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Combined heart-lung-liver, double lung-liver, and isolated liver transplantation for cystic fibrosis in children

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Abstract Between June 1990 and September 1995, 8 of 24 children with cystic fibrosis (CF) who were accepted either for combined transplantation or isolated liver transplantation died while waiting for a graft; 11 underwent transplantation and 5 are currently on the waiting list. Of the 11 children who had surgery, 7 (group 1) underwent one of the following procedures: heart-lung-liver ($n = 4$), sequential double lung-liver ($n = 2$), or bilateral lobar lung from a split left lung and reduced liver ($n = 1$). During the same period, the four other children (group 2) underwent isolated liver transplantation (three full-size livers, one partial liver). There was one perioperative death in each group. Pulmonary infection was the most common cause of morbidity in group 1. Other complications in group 1 included tracheobronchial stenosis ($n = 2$), biliary stricture ($n = 2$), and severe ascites ($n = 2$). All were successfully treated. Obliterative bronchiolitis developed in three patients. This was treated with FK 506. In group 2, pulmonary function tests improved or remained stable after liver transplantation. Surgical complications in group 2 included severe ascites ($n = 1$), biliary stricture ($n = 1$), and abscess of the liver ($n = 1$). Actuarial survival was 85.7 % ± 2 % in group 1 at 1 year; it remained unchanged at 3 years and was 64.2 % at 5 years.

Key words Cystic fibrosis, multiple organ transplantation · Lung, heart, liver transplantation, in cystic fibrosis · Multiple organ transplantation, cystic fibrosis

Introduction

Cystic fibrosis (CF) is a multisystem genetic disease carried by 5 % of the population [25]. In spite of new medical therapies, life expectancy is approximately 50 % at 30 years [13]. Once bronchopulmonary infection is established, most CF patients die of severe bronchiectasis caused by inspissated pulmonary secretions. Pulmonary transplantation is indicated in these patients. Hepatic multilobar cirrhosis occurs in 5 %–15 % of CF patients [27], with onset in the first decade of life, and progresses to portal hypertension, hypersplenia, and variceal bleeding [12]. For these patients, liver transplantation is the only effective treatment option to prolong survival and to improve the quality of life.

To date, the presence of associated significant lung destruction has prevented many teams from embarking on liver transplantation, as only the combined replacement of irreversibly damaged lung and liver can offer hope of prolonged survival. Nevertheless, in cases of mild to moderate lung disease, pioneering teams have demonstrated that pulmonary function tests either remained stable or improved significantly after liver transplantation in CF patients [21].

The purpose of this study was to emphasize our indications and to analyze our results of isolated and combined liver transplantation in CF patients with advanced

liver disease associated with either end-stage or mild respiratory failure.

Patients and methods

Between April 1989 and March 1995, 32 patients with CF were referred and accepted either for liver and lung transplantation or for isolated liver transplantation in Broussais and Cochin Hospitals. Patients were assessed by physicians experienced in the management of CF, and a consensus was reached by the CF French Transplant group regarding the suitability and acceptance of candidates. Patients were selected either for single liver transplantation or for associated combined procedures (i.e., heart-lung-liver, double-lung liver) on the basis of a deteriorating clinical status indicating a very limited life expectancy. Evidence of such a critically ill condition was suggested by: (1) frequent hospitalizations for pulmonary infection and loss of functional lung capacity; (2) complications of portal hypertension, such as variceal hemorrhage; (3) emaciation in spite of parenteral feeding; (4) the need for nasal intermittent positive pressure ventilation for severe hypoxemia and hypercapnia used for sudden deterioration and as a bridge to lung transplantation [16]; and (5) life-threatening pulmonary and liver complications, such as pneumothorax, hemoptysis, or severe gastrointestinal bleeding.

