


Intensive Care of Liver Transplant Patients

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Intensive Care of Liver Transplant Patients

A. Recent advances in human orthotopic liver transplantation

1. Introduction and historical perspective

The first human liver transplantation was performed by Thomas Starzl in 1963.¹ During the next 12 years, however, only 169 additional liver transplantations were performed.² During this early interval, difficulties with donor liver procurement, surgical technique, and postoperative rejection placed the future of liver transplantation in doubt. Nevertheless, as experience grew and new techniques developed in liver transplantation, the number of patients successfully undergoing this procedure accelerated. Accordingly, the 1983 Consensus Development Panel at the NIH concluded that liver transplantation was an acceptable therapeutic modality for the treatment of end-stage liver failure.³ Associated with this acceptance, the number of centers in the United States performing liver transplantations increased several fold: by the end of 1985, 1441 liver transplant procedures had been performed (fig. 1). Similarly, at the University of Pittsburgh the number of liver transplant procedures has grown each year (fig. 2). A 1984 survey by Starzl et al.⁴ revealed that since the start of human liver transplantation in 1963, 269 (47.3%) of 569 North American recipients were still alive. The overall 1-year survival improved from 32.9% in 1979 to 75% in 1984. During the years 1981 to 1985, 653 liver transplantations were performed at the University Health Center of Pittsburgh. During these 5 years, our postoperative care in the intensive care unit (ICU) evolved on the basis of numerous observations

of the variable postoperative course of these patients. ICU care is also determined to a large extent by the surgical procedure, which has seen significant changes over the last 5 years. The first part of this chapter will describe recent trends in liver transplantation as they may reflect on ICU care, while the second part will focus on the specifics of postoperative management.

2. Patient population and pretransplantation care in the ICU

a. End-stage liver failure as a disease

Patients awaiting liver transplantation are usually chronically ill, as would be expected from the indications for liver transplantation (fig. 3). When portal hypertension is present, gastrointestinal hemorrhage is common. Most adult liver transplant candidates have had at least one episode of acute upper gastrointestinal bleeding. Similarly, most have abnormal coagulation profiles, hypoalbuminemia, and an altered cardiovascular profile that reflects a high output, low peripheral vascular resistance state. It has recently been suggested that end-stage liver failure predisposes to multiple organ system failure.^{5,6} If so, then our liver transplant candidates are at an increased risk to develop remote organ system failure while awaiting surgery. Recently, Matuschak and Martin⁷ described the cardiovascular response to sepsis of patients with end-stage liver failure. They found no difference in the hemodynamic profile between stable preoperative patients awaiting liver transplantation and similar patients with liver failure during or after an acute septic episode. This finding underscores the previously held clinical impression that it is difficult to diagnose sepsis in patients with liver failure. More important,

however, these data suggest that end-stage liver failure coexists with a generalized toxemia due to failure of hepatic defense and clearance mechanisms. In further support of this hypothesis, Matuschak et al.⁸ found that when patients with end-stage liver failure developed hypoxemic respiratory failure, (i.e., adult respiratory distress syndrome) their clinical course uniformly led to death. That this lethal interaction may be reversed by liver transplantation is suggested by Esquivel et al.⁹ who found that 9 of 22 children (40%) with liver failure and remote organ failure survived liver transplantation. Given the high mortality of multiple organ system failure, these results suggest that an irreversible process may be reversed by changing the internal environment.

b. Treatment for metabolic diseases

Perhaps the most exciting application of liver transplantation is in the treatment of metabolic diseases (inborn errors of metabolism). If a metabolic disease damages the liver, then such patients have clear benefit from liver transplantation. Since the mortality after liver transplantation is decreasing, it may become reasonable in the future to transplant livers in patients who are not yet in end-stage liver failure, but have a fatal or a very disabling primary metabolic disorder. Patients with alpha-1 antitrypsin deficiency and tyroseinemia have not only benefited from having their failing liver replaced, but have also been cured of their underlying metabolic disease.⁴ Patients with other metabolic diseases, such as familial hypercholesterolemia, also may benefit from liver transplantation.¹⁰ A partial list of these diseases is given in table 1.

c. HLA tissue typing

Experience with both renal and cardiac allograft transplantation suggests that human lymphocyte antigen (HLA) matching is important for subsequent donor organ viability.¹¹ Nevertheless, an early study at our institution failed to demonstrate any relation between HLA compatibility or positive cross-match and liver transplant survival.² In fact, experience with combined liver-kidney transplants at our institution suggests that preformed donor-specific antibodies are removed from the circulation by the donor liver without apparent adverse effects.¹² In contrast, Knechtle et al.¹³ found that under certain instances, the liver allograft may undergo hyperacute rejection. Recently, Markus et al.¹⁴ reexamined the relation between HLA compatibility and liver transplant survival in our institution between March 1980 and December 1985 (667 liver transplantations in 517 patients). Complete data were available for HLA-A and B antigens in 332 donor-recipient pairs. Survival of primary grafts with no HLA-A antigen mismatch was less than survival of those with one or two HLA-A antigen mismatches (fig. 4). The HLA-B data showed no effect of compatibility on liver survival. Complete typing data were available also for HLA-DR antigens in 292 donor-recipient combinations. Again, one and two DR-mismatched liver allografts had a better 1-year survival than HLA-DR-matched patients (fig. 5). These findings suggest that histocompatibility does not improve graft survival and may adversely affect liver transplants. Similarly, successful liver transplantation across ABO blood groups from cross-match positive donors suggests a relative resistance of the liver allograft to the deleterious effects of ABO and donor-specific antibodies.^{15,16}

