

Liver transplantation at the Cleveland Clinic¹

Early results

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Seventeen patients received 19 orthotopic liver transplants at the Cleveland Clinic in the initial clinical phase of the liver transplantation program developed by a team of surgeons, gastroenterologists, anesthesiologists, psychiatrists, and social workers. The survival rate of 71% after a mean follow-up of six months is equal to that seen in other centers. The technical demands are high, and postoperative complications are many. The demands on limited resources, such as blood for transfusion, are modest. The quality of life among survivors has been, with two exceptions, excellent. The indications for liver transplantation are evolving. It is anticipated that this operation will be performed more often. Patients to be considered for transplantation need to be referred before they have deteriorated too much to be operated on.

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The first human liver transplant was performed by Starzl in 1963.¹ At about this time, surgeons at the Cleveland Clinic became interested in experimental canine heterotopic liver transplantation.^{2,3} An auxiliary liver transplant was performed at the Cleveland Clinic for biliary atresia, unsuccessfully. Until a few years ago, liver transplantation continued as an experimental procedure performed infrequently in this country with unsatisfactory results. In the early 1980s, a number of advances were made that improved the results of liver transplantation sufficiently to gain more widespread acceptance.⁴ Yet, the limited availability of the operation with subsequent long delays and frequent deaths made it apparent that more centers were

Table 1. Diseases that may be indications for liver transplantation

Advanced cirrhosis
Primary biliary cirrhosis
Chronic active hepatitis
Cryptogenic cirrhosis
Secondary biliary cirrhosis
Sclerosing cholangitis
? Hepatitis B
Metabolic disorders
Wilson's disease
Protoporphyrria
Hemochromatosis with cirrhosis
Alpha-1-antitrypsin deficiency
Type IV hyperlipidemia
Vascular disease
Budd-Chiari syndrome
Neoplasms
Primary hepatocellular carcinoma (especially fibrolamellar)
Life-threatening multiple adenomas
Fulminant or submassive hepatic failure from drugs, toxins, or infection
Diseases in children
Biliary atresia
Congenital biliary cirrhosis
Congenital hepatic fibrosis
Tyrosinemia
Galactosemia
Glycogen storage disease I and IV
Byler's disease
Sea blue histiocyte disease
Alagille syndrome

necessary to provide the needed service. This article summarizes the development and early results of the liver transplant program at the Cleveland Clinic.

Methods

Organization

Liver transplantation is a major institutional undertaking. Resources deemed essential for implementing a successful program include suitable operating room facilities and personnel, anesthesia support, hospital beds and outpatient follow-up facilities, medical and nursing support personnel, psychiatric and social service support, donor procurement systems, and a blood product support system. In addition to the availability of such services, organization for timely delivery is essential.

The Cleveland Clinic Liver Transplant Group assembled in January 1983 to make plans for our

transplantation program. Twenty-three months later, the first transplant was carried out. Key members of the surgical team, hepatologists, anesthesiologists, blood banking specialists, and psychiatrists were trained extramurally. Several working subgroups were established, including a patient selection committee. This committee meets regularly to discuss potential transplant candidates and comprises physicians, surgeons, social workers, psychiatrists, and bioethicists. Other committees were convened to provide a liaison with organ procurement agencies and ensure effective internal communication among the disparate health-care providers. The entire administrative effort is led by a transplant surgeon and a hepatologist.

A unique organizational feature of transplantation in Ohio is the Ohio Consortium of Solid Organ Transplantation. The consortium is a state-mandated oversight committee. Its purpose is to make the most efficient use of scarce resources within the state and to ensure that patients in need of transplantation are dealt with equitably. A liver transplant cannot be done without the approval of the consortium. Importantly, state residents are given full consideration for transplantation, regardless of their economic status. This has removed considerable constraints on the performance of this expensive procedure for Ohio residents.

Patient Selection

Patients with end-stage liver disease are seen primarily by a hepatologist. Before a case is presented to the patient selection committee, the patient is evaluated, if indicated, by other medical specialists. Most patients are physician-referred, but some are self-referred. A patient is considered a transplant candidate if one of two conditions is met: end-stage liver disease with a life expectancy of less than a year or a quality of life poor enough to justify the risks of transplantation. Acute liver failure patients are considered candidates, recognizing that the logistics are formidable and the results are inferior to those for more stable patients. Finding a suitable donor in the very narrow "window period" when the patient can be saved is not always possible. Patients under age 60 are considered the best candidates, but those over 60 may be considered if their health is otherwise excellent.

