Part III: Gastroenterological Disorders

Chapter 34: Liver Transplantation

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Introduction

The first human liver transplant operation was performed in 1963 but extended survival (1.5 years) was not achieved until 1967. Since then, results have improved and liver transplantation has become accepted as a service rather than an experimental operation. Intensive care management of such patients is thus vital. Two forms of liver transplantation have been used clinically:

1. *Orthotopic* (OLT) - the recipient's diseased liver is replaced with a donor liver (homograft); and

2. *Heterotopic* - the diseased liver is left in situ with the new liver transplanted in an ectopic site.

OLT has been more successful and constitutes the vast majority of the total experience.

Recipient Selection

Liver transplantation is indicated in chronic, irreversible and progressive liver disease intractable to medical or alternative surgical therapy. It may also be indicagted when patients experience severe subjective symptoms, such as fatigue in primary biliary cirrhosis. Transplantation may be appropriate in the following diseases.

1. Biliary atresia.
2. Inborn error of metabolism, eg, alpha-1 antitrypsin deficiency, Wilson's disease and tyrosinaemia.
3. Chronic active hepatitis.
4. Primary biliary cirrhosis.
5. Sclerosing cholangitis.
6. Primary hepatic malignancy.
7. Subacute hepatic necrosis.

Major contraindications include extrahepatic malignancy and severe sepsis and active alcoholism. Portal vein thrombosis, severe cardiopulmonary or renal disease, age over 55 years, past multiple abdominal operations, psychological instability and positive hepatitis B e-antigen infection are relative contraindications. Fulminant hepatic failure (FHF) and advanced encephalopathy are by themselves, not outright contraindications.

Donor Selection

All necessary medical and legal formalities for organ harvesting are met beforehand. It is usual to obtain other organs at the same from the liver donor. The clinical criteria for postmortem liver donors are more restrictive than for renal donation (Table 1). The criteria for donor selection is less stringent when transplantation is urgent (eg, with FHF or retransplantation). Histocompatibility matching between donor and recipient is not undertaken because of the time involved and the small recipient pool. Lymphocytotoxic crossmatching (testing recipient serum against donor lymphocytes) is controversial, but positive matches may predispose to humorally mediated rejection.

Table 1. *Clinical Criteria for Cadaveric Liver Donors*

1. Age less than 55 years.
2. No hepatobiliary disease or severe liver trauma.
3. Acceptable liver function tests and coagulation profile.
4. Size and ABO compatibility with available recipient.
5. No extracerebral malignancy.
6. No active systemic or hepatic infection.
7. Negative HIV and hepatitis B serology.
8. Negative cytomegalovirus (CMV) serology (if recipient is CMV negative).

Operation

There are three components to the entire procedure for liver transplantation.

1. Donor hepatectomy.

2. Recipient hepatectomy and establishment of veno-venous bypass during the anhepatic period. Routine use of bypass has resulted in improved haemodynamic stability, less blood loss and postoperative renal failure, and better survival.

3. Liver implantation by anastomoses of the liver vessels and biliary tract reconstruction. The recipient operation takes 6-16 hours. A recently developed University of Wisconsin perfusion solution, has increased liver preservation times from approximately 8 to 20 hours. This may allow transplantation to be undertaken on a more elective basis.

Blood loss can reach 1500 mL/min, and blood requirements may range from 10-100 units. In general, one unit each of fresh frozen plasma (FFP) and platelets are required for each unit of blood. The anhepatic phase (when metabolic acidosis may develop) and the revascularization phase (when disseminated intravascular coagulation (DIC) may occur) are critical times during the operation.

Postoperative Management

The postoperative care of liver tranplant recipients is potentially difficult and patients should be admitted to the ICU.

1. *Mechanical ventilatory support* is required for the first 12-48 hours.

2. *IV fluids and blood products* are administered as required. Excessive drainage of ascites will require increased fluid and protein volumes. This occurs mostly in those with gross ascites preoperatively, but may rarely signify development of an acute Budd-Chiari syndrome.

3. *Surgical drains* are monitored for volumes and presence of frank blood or bile which may be indications for reoperation.

4. *Routine medications* include a broad spectrum antibiotic (eg, cefotaxime) for 5 days, stress ulcer prophylaxis (eg, IV ranitidine 50 mg tds), vitamins and minerals, oral and nasogastric nystatin and immunosuppressive drugs (see below). If the patient has negative cytomegalovirus (CMV) serology, CMV hyperimmune globulin (10.000 units) is administered daily for at least one week. In some centres selective decontaminatino of the digestive tract is practised.