d. Viral hepatitis

Liver transplantation in patients with cirrhosis due to viral hepatitis is controversial. Despite the fact that the liver, which houses the major viral "load", is removed during liver transplantation and that the circulation is flushed with large quantities of blood and plasma products, in our experience many of these patients have a persistent hepatitis B surface antigenemia postoperatively and develop evidence of recurrent chronic hepatitis in the newly transplanted liver.¹⁷ Until it is shown that the virus can be eliminated in e antigen-positive patients, transplantation remains controversial for this group. At present, use of antiviral therapy associated with liver transplantation in this group of patients is being examined.

e. Age limitations

Although 55 years had been the arbitrary cut-off point for liver transplantation, significantly older individuals recently have been considered as candidates. The survival of patients following liver transplantation does not correlate with age (fig. 6). In our institution, the oldest patient to receive a liver transplant was 76 years old and she remains well after 6 months. These older patients may have concomitant cardiac, pulmonary, and renal diseases, however, that may complicate perioperative therapy.

3. Surgical procedure - Improvements in technique

a. Donor liver management

Once a patient's condition is considered hopeless and brain death is imminent, the focus of care is directed at donor organ maintenance.

After brain death certification, all measures are directed at preserving donor organs, not neurologic function. In the operating room during organ procurement, the donor's cardiac output and oxygenation should be maximized. Extensive surgical dissection in the chest and abdomen are performed before cold flushing with the preservation solution. This sequence is used to minimize ischemic injury.¹⁸ Although numerous groups have attempted to prolong the ischemic time limit by altering the preservation solution, none has been shown to be superior to Euro-Collins solution.¹⁹ The primary goal in organ procurement is to minimize organ ischemic time during and after organ harvesting.

b. Venovenous bypass without systemic anticoagulation.

The anhepatic phase of liver transplantation is the time from removal of the native liver to return of blood flow to the donor liver. During this time, the inferior vena cava is cross-clamped both at the diaphragm and above the renal veins. The portal vein is also clamped. This procedure results in an almost complete cessation of venous return from below the diaphragm, excepting the flow that reaches the right atrium via the azygos veins and other collaterals. These occlusions of the portal vein and inferior vena cava result in: 1) a significant decrease in cardiac output due to pooling of blood below the diaphragm, 2) marked deterioration in renal function because of renal venous occlusion, and 3) worsening of portal venous hypertension, which may result in greater blood loss during the entire procedure.

Because of these considerations, we began using, in adult liver transplantations, a heparin-bonded venovenous bypass system that drained both the inferior vena cava and portal vein through a centrifugal force pump into an axillary vein.²⁰ Fifty-seven patients

supported with veno-venous bypass were compared with a control group of 63 previous patients who had liver transplantation without bypass. Although long-term (90-day) survival was similar in both groups, the non-bypass group required more blood products (33 ± 25 vs. 19 ± 8 units, $x \pm SD$, $p < 0.01$) and had a higher serum creatinine on the third postoperative day (3.0 vs. 1.5 mg/dl). Although such factors as surgical experience and patient selection also may have affected these results, this study suggests that veno-venous bypass improves postoperative status after liver transplantation. Not all centers use veno-venous bypass. Wall et al.²¹ reported their results in 61 liver transplantations without veno-venous bypass. They found no incidence of renal failure after liver transplantation in those patients with good renal function before surgery. Patients with preoperative hepatorenal syndrome required dialysis postoperatively. In agreement with Griffith et al.,²⁰ Wall et al.²¹ found that both mean arterial pressure and cardiac output decreased during the anhepatic phase when veno-venous bypass was not used. From these studies, it is unclear whether veno-venous bypass improves postoperative results. However, our experience with a large series of high risk patients suggests that improved operative survival of many of these patients may be related to routine use of veno-venous bypass. Furthermore, veno-venous bypass allows surgeons-in-training to perform the difficult vascular anastomoses without undue time constraints.