Diseases for which transplantation is currently deemed appropriate are listed in *Table 1*. Contraindications to liver transplantation are listed

in *Table 2*. Before acceptance as a candidate for transplantation, the patient is seen in consultation by a surgeon, psychiatrist, social worker, and a bioethicist, all of whom participate on the patient selection committee.

The donor operation

Successful management of donor procurement is of utmost importance for the success of a liver transplant program. The donor team consists of one staff surgeon, two surgical residents, and two support personnel. Cleveland's geography allows timely travel to either coast of the continental United States or to Canada. However, harvest sites within 1500 miles are preferred in order to reduce ischemia time. Deranged serum liver tests or an unsuitable size mandates refusal of an organ.

Initially, organs were harvested using the technique of complete dissection before removal.⁴ This operation is tedious and time-consuming and may require two to four hours, especially if arterial anomalies are encountered. Six of our first 19 grafts had an anomalous blood supply; five had a replaced, right hepatic artery from the superior mesenteric artery; and in one the left hepatic artery arose from the left gastric artery. For the last patient in this series we used a new method of harvesting, adopted from Starzl and colleagues. Catheters are placed in the inferior mesenteric vein and the aorta. These vessels are then flushed with a modified Collins solution. All of the dissection is done after the viscera are cooled and bloodless. This modification has allowed liver harvesting to take place in one hour. Our average ischemia time is six hours.

It is important that a surgeon from the recipient hospital perform the donor operation. This physician bears the responsibility of the patient's life in obtaining a healthy organ for implantation. Multiple organ retrieval requires cooperation between the local renal procurement surgeon and the visiting heart and liver teams. The optimal sequence of dissection and harvest is heart, liver, and kidneys. This sequence affords the best chance of providing each team with viable organs.

The recipient operation

The recipient hepatectomy is the most demanding phase of the transplant procedure. The patient is given 1 g each of cefotaxime and ampicillin preoperatively. Previous operations, por-

Table 2. Current contraindications for liver transplantation

Active infection outside the biliary tree
Malignancy outside the liver and/or biliary tree
Advanced extrahepatic organ damage (particularly heart or lung disease)
Insulin-dependent diabetes mellitus
Alcoholism (those who are known to be abstinent for at least 6 months may be accepted)
Other chemical dependence
Insufficient personal strength and/or social resources to adapt to the demand of life with a liver transplant

tal hypertension, and preoperative coagulopathy contribute to the complexity of the procedure. The portal structures are dissected first, followed by mobilization of the vena cava from the diaphragm to the renal veins. In adults, the saphenous and axillary veins are exposed for the venovenous bypass. The bypass returns lower extremity and portal blood to the axillary vein via a small pump. The diseased liver is left in situ until the donor liver arrives in the operating room so that the operation can be terminated if the donor liver does not arrive. After the diseased liver is excised, the portal vein is added to the venovenous bypass circuit.

Hemostasis during the dissection is paramount. The Cell-Saver Haemonetics (Haemonetics Co., Braintree, MA) machine, primed with citrate, allows some shed blood to be captured, and a rapid infusion device ensures prompt blood replacement and maintains intravascular volume. Coagulation is monitored at frequent intervals by a thromboelastograph, which aids in the proper selection of replacement blood components.

Implantation of the donor organ is the final phase of the transplant procedure. The upper and lower vena caval anastomoses are completed first, followed by the portal vein anastomosis. Partial circulation is restored to the liver in 45 to 60 minutes. Finally, the hepatic artery anastomosis is performed. Biliary reconstruction is the final phase of the recipient operation. A Roux-Y choledochojejunostomy is constructed in those patients with an absent or diseased bile duct, but, in all other circumstances, a primary duct-to-duct repair is fashioned over a T-tube. The donor gallbladder is then removed, and a cystic duct cholangiogram is obtained to detect technical problems with the biliary anastomosis. A needle biopsy of the liver is performed, drains are placed, and the abdomen is closed. The op-

