

Lecture

Overview of Liver Transplantation for the Perfusionist

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Introduction

End stage liver disease is manifested by portal hypertension and impaired hepatic synthetic, metabolic, and immune function. Orthotopic liver transplantation is recognized as a therapeutic option for patients with end stage liver disease (ESLD). It is the only option which offers a chance for return to a relatively normal existence.

This therapeutic option is currently offered at 92 medical centers in the United States with approval from the United Network for Organ Sharing (UNOS). About 2,700 liver transplants were performed in the U.S. in 1990 and more than 90% of patients had successful surgical outcomes. Currently about 75% of transplant recipients are alive at 1 year and 60% are alive at five years following liver replacement (1).

Patient Selection

Patients considered for liver transplantation have irreversible liver disease that is intractable to other forms of therapy. The indications for liver transplantation in adults are listed in Table 1. Nationally about 21% of patients undergo liver replacement for cholestatic liver disease, 45% for other causes of cirrhosis such as viral infections, alcohol and autoimmune hepatitis, 8% for fulminant hepatic failure, 12% for biliary atresia, 6% for metabolic deficiencies, and 6% for neoplasms (1). In children the most common indication for liver replacement is biliary atresia after a failed portoenterostomy (2). Contraindications to liver transplantation include extrahepatic malignancy, uncontrolled extrahepatic sepsis, AIDS, active alcoholism or drug abuse, advanced cardiopulmonary disease, or other irreversible organ failure.

Advanced age alone should not preclude transplantation in patients with uncomplicated liver failure. Currently approximately 50% of all patients formally considered for liver transplantation actually undergo the procedure, while the rest are excluded by the evaluation process or die while awaiting a suitable donor (1).

Patient evaluation should establish a specific diagnosis and determine the current severity of the illness in relation to the natural history of the underlying disease so that the timing of the transplant can be optimized. Table 2 summarizes our criteria for establishing the need and timing of liver transplantation. Co-existing medical disorders, which can potentially complicate the operative or post-operative course, need to be identified, evaluated, and managed. Prior abdominal surgery often results in dense vascular adhesions which may complicate the recipient hepatectomy and significantly increase blood loss. Prior portosystemic shunting or portal vein thrombosis present technical problems which may contribute to perioperative morbidity and mortality. These problems underscore the need for careful delineation of the portal anatomy prior to liver transplantation.

In addition the transplant recipient selection committee should assess the patient's ability to comprehend the magnitude of the operation, and the need for life-long medical follow-up and compliance with medication schedules. Patients need a strong social support system to help ensure physical and emotional stability. The ultimate decision whether or not to transplant a patient is best made by a multidisciplinary selection committee that evaluates all aspects of transplantation as they relate to each patient.

According to UNOS statistics for 1988 and 1989 (1) there was about equal distribution of liver transplants between men and women. The median age for all recipients in 1989 was 42 years. About 19% of all recipients were under the age of 18, and 11% were less than 3 years of age. In 1988 and 1989 approximately 54% of recipients were hospitalized pretransplantation; 27% in an ICU and 56% of these patients were on life support. An additional 43% were partially disabled or homebound with failure to thrive. Less than 4% were working full-time or attending

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**TABLE 1
DISEASES TREATED BY LIVER TRANSPLANTATION
IN ADULTS**

1. Primary Biliary Cirrhosis
2. Sclerosing Cholangitis
3. Chronic Active Hepatitis
 - A. Viral
 - B. Autoimmune
4. Cryptogenic Cirrhosis
5. Alcoholic Cirrhosis
6. Budd-Chiari Syndrome
7. Polycystic Liver Disease
8. Hepatocellular Carcinoma
9. Fulminant Hepatic Failure
 - A. Toxic
 - B. Viral
10. Metabolic Disorders
 - A. Wilson's Disease
 - B. α_1 antitrypsin Deficiency
 - C. Hemochromatosis
 - D. Glycogen Storage Disease
 - E. Tyrosinemia
11. Failed Prior Transplant

school. In our experience about one third of patients had previous right upper quadrant abdominal surgery.

Donor Information

Selection of a donor liver is based primarily on ABO blood type and liver size. HLA tissue typing is currently not used. In 1988 and 1989, 87% of transplant recipients received ABO identical livers, 10% received ABO compatible grafts and 3% received ABO incompatible liver grafts (1). Because of diminished graft and patient survival, the use of ABO incompatible grafts are reserved for patients with severe liver failure in whom survival is dependent on liver replacement within 24-72 hours. Table 3 outlines our current criteria for donor selection. According to UNOS data the median waiting time was 2-3 months for a recipient, and about 25% of patients died before a suitable donor liver became available (1).