c. Biliary tract reconstruction

Problems associated with the biliary tract anastomosis are the most common and may be difficult to correct. Today all biliary tract reconstructions are performed by either a choledocho-choledochostomy

with a T-tube stent or a choledochojejunostomy to a Roux-en-Y limb of jejunum (fig. 7). Bile duct complications have decreased in frequency with this standardized reconstruction.²² The biliary tree is also flushed during procurement of the liver to decrease the subsequent development of biliary sludge. Casts may still form within the biliary tract up to 8 weeks after transplantation. Intraoperative attention to preserving the blood supply to the donor common bile duct improves the integrity of the biliary anastomosis. Finally, an intraoperative cholangiogram is performed in most patients and aids in identifying technical problems for immediate correction in the OR.

d. Rapid infusion system

Liver transplantation often requires the transfusion of massive quantities of blood over very short intervals to maintain adequate cardiac output. Transfusion requirements vary by patient, previous surgery, and skill of the surgeon. In the period 1983 through 1985 our experience with 200 adult liver transplant recipients showed that 75% required more than 10 units of blood intraoperatively, 30% required more than 30 units, and 6% more than 100 units.²³ Standard transfusion methods are not able to infuse warm blood rapidly enough for this procedure. Accordingly, Sassano in collaboration with Haemonetics^R Corporation developed a device that could deliver diluted warm blood at rates up to 2000 ml/min. This device is called the Rapid Infusion System.

The system infuses a mixture of 2 units packed red blood cells (600 ml), 2 units fresh frozen plasma (400 ml), and 500 ml Plasmalyte^R (total volume, 1500 ml). This solution was selected to provide adequate oxygenation and minimize viscosity. The final hematocrit is

approximately 28%. We use the Rapid Infusion System in most adults undergoing liver transplantation but not in children since their transfusion requirements are less. Its ability to easily infuse warm blood at the required rate has made it invaluable in the intraoperative management of these patients. Its use in other situations where massive blood transfusions are required is being investigated. When the Rapid Infusion System is used, most patients have a hematocrit in the immediate postoperative state equal to that of the blood mixture (28%).

Although the primary advantage of the Rapid Infusion System is the adequate infusion of warm blood with minimal number of personnel, it also tends to maintain more stable intraoperative hemodynamics, which may be reflected postoperatively in better overall organ function.

e. Postperfusion syndrome

Reperfusion of the graft liver after the anhepatic phase is frequently associated with cardiovascular collapse. These dramatic cardiovascular changes, termed the postperfusion syndrome, are characterized by systemic hypotension, bradycardia, increases in central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP), and a decrease in calculated systemic vascular resistance. These changes may occur within 30 seconds of reperfusion and last from 5 to 30 minutes.²⁴ The cause of the postperfusion syndrome is unknown but has been postulated to be the washout of cold, high potassium-containing, acidic fluid from the donor liver.^{25,26} To define the determinants of the postperfusion syndrome, Aggarwal et al.²⁴ studied 69 consecutive liver transplantations. They defined the postperfusion syndrome as a sudden decrease in mean arterial pressure (MAP) greater than or equal to 30% for at least 1 minute within the first 5 minutes after unclamping.

The postperfusion syndrome occurred in 20 patients (30%) (responders). This subgroup also had a higher potassium level (5.3 ± 0.8 vs. 4.0 ± 0.5 mEq/L, $p < 0.5$) than the nonresponder group. All patients demonstrated increases in potassium and decreases in both pH and blood temperature after reperfusion. Although the changes in potassium level were different between the two subgroups, they did not explain most of the variance in MAP. Thus, factors other than hyperkalemia may be involved in the postperfusion syndrome. That the postperfusion occurred in only 20% of the patient sample,²⁴ as opposed to 50% in previous studies,^{25,26} suggests that attention to all intraoperative details, including ionized calcium, blood volume and acid-base balance, may minimize this serious complication.

4. Postoperative care: Immunosuppression with cyclosporine and OKT-3

One of the major breakthroughs in the postoperative management of organ transplantation was the introduction of cyclosporine. Previously, the immunosuppressant regimen was a combination of steroids, azathioprine, and pulse therapy with rabbit antithymus globulin (RATG). With the substitution of cyclosporine for azathioprine, overall survival of primary liver transplants improved from 16.5% to 68.6% (table 2). Actuarial survival was also superior with cyclosporine (fig. 8). At present, all patients receive cyclosporine as the mainstay of immunosuppression.

In an attempt to further improve liver survival, Starzl and Fung²⁷ instituted a randomized trial of mouse anti-human T-cell antibody (OKT-3) for treatment of acute allograft rejection. By June 1986, 250 liver transplant patients had received a course of OKT-3.²⁸ Baseline

immunosuppression consisted of cyclosporine and steroids. Patients were separated by time of rejection episode into group 1, less than 10 days postoperatively; group 2, between 10 days and 3 months postoperatively; and group 3, greater than 3 months after surgery. Results are shown in table 3. The maximal beneficial response occurred in group 2 patients, in whom cell-mediated rejection was the primary cause of postoperative liver allograft dysfunction. Rejection is a major factor influencing the need for retransplantation.²⁹ The rate of retransplantation was greatly diminished in group 2 patients. This group represented the period during which cell-mediated rejection commonly occurs. The high rate of retransplantation in groups 1 and 3 probably reflects the inability of OKT-3 to reverse other causes of liver failure, since the survival rate of transplanted livers in groups 1 and 3 was similar to that of a historical control group that received no OKT-3. Thus OKT-3, in conjunction with cyclosporine and steroid, has improved the treatment of hepatic allograft rejection due to cell-mediated immune mechanisms. In patients with impending renal failure because of cyclosporine renal toxicity, OKT-3 also has been used to maintain immunosuppression, allowing cyclosporine dosage to be reduced.