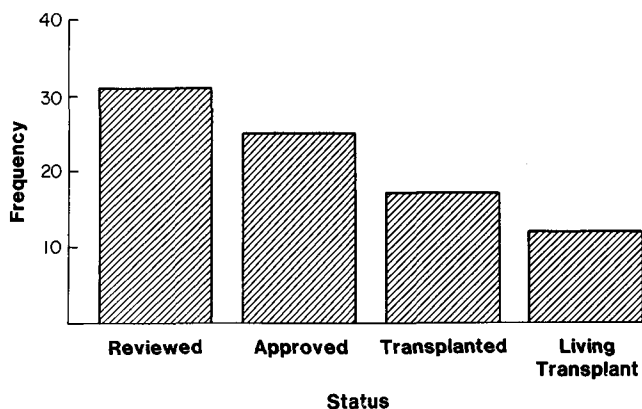


Fig. 1. Liver transplant program experience from October 1984 through July 1986.

erative time for the recipient phase has ranged from eight to 16 hours, most averaging 12 hours.

The postoperative course begins in the surgical intensive care unit. Antibiotics begun preoperatively are continued for two days postoperatively. The patient is transferred to a specially designated regular nursing floor when appropriate. Corticosteroids and cyclosporine for immunosuppression are given intravenously in the early postoperative period but are given orally as the gastrointestinal tract becomes functional. The maintenance dose of prednisone is 20 mg per day; cyclosporine is titrated by measuring trough blood levels and renal function. Ideally, a whole-blood level of 200–300 ng/mL of cyclosporine

(as measured by high-performance liquid chromatography) is the goal. Azathioprine has occasionally been used because of intolerance to cyclosporine or when enhanced immunosuppression is needed. Liver biopsies are performed before implantation and immediately after revascularization to assess the status of the liver and to serve as a baseline for subsequent biopsies. Protocol biopsies are performed weekly for the first month and whenever rejection is suspected. The diagnosis of rejection requires histologic confirmation. It was initially treated by bolus infusions of 500 mg of methylprednisolone, but because of apparent lack of effect, later cases were most often treated by recycling treatment. Rejection episodes not responsive to a recycle of steroid are treated with OKT-3, a mouse monoclonal antilymphocytic globulin.

Follow-up

Whenever possible, patients are seen weekly in our Liver Transplant Clinic. The frequency of visits gradually decreases to four visits per year. Adjustment of medications, frequent liver biopsies, and liver tests are done in the clinic. An important part of the follow-up is psychosocial, and a member of the psychiatry department is in attendance.

Results

Figure 1 summarizes the activity of the Liver Transplantation Program from October 1984

Table 3. Patient characteristics and outcomes

Pt. no.	Age	Sex	Liver diagnosis	Wait before transplant (days)	No. units blood at operation	Status*
1	42	F	Postnecrotic cirrhosis	2	23	D (3 mo)
2	50	M	Budd-Chiari syndrome	3	56	D (2.5 mo)
3	28	M	Wilson's disease	na	39	D (1 mo)
4	19	M	Chronic active/cirrhosis	na	145	A (17 mo)
5	38	F	Primary biliary cirrhosis	5	15	D (2 mo)
6	36	M	Laennec's cirrhosis	15	70	A (13 mo)
7	36	M	Sclerosing cholangitis	7	17 (+44)†	D (3.75 mo)
8	18	M	Postnecrotic cirrhosis	9	9	A (7.5 mo)
9	36	M	Sclerosing cholangitis	32	10	A (6 mo)
10	36	F	Hepatitis B/cirrhosis	5	7	A (6 mo)
11	52	M	Primary biliary cirrhosis	1	8	A (5 mo)
12	42	M	Postnecrotic cirrhosis	46	13	A (5 mo)
13	49	F	Hepatitis B/cirrhosis	2	13	A (4 mo)
14	52	M	Sclerosing cholangitis	25	11 (+6)†	A (4 mo)
15	30	F	Wilson's disease	83	8	A (3 mo)
16	50	F	Chronic active/cirrhosis	2	14	A (2 mo)
17	33	F	Chronic active/cirrhosis	21	8	A (1 mo)

* Dead (D) or alive (A) as of 8/31/86.

† Figure in parentheses indicates blood used at retransplantation.

