Liver Transplantation in Hawaii

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The first liver transplant performed in Hawaii was on May 17, 1993 in a patient with end-stage liver disease caused by autoimmune hepatitis. Liver transplantation is a well-accepted treatment for end-stage liver disease with a 1-year patient survival of 80% to 85%. Early recognition of the appropriate candidate by primary care physicians and prompt referral to a liver transplant center are essential for optimal results. The indications, contraindications, organ procurement and allocation, complications, and results of liver transplantation are described. Finally, several controversial areas will be introduced, including liver transplant for alcoholic cirrhosis and hepatitis B, and use of transjugular intrahepatic portosystemic shunts (TIPS).

Case 1

In 1989 a 60-year-old woman who has a very distant history of breast cancer had a CT scan that noted a cirrhotic liver. A follow-up CT scan in 1990 showed the cirrhosis was unchanged. She had received no blood transfusions and was asymptomatic. In 1990, she developed intermittent mental slowness and fatigue. She was admitted in August 1992 for mental status changes, lethargy, and severe anemia. Her past medical history was significant only for a moderate amount of alcohol use, but none for more than a year.

Her physical examination was notable for mental slowness and encephalopathy, jaundice, scleral icterus, spider angiomata, and severe lower extremity edema. Her abdomen was distended with ascites and an umbilical hernia was present.

Her laboratory data was:

WBC: 5.2 x 10^9cells/mm^3 Hgb - 10.3 gm/dl; Hct 28.8%; Platelets 98K; Protime: 18.2 sec; PTT 41 sec; Albumin 2.5 gm/dl; Alk phos: 16.1 IU/l; Total Bilirubin: 7.6 mg/dl; AST: 91 IU/l; ALT: 37 IU/l; GGTP: 56 IU/l; Hep A,B,C; HIV: all negative; ANA titer 1:640; Antimitochondrial Ab<20; Alphafetoprotein 11.75.

Studies performed included CT scan and ultrasound of the abdomen which confirmed cirrhosis, splenomegaly, and patent vessels (portal vein, hepatic artery, hepatic veins, and vena cava).

In summary, she had end-stage liver disease probably from autoimmune hepatitis with manifestations of encephalopathy, ascites, malnutrition, and severe fatigue. She was evaluated by the members of the Liver Transplant Selection Committee at St. Francis Medical Center who agreed she was a suitable candidate for transplant; she was placed on the waiting list in April 1993.

On May 17, 1993, a suitable donor of identical blood type became available. The donor was hemodynamically stable and had good liver function prior to procurement. The donor procedure was done by the en-bloc technique, to include removal of the liver, pancreas and both kidneys. The donor organs were flushed with University of Wisconsin solution at 4°C. The pancreas was sent for use in Islet cell transplantation. The heart was procured by a separate heart team.

The liver recipient procedure began shortly thereafter. The cirrhotic liver was removed and the new liver was placed in the standard fashion using veno-venous bypass to maintain hemodynamic stability and prevent lower extremity swelling. The anastomoses included suprahepatic inferior vena cava (IVC), infrahepatic IVC, portal vein, hepatic artery, and bile duct. The entire procedure took 10 hours; cold ischemic time was 11 hours, and a total of 26 units of PRBCs were transfused.

Postoperatively, she maintained excellent liver allograft function. Her coagulopathy resolved (protime 11.3 sec., fibrinogen 458 mg/dl on the first post-operative day), she had no acidosis, and bile production was good. She also maintained good cardiovascular and renal function. She was given antilymphocyte globulin (ATGAM®) for induction therapy. Maintenance immunosuppression included prednisone, azathioprine, and cyclosporine. Her postoperative problems included febrile reactions to ATGAM®, and a mild rejection on the twelfth postoperative day which was treated with high-dose steroids. She was discharged on 21 days after the operation. She subsequently developed elevation of alkaline phosphatase and bilirubin, and cholangiograms suggested an extrinsic compression of the bile duct. She was found to have a mucocele of the cystic duct stump, which was drained intraoperatively. Her liver function tests returned to normal.

She is currently 6 months postop with continued good liver allograft function and no further rejection episodes. Her immunosuppression consists of prednisone and cyclosporine. She has gained weight (albumin 4.5 gm/dl), walks 3 miles each day, and performs household work.

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Discussion

Few medical discoveries have been as exciting as the development of liver transplantation. The first human liver transplant was performed in 1963 by Dr Thomas Starzl. His patient was a 3-year-old boy with liver failure caused by biliary atresia; he died intraoperatively from uncontrollable hemorrhage.[1] Liver transplantation has come a long way since then—with numerous advancements in preservation solutions, surgical techniques, and immunosuppression. Liver transplantation now has become an accepted treatment for end-stage liver disease—more than 2,900 liver transplants were performed in the United States in 1991, with one-year survival rates as high as 80% to 90%.

