Liver Transplantation
By: Kay R. Brown, CLCP

Dr. Jeffrey Crippin, Director of Hepatology at the Baylor Institute of Transplantation in Dallas, Texas outlined during the Transplantation '97 seminar the primary indications for liver transplantation in adults to be advanced chronic liver disease, unresectable hepatic malignancies, fulminant hepatic failure and metabolic liver disease. Advanced chronic liver diseases are cholestatic, hepatocellular, vascular and polycystic. Examples of cholestatic diseases are primary biliary cirrhosis, which Dr. Crippin indicated is usually diagnosed in middle age women. Primary sclerosing cholangitis is usually diagnosed in middle age men. Other cholestatic diseases include biliary artresia, familial cholestatic syndromes and secondary biliary cirrhosis, which can be caused by a stricture occurring during the removal of the gall bladder. Hepatocellular diseases are chronic viral-induced liver disease such as Hepatitis C, chronic drug-induced liver disease, alcohol liver disease, and autoimmune liver disease. Unresectable hepatic disorders are associated with malignancies, hepatocellular carcinoma, and epithelioid hemangioendothelioma.

According to Dr. Crippin the necessary preconditions for liver transplantation are that the patient is an acceptable surgical risk, that they are reliable and compliant, and that they have an adequate support system. Contraindications for liver transplantation are active alcohol or chemical abuse; metastatic malignancy or non-hepatic primary malignancy; other serious diseases; HIV positive status; and angiosarcoma. Patients should be considered for transplantation when their quality of life deteriorates to an unacceptable level, when there is no reasonable alternative treatment, when the complications of End Stage Liver Disease (ESLD) reach a point at which there is no alternative treatment, when a patient has fulminant hepatitis, and with certain inborn errors of metabolism.

The most significant development in liver transplantation in the United States over the past year was the full implementation of the MELD and PELD based allocation policy, which has shifted emphasis from waiting time within broad medical urgency status to one based on prioritization by risk of waiting list death. (2003 OPTN/SRTR Annual Report). The MELD system is a unified, objective system. It takes into account creatinine, INR and total bilirubin, then correlates with 3-month mortality and correlates with outcomes by using a complex logarithmic formula. (Manzarbeitia, C. M.D. 2003).

Cosme Manzarbeitia, M.D., Chairman, Division of Transplant Surgery; Director, Liver Transplant Program at Albert Einstein Medical Center in Philadelphia P A. outlined the following information regarding liver transplantation during the United Resource Network's, A Course In Transplantation For Case Managers in Newport, RI in October 2003.

Contraindications for liver transplantation
Absolute:
* Extrabiliary infection.
* Extrabiliary malignancy.
* Severe cardiopulmonary disease.
* Uncontrollable, life limiting congenital anomalies.
* Active addiction / ETOH.
* Noncompliance (Manzarbeitia, C., M.D. 2003).

Relative:
* ETOH/VDA (Document rehab with 6 months of abstinence.)
* HIV without AIDS (Because of the effect of immunosuppression and antiviral meds on the liver.)
* Hepatic metastasis (only done with slow growing cancerous tumors.)
* Portomesenteric thrombosis.
* Large HCC (cancer) - Some are transplanted with living donors.
* Prior portocaval shunt (Manzarbeitia, c., M.D. 2003).

Testing for work-up: (Billed according to insurance contract and transplant centers billing methods.)
* Blood work - CBC, Coagulation profile, SMA-12, LFT, Blood type and screen.
* Oncological screening - Anergy panel, Immunizations, Tumor markers.
* Viral and Infectious Disease - HIV, CMV, HSV, EBV (Epstien Bar), Varicella; VDRL; Toxoplasma titer; Hepatitis A, B, C.
* Directed Testing - Genetic markers of liver disease (Ceruloplasmin, Alpha-I-antitrypsin level and phenotype); ANA, AMA, ASMA autoimmune antibodies); Antimicrosomal antibody, serum iron, TIBC, ferritin, serum protein, electrophoresis, IPEP.
* General imaging (Chest x-ray, Duplex ultrasound, CT, MRI.)
* Directed screening (Upper GI Endoscopy, Colonoscopy, PAP smear, Mammogram.) (Manzarbeitia, C., M.D. 2003).

Consultations:
Surgical, Cardiac / Pulmonary, Psychosocial, Renal, Nutrition, Dental, Oncological (if necessary). (Manzarbeitia, C., M.D. 2003).


Alcoholic liver disease - Survival ≥ non-alcoholics. Death and graft loss uncommon.

Hepatocellular Carcinoma (BCC) - Survival depends on size of tumor, vascular invasion, lymph node involvement and presence of cirrhosis. Success depends on role of chemoembloization and Radio frequency ablation given while waiting on transplant.