Some of the improving success of liver transplantation can be attributed to improvements in preservation of hepatic allografts. The University of Wisconsin (U.W.) solution provides excellent preservation of hepatic allografts for up to 24 hours. This solution helps 1) minimize hepatocyte edema by maintaining a high extracellular oncotic pressure with lactobionate and hydroxyethyl starch, 2) decrease anaerobic glycolysis by using an impermeable trisaccharide (raffinose), 3) and maintain cell integrity by providing ATP precursors (adenosine), an antioxidant (glutathione), and an oxygen free radical scavenger (allopurinol) (3).

Standardization of techniques for multiple organ retrieval facilitates cooperation among procurement teams, and efficient

**TABLE 2
CRITERIA FOR ESTABLISHING THE TIMING OF
LIVER TRANSPLANTATION**

Chronic Liver Disease

Hepatocellular dysfunction
nutritional deficiency and fatigue, serum albumin < 3.0 mg/dL, uncontrollable encephalopathy

uncorrectable coagulopathy, prothrombin time > 15 seconds, fibrinogen < 150 mg/d L

hepatic osteodystrophy, especially spontaneous fractures

Cholestasis

jaundice and pruritus, bilirubin > 10 mg/dL

recurrent biliary sepsis

Complications of portal hypertension

refractory variceal hemorrhage

refractory ascites

spontaneous bacterial peritonitis

progressive hypersplenism

hepatorenal syndrome

Fulminant Hepatic Failure

biopsy (if possible) proof of confluent necrosis

progressive encephalopathy, especially stage III-IV

prothrombin time of 25 seconds and rising, especially > 50 seconds

bilirubin of 10 mg/dL and rising, especially > 20 mg/dL

progressive renal dysfunction, especially Cr > 3.0 mg/dL

removal of heart, liver, lungs, kidney and pancreas allografts from a single donor. A midline incision is made from the sternal notch to the pubis and all potential organ grafts are visually and palpably inspected. If there is concern about the liver's appearance, a biopsy is obtained and examined for fatty infiltration and hepatocyte degeneration or necrosis. If the liver is found to be

TABLE 3
DONOR CRITERIA FOR LIVER TRANSPLANTATION

1. Brain dead, usually from spontaneous intracranial hemorrhage, head trauma, gunshot wound, anoxia, or primary brain tumor
2. Age: term newborn - 70 years of age
3. No uncontrolled systemic infection
4. No history of cancer except for brain or skin
5. No history of hepatitis, syphilis, TB, hemophilia; AIDS, HIV and Hb,Ag negative
6. No history of illicit IV drug use within the past year
7. No history of alcoholism
8. No severe liver trauma
9. Relatively stable hemodynamics with acceptable blood gases
10. Relatively normal liver function tests
11. Avoidance of extreme obesity

acceptable, it is partially mobilized by incising the various ligaments, and the arterial and portal blood supply to the liver are isolated. The common bile duct is transected distally and the biliary system flushed with saline via the gall bladder. A portal vein tributary is cannulated, and slowly infused with lactated Ringer's solution in anticipation of portal flushing and cooling.

If the kidneys and pancreas are to be retrieved they are mobilized and the ureters identified. The donor is then heparinized systemically and the distal aorta is cannulated in preparation for arterial perfusion with U.W. solution (See Figure 1). The vena cava can be drained distally through a cannula or into the chest by incising the atriocaval junction. The supraceliac aorta is clamped and the liver, pancreas and kidneys are perfused via the portal and aortic cannulas. At the same time the abdominal cavity is filled with an iced slush solution to help with rapid cooling of donor organs. After cardiectomy the liver is removed followed by pancreatectomy and en bloc nephrectomy. Donor iliac arteries and veins are also retrieved for potential use as vascular conduits during allograft implantation.