The above case illustrates the course of a fairly typical liver transplant. What follows is a discussion of liver transplantation to include indications/contraindications, the evaluation process, complications, and controversies.

Who needs a liver transplant?

There are 4 primary indications for liver transplant:

1. Irreversible advanced chronic liver disease
2. Neoplastic diseases
3. Metabolic liver diseases
4. Fulminant liver failure (usually from hepatitis B, autoimmune hepatitis or acetaminophen overdose)

Not all patients with the above-listed diseases will need a liver transplant; proper selection of patients and timing of surgery are essential. The patient should have advanced liver disease with complications such that liver transplant will improve survival and quality of life. General criteria for patient selection include:

1. Intractable ascites, not responsive to diuretic therapy
2. Uncontrolled variceal bleeding
3. Poorly controlled encephalopathy
4. Malnutrition
5. Fatigue, interfering with normal daily activities
6. Hepatorenal syndrome
7. Recurrent spontaneous bacterial peritonitis

Although the contraindications to liver transplant have become fewer with time, there are still 4 main contraindications:

1. Active sepsis outside the hepatobiliary tree
2. Malignancy outside the liver
3. Advanced cardiopulmonary disease
4. AIDS

Age, prior portacaval shunt, chronic alcoholism, and portal vein thrombosis are not absolute contraindications; however, these patients must be selected carefully. Advanced chronic renal failure may be a contraindication in certain scenarios, but a combined liver-kidney transplant can be performed.[2,3]

Who gets a liver transplant?

Before becoming a liver transplant candidate, the patient must be formally evaluated by a team of health professionals to include a transplant surgeon, hepatologist, anesthesiologist, nurses, and social workers. Multiple laboratory tests are obtained to assess the extent and etiology of liver failure. Serologic tests and tumor markers are also checked. An ultrasound examination and CT scan of the liver are used to look for tumors and determine vessel patency. All patients undergo cardiac evaluation with an EKG and echocardiogram and further testing is done for high risk patients. Psychosocial assessment is made to establish whether or not if the patient can adapt to the stresses of having a liver transplant, will be compliant with medications and postoperative care. Finally, the patient meets with a financial counselor. Members of the transplant selection committee will then meet to determine if a patient is an appropriate candidate.

How does a candidate get a liver?

When a patient is accepted as a candidate, he or she is placed on a waiting list. How a patient then gets a liver is largely regulated by a national organization called UNOS (United Network for Organ Sharing). It dictates the policies as to how donor organs are procured and distributed fairly. It oversees the actions of 261 transplant centers and 65 organ procurement organizations in order to distribute organs from nearly 4,300 cadaveric donors to the more than 22,000 patients waiting for transplants. This data includes all types of organs—most are waiting for kidneys and about 1,300 are waiting for liver transplants.

UNOS has divided the United States into 11 regions (Fig 1). When a donor liver becomes available, it is first used locally within the area of the organ procurement organization. If no suitable candidates are found, it is then offered within the region, and then nationally. The appropriate candidate for a donor liver is determined by the patient's size, blood type, time waiting on the list, and medical urgency status. Urgency status is the most important factor, and each patient is categorized into one of the 4 statuses listed.[3]

Status 1: Patient's level of functioning and overall health status are not yet affected by liver disease.

Status 2: Patient requires ongoing/frequent medical care, hospitalizations may be necessary.

Status 3: Patient is hospitalized and cannot be discharged.

Status 4: Patient is in the intensive care unit with liver failure and life expectancy is less than 7 days.

The entire system is continuously evaluated and improved by UNOS. Currently there is much debate as to whether major changes should be made in the allocation process. Some believe that giving priority to the sickest patients (Status 4) may not be practical because these patients already have many complications and are likely to have a higher mortality.

What is the hospital course of a liver transplant patient?

Performing the recipient operation of a liver transplant is probably the most complex and difficult of all abdominal surgical procedures. The procedure can take anywhere from 6 to 18 hours and requires meticulous technique and a tremendous amount of patience (Fig 2). Intraoperative problems can include hypothermia, coagulopathy, hypocalcemia due to multiple transfusions, and many hemodynamic changes caused by blood loss and reperfusion of the new liver.