5. *Routine investigations* include regular arterial blood gas measurements, 6 hourly measurements (for the first 24 hours) of full blood count, coagulation profile, plasma electrolytes, glucose, creatinine, ionised calcium and liver function tests. Plasma concentrations of magnesium, phosphate, albumin and amylase are measured daily. Cyclosporin levels are measured daily and other drug levels are determined when indicated. A chestX-ray and 12-lead ECG are performed daily. Cultures of drains and body fluids are performed every second day. The function of the allograft is routinely monitored by radionucleide scanning on day 2 and day 5.

6. *Narcotic analgesics* are administered by infusion (eg, morphine 1-10 mg/h). Analgesic requirements usually decrease markedly after the first few postoperative days.

7. *Active chest physiotherapy* is required.

8. *Psychiatric and emotional support* for both the patient and relatives should be continued.

9. *Nutritional support* by enteral or parenteral (TPN) feeding should be given. Resting energy expenditure (REE) is increased in chronic liver disease. Hypercatabolism is present in the early period after OLT. Lipid and carbohydrate intolerance occur, and high caloric TPN should be avoided.

Immunosuppression

Methylprednisolone (1 g IV) is administered intraoperatively before revascularization of the liver. A further 500 mg IV is administered postoperatively. The dose is then tapered daily to give a maintenance dose of 0.5 mg/kg by the end of the first 2 weeks.

Cyclosporin 10 mg/kg is given orally preoperatively. If renal function is stable, 4 mg/kg/day is given IV in 2-3 divided doses from the first postoperative day. Once oral intake

is established, 12 mg/kg/day is given orally in 2 divided doses. Cyclosporin absorption depends on enterohepatic circulation and requirements may decrease when the T-tube is clamped. Therapeutic levels are 400-800 ng/mL. Adverse effects of cyclosporin are shown in Table 2.

Table 2. *Adverse Effects of Cyclosporin*

1. Nephrotoxicity.
2. Neurotoxicity.
3. Hepatotoxicity.
4. Hypertension.
5. Hirsutism.
6. Gingival hyperplasia.
7. Flushing, nausea and abdominal discomfort.
8. Thromboembolism.
9. Lymphoproliferative disease.

Azathioprine or other immunosuppressive agents should be substituted if renal dysfunction is present, until cyclosporin can be introduced.

Postoperative Complications

Patients with endstage liver disease frequently have profound nutritional depletion, debility and multiple organ dysfunction preoperatively. Hence, 85% develop at least one postoperative complication.

1. Bleeding

Continuing postoperative bleeding is usually of surgical origin. Urgent re-exploration is often required. Bleeding associated with coagulopathy can usually be corrected with infusion of fresh frozen plasma and platelets. Inability to correct the coagulopathy is usually a sign of poor graft function. Thrombocytopenia is common in the first week. The aetiology is unclear but patients usually have a hyperplastic bone marrow. The allograft itself, with ischaemic damage, may be the major site of platelet sequestration.

2. Metabolic Complications

(a) *Hypothermia* occurs despite intraoperative use of warming blankets and requires continuing treatment.

(b) *Hypokalaemia* is probably secondary to preoperative potassium depletion and uptake into the allograft, following loss from the hepatic cells during the period of cold preservation. Controlled replacement is indicated. Persistent hyperkalaemia postoperatively is an ominous sign of poor liver function.

(c) *Metabolic alkalosis* is frequent during the early postoperative period and is probably due to the large amounts of citrate infused with stored blood as well as hypokalaemia.

(d) *Hypocalcaemia* is also due to the citrate load from massive transfusion. Calcium deficits should be replaced.

(e) *Hypomagnesaemia* is implicated in postoperative seizures. Postoperative magnesium deficits should be corrected.

(f) *Hyperglycaemia* occurs frequently and is probably secondary to steroid therapy. Insulin by infusion may be required. Persistent hypoglycaemia in the early postoperative period suggests poor liver function and a grave prognosis.

3. Pulmonary Complications

Patients are electively ventilated in the initial postoperative period. The most common pulmonary complications are infections including pneumonia, empyema and lung abscess, caused by bacteria, viruses, fungi, or *Pneumocystis carinii.* Pleural effusions, primarily right-sided, are common. The majority resolve spontaneously or respond to diuretic therapy. If the adult respiratory distress syndrome (ARDS) occurs after liver transplantation, an intra-abdominal catastrophe should be suspected. ARDS is associated with acute allograft rejection, hepatic artery thrombosis, and most commonly, sepsis.