Recipient Operation

The recipient operation begins with preoperative preparation by the surgical and anesthesiology teams. The anesthesiology

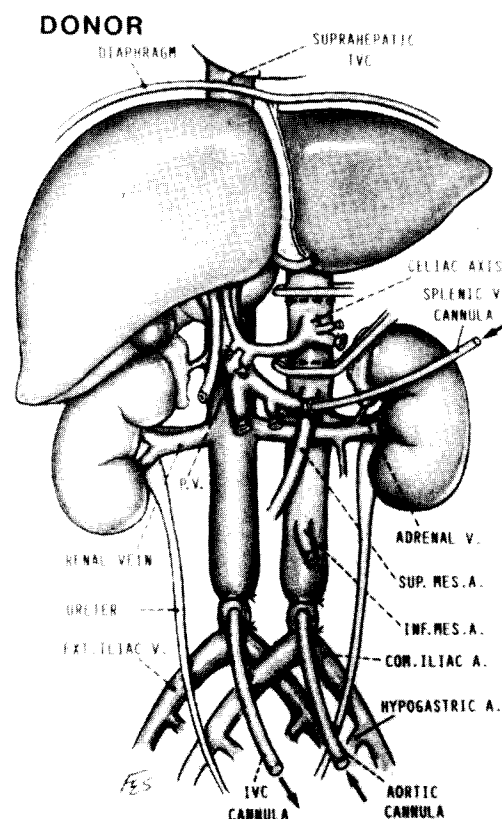


Figure 1

This diagram demonstrates the flushing of the donor liver and kidneys by two routes: arterially via a cannula in the distal aorta and into the portal circulation via a cannula in the splenic vein. The aorta cannula is flushed with 2 liters of U.W. solution. Drainage is via a cannula in the inferior vena cava or alternatively the atriocaval junction is divided. A cuff of donor aorta is taken with the graft between the dotted lines.

team develops an anesthetic plan for each particular patient based on the degree of hepatic dysfunction and associated complications, other pertinent medical conditions, and the patient's overall clinical condition. Preoperative medications may include an H₂-blocker or sodium bicarbonate for aspiration prophylaxis since delayed gastric emptying often accompanies severe liver disease. Preoperative sedation is usually not needed and may be contraindicated in the face of hepatic encephalopathy. Every effort should be made to maintain normothermia by heating the operating room prior to patient arrival and warming all intravenous fluids during the operation. Anesthetic induction should attempt to meet the following goals: 1) render the patient unconscious, unaware, and analgesic, 2) maintain hemodynamic stability, 3) avoid gastric regurgitation and aspiration, and 4) avoid increasing intracranial pressure in patients with existing elevated intracranial pressure. These goals are commonly achieved

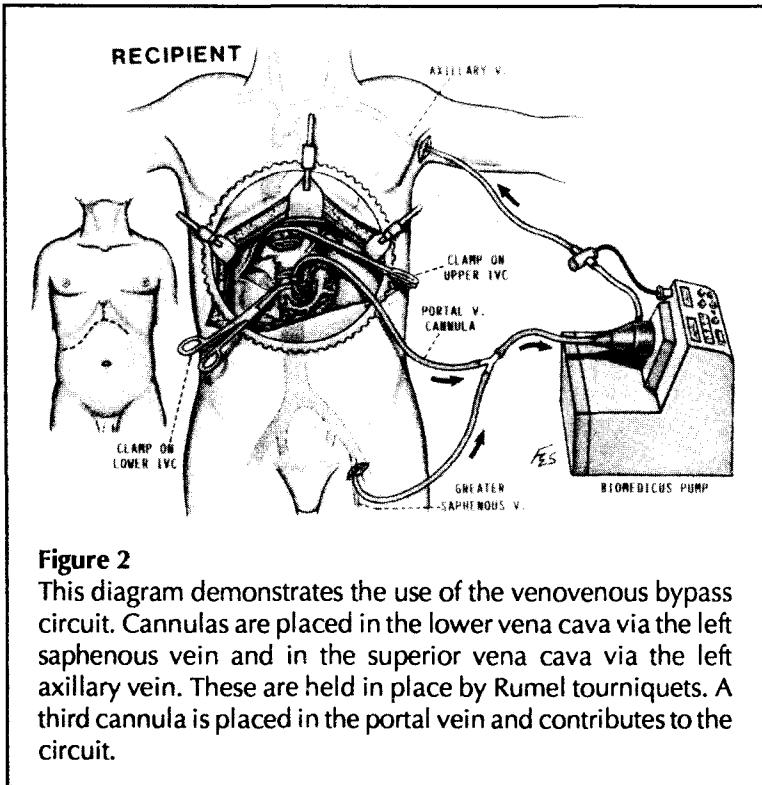


Figure 2
This diagram demonstrates the use of the venovenous bypass circuit. Cannulas are placed in the lower vena cava via the left saphenous vein and in the superior vena cava via the left axillary vein. These are held in place by Rumel tourniquets. A third cannula is placed in the portal vein and contributes to the circuit.