B. Postoperative intensive care of the liver transplant patient

The postoperative care of the liver transplant patient in the ICU is similar in many ways to the routine postoperative care of any patient who has undergone extensive intraabdominal surgery. Strict attention is given to intravascular fluid status, electrolyte balance, coagulation, liver and renal function, and cardiovascular performance. We closely monitor MAP, PCWP, CVP, arterial blood gases, cardiac rhythm, cardiac output, and urine output, as well as the output from all surgical drains. Therapy is directed initially at achieving hemodynamic stability by the titration of routine resuscitative care, which is guided by clinical signs, laboratory data, and the invasive hemodynamic monitoring mentioned above. Beyond this resemblance to the routine postoperative patient care in the ICU, the liver transplant patient has unique problems that stem from the newly transplanted liver and the necessity of immunosuppression.

The routine orders for care of the postoperative liver transplant patient are based on standard principles of surgical management (table 4). Electrocardiogram (ECG), and arterial, central venous, and pulmonary arterial pressures are monitored continuously, as are respiratory variables during mechanical ventilation. Vital signs and fluid balance are recorded frequently, because these patients are often unstable in the immediate postoperative period. Many patients have oliguria in the first 24- to 48-hour period because of intraoperative blood loss and its replacement as well as transient hypotension and/or inferior vena caval cross-clamping. Patients may need furosemide and/or colloid therapy during this interval. Excessive use of crystalloids,

however, can result in pulmonary edema. Therefore, fluids are administered as necessary to maintain CVP at approximately 10 cm H₂O.

Hypertension is a common postoperative problem. We use hydralazine and beta-adrenergic blocking agents such as labetalol and propranolol as initial antihypertensive therapy. These agents are given as intravenous boluses and titrated to effect. In patients who require other antihypertensive therapy because they either cannot receive the above agents or are refractory to them, we use minoxidil, clonidine, and captopril. We avoid using alpha methyldopa because of its hepatotoxic potential. In acute hypertensive emergencies, nifedipine, 10 mg sublingually, is a useful immediate agent in addition to more definitive long-term therapy is given. In cases of refractory hypertension, labetalol can be given intravenously as 20 mg over 2 minutes, repeated as necessary every 10 minutes to a total dose of 300 mg. Labetalol can also be given as a continuous infusion at an initial dose of 2 mg/min, adjusted according to the arterial pressure.

The patient is kept NPO until gastrointestinal mobility resumes. A nasogastric tube, inserted during the operation, is kept to low continuous suction and irrigated hourly with saline. Antacid (Mylanta, 30 ml or Riopan, 5 ml) is given via the nasogastric tube every 4 hours to keep the gastric pH >5. This dose of antacid is doubled when gastric pH is <5. Previous studies have demonstrated significantly less upper gastrointestinal hemorrhage in patients whose gastric pH is >5.³⁰

Pulmonary complications are common and should be treated aggressively. The patient is turned every 2 hours. Pulmonary toilet is achieved by endotracheal suctioning, manual hyperinflations using a self-inflating ventilation bag and instillation of 3 ml saline with

repeat suctioning as needed every 2 hours. Sustained (15 second) manual hyperinflations of the lungs to recruit are used if arterial hypoxemia develops. The patient is weaned from mechanical ventilation using standard criteria for extubation (table 5). If there are no special problems, the patient can be extubated within 12-24 hours of surgery.

Fluid management is very important. Most patients arrive in the ICU in a nonsteady state characterized by a much expanded extracellular fluid volume, increasing vasomotor tone, and hypothermia. We start basal fluid resuscitation with 5% dextrose in half-normal saline, infused at 125 ml/hr. Since excessive administration of crystalloids may precipitate pulmonary edema, we use either plasma protein fraction or fresh frozen plasma to provide oncotic pressure and maintain intravascular volume. The goal of this initial therapy is to keep CVP at about 10 cm H₂O and urine output at 0.5 ml/kg/h. Hypovolemia must be avoided since the combination of hypovolemia and cyclosporine increases the risk of postoperative renal failure.