4. Cardiovascular Dysfunction

Hypertension is a frequent complication when cyclosporin is used, and antihypertensive agents are required. When sustained and refractory, infusions of hydralazine or sodium nitroprusside may be indicated. Hypertension is thought to be due to effects of cyclosporin, although the mechanism is unknown. Other cardiovascular complications are rare.

5. Renal Dysfunction

Postoperative renal dysfunction occurs in up to 2/3 of liver transplant recipients. Preexisting renal failure is exacerbated. Raised plasma creatinine levels and the need for haemodialysis are poor prognostic indicators. Persistent renal failure may result from continuing bleeding, sepsis or poor allograft function (possibly further compromised by nephrotoxic drugs, especially cyclosporin, aminoglycosides and amphotericin). Preoperative renal failure due to the hepatorenal syndrome, usually resolves postoperatively. The use of venovenous bypass and low-dose dopamine infusion (2 microg/kg/min) have decreased the incidence of postoperative renal failure.

6. Neurological Complications

Neurological complications occur in 1/3 of liver transplantation patients. Fits are common, usually associated with cyclosporin toxicity or hypomagnesaemia. Clinical features of cyclosporin neurotoxicity range from minor neuropsychiatric syndromes through to the syndrome of encephalopathy, seizures and white matter oedema, sometimes associated with cortical blindness. Cyclosporin neurotoxicity occurs in 30% of liver transplantation patients, but in only 0.5% of other organ transplantation. If no cause can be demonstrated for neurological compilcations, cyclosporin dosage should be reduced. Other neurological complications include hypoxic encephalopathy, air embolism, intracerebral haemorrhage,

central pontine myelinolysis, hepatic and metabolic encephalopathy, and opportunistic infection (with listeria, cryptococcus and viruses being most common).

7. Infection

Up to 80% of liver transplant patients have at least one infection postoperatively. The majority are bacterial infections and appropriate antibiotics should be given. Fungal infections (42%, with Candida and aspergillus being most common) should be treated with amphotericin B. The most common viral infections are of Herpses and CMV, and should be treated respectively with acyclovir 5 mg/kg tds and gancyclovir 5 mg/kg/day. Abdominal infection occurs in approximately 20%. Diffuse peritonitis has a mortality rate of 75%, due more to mixed infections than isolated bacterial infection. Localized intra-abdominal abscesses occur most commonly in the right subphrenic space. Immunosuppressive therapy should be reduced in significant infection.

8. Liver Dysfunction

Immediately after transplantation, plasma transaminases are elevated, due to unavoidable ischaemic injury. Concentrations are usually less than 1000 IU/mL. Levels above 3000 IU/mL usually indicate significant damage. Plasma bilirubin is often lower than preoperative levels due to "wash-out" from massive transfusion. Liver function usually returns towards normal relatively quickly but up to 2/3 patients have a degree of liver dysfunction after this initial ischaemic episode.

(a) *Ischaemic Injury* - A non-functioning graft is an extreme form of ischaemic injury. There is total hepatic failure with profound hypoglycaemia, coagulopathy and coma. Treatment is retransplantation, although only 20% of those retransplanted survive.

(b) *Technical Consultations* - Bleeding is the most frequent postoperative technical complication. Graft failure may result from occlusion of any of the four vascular anastomoses. Hepatic artery thrombosis occurs in approximately 3% of adults and 12% of children. It may present as massive liver necrosis, bile duct necrosis, or liver abscesses. Problems with the biliary anastomosis occur in 10-15%. These include biliary leaks, strictures, and obstruction. Biliary tract problems are diagnosed by a T-tube cholangiogram or by percutaneous cholangiography.

(c) *Rejection* - Rejection is the commonest cause of graft dysfunction and occurs to some extent in every patient in the 2nd and 3rd week. The clinical picture and severity are variable. There is frequently general malaise, fever and abdominal pain associated with firmness and tenderness of the graft. Rejection may develop slowly and progressively or acutely and rapidly, which is difficult to treat. The diagnosis is made by liver biopsy. In acute rejection there is infiltration of the portal tracts, particularly the bile ducts, with lymphoid cells and associated endothelitis. A common form of chronic rejection is the vanishing bile duct syndrome, which has been associated with a mismatch for class I HLA antigents. Treatment of rejection episodes consists of increasing steroid doses, antilymphocyte globulin (ALG) and/or a monoclonal antilymphocyte antibody such as OKT3. The latter has been shown to improve graft survival when steroid therapy is unsuccessful.