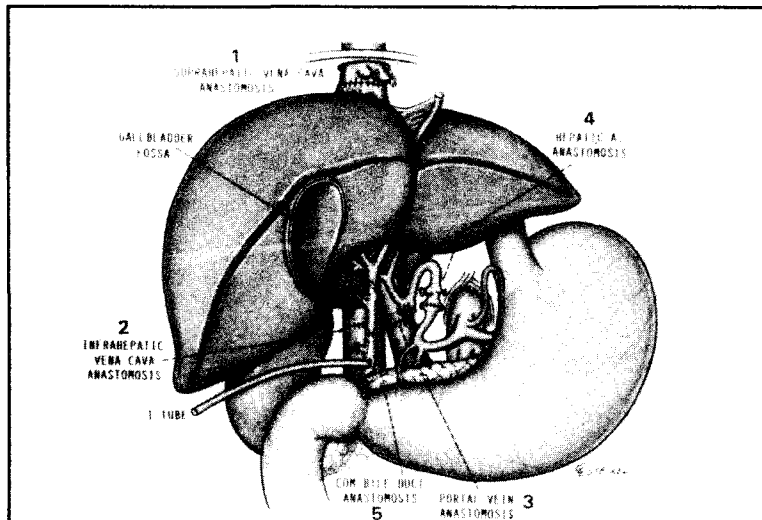


Figure 3
This figure demonstrates the 5 anastomoses in the recipient that are performed during the implantation of the graft.

liters/minute may be generated, if needed, during periods of heavy blood loss. Use of the automated cell saver system decreases the amount of bank blood transfused. Since these autologous red blood cells are deficient in clotting factors and platelets, they are infused with fresh frozen plasma and platelet concentrates.

After line placement, attention is given to patient positioning and padding. Hypothermia, episodic hypotension, surgical retraction, and length of case may all contribute to increased susceptibility to pressure sores and nerve palsies. The maintenance anesthetic most commonly used is isoflurane in an air-oxygen mixture (4). Narcotic may be added if desired. A long-acting muscle relaxant is administered to facilitate surgical exposure. Nitrous oxide is avoided because it will increase the size of any air emboli. Frequent (at least every 30 minutes) blood samples are sent to the laboratory to monitor blood gases, serum electrolytes, glucose, hematocrit, platelets, prothrombin time, partial thromboplastin time, fibrinogen, calcium, magnesium, and lactate. Thromboelastography greatly aids in assessing whole blood clotting and planning treatment for existing coagulopathy. We have found it beneficial to have a member of the clinical pathology/blood bank department present in the operating room for most of the operation. Intracranial pressure may be continuously monitored if necessary. The pulmonary artery catheter helps optimize fluid management and assess cardiac output. Frequently, low-dose dopamine is used to provide inotropic support, renal protection, and to limit the volume of fluid infused.

The first part of the surgical procedure is the recipient hepatectomy. This is the most demanding part of the overall procedure since this dissection is carried out in the face of portal hypertension, neovascularization of adhesions, and co-existing coagulopathy. Exposure to the liver is best achieved with a bilateral subcostal incision with the midline extension cephalad to the xiphoid. Fixed table retraction is helpful. The hepatic ligaments are divided and the supra- and infrahepatic vena cava, portal vein, hepatic artery and common bile duct are skeletonized. Liberal use of electrocautery, the argon beam coagulator, and suture ligation of the retroperitoneum help with hemostasis.

While the recipient hepatectomy is performed, the donor liver is prepared by skeletonizing and tailoring the blood vessels for future anastomosis. If replaced hepatic arteries are present, reconstruction is performed so that a single anastomosis between recipient and donor arteries will be possible.

The second phase of the recipient operation is the establishment of venovenous bypass. In adult patients the anesthesiology and surgical teams must decide whether or not to employ venovenous bypass. Clamping the IVC and portal vein dramatically decreases venous return to the heart and creates splanchnic and lower systemic venous hypertension. Physiologic changes

through the use of short-acting barbiturates and/or narcotics, muscle relaxants, and lidocaine.