Immunosuppression is begun preoperatively. Cyclosporine and prednisone are the mainstays of immunosuppression in the liver transplant patient. The first dose of cyclosporine, 17.5 mg/kg, is given orally just before surgery, and the first bolus of steroids, 1 g methylprednisolone, is given intravenously at the time that the donor liver is revascularized. Postoperatively, 2 mg/kg cyclosporine is given intravenously every 12 hours until the patient resumes oral intake. Once the patient is able to take medications orally, 17.5 mg/kg cyclosporine is given in divided doses twice a day, as well as 2 mg/kg intravenously every 12 hours. Methylprednisolone, 200 mg, is given intravenously on the first day in 4 divided doses and tapered by 40 mg

per day until a maintenance dose of 20 mg/day is reached. Once the patient resumes oral intake, we switch to prednisone, 20 mg/day, orally. Cyclosporine dosage is monitored by daily cyclosporine trough levels in blood samples drawn one-half hour before the evening dose. Generally, whole-blood trough levels (by radioimmunoassay) of 800-1000 ng/ml are considered optimal.

Since all patients are immunosuppressed and the procedure requires anastomosis of donor and recipient bile ducts, antibiotics with a spectrum appropriate for biliary tract pathogens such as *Klebsiella*, *E. coli*, and *enterococcus* are started preoperatively. Our practice is to give all patients ampicillin and cefotaxime, 1 g each intravenously every 6 hours. Other antibiotics are given as guided by culture results. Oral and vaginal candidiasis occur frequently in the liver transplant patient. To suppress these infections, we give mycostatin oral suspension four times a day and, for female patients, mycostatin vaginal suppositories three times a day.

If hypokalemia occurs during the initial postoperative period, it is best treated with infusion of 20 mEq KCl rather than by adding KCl to the maintenance intravenous fluids. Caution must be exercised to avoid hyperkalemia. The patient may be unable to excrete excess potassium since some degree of oliguria is common postoperatively. Further, graft necrosis may occur, with either primary nonfunction or hepatic artery thrombosis, and result in rapid increases in serum potassium.

Although other centers treat postoperative liver transplant patients with narcotics, we generally avoid narcotics and sedatives, as these medications depend on hepatic metabolism. In addition, these drugs cause hypoventilation and secretion retention, increasing the risk

of postoperative pulmonary infection. Narcotics and sedatives also may alter mental status. Since improvement in mental status is an important sign of a functioning donor liver, we tend to avoid giving any drugs which may alter mental status. Instead of narcotics, we use mild sedatives such as antihistamines to blunt postoperative pain. If necessary, small doses of morphine sulfate or fentanyl are given, but only to patients who are awake and alert. To pediatric patients, however, we routinely give morphine sulfate for postoperative pain.

If there are no special problems or complications, the patient can usually be transferred to a surgical ward by the second or third postoperative day.

2. Complications following liver transplantation

a. Pulmonary complications

The most common complications in the early postoperative period are pulmonary atelectases and pleural effusion. Atelectasis may lead to lobar collapse, which compromises oxygenation and, in these immunocompromised patients, rapidly leads to pneumonia. For these reasons, we aggressively treat atelectases with chest physical therapy, positioning, and nasotracheal suctioning. Since frequent nasotracheal suctioning can cause significant bleeding in these patients, we reintubate the trachea early if routine recruitment and pulmonary toilet procedures are ineffective. In patients with retained secretions, flexible fiberoptic bronchoscopy is performed repeatedly to help remove secretions. This aggressive treatment of segmental or lobar atelectasis has frequently improved oxygenation and reduces the risk of infection.

Pleural effusions, primarily right-sided, are commonly seen postoperatively. During surgery when the suprahepatic inferior vena cava is clamped, a small portion of the right hemidiaphragm is usually included in the clamp. This trauma promotes right-sided pleural effusions. If the pleural effusion is small, it often resolves after several days of diuretic therapy. If the effusion is large, it may compress the underlying lung and cause atelectasis and pneumonia. In such cases, tube thoracostomy is indicated. Since liver transplant patients often have both abnormal coagulation and engorged intercostal collateral vessels, extreme care is exercised in placing the drainage catheter. We have seen massive bleeding in cases where these collaterals were injured. Accordingly, we often use a small, pigtail catheter inserted using the guidewire technique.

In many patients a significant postoperative metabolic alkalosis develops with partially compensatory respiratory acidosis. The degree of metabolic alkalosis is not related to the amount of bicarbonate given to the patient intraoperatively.³¹ This condition is usually seen in situations where there is primary graft failure.

b. Hepatic complications

Function of the transplanted liver may be altered by primary nonfunction, technical complications, or rejection. Primary nonfunction implies no evidence of initial function of the hepatic allograft after transplantation. It occurs infrequently, but is a very serious complication. Evidence of total hepatic failure includes profound hypoglycemia, uncorrectable coagulopathy, stage IV coma, new onset of renal failure, profound metabolic acidosis, cardiogenic shock, and markedly abnormal liver function tests. Prolonged ischemia of the liver

before transplantation may lead to primary nonfunction. Donor hypoxemia before or during procurement and cold ischemia beyond 8-10 hours appear to be the most common reasons for primary nonfunction. However, some hepatic allografts, for unknown reasons, fail to function despite apparently uneventful procurement and transplantation. These allografts produce small amounts of thin watery bile, and the patient exhibits hypoglycemia, uncorrectable coagulopathy, depressed mental status, and abnormal liver function values. Infrequently, these allografts begin to function if the patient is carefully supported, but improvement rarely occurs after 48 hours of nonfunction. Patients with primary nonfunction should be considered for immediate retransplantation. Such patients are supported with infusions of fresh frozen plasma every 4 to 6 hours.