All patients accepted for a combined procedure had severely compromised pulmonary function; their mean forced vital capacity (FVC) was 35 % and their mean forced expiratory volume in 1 s (FEV_1) was 29 % of predicted values. All patients were hypoxic and required supplemental oxygen. All had end-stage liver disease with severe cirrhosis and portal hypertension, and all had esophageal varices seen on endoscopy. One patient had hepato-pulmonary syndrome with severe hypoxemia and an intrapulmonary shunt of 35 % despite well-preserved pulmonary function tests. Patients accepted for isolated liver transplantation had mild to moderate lung disease; their mean FEV_1 was 65 % and their mean FVC was 70 % of the predicted values. All had end-stage liver cirrhosis and previous portosystemic shunts.

The clinical status of all patients is outlined in Table 1. Sputum cultures before transplantation grew mainly *Pseudomonas* species (Table 2).

Prospective candidates were evaluated to identify relative contraindications to transplantation, which included poor nutritional status and renal dysfunction. Controlled diabetes mellitus, previous thoracic surgery (lobectomy, pleurodesis), and colonization of sinuses or respiratory passages are no longer considered to be contraindications. As waiting periods for transplantation can be protracted and patients often deteriorate during this time, all patients in this group participated in a preoperative program of pulmonary rehabilitation with regular intensive physiotherapy. Noninvasive mechanical ventilation was instituted, if required, in deteriorating situations of severe hypoxemia and hypercapnia. Patients with inadequate nutritional status benefited from parenteral nutrition or jejunostomy feeding. In cases of chronically infected paranasal sinuses, bilateral antral washouts or antrostomies were performed [16]. At the beginning of our experience, when heart-lung transplantations were being performed, recipients were all evaluated and accepted for domino procedures.

Donor organs and procurement

The selection of donors was based on standard accepted criteria for separate heart-lung or lung, and liver transplantation. Particularly important were: good pulmonary function, as determined by a PaO_2 of 150 mmHg or greater for an inspired oxygen concentration of 40 %, adequate size matching, chest roentgenogram showing no abnormalities, viral studies negative for HTLV1, HTLV2, and hepatitis B and C, ABO compatibility, a negative history of lung disease, negative sputum gram stain, and short periods of mechanical ventilation. Only heavy cigarette smokers were not accepted as donors. Unless transplantation was urgent, CMV mismatching was not accepted for a CMV-negative recipient. For the liver to be accepted, normal liver function tests were required, but matched CMV was not required for isolated liver transplantation.

Table 1 Patients' clinical status

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
End-stage respiratory failure	6	–
O_2-dependent	7	–
History of hemoptysis/pneumothorax	4	–
Hepatopulmonary syndrome (major hypoxemia)	1	–
End-stage liver failure		
Cirrhosis and portal hypertension	7	4
Hepatic failure	2	3
History of variceal bleeding	3	4
Previous portosystemic shunts	1	3

Table 2 Infection status before transplantation

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Pseudomonas aeruginosa	6	4
Pseudomonas cepacia	2	–
Pseudomonas maltophilia	1	–
Staphylococcus aureus	2	–
Aspergillus	2	–
Candida	2	–

Donor and recipient operations

Donor operation

Surgical techniques have been described elsewhere in detail [7]. Briefly, for the combined procedure, all organs were obtained from a single donor employing standard harvesting techniques. Before retrieval of the heart and lungs, all donors were given heparin intravenously (250 U/kg) and a bolus of i.v. methylprednisolone (1 g). Prostaglandin (PGE1, 1000 µg) was administered directly and rapidly into the pulmonary artery. Cold Papworth solution (20 mg/kg) was then infused into the pulmonary artery with simultaneous infusion of crystalloid cardioplegia solution into the ascending aorta for heart and lung preservation [9]. The liver graft was cooled and preserved with University of Wisconsin (UW) solution, as described elsewhere [17].

Recipient operation

In group 1, the combined procedures of thoracic and abdominal organ transplantation were performed in the same operative setting. All combined operations were performed with the use of cardio-

pulmonary bypass because of the critical nature of the recipient's condition. We proceeded with liver transplantation following the completion of the lung implantation, termination of bypass, and reversal of heparinization. The sternotomy remained open as the liver transplantation proceeded to allow access for temporary portoatrial shunting. This was required in only one patient. The sternotomy and chest wound were closed before the biliary anastomosis was fashioned in order to minimize the risk of contamination.