(d) *Hepatic Infection* - Infection of the transplanted liver with viruses may occur at any time but usually between 2 weeks and 3 months. Pathogens include Hepatitis B, CMV, Herpes simplex and zoster, adenovirus and Epstein Barr virus.

(e) *Drug Induced Injury* - Virtually all groups of drugs have been associated with liver injury. Cyclosporin, azathioprine, methyldopa, phenytoin and many antibiotics have been incriminated.

(f) *Cholestasis* - Cholestasis may occur in the first two weeks after srugery. The causes are multifactorial and similar to the "benign postoperative cholestatic syndrome" or "ICU jaundice", and it usually settles by the end of the third week. A schema for the diagnosis and treatment of postoperative liver dysfunction is shown in the figure.

1. Liver Dysfunction --> Sepsis Cholangitis Vascular
    a. No - Go to 2.
    b. Yes - Go to 3.
2. Liver Biopsy --> Rejection
    a. No - Go to 4.
    b. Yes - Go to 5.
3. Treat Appropriately
4. a. Drugs
    b. Surgical Cholestasis
    c. Viral
5. Anti-Rejecton Therapy.

Paediatric Considerations

The major indications for OLT in children are biliary atresia and genetic and metabolic disorders. Chronic liver disease, FHF and liver tumours are less common indications. The long term survival rate is higher than for adults, and as many as 80% survive for 2-3 years. Paediatric liver transplantation has been impeded by a shortage of paediatric donors. This has led to the technique of reduction hepatectomy of adult donor livers by performing an in-vivo or ex-vivo right hepatic lobectomy or trisegmentectomy. Complex vascular techniques are required to reduce adult major blood vessels to a size suitable for anastomosis. Technical complications, particularly hepatic artery thrombosis, are more common in children. Venovenous bypass is not always used in paediatric patients as they generally remain haemodynamically stable during the anhepatic phase. Most children exhibit normal or accelerated growth following a successful liver transplant, and the majority have an excellent quality of life.

Retransplantation

In the early postoperative period, retransplantation is indicated if the primary graft fails (up to 20% of cases). Survival rates approach 50% except those in coma. The most frequent indications are primary graft nonfunction, intractable rejection or complications arising from technical problems. Retransplantation may also be required some time after transplantation, usually because of intractable chronic rejection.

Liver Transplantation for Fulminant Hepatic Failure

Currently, worldwide survival rates for OLT in FHF (41 cases) is 61%, and hence transplantation is rapidly becoming a standard option in the treatment of FHF. The key issues are:

1. Rapid diagnosis and estimation of prognosis. The best clinical predictor of outcome is the degree and rate of deterioration of encephalopathy. Rising prothrombin time, renal impairment and hypoglycaemia are all ominous signs that influence the decision towards liver transplantation.

2. Meticulous medical support. (See Chapter 33, Hepatic Failure.)

3. Ready availability of donor.

Liver transplantation for FHF is technically less difficult because of the abscence of established porto-systemic collateral blood channels. Despite the coagulopathy, massive blood loss is not usually a major problem. Successful liver transplantation is followed by rapid return of consciousness within the first few days. Results have been poor with grade IV encephalopathy, severe renal failure and massive gastrointestinal bleeding. Improving survival rates suggest liver replacement may be justified in somewhat earlier stages of FHF. Viral hepatitis is the most common cause of FHF. Hepatitis B immunoglobulin, injected during the anhepatic phase, does not seem to be effective in preventing recurrent disease (and may be associated with fatal intraoperative thromboembolism).

Outcome

Early death is related to infection, multi-organ failure and uncontrollable rejection. One year survival can be as high as 80% and 5 year survival 60%, and the majority of patients experience a good quality of life. Most mortality occurs in the first 6 months after transplantation, and in patients who survive 1 year, the chance of dying each year afterwards, is < 3%. Deaths after the first year are due chiefly to recurrence of primary liver malignancy, graft rejection, lymphoproliferative disease, opportunistic infections or late bile duct complications. Recurrent tumour can be expected in up to 80% patients transplanted for primary hepatic malignancy.