Technical complications during surgery can affect hepatic function. These include surgical bleeding and graft failure from vascular occlusion at any of the four anastomoses as well as from problems with biliary tract reconstruction. The most common and devastating vascular complication of transplantation is hepatic artery thrombosis. Hepatic artery thrombosis presents with fever, malaise, and a positive blood culture for *Klebsiella*, *E. coli*, *Pseudomonas*, or enterococci. Signs of hepatic artery thrombosis usually occur in one of three general patterns (table 6).³² The first presentation, acute hepatic gangrene with sepsis and fulminant liver failure, necessitates urgent retransplantation. The second, delayed bile leak resulting from ischemic necrosis of the common bile duct, also requires retransplantation. The third, relapsing bacteremia, has been managed successfully with antibiotic therapy in some pediatric patients. A full course of intravenous antibiotics is given followed by a course of oral

suppressive antibiotic therapy. If the patient remains afebrile, with good liver function, retransplantation is not necessary. Most patients, however, will have persistent bacteremia and liver abscesses, eventually requiring retransplantation. Hepatic artery thrombosis should be suspected in all patients after liver transplantation who have unexplained fever, a bile leak, or a positive blood culture for gram negative organisms. Doppler ultrasonography of the liver has proven to be a useful screening device if a pulsatile artery is seen. If the vessel is not well seen, arteriography is required to make the definitive diagnosis.

Because of the threat of hepatic artery thrombosis, we do not vigorously treat elevated prothrombin time or low platelet count with fresh frozen plasma and platelet transfusions. Platelet count as low as 30,000 and prothrombin time less than 30 seconds are not treated except in patients with active bleeding.

Recurrent hepatic vein thrombosis in patients with the Budd-Chiari syndrome also has been seen. Because of the tendency to rethrombosis as well as primary hepatic artery thrombosis, anticoagulation therapy is given postoperatively. Adult patients are started on 10 ml per hour of Dextran 40 for 5 days. As soon as the prothrombin time is less than 18 seconds, 50 units/kg of heparin is given intravenously every 12 hours. Aspirin, 40 mg, is given daily once the patient is on oral intake. Rapid development of ascites and abdominal pain has been reported by Calne in association with acute portal vein thrombosis.³³ Severe variceal bleeding has been seen in the Pittsburgh series in acute portal vein thrombosis and associated rapidly deteriorating liver function. Retransplantation is indicated in these conditions.

The incidence of bile duct complications has decreased with standardization of the technique of biliary duct reconstruction. Most bile leaks are delayed and, if suspected, must be promptly investigated and treated surgically to avoid sepsis. Suspected leakage can be confirmed through direct cholangiography, if a T-tube is present, or through endoscopic retrograde cholangiopancreatography in cases of choledocho-choledochostomy. None of these techniques can be used in patients who have a choledocho-jejunostomy. In these patients, a percutaneous transhepatic cholangiogram is necessary to define the biliary tract anatomy.

Rejection is the most common cause for hepatic allograft dysfunction. It is often difficult to determine, however, whether poor hepatic function is due to rejection, infection, ischemia, a technical problem, or a combination of these. Often, fever in the early postoperative period may be the first indication of rejection. Other symptoms include loss of appetite, depression, vague upper abdominal pain, arthralgias, and myalgias. Examination of the allograft may disclose a swollen and hard liver and a tender abdomen with ascites. Deterioration in liver function tests and decreased quantity and quality of bile suggest rejection. Prolonged prothrombin time is rarely seen in rejection and occurs only in severe cases. The differentiation of infection from rejection is very important, since infection requires a decrease in immunosuppression, while rejection often requires an increase in immunosuppressive therapy. Acute rejection occurs most commonly in the second week after transplantation.

We find liver biopsy to be invaluable in differentiating rejection from both ischemic injury and various forms of viral hepatitis,

especially that caused by cytomegalovirus. Hepatic rejection is characterized histologically by the triad of portal inflammation with mononuclear cells, bile duct damage, and venous endothelialitis.³⁴ Other findings suggestive of rejection include intralobular hepatocellular regeneration, centrilobular bland hepatocellular necrosis, and few bile ducts.³⁵ Liver biopsy in late rejection reveals less inflammatory infiltrate than in acute rejection, sparing centrilobular areas and demonstrating extensive periportal fibrosis³⁴ with disappearance of bile ductules.