Following induction the anesthesiology team inserts two arterial lines, an oximetric pulmonary artery catheter and two 8.5 Fr intravenous catheters for use with a rapid blood infusion system. An automated cell salvaging system is used in conjunction with the rapid infusion system and infusion rates up to 1-2

during the transplant operation are most dramatic during this anhepatic phase. In the early days of clinical transplantation liver replacement was performed without venous bypass (5). In 1979 Dr. Calne (6) reported the use of femoral vein to femoral artery partial cardiopulmonary bypass during liver transplantation. This bypass circuit improved the hemodynamic alterations of liver transplantation but the systemic heparinization contributed to significant hemorrhage. In 1983 the Pittsburgh group (7) reported the successful use of a heparin-less veno-venous bypass during liver transplantation. One year later they compared 57 patients transplanted with this heparin-less venovenous bypass to a group of historical controls transplanted without bypass (8). They reported better hemodynamics, better postoperative renal function, less blood loss and better operative survival in patients transplanted with venovenous bypass. Since then, most transplant centers use venovenous bypass routinely.

However, a few centers report excellent results without the use of venovenous bypass (9,10). With operative technical improvements, improved anesthesia expertise, use of vasoactive drugs, and adequate volume loading, Wall and colleagues (9) feel that the altered physiology during the anhepatic phase can be anticipated, monitored, and managed satisfactorily without venovenous bypass. Stock et al. (10) report that the rapid infusion technique is a safe alternative to venovenous bypass for improving hemodynamic stability during liver transplantation.

The potential benefits of venovenous bypass include decompressing the portal system which may help diminish venous bleeding in the peritoneal cavity and retroperitoneum, and increasing venous return to the heart which supports higher levels of cardiac output and renal perfusion during the anhepatic phase. Continuous venous return from the splanchnic and lower systemic systems also helps decrease edema of the bowel and pancreas during the anhepatic phase and minimize hyperkalemia and lactic acidemia at the time of graft reperfusion. The venovenous bypass circuit itself does not contribute to the coagulopathy (11). However, the use of venovenous bypass poses some additional risks including air embolus, thromboembolism, heat loss and local wound problems (5,11,12). Axillary and iliofemoral venous thromboses can occur and peripheral nerve injuries have been reported (13,14). While serious complications are rare, lymphatic leaks and seromas occur in 25% of patients (5).

When we (12) compared the results of liver transplantation with and without venovenous bypass in selected patients we found similar hemodynamic alterations, and no difference in renal function or operative and six-month survival in the two groups. We also found shorter operating time and less blood use in patients transplanted without the use of venovenous bypass. In selected patients hemodynamic stability during the anhepatic phase may be facilitated by the use of venovenous bypass, especially in more critically ill patients with less hemodynamic reserve. We currently advocate selective use of venovenous bypass, reserving its use for patients who do not tolerate vena caval clamping, or in patients with cardiac disease, severe renal insufficiency, or extreme portal hypertension with excessive adhesions.

Venovenous bypass is instituted by placing heparin-bonded #7 Gott shunts in the femoral and axillary veins and a #9 Gott shunt in the portal vein, creating an extracorporeal bypass circuit. After all air is removed from the circuit blood is circulated through a 3/8" polyvinyl chloride tubing driven by a centrifugal force pump (see Figure 2). Saphenofemoral and axillary venous cannulation sites are often prepared prior to recipient hepatectomy so that rapid cannulation can be performed in the event of sudden blood loss and hypotension. Systemic heparin is not used. The lower systemic and splanchnic venous systems are decompressed and blood is returned to the right heart via the axillary cannula. Flow rates of 1-5 liters/minute can be achieved with the centrifugal force pump (4). Flow rates below 1 liter/minute have been associated with thromboembolism (7).

The third part of the recipient operation consists of allograft implantation by establishing 4 vascular and 1 biliary anastomoses. The suprahepatic vena caval anastomosis is performed first followed by the infrahepatic vena caval anastomosis. The allograft is then flushed with cold lactated Ringer's solution via the portal vein to remove the preservation solution. The portal cannula is removed (peripheral bypass is continued) and the portal vein is reconstructed in an end-to-end fashion. The allograft is then perfused with portal blood, and aerobic cellular metabolism resumed. At this point venovenous bypass, if used, is terminated and cannulas are removed from the axillary and saphenous veins.