We performed heart-lung transplantation in the first four patients with a full-size liver. As the technique of lung transplantation evolved, we performed in the following two patients bilateral, sequential, double-lung implantations in combination with liver transplantation. Most recently, due to a major size discrepancy between the donor and recipient, we performed a bilateral, sequential lobar transplantation from a split left lung associated with a reducedliver transplantation in one patient. Another patient (group 2) also received a reduced-size liver. Techniques of split lung with lobar lung implantation and partial liver transplantation have been described elsewhere [6, 24].

In both groups, liver transplantation was straightforward in six patients. In five patients who had had previous abdominal operations (four portosystemic shunts and one laparotomy exploration for meconium ileus), there was increased technical difficulty and increased intraoperative blood loss. To minimize ischemic time, "bench work" of the liver was performed during implantation of the lungs in group 1. This was particularly useful for the patient who received a reduced-size liver. Biliary reconstruction was by choledochocholedochostomy (CDCD) with a T tube in three patients or by Roux-en-Y choledochojejunostomy (CDJ) in eight patients. Temporary portosystemic shunting was mandatory in one patient in group 2.

Postoperative management

In group 1, postoperative immunosuppression was based on our standard triple drug therapy for isolated lung transplantation: azathioprine, 2–3 mg/kg, together with three doses of equine antithymocyte globulin (ATG) and methylprednisolone (1 g at operation and 125 mg three times daily for the first 24 h). Steroids were then withheld for 8 days and resumed at a dosage of 1 mg/kg per day, tapering to 0.2 mg/kg per day by 6 months. Cyclosporin was given intravenously (1–2.5 mg/kg per day) for 8 days, with doses adjusted according to renal function and cyclosporin blood concentration. Oral cyclosporin was then started to maintain a serum level of 150–250 mg/ml.

Episodes of acute lung rejection were treated with bolus intravenous methylprednisolone (15 mg/kg for 3 days) for grades 1 or 2 rejection. ATG was added for persistent grade 1–2 or for grade 3 rejection. Diagnosis of rejection was based on clinical grounds in the 1st postoperative week and on transbronchial biopsy (TBB) results thereafter. Postoperative management in the early phase was aimed at maintaining optimum hemodynamics with restriction of fluid intake to avoid pulmonary edema and to allow early extubation. Bronchoscopy, TBB, and bronchioalveolar lavage were performed routinely and when indicated on clinical grounds. Ultrasound of the liver with Doppler evaluation of the hepatic artery and portal vein were done on a daily basis.

In group 2, patients were given a double drug therapy (steroids and cyclosporin).

Table 3 Demographic characteristics of CF patients

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Age (years)	12 (10–17)	16.5 (14–18)
Weight (kg)	29.5 (23–45)	42.5 (40–49)
Height (cm)	138 (122–160)	155 (140–161)
Gender (m/f)	5/2	3/1

Table 4 Perioperative data

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Ischemic time (min)		
Heart-lung	229 ± 7.5	–
First lung	125 ± 5.4	–
Second lung	191 ± 6.3	–
Liver	620 ± 9.2	415 ± 8.2
Duration of operation (hours)		
Mean	12	6
Range	10–17	5–7
Duration of ventilation (days)		
Mean	1	1
Range	1–21	1–8
ICU stay (days)		
Mean	17	12
Range	10–60	5–18
Hospital stay (days)		
Mean	45	42
Range	10–90	8–58

Results

From April 1989 through March 1995, 24 children with CF were placed on the transplant waiting list either for isolated liver transplantation or for combined heart-lung-liver or double lung-liver transplantation. Eleven children underwent transplantation, with four (group 2) receiving isolated livers and seven (group 1) having a combined procedure, i.e., heart-lung-liver, sequential bilateral lung-liver, or sequential, bilateral lobar and reduced liver transplantation. Demographic characteristics are depicted in table 3. The average waiting time for isolated lung transplantation was 6 months, compared to 9 months (range 2–30 months) for combined transplantation. Ten patients died while on the waiting list, and six are currently still awaiting a combined transplantation. Length of postoperative follow-up ranged from 11 months to 5 years.