If a T-tube is present, liver rejection is initially assessed with a T-tube cholangiogram. Comparison with the intraoperative cholangiogram is important. Pruning of the bile ducts within the liver suggests rejection. If a T-tube is not present, an ultrasound examination of the liver can be obtained to rule out bile duct obstruction. Finally, a computed tomogram of the liver may reveal areas of decreased attenuation, which are consistent with rejection.

Initially, acute rejection is treated with steroid pulse therapy similar to the tapered steroid therapy given in the initial postoperative period. The 6-day steroid pulse is outlined in table 6. The cyclosporine trough level (whole blood RIA) is maintained at 800-1000 ng/ml. Patients whose liver function appears to be getting worse despite steroid pulse therapy should be considered candidates for antilymphocyte globulin (OKT-3).

The monoclonal antibody OKT-3 (Orthoclone^R, Ortho Pharmaceuticals, Ravitan, NJ), a T-cell-specific antilymphocyte globulin produced with the mouse hybridoma technique has been used in Pittsburgh for the treatment of acute rejection since 1984. It is given as a single daily

dose of 5 mg intravenously over 15 minutes. The duration of therapy depends on graft response, but averages from 5 to 7 days. The most remarkable side effect of OKT-3 is bronchospasm, which is readily reversed with systemic epinephrine. Other side effects include fever, rigors, diarrhea, nausea, vomiting, chest tightness, and exacerbation of pulmonary edema in hypervolemic patients.³⁶ The protocol for administration of OKT-3 is given in table 7. Pulse steroid therapy and OKT-3 therapy now comprise a single course of antirejection therapy.

In the first 11 months of 1984, 20% of all liver transplant patients in Pittsburgh underwent retransplantation.³⁷ There were two clusters of retransplantation times, early (mostly for technical failures or primary non-function) corresponding to rejection at 1 and 2 months postoperatively usually for acute rejection. Retransplantation within the first postoperative month is considered in patients with persistent hyperbilirubinemia of >10 mg/dl, rejection unresponsive to two full courses of antirejection therapy, or no evidence of correctable lesions. Patients with late rejection seldom respond to manipulation of immunosuppression and if they have marked elevation of hepatic enzymes should be considered early for retransplantation.

Cyclosporine and prednisone are the mainstays of immunosuppression. Cyclosporine toxicity is a constant fear. As mentioned earlier, cyclosporine trough blood levels should be kept at between 800 and 1000 mg/ml. Since cyclosporine is lipid soluble and dependent on the enterohepatic circulation, its blood level may increase after T-tube clamping. Cyclosporine toxicity is manifest as hypertension, tremulousness, hypertrichosis, gingival hyperplasia, and nephrotoxicity (table 8). Cyclosporine may also impair liver function,

but this is less common than acute or chronic nephrotoxicity. The most common cause of an increase in blood urea nitrogen and creatinine after transplantation is cyclosporine toxicity, which will respond promptly to reduction in the dosage given. Cyclosporine can produce a chronic interstitial fibrosis of the kidney, which may not be clinically apparent for many months³⁸ (Meyers NEJM). This lesion will significantly impair glomerular filtration rate and alter filtration fraction long before changes in serum creatinine or even creatinine clearance are detected. For these reasons, every effort is made to reduce cyclosporine doses to the lowest levels possible without compromising the immunosuppression of the patient.

c. Renal complications

Some degree of renal impairment develops in many patients after liver transplantation, even though most have normal renal function preoperatively. Most patients arrive in the ICU with an expanded extracellular fluid volume. Despite this, they frequently have relatively low filling pressures (CVP less than 10 torr and pulmonary artery diastolic pressure less than 15 torr). If the urine output is greater than 20 ml/h, these patients require no diuretics, and usually the only fluid given is fresh frozen plasma or red blood cells to reverse coagulopathy or raise the hematocrit, respectively. Patients whose urine output falls below 20 ml/h and whose ventricular filling pressures are low are given boluses of crystalloids (Plasmalyte^R or normal saline) or colloids (purified protein derivative) as necessary until urine output increases. Significant loss of third-space volume may necessitate massive, continuous fluid replacement, similar to the fluid requirements of septic patients.

In patients with reduced renal function preoperatively, renal failure often occurs postoperatively, occasionally severe enough to require hemodialysis. If the new liver functions promptly, however, renal function usually improves rapidly. Persistent postoperative renal failure, even in patients with the hepatorenal syndrome, is uncommon except when associated with systemic infection, poor allograft function, or other complications.