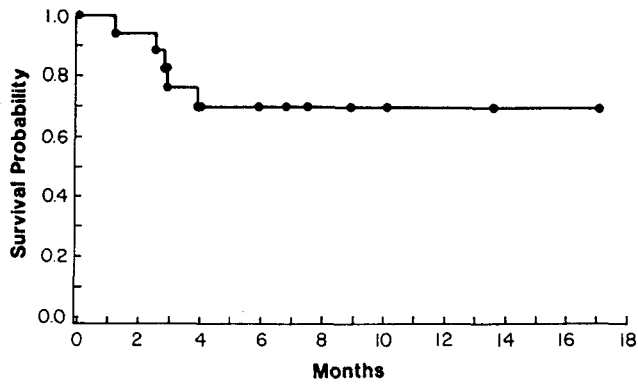


Fig. 2. Survival probability of liver transplantation patients.

through July 1986. Thirty-two cases were presented to the patient selection committee. Of these, 17 were selected for transplantation. Two required retransplantation because of hepatic artery thrombosis, for a total of 19 operations. Information about these patients is presented in Table 3.

The average waiting time for a donor organ was 17.2 days (range 1-83) (Table 3). The average recipient age was 35. The 17 recipients included 5 women and 12 men. All had cirrhosis, except one patient with the Budd-Chiari syndrome. Two patients had cirrhosis from chronic hepatitis B; neither was e-antigen positive and one had anti-e antibody. Both have had relatively uncomplicated postoperative courses. Both remained HbsAg positive despite administration of hyperimmune B globulin immediately after the operation. One patient has developed histologic evidence of recurrent hepatitis in the transplanted liver, with only mild elevation of transaminases and no clinical symptoms.

All of the deaths occurred early in the series. All but one of these patients were hospital-bound before transplantation, indicating the severity of their illness. No patient who died ever became well enough postoperatively to be discharged from the hospital. None have had primary graft failure, and there were no intraoperative deaths. The principal cause of death has been systemic infection, usually viral. In one case, hepatic artery thrombosis contributed to a number of complications that resulted in death despite retransplantation. The only other patient who developed hepatic artery thrombosis underwent retransplantation and has done well.

Twelve of 17 patients (71%) survive. Actuarial survival rates are shown in Figure 2. Patients who

died were of similar mean age (38.8) to those who survived (37). The patients who died were sicker before surgery. Four of five deaths occurred in patients hospitalized and in unstable condition immediately before transplantation. Laboratory tests performed closest to the cut-off time for this analysis revealed normal mean values for bilirubin (1.1 mg per dL), SGPT (36 units per liter), and alkaline phosphatase (88 units per liter). The mean value for gamma glutamyl transpeptidase is 202 units per liter (normal less than 44 units per liter). We found levels of this enzyme to be significantly above normal in most patients who are well, and to be without apparent clinical significance. The mean creatinine level for the 10 patients maintained on cyclosporine is 1.4 mg per dL. We attribute this slight elevation to cyclosporine therapy. Seven patients have had hypertension secondary to cyclosporine of sufficient magnitude to require pharmacotherapy. The mean creatinine level in those requiring anti-hypertensive treatment was 1.34 mg/dL, compared with 1.18 mg/dL for those not hypertensive.

Blood use

The volume of blood used during liver transplant surgery ranged from 8 to 145 units. Although the range of blood requirement was great, most patients required fewer than 20 units (Fig. 3). A median of 20 units of platelets (range 0-80), 17 units of fresh-frozen plasma (range 6-118), and 4 units of cryoprecipitate (range 0-70 units) was needed for each case. Only one patient developed a severe, massive intraoperative coagulopathy, requiring 141 units of blood, 80 units

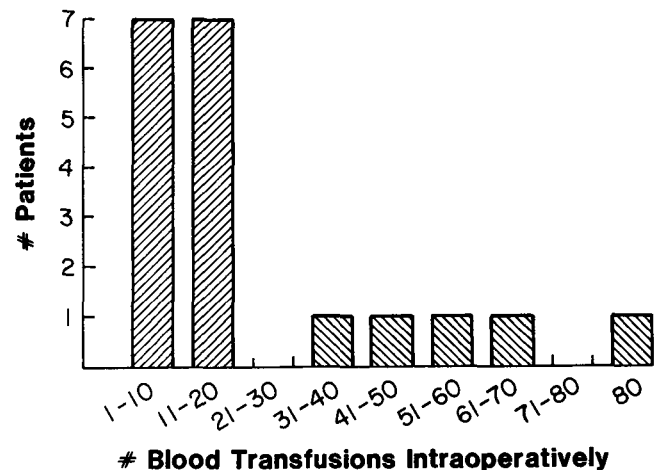


Fig. 3. Blood use during transplant surgery.