Perioperative outcome

Operative and postoperative data are presented in table 4. Ischemic times are given for both lungs, the left lung being implanted after the right lung. Ischemic time for the liver in the combined procedure ranged from 390 to

Table 5 Mortality

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Early mortality (< 3 months post-transplantation)		
Liver surgical complication (abscess)	1	
Respiratory failure (patient could not be weaned from ventilator)		1
Late mortality (> 3 months post-transplantation)		
Cerebral hemorrhage	1	
Obliterative bronchiolitis (retransplantation)	1	

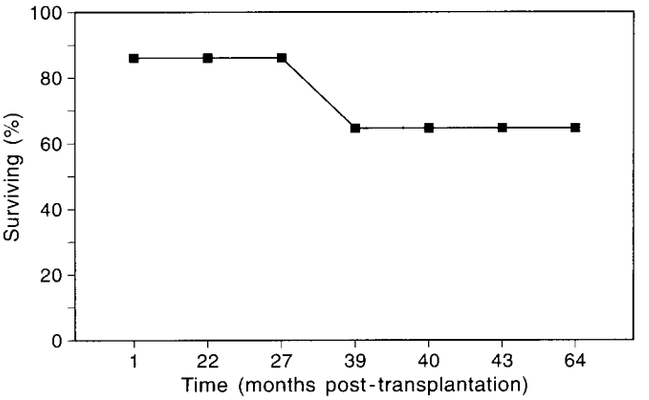

Fig. 1 Actuarial survival rate (Kaplan-Meier) of patients with CF after combined lung-liver transplantation

780 min (mean 620 min), which is acceptable for liver grafts preserved with UW solution.

Bleeding problems were minimal and no patient required either rethoracotomy or relaparotomy for hemorrhage. Coagulation complications were not noted since we did not have any primary liver failure. Coagulation factors were adjusted as required. The amount of blood transfused never exceeded 10 packs of red cells in the postoperative period.

Perioperative mortality, as defined by death within the 1st 90 days after transplantation or before patients were discharged from the hospital, was 14 % ($n = 1$) in group 1. One patient in group 2, who was initially accepted for combined transplantation, suffered from severe deterioration of the liver disease with considerable ascites and, consequently, was switched to isolated liver transplantation. He underwent a successful liver transplantion but could not be weaned from the ventilator; he underwent an urgent lung transplantation on postop day 8 but subsequently died from medical complications. Causes of early and late deaths are summarized in table 5. Actuarial survival was 85.7 % ± 2 % at 1 year and has remained unchanged at 3 years in group 1 (Fig. 1).

Postoperative complications are documented in tables 6 and 7. Airway complications occurred in two children, one tracheal stenosis and one bronchial stricture on the left side of the bilateral lobar transplant patient. Both were successfully managed with laser and /or dilatation therapy. Airway stenting was not employed in either of these patients. Three patients had prolonged thoracic drainage for pleural effusion or pneumothorax. Abdominal complications occurred in nine patients, six of whom had a relaparotomy. Three patients developed ascites. One proved to be a chyloperitoneum, and after laparotomy on postoperative day 30 for ligation of lymphatic ducts around the hepatic pedicle, he recovered uneventfully. Three other patients with choledochocholedochostomy developed a biliary stricture 3 weeks, 6 months, and 7 months postoperatively that were successfully managed by conversion to choledochojejunostomy. One patient had a meconium ileus equivalent obstruction. This was successfully relieved with gastrografin enemas and oral acetylcysteine. Three patients in group 1 had grand mal seizures after transplantation; among them were two patients who suffered reversible cerebral abnormalities that were identified on computed tomographic scanning. One patient suffered cerebral hemorrhage in the 6th postoperative month secondary to systemic hypertension and eventually died. All patients who had seizures also had elevated systemic blood pressure. Four patients developed de novo insulin-dependent diabetes mellitus.