Immunosuppression is started at the time of surgery and will continue throughout the patient's life. Each transplant center has

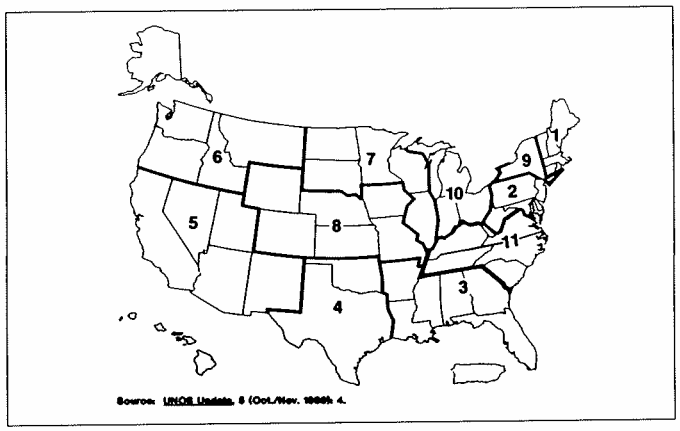

Figure 1.—Organs are distributed to local centers first, then within each of the 11 regions as determined by the UNOS map. (Courtesy of Thomas L. Fabry, MD and Franklin M. Klion, MD from the book *Guide to Liver Transplantation,* Ikagu-Shoin Medical Publishers, New York, New York; 1992)

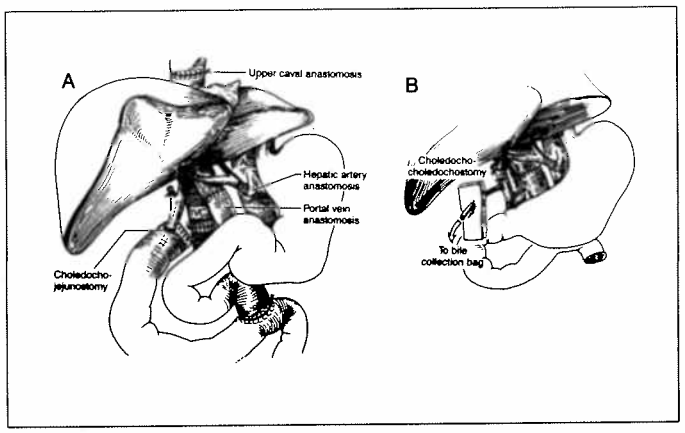

Figure 2.—The completed liver transplant. Two methods of connecting the bile duct are depicted. (Courtesy of Thomas L. Fabry, MD and Franklin M. Klion, MD from the book *Guide to Liver Transplantation,* Igaku-Shoin Medical Publishers, New York, New York; 1992)

its own protocol and new drugs are continually introduced and tested. In general, maintenance immunosuppression is with a combination of steroids, azathioprine, and cyclosporine. Drugs such as antilymphocyte globulin and OKT3 (monoclonal antibody directed against CD3 molecule on T-cells) are used as induction therapy and to treat severe rejection episodes. FK506 is a drug with properties similar to cyclosporine and can be used as maintenance therapy in place of cyclosporine for those patients with refractory rejection or intolerance to cyclosporine. FDA approval of this drug is expected in early 1994.

What are the complications?

Because liver transplants are such complex procedures and the patient is wrought with portal hypertension and coagulopathy, complications are common. About 20% to 40% of all patients will have a surgical complication requiring re-operation. Most common indications for operative intervention include bleeding, infection, and bile duct problems.[4,5]

Medical complications usually are related to immunologic problems, infections, or the side effects of medications. Rejection is common, and histologically proven rejection has been shown in one study to occur in 73% of patients.[6] Primary graft nonfunction or dysfunction may be due to immunologic problems or problems during the organ procurement. Early infectious complications usually are related to surgery. Later infectious complications include viruses (cytomegalovirus, Epstein-Barr virus) or opportunistic pathogens (pneumocystis, listeria). Finally patients may be at risk for lymphoproliferative disorders (due to immunosuppression) or recurrence of their original disease (especially hepatitis B and neoplasms).

What are the results of liver transplantation?

When patients are carefully selected and managed, the 1-year survival rate is 80% to 90% and the 5-year survival rate is 60% to 65%; however, these numbers will vary depending on the patient's original disease. The most favorable survival is obtained when patients are transplanted for primary biliary cirrhosis and sclerosing cholangitis. Results are less favorable for hepatic neoplasms and hepatitis B.

Should patients with alcoholic cirrhosis be transplanted?