Table 4. Major complications after liver transplantation

	Survivors	Nonsurvivors	Total (%)
Rejection	12	5	17 (100)
Infection			
Viral	1	4	5 (29)
Bacterial	5	3	8 (47)
Fungal		1	1 (6)
CNS disturbances			
Seizures	5	4	9 (53)
Psychosis		1	1 (6)
Coma	2		2 (12)
Neurologic impairment	2		2 (12)
Hepatic artery thrombosis	1	1	2 (12)
Intra-abdominal bleeding	0	2	2 (12)
Renal insufficiency (dialysis needed)	1	2	3 (18)
Respiratory failure	1	1	2 (6)
Symptomatic pleural effusion	1	2	3 (18)
Perforated viscus		1	1 (6)
Hypertension	7	1	8 (47)
Other*	5	3	8 (47)

* Includes: seroma (3), tracheomalacia, bone marrow suppression, intraoperative coagulopathy, cyclosporine liver toxicity, transient heart failure.

of platelets, 118 units of fresh-frozen plasma, and 70 units of cryoprecipitate. Several patients had special blood drives conducted on their behalf. Over 3000 units of blood were donated in these efforts. No surgery has had to be cancelled in the hospital or the community because of blood used for liver transplantation.

Complications

Rejection, renal dysfunction, hypertension, vascular thrombosis, sepsis, pulmonary and neurologic problems, and intra-abdominal bleeding constituted the bulk of the postoperative complications (Table 4). Almost all patients had more than one complication. All had biopsy-confirmed rejection requiring increased dosages of corticosteroids. Never was graft or life lost because of rejection, although, in some, the treatment of rejection may have set the stage for mortal infections. Perhaps the most difficult complication to understand is a rather devastating diffuse neurologic motor disturbance that has occurred in two patients. This is characterized by major speech disorders and quadriplegia. One patient has demonstrated considerable improvement a year after transplantation with intensive physical therapy, but considerable speech difficulty remains. This patient lives at home and is largely self-sufficient. In the other patient, slow improvement is apparent, but he is still institutionalized.

Hospitalization

As of 8/31/86, 12 patients had survived liver transplantation and had been discharged from the hospital. For this group, the survival period is from 1 to 15 months (average, 6.2). The time spent in the hospital after transplantation averaged 38.5 days (range 19–134 days). Seven patients (64%) required 25 or fewer days. At least one readmission was necessary in 55%. The average additional hospitalization for the group was 13.5 days. Thus, after successful liver transplantation, the majority can look forward to a three- to four-week hospitalization and relatively little need for in-hospital care afterward.

Rehabilitation

Four of the five employed outside the home within six months before transplantation are back at work. Two patients who were homemakers before transplantation have been able to resume these activities. Five patients were unemployed for the six months before transplantation. Three of these had never worked: two were school-age, and the third had never been well enough to work. One of these five has obtained a full-time job for the first time in his life. Another has definite plans to return to her nursing job. Three remain unemployed. Only the two patients who developed severe neurologic syndromes seem unlikely to be employable in the foreseeable future.

The vast majority of patients consider their lives to be substantially improved by transplantation. The exceptions are the two patients who developed severe neurologic problems postoperatively. One of these also had a major depressive episode, which was successfully treated. Despite his neurologic deficit, he feels his life to be worthwhile and is pleased that he opted for the transplant. The second patient with severe neurologic sequelae remains quite ill and is in the process of rehabilitation.