Infection was a significant cause of morbidity in group 1 despite antibiotic prophylaxis administered to all recipients based on the most recently available gram stain, culture, and sensitivity of the recipient's upper respiratory tract. Antibiotic prophylaxis was given for 2 weeks and stopped if no evidence of infection was present. The linearized infection rates were 2.2 episodes /100 patient-days in group 1. There was a high predominance of bronchitis and pneumonia with *Pseudomonas aeroginosa*. Two patients developed bronchial *Aspergillus fumigatus* infections. One patient suffered from meningoencephalitis secondary to herpes virus infection. The incidence of pulmonary infection was very low in group 2.

Rejection

In the combined procedure, rejection episodes were most frequent during the first 3 postoperative months. The incidence of lung rejection episodes was three times greater than of hepatic rejection (15 episodes vs 5 episodes). Acute episodes of lung and liver rejections were dissociated in our series. The incidence of rejection episodes was not significantly different in CF patients with combined transplantation than in patients with isolated lung transplantation. In group 2, only one patient had an acute liver rejection episode.

Table 6 Medical complications

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Pulmonary infections	21	3
Acute rejection episodes		
Lung	15	–
Liver	5	1
Obliterative bronchiolitis	3	–
Seizures	3	–
Toxic cardiomyopathy	1	–
De novo diabetes mellitus	4	–
Hypersplenism	–	1

Table 7 Surgical complications (*CDCD* choledochocholedochostomy, *CDJ* choledochojejunostomy)

	Group 1 ($n = 7$)	Group 2 ($n = 4$)
Ascites (chyloperitoneum) Required laparotomy in two patients	2	2
Biliary obstruction (strictures) CDCD converted to CDJ	2	1
Stenosis of hepatic artery and hepatic abscess		1
Portal vein stenosis		1
Bowel obstruction Meconium ileus equivalent	1	
Tracheal stenosis Laser and dilatation	1	
Bronchial stenosis Dilatation	1	
Prolonged thoracic drainage	2	1

Obliterative bronchiolitis (OB)

Obliterative bronchiolitis, diagnosed according to established criteria, developed in three patients [5]. One of two patients with grade 3 OB was retransplanted on postoperative month 38 but subsequently died from bleeding. The second patient chose not to be listed for retransplantation and is currently in poor clinical condition. A third patient with grade 1–2 OB has been stabilized with FK 506 and has a normal life style.

Discussion

Since the first clinical experience with heart-lung transplantation for CF was reported in 1984, encouraging results with both heart-lung and lung transplantation in Cf patients have been published [9, 11, 20, 26]. The occurrence of hepatic cirrhosis and portal hypertension in 5 %–15 % of these patients may preclude a successful outcome of lung transplantation and has been generally considered to be an absolute contraindication. Satisfactory preliminary results with isolated liver transplantation in CF patients were reported in 1989. Improved management of pulmonary problems in CF patients has increased life expectancy, and now patients are increasingly developing extrapulmonary complications [23]. The onset of liver disease is usually in the first decade of life. The earliest characteristic of a hepatic lesion is a focal biliary fibrosis, which is thought to result primarily from the accumulation of abnormally tenacious bile in intrahepatic ducts. This impedies bile flow and causes biliary fibrosis and consequent cirrhosis. This may progress to severe portal hypertension, as occurred in our 11 patients who, at the time of assessment, had splenomegaly, indices of hypersplenism reflected in white cell counts and platelets, and large varices shown at endoscopy [31].

Hepatocyte function, as estimated by serum albumin, prothrombin time, and transaminases, may be normal or slightly impaired in spite of advanced multilobular cirrhosis [12]. In our series, only five patients had hepatic failure. The combination of end-stage lung and liver disease in these patients is particularly challenging for surgery and postoperative management. Questions have been raised regarding the suitability of such candidates for transplantation, particularly in the global context of the organ shortage [11]. These patients are often in poor nutritional condition as a result of severe intestinal malabsorption and chronic infection wth multiresistant organisms. Their poor clinical status is aggravated by portal hypertension with such episodic life-threatening complications as gastrointestinal bleeding. Ileus may cause abdominal distension and diaphragmatic splinting. All of these problems may impair the results of combined transplantation.

