FVC | 86%<br>93% | 110%<br>103% | 39.6%<br>75.3% | 65.9%<br>85.6% |
| GFR (ml/min/1.73m$^2$) | 69 | 128 | 27 | 43 |
| Bilirubin (micromol/L) | 32 | 17 | 13 | 3 |
| ALT (IU/L) | 79 | 15 | 81 | 38 |
| GGT (IU/L) | 25 | 13 | 388 | 14 |
| Albumin (g/L) | 35 | 38 | 32 | 36 |
| INR | 1.3 | 1.1 | 1.4 | 1.1 |
| Platelet count (x10$^9$/L) | 31 | 74 | 45 | 94 |
| **Transplant** | | | | |
| Type of transplant | Whole liver graft + heterotopic pancreas | | Whole liver graft + heterotopic pancreas | |

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| | | |
|---|---|---|
| Biliary anastomoses | Roux-en-Y jejunal anastomosis | Duct to duct anastomosis |
| Exocrine drainage | Enteric | Enteric |
| Venous drainage | Systemic | Systemic |
| Type of immunosuppression | Basiliximab on induction Tacrolimus, Mycophenolate mofetil and steroids | Basiliximab on induction Tacrolimus, Mycophenolate mofetil and steroids |
| Complications | None | ? Antibody-mediated pancreatic rejection |
| Duration of follow-up | 30 months | 12 months |
| Pancreatic function at last follow up | Normal exocrine and endocrine function | Normal exocrine and endocrine function |

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