Alcoholic liver disease is the single most-common cause for liver problems in the United States, but transplantation for this is somewhat controversial. The argument against transplantation is that these patients are "morally blameworthy", have associated medical problems, and are prone to recurrent disease. A number of studies have refuted this theory: The University of Pittsburgh demonstrated that 85.9% of the survivors remain abstinent post-transplant, and 74% return to some type of productive work. Factors that were predictive of abstinence include 1) support of a significant other, 2) acceptance of alcohol as the cause for liver disease, 3) active involvement in an alcohol treatment program, and 4) existing job or education allowing subsequent employment.[7] In general, patients with alcoholic liver disease can do well following liver transplant. Survival rates are comparable to patients with liver failure for nonalcoholic causes. Patient selection is absolutely essential, as only about 50% of all patients referred for transplant will be suitable candidates.[8]

Should patients with viral hepatitis B be transplanted?

An estimated 300,000 people will develop hepatitis B annually, with 15,000 having chronic hepatitis B and 300 progressing to fulminant liver failure.[7] Many of these patients will need liver transplants, however, there is concern over the significant rate of recurrence of hepatitis. We have learned a few things about the patterns of recurrent disease following transplant. It occurs more commonly in those with chronic Hepatitis B with cirrhosis, and less frequently in those with fulminant disease. High recurrence is thought to be due to extrahepatic replication of the viruses in such areas as bone marrow, spleen, and pancreas. Immunosuppression post-transplant also has been shown to enhance viral

replication; specifically steroids were found to increase hepatitis B surface antigen production. A number of centers are using hepatitis B immune globulin as prophylaxis with improved results. The 5-year survival is generally lower (60%) when compared to transplantation for other disease (80%).[9] Liver transplant for hepatitis B remains controversial; however, it is beneficial when performed in the proper setting. As we begin to understand immunoprophylaxis and develop new antiviral agents, perhaps we can learn to control recurrent disease.

What is TIPS?

The latest addition to the armamentarium of treatments for liver failure is the transjugular intrahepatic portosystemic shunt (TIPS). TIPS is a shunt that connects the portal venous system to the systemic circulation via the hepatic veins. It is essentially a portacaval shunt within the liver. These stents are placed by a skilled interventional radiologist with the assistance of high-resolution fluoroscopy, digital subtraction angiography, and ultrasound. Indications include portal hypertension with complications of bleeding varices, failed sclerotherapy, or ascites.[10] TIPS serves as a good bridge to liver transplant by decreasing the intraoperative and perioperative blood loss.[11]

Conclusions

The field of liver transplantation is exciting and dynamic. It is a well-accepted treatment for end-stage liver disease and when patients are carefully selected and managed, the 1-year survival rate is 80% to 90%. These are extraordinary results when it is considered this population of patients would not have survived their liver failure. With constant new developments in organ preservation, immunosuppression, immunoprophylaxis, and surgical techniques, results are likely only to improve.

References

1. Starzl TE, Marchioro TL, von Kaulla KN, Hermann G, Brittain RS, Waddel WR. Homotransplantation of the liver in humans. *Surg, Gyn & Obst.* 1963;117:659-676.
2. Maddrey WC. *Transplantation of the liver.* New York, NY: *Elsevier Science Publishing Co.* 1988.
3. Fabry TL, Klon FM. *Guide to liver transplantation.* New York, NY: *Igaku Shoin,* 1992;
4. Wood RP, Rosenlof LK, Shaw BW, Pillen TJ, Williams L. Complications requiring operative intervention after orthotopic liver transplantation. *Am J Surg.* 1988;156:513-518.
5. LeBeau G, Yanaga K, Marsh JW, Tzakis AG, Makowka L, Gordon RD, Todo S, Stieber AC, Iwatsuki S, Starzl TE. Analysis of surgical complications after 397 hepatic transplantations. *Surg Gyn & Obst.* 1990;179:317-322.
6. Stock PG, Snover D, Payne W. Biopsy-guided immunosuppressive therapy in the treatment of liver transplant rejection: an individualized approach. *Clin Transp.* 1987;1(4):179.
7. Van Thiel DH, Carr S, Iwatsuki S, et al. Liver transplantation for alcoholic liver disease, viral hepatitis and hepatic neoplasms. *Trans Proc.* 1991;23(3):1917-21.
8. Lucey MR, Merion RM, Henley KS, et al. Selection for and outcome of liver transplantation in alcoholic liver disease. *Gastroenterology.* (in Press).
9. Todo S, Demetris AJ, Van Thiel D, et al. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology.* 1991;13:619-626.
10. Conn HO. Transjugular portalsystemic shunts: The state of the art. *Hepatology.* 1993; 17(1):148-158.
11. Esquivel CO, Menegaux F, Egawa H, Keefe EB, et al. Impact of Transjugular Intrahepatic Protosystemic Shunts (TIPS) on transfusion requirements during orthotopic liver transplantation (by communication).

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