In spite of these increased preoperative risk factors, our actuarial survival rate of 85.7 % at 3 years in the combined transplant group is similar to that reported for isolated lung transplantation in CF patients with a good quality of life [10, 11]. The genetic nature of the disease is such that recurrence in transplanted organs is highly unlikely. This has been demonstrated for lung transplantation [33] but not for liver transplantation. Nevertheless, our first patient with a 5-year follow-up has not demonstrated recurrence of the disease on repeated liver biopsies taken when indicated for suspected rejection episodes.

In this report, 50 % of the patients accepted for combined transplantation died while awaiting a transplant, and this was essentially due to an unacceptably protracted mean waiting time of 9 months. To improve this situation, the regulations regarding organ sharing should be reconsidered so as to give priority to patients suffering from combined end-stage lung and liver disease.

The important question, then, is: which patients with CF and associated lung and liver diseases should be referred and accepted for combined transplantation or for isolated liver transplantation and when? Treatment of portal hypertension with splenomegaly by isolated liver transplantation has been reported in CF patients with encouraging results [21, 22]. In these reports, patients had mild to moderate lung disease, and with a mean FEV_1 of approximately 70%, they would certainly not be candidates for lung transplantation. Noble-Jamieson et al. [22] reported an impressive improvement in subjective pulmonary symptoms in five CF children after isolated liver transplantation with greatly improved exercise tolerance and even decreased sputum production. Improvement in pulmonary function was also reported by Cox [8], but three of a total of ten patients died from infectivous complications (two from *Pseudomonas* and one from *Aspergillus*). Mieles et al. [21] reported on four children and five adults. Two died due to operative problems; in the seven survivors, pulmonary function remained stable or improved. Three patients in our series stabilized and improved after isolated liver transplantation. One patient in our series had mild lung disease but presented with a hepatopulmonary syndrome with extensive pulmonary shunting (35%), as measured with albumin macroaggregates, and with severe hypoxemia (pO_2 of 35 mmHg) [19]. Isolated liver treatment has occasionally been able to reverse hypoxemia in this syndrome [32]; however, a recent report by our group showed poor results, with increased mortality in patients with hypoxemia of pO_2 less than 60 mmHg [15]. Therefore, we considered isolated liver transplantation contraindicated for this patient.

Of the various surgical options available for combined transplantation, the separated procedure was adopted, with completion of the heart-lung or bilateral, sequential double-lung transplantation before the start of liver transplantation. This procedure allows time for "bench work" on the liver to be performed during implantation of intrathoracic organs and, thus, minimizes hepatic ischemic time. As the technique of lung transplantation has evolved [1], the introduction of the anterior bithoracosternotomy approach for sequential, bilateral lung transplantation has meant that the separate implantation of lungs and liver is the only possible surgical option.

Although biliary reconstruction, once considered the "Achilles heel" of liver transplantation [4], has become standardized, biliary strictures remain a significant source of complications in our CF patients. The only three patients who had biliary reconstruction by choledochocholedochostomy developed biliary strictures and were managed by conversion to a Roux-en-Y choledochojejunostomy. We believe that choledochocholedochostomy should be avoided in CF patients because the diseased recipient bile duct may play a major role in developing stricture.

The scarcity of suitable donor organs, even more critical in the pediatric population, has prompted surgeons to develop techniques of liver [24] and pulmonary reductions. We recently developed a split lung technique with the use of bilateral lobar transplants from a donor left lung [6]. The technique of combined reduced liver and bilateral lobar lung transplantation was successfully performed in one child. The use of lobar transplantation from living related donors has been proposed for isolated lung [30] or liver transplantion in children [2]. Discharged patients showed a dramatic improvement in pulmonary function as reflected by FEV_1 and FVC, with satisfactory blood gases on exertion and improved quality of life despite the morbidity caused by complications. The incidence of lung or liver rejection episodes was comparable to that of isolated repeated organ transplants, and there was no demonstrable immunosuppressive effect of an additional liver allograft from the same donor, as has been reported in clinical [14] and experimental settings [3, 18]. There was a disappointingly high incidence of OB (40%). The response to augmented maintenance immunosuppression was inconsistent, but two patients were stabilized by converting cyclosporin therapy to FK 506. Retransplantation was performed in an additional patient. Retransplantation remains controversial for OB because of very poor reported results and the scarcity of donor organs [28].