Discussion

Until a few years ago, orthotopic liver transplantation was a procedure of uncertain value. As reports of improved survival began to appear, great interest in liver transplantation emerged. Improvement is credited to a number of factors, including better harvesting and preservation of donor livers, intraoperative developments such as venovenous bypass, reliable methods of biliary reconstruction, and improved immunosuppression with cyclosporine.⁵ Further stimulus to in-

creased applicability occurred in 1983 when the National Institutes of Health sponsored a consensus development conference on liver transplantation. It concluded that, for certain diseases, transplantation is not experimental but established therapy.⁶

Recent reports from Los Angeles, Boston, and Rochester, MN, document the successful establishment of liver transplantation programs.⁷⁻⁹ Our own development of a successful liver transplantation program has occurred along similar lines. The survival rate by life-table analysis at the Cleveland Clinic, 71% at four months, is remarkably similar to the results from other newer programs.^{7,8,10} These results also compare quite favorably to results from established programs in Germany¹¹ and the Netherlands,¹² and are similar to results reported for adults from Pittsburgh with comparable diseases.

Many reports detail the skills and resources required for the successful development of a liver transplantation program. All stress that this procedure, its antecedents, and sequelae are so complex that it cannot be done by one person or one department.¹⁴⁻¹⁶ A multidisciplinary team approach in a tertiary care facility is an absolute requirement. Our experience has certainly borne this out. Our patients have frequently required consultation not only with surgeons and hepatologists, but also with specialists in pathology, infectious disease, nephrology, neurology, blood banking, intensive care, psychiatry, social work, and others. It would seem unwise to commit institutional resources to liver transplantation unless these services are of high caliber and readily available.

The indications for liver transplantation are evolving as experience increases. A broad consensus exists regarding the types of diseases for which transplantation is most appropriate (*Tables 1 and 2*). Although alcoholic liver disease is the commonest cause of cirrhosis in the United States, only very occasionally is it considered appropriate to provide liver transplantation to such patients. Two reasons for this are apparent: first, such individuals are likely to continue drinking and neglect follow-up care; second, alcoholism often results in multiorgan disease, which may jeopardize survival. A review of the experience from four centers indicates that one-year survival for transplantation for Laennec's cirrhosis to be only 25%.¹⁷ One of our patients was a recovered alcoholic and has survived, but with a severe, slowly improving neurologic impairment.

The majority of adult patients in our series and others have had posthepatic cirrhosis, primary biliary cirrhosis, or sclerosing cholangitis. Children are most likely to have biliary atresia or an inherited metabolic disorder such as α -1-antitrypsin deficiency or Wilson's disease.

No consensus has emerged about liver transplantation in patients with liver disease due to hepatitis B. Our two patients are well 22 and 17 weeks later, although one has evidence of subclinical, recurrent hepatitis B. Neither was HBeAg positive before transplantation. Although both were given repeated doses of hyperimmune B globulin, neither lost HBsAg even transiently after transplantation. While some consider HBsAg, especially if HBeAg is present, to be a contraindication,^{5,18} others do not.¹⁹ Our early experience does not allow firm conclusions to be drawn yet. It is our conviction that such patients should undergo transplantation only in an environment where most health care workers dealing with such patients have been immunized.

When a major operation or program is started, it may take a some time for the team to learn the nuances that enhance the likelihood of survival (the "learning curve"). Most of the deaths occurred early in our series. A major contribution to less favorable early results is the tendency to select patients who are simply too sick to benefit from such a major undertaking. Four of the five deaths were in our patients who, before the transplant, were hospitalized and in unstable condition. In only one case (where hepatic artery thrombosis occurred) can faulty surgical technique be implicated in an early death. In the others, infection compounded by immunosuppression was the major contributor to mortality.

We learned that the team could develop skill rapidly and that entirely satisfactory survival rates can be attained from a less experienced center if a major commitment is made to the operation. It is hoped that the markedly reduced waiting time for transplantation in newer programs will save lives. In some centers, a significant number of patients die of their underlying liver disease while awaiting their turn for transplantation.¹⁵ Our patients waited only days to a few weeks for a donor to become available.

Conclusions

We have been able to develop a successful liver transplantation program, achieving early results that equal those of more experienced centers.

Most patients who undergo this life-saving operation survive with good quality of life. Considerable effort needs to be spent on improving results by better patient selection and by increasing the chances for success in those too ill to benefit from this operation now. This procedure can be safely performed by major institutions only with the commitment of a team from many disciplines.

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