Hepatitis B (HBV) - Depends on HBV -DNA negativity - more recurrence after
transplant if active viral replication. Fulminant B or D have a better prognosis. Management of Hep B with HBIG (AIDS meds that work well with Hep B); lamivudine (Epivir) and new meds Adefovir (Hepsera).

**Hepatitis C (HCV)** - Poor risk for transplant because there is no cure for Hep C. 100% recurrence of Hep C with graft loss within 3 years. Never re-transplanted. HCV kills more people than AIDS. Steroids are needed post transplant and the steroids make the Hep C virus grow.

**Primary Biliary Cirrhosis (PBC)** - Very good outcome after transplant, but patients have an increased incidence of breast cancer so mammogram is needed to monitor for this. Patients have better outcome if they do not have renal dysfunction and encephalopathy.

**Fulminant Liver Failure (FHF)** - FHF has a very fast progress, so patients need emergent transplant. Graft survival depends on careful recipient selection and management. Bridges are often used with these patients while waiting on transplant, such as artificial liver (pig liver).

**Hereditary Hemochromatosis** - High prevalence of HCC and/or Dysplasia 46%. Cardiac involvement and infection risk lead to poorer survival.

**Other indications for transplant:**
- *TPN dependence with cholestatic liver failure - Need liver and small bowel transplant.
- *ESLD and ESRD - need liver and kidney. Liver transplant alone will not cure renal failure if have the patient has hepatorenal syndrome.
- *ESLD and cardiac failure - Coronary artery disease is important problem in >50% of population (Manzarbeitia, C., M.D. 2003).

**Living-related Liver Transplants:**
- *Only 15% of all patients are ultimately eligible for LR donor.
- *Not good for HCV cases.
- *Ideal for PBC and PSC (primary sclerosing cholangitis) with poor MELD priority (Manzarbeitia, c., M.D. 2003).

**Complications after transplant:**
- *Primary graft non-function.
- *Infections.
- *Acute cellular rejection.
- *Systemic problems (renal failure, neurological tremors, seizures, diabetes, hypertension.)
- *Disease recurrence (HCV, HBV, HCC.)
- *Lymphoproliferative disorder (with over immunosuppression.)
- *CMV infections.
- *Chronic rejections.
*Cardiovascular disease (Manzarbeitia, C., M.D. 2003).

Dr. Manzarbeitia outlined post-transplant medications as follows:
* Corticosteroids.
* Cyclosporine/tacrolimus
* Azathioprine/mycophenolate/cyclophosphamide,

The OPTN/SRTR Annual Report 2003 noted that the data on calcineurin inhibitors and antimetabolites indicate the widespread use of tacrolimus where previously cyclosporine was the favored calcineurin inhibitor and the reduction in use of azathioprine and concomitant adoption of mycophenolate mofetil as the antimetabolite of choice. A small but significant percentage of patients also received rapamycin. In 2001, more that 80% of liver transplant recipients were receiving at least two immunosuppressives (both corticosteroids and tacrolimus) and approximately half were receiving three (OPTN/ SRTR Annual Report 2003).

Dr. Manzarbeitia outlined immunosuppression side effects as follows:
* Tremulousness.
* Increased BUN, creatinine, potassium.
* Hypertension.
* Headaches, seizures, parasthesias.
* Bone marrow suppression.
* Hyperlipidemia.
* Weight gain.
* Diabetes mellitus.

Precautions
* Avoid direct unprotected sun exposure (10x more prone to develop skin cancer.)
* Eat in moderation to avoid weight gain.
* Use aspirin daily.
* Exercise judiciously (Manzarbeitia, C., M.D. 2003).

Allograft dysfunction needs sonogram and biopsy also serial LFTs, CMV cultures, Cholangiography, duplex ultrasound and CT scan will be needed (Manzarbeitia, C. M.D. 2003).

Experimental alternatives or bridges to transplantation are artificial liver support, such as Extracorporeal liver assist device (ELAD), which is in clinical trials. Other experimental techniques in clinical trails are intraportal hepatocyte transplantation, splenic hepatocyte transplantation and Hemocleanse system (Manzarbeitia, C. M.D. 2003).

Milliman USA Research Report 2002 indicates that survival rates for liver transplant recipients has improved since 1994, primarily due to the
immunosuppressant drug Tacrolimus, formerly known as FK506. One-year, three-year and five-year survival rates equaled 88%, 79% and 74% respectively. The median waiting time for a donor liver was 517 days. The median waiting time for children less than one year old was 140 days, and the median waiting time for persons ages 50-64 was 628. Milliman outlined the cost of liver transplantation through the first year following transplant as follows: Evaluation - $17,200; Procurement $54,100; Hospital $131,800; Physician $42,700; Follow-up $58,400 and Immunosuppressants - $9,400. (2002, Milliman, USA).

Works Cited:
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