Reperfusion of the grafted liver is both an exciting and potentially dangerous event. Occasionally bradycardia, hypotension and increased filling pressures may ensue and rarely progress to ventricular fibrillation. The etiology of this post-perfusion syndrome is not clear, but may partially be due to rapid influx of cold, acidemic, hyperkalemic blood from the grafted liver and splanchnic and lower systemic circulation. Treatment consists of small doses of epinephrine (5-10 micrograms), calcium chloride and sodium bicarbonate. Defibrillation is rarely required.

The hepatic artery is reconstructed next. Usually the donor celiac origin is sutured end-to-end to the recipient common hepatic artery. Occasionally, if the recipient hepatic artery is not suitable, or inflow is poor, an arterial conduit from the aorta is constructed with the donor iliac artery. Once all the vascular anastomoses are completed, hemostasis is achieved and the donor gallbladder removed. Biliary reconstruction is by end-to-end choledochocholedochostomy in about 85% of adults (15). In adult patients with intrinsic biliary disease, such as sclerosing cholangitis, and in pediatric patients, a Roux-en-y choledochojejunostomy is used. (See Figure 3)

Closed suction drains are placed around the liver and near the biliary anastomosis. The fascia and skin are closed except in the sub-xiphoid midline where a transfascial defect is left to allow for future allograft biopsies. The median length of operation in our experience is 8 hours, ranging from 3.5 to 16.25 hours. The median blood products used were 12 units of packed red blood cells, 3 units of auto saved packed cells, 18 units of fresh frozen plasma and 30 units of platelets.

Postoperative Care and Complications

Liver transplant recipients are monitored initially in the intensive care unit. Adequate circulating blood volume is maintained with crystalloid or blood products as indicated. Allograft function is monitored by following the prothrombin time, fibrinogen, clearance of serum lactate, bile production, and liver function tests. Prothrombin times > 20 seconds, platelets counts < 50,000/mm³, and fibrinogen levels < 100 mg/dL are corrected. If there is satisfactory allograft function, the coagulopathy and lactic acidosis will usually correct within 24-48 hours. Patients with satisfactory allograft function generally have a more benign postoperative course and transfer to a ward may take place on the first or second postoperative day.

Maintenance immunosuppression usually includes Cyclosporine A, corticosteroids, and Azathioprine. 60-70% of patients will experience some rejection in the early post-transplant period; however this acute rejection usually responds to high-dose steroids. Steroid-resistant rejection is treated with an antilymphocyte preparation such as OKT3 or antilymphocyte globulin. Failure to control acute rejection leads to extensive hepatic necrosis necessitating urgent retransplantation.

Due to the complexity of the transplantation procedure a broad spectrum of complications occurs in more than 50% of the recipients (16). About 5-10% of transplant recipients will suffer from primary graft nonfunction or severe dysfunction resulting in profound metabolic, hematologic, and neurologic abnormalities (12). Patients with early graft failure will need urgent retransplantation. About 15% of patients will need surgical exploration for ongoing intra-abdominal hemorrhage or to evacuate intraabdominal blood to prevent secondary infection (16). Biliary tract complications occur in 13 to 34% of patients and may require surgical correction (16-18). Vascular thrombosis, usually involving the hepatic artery, complicates about 1-10% of transplants particularly in children, and generally results in graft failure (19,20). Constant surveillance for bacterial, viral and fungal infections is necessary in the immunocompromised transplant recipient. Post-transplant complications need to be diagnosed and treated promptly if hepatic allograft and patient survival are to be maximized.

Results

Patient survival following liver replacement has increased over the past 10 years. Nationally, patient survival rates reported from the Pittsburgh-UNOS registry was 78% at 6 months, 75% at one year, and 69% at 2 years (1). The median length of hospital stay in our experience was 28 days, with the range from 11-356 days. The Mayo Clinic reported that more than 90% of their patients alive more than 1 year after transplantation were able to return to full- or part-time work (21). 75 % of our surviving patients have resumed normal activities including work, while 14% are able to care for themselves and enjoy relatively normal activities but have not returned to work. 12% require some medical assistance. The long-term prognosis after liver trans-

plantation is excellent and the quality of life approaches that of the normal population. This is remarkable considering the degree of debilitation and short-term life expectancy that these patients experienced prior to transplantation. Transplant recipients require ongoing medical follow-up and periodic laboratory testing. Compliance with lifelong daily medication schedules is of utmost importance. Such impositions are surmountable if these transplant recipients become active participants in their own medical care.

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