This report shows encouraging results for combined lung and liver transplantation, with a morbidity and mortality equalling those of separate replacements. It demonstrates the feasibility and potential of the combined procedure in carefully selected CF patients suffering from chronic respiratory failure with advanced cirrhosis and, thus, a low minimal life expectancy. CF patients with end-stage respiratory failure and mild to moderate liver cirrhosis who have been considered poor candidates for isolated lung transplantation are potentially good candidates for the combined procedure. On the other hand, isolated liver transplantation has emerged as an effective therapy for CF patients with mild lung disease and advanced cirrhosis. Close cooperation between clinicians and specialists is of utmost importance.

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References

1. Bismuth H, Houssin D (1984) Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 95: 367–370
2. Broelsch CE, Emond JC, Whitington PF, Thistlethwaite JR, Baker AL, Lichtor JL (1990) Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. Ann Surg 212: 368–377
3. Calne RY, Sells RA, Pena JR, Davis DR, Millard PR, Herbertson BM, Binns RM, Davies DAL (1969) Induction of immunological tolerance by porcine liver allografts. Nature 223: 472–476
4. Colonna JO II, Shaked A, Gomes AS, Colquhoun SD, Jurim O, Mc Diarmid SV, Millis JM, Goldstein LI, Busuittil RW (1992) Biliary strictures complicating liver transplantation. Ann Surg 216: 344–352
5. Cooper JD, Bilingham M, Egan T, et al. (1993) A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. J Heart Lung Transplant 12: 713–716
6. Couetil JP, Grousset A, Benaim D, Sapoval M, Hernigou A, Coppens P, Fayolle P, Carpentier A (1994–95) Mise au point experimentale de la bipartition pulmonaire avec transplantation lobaire bilaterale chez le chien et application en clinique humaine. Chirurgie 120: 512–517
7. Couetil JP, Houssin D, Soubrane O, Chevalier P, Dousset B, Loulmet D, Achkar A, Tolan M, Amrein C, Guinvarch A, Guillemain R, Birnbaum P, Carpentier A (1995) Combined lung and liver transplantation in cystic fibrosis. A 4.5 year experience. J Thorac Cardiovasc Surg 110: 1415–1423
8. Cox KL (1990) The role of liver transplantation in cystic fibrosis patients. Cystic Fibrosis Conference S1.4: 78–79
9. de Leval MR, Smyth R, Whitehead B, et al. (1991) Heart and lung transplantation for terminal cystic fibrosis: a 4 1/2-year experience. J Thorac Cardiovasc Surg 101: 633–642
10. Dennis C, Caine N, Sharples L, et al. (1993) Heart lung transplantation for end stage respiratory disease in a cystic fibrosis patient at Papworth Hospital. J Heart Lung Transplant 12: 893–902
11. Egan TM, Detterbeck FC, Mill RM, Paradowski LJ, Lackner RP, Ogden WD, Yankaskas JR, Westerman JH, Thompson JT, Weiner MA, Cairns EL, Wilcox BR (1995) Improved results of lung transplantation for patients with cystic fibrosis. J Thorac Cardiovasc Surg 109: 224–235
12. Feigelson J, Anagnostopoulos C, Poquet M, Pecau Y, Munck A, Navarro J (1993) Liver cirrhosis in cystic fibrosis – therapeutic implications and long term follow up. Arch Dis Child 68: 653–657
13. Geddes DM (1988) Cystic fibrosis Future trends in care. Thorax 43: 115–130
14. Gonwa TA, Nery JR, Husberg BO, Klintmalm GB (1988) Simultaneous liver and renal transplantation in man. Transplantation 46: 690–693
15. Hobeika J, Houssin D, Bernard O, Devictor D, Grimon G, Chapuis Y (1994) Orthotopic liver transplantation in children with chronic liver disease and severe hypoxemia. Transplantation 57: 224–228
16. Hodson ME, Madden BP, Steven MH, Tsang VT, Yacoub MH (1991) Non-invasive mechanical ventilation for cystic fibrosis patients – a potential bridge to transplantation. Eur Respir J 4: 524–527
17. Kalayoglu M, Sollinger HW, Stratta RJ, et al (1988) Extended preservation of the liver for clinical transplantation. Lancet I:617–619
18. Kamada N, Davies HS, Roser B (1981) Reversal of transplantation immunity by liver grafting. Nature 292: 840–842
19. Lange PA, Stoller JK (1995) The hepatopulmonary syndrome. Ann Intern Med 122: 521–529
20. Madden BP, Hodson ME, Tsang V, Radley-Smith R, Khaghani A, Yacoub MH (1992) Intermediate-term results of heart-lung transplantation for cystic fibrosis. Lancet I: 1583–1587
21. Mieles LA, Orenstein D, Teperman L, Podesta L, Koneru B, Starzl TE (1989) Liver transplantation in cystic fibrosis. Lancet I: 1073
22. Noble-Jamieson G, Valente J, Barnes ND, Friend PJ, Jamieson NV, Rasmussen A, Calne RY (1994) Liver transplantation for hepatic cirrhosis in cystic fibrosis. Arch Dis Child 71: 349–352
23. Park RM, Grand RJ (1981) Gastrointestinal manifestations of cystic fibrosis: a review. Gastroenterology 81: 1143–1161
24. Pasque MK, Cooper JD, Kaiser LR, Haydock DA, Triantafillou A, Trulock EP (1990) Improved technique for bilateral lung transplantation: rationale and initial clinical experience. Ann Thorac Surg 49: 785–791
25. Penketh ARL, Wise A, Mearns MB, Hodson ME, Batten JC (1987) Cystic fibrosis in adolescents and adults. Thorax 42: 526–532
26. Ramirez JC, Patterson GA, Winton TL, de Hoyos AL, Miller JD, Maurer JR (1992) Bilateral lung transplantation for cystic fibrosis. J Thorac Cardiovasc Surg 103: 287–294
27. Scott-Jupp R, Lama M, Tanner MS (1991) Prevalence of liver disease in cystic fibrosis. Arch Dis Child 66: 698–701
28. Smith J, Wallwork J (1995) Retransplantation in heart-lung recipient with obliterative bronchiolitis (letter). J Thorac Cardiovasc Surg 109: 818
29. Starnes VA, Lewiston N, Theodore J, Stoehr C, Stinson E, Shumway NE, Oyer PE (1992) Cystic fibrosis. Target population for lung transplantation in North America in the 1990s. J Thorac Cardiovasc Surg 103: 1008–1014
30. Starnes VA, Barr ML, Cohen RG (1994) Lobar transplantation. Indications, techniques and outcome. J Thorac Cardiovasc Surg 108: 403–411
31. Stern RC, Stevens DP, Boat TF, Doershuk CF, Izant RJ Jr, Matthews LW (1976) Symptomatic hepatic disease in cystic fibrosis: incidence, course, and outcome of portal systemic shunting. Gastroenterology 70: 645–649
32. Van Obbergh L, Carlier M, de Clety SE, Sokal E, Rennotte MT, Veyckemans F, Dekock M, Frans A, Otte JB (1993) Liver transplantation and pulmonary gas exchanges in hypoxemic children. Am Rev Respir Dis 148: 1408–1410
33. Wood A, Higgenbottam T, Jackson M, Scott J, Stewart S, Wallwork J (1989) Airway mucosal bielectric potential difference in cystic fibrosis after lung transplantation. Am Rev Respir Dis 140: 1645–1649