The administration of such nephrotoxic drugs as antibiotics and cyclosporine must be carefully monitored and dosages manipulated according to renal function and serum levels. Cyclosporine nephrotoxicity usually complicates renal insufficiency rather than induces it, provided trough levels are kept in the recommended range (800-1000 ng/ml).

d. Bleeding and coagulation problems

Substantial improvement in the technical aspects of both anesthetic and surgical management of liver transplantation has significantly reduced the perioperative coagulopathy uniformly seen in the past. The coagulation defects seen most commonly on arrival in the SICU are prolonged prothrombin time, partial thromboplastin time, and thrombocytopenia. However, with appropriate blood component therapy (such as packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, and epsilon aminocaproic acid), bleeding due to coagulopathy is rarely a problem in the SICU. Inability to correct coagulopathy by routine replacement of blood components suggests poor graft function. A continued need for red blood cell transfusions

postoperatively generally indicates the need for early reexploration for hemostasis, not the presence of coagulopathy.

e. Infection

We do not place the liver transplantation patient in a protective isolation environment in the ICU. This is in contrast with the 7-day obligatory protective isolation in the ICU used by the Cambridge group. Rigid application of standard hygienic principles limits the spread of infection by personnel. Indeed, the overwhelming threat to these immunocompromised individuals is their own gastrointestinal flora.

During the initial postoperative period, fever is uncommon. If fever is present, it must be thoroughly evaluated. Our protocol for postoperative fever evaluation is shown in table 9. In addition, other tests are used as indicated. For example, acute serum titers for CMV, tuberculosis skin test, legionella titers, and hepatitis screening may be obtained. If indicated by clinical examination, a lumbar puncture is performed to rule out central nervous system infection. Ultrasonography and computed tomography of the abdomen are very useful in evaluating hepatobiliary duct size and to look for intraabdominal fluid collections. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and open lung biopsy are also useful techniques to identify the causative agent in the presence of pneumonia, especially if pneumocystis carinii infection is suspected. We treat new pulmonary infiltrates of unknown etiology empirically with erythromycin and sulfamethoxazole-trimethoprim to cover both legionella and pneumocystis carinii infections until final culture results are known.

From 1981 to 1983, 81% of all liver transplant patients in Pittsburgh had at least one infection.³⁹ This high infection rate is most likely related to immunosuppression, use of antibiotics, and preoperative malnutrition. Further, use of antacids permits bacterial overgrowth in the stomach. Gastrointestinal surgery for biliary reconstruction also may contribute to the high frequency of postoperative infection, as does a defective reticuloendothelial system. Sepsis remains a major cause of morbidity and mortality in patients after retransplantation.³⁷

Fungal infection occurs in 42% of our liver transplant patients, usually within 1 month of transplantation. Fungal infections are more common when steroids and antibiotics are used preoperatively and if the duration and number of operative procedures increase. Fungal infections are also associated with increasing duration of perioperative antibiotic administration, bacterial infections, and rejection treated with steroid boluses. For unknown reasons, patients with primary biliary cirrhosis have a low incidence of fungal infections. *Candida* is the most common fungal organism isolated from these patients, while *aspergillus* is the next most frequent. Invasive aspergillosis has been uniformly fatal.⁴⁰ Significant monilia in the sputum, blood, urine, bile, or drains is treated with intravenous amphotericin B.

Both herpesvirus and CMV have caused significant infections in liver transplantation recipients. Overwhelming infections with these viruses have been fatal. Documented herpesvirus infections are treated with daily acyclovir, 5 mg/kg, in 3 divided doses for 10-14 days. At present, there is no treatment for CMV infections. As is the case for all significant infections in these immunocompromised hosts, one of the

first steps of therapy is a significant reduction in immunosuppression. Use of bolus injections of steroids for "stress" in the presence of major infection is unwarranted and dangerous. However, maintenance doses of steroids in steroid-dependent patients should be continued.

f. Nutrition

Postoperative ileus usually resolves by the third or fourth postoperative day. Assuming that liver function is acceptable and there are no other contraindications, progressive oral intake is initiated with liquids and advanced to an unrestricted diet. For patients who have a functional gastrointestinal tract, but are either unable to eat or at high risk for aspiration, a thin silastic feeding tube is passed beyond the pylorus, and enteral feeding is begun. Intravenous hyperalimentation is reserved for patients whose gastrointestinal tract cannot be used for nutrition. In contrast, Calne begins total parenteral nutrition on postoperative day 2 via an intraoperatively placed central venous catheter.³³

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Table 1. Metabolic Diseases of the Liver

Associated with liver injury

Wilson's disease

Hemochromatosis

Alpha-1 antitrypsin deficiency

Tyrosinemia

Glycogen storage disease types I and IV

Protoporphyrria

Not associated with liver injury

Hemophilia

Urea cycle enzyme deficiencies

Phenylketonuria

Hyperlipoproteinemia type 2

Crigler-Najjar syndrome

Table 2. Effect of Azathioprine Versus Cyclosporine on Survival After Primary Liver Transplantations*

	Azathioprine and Prednisone	Cyclosporine and Prednisone	Total
Number of			
Patients (%)	170 (19.1)	720 (80.9)	890 (100)
Survived	28 (16.5)	494 (68.6)	522 (58.6)
Died	142 (83.5)	226 (31.6)	368 (41.4)

*890 primary liver transplantations with observations through November 1, 1986.

Table 3. Graft Status at the Beginning of March 1987 and One-year Survival in Liver Transplant Recipients Treated with OKT3

Group	Number of Grafts	Graft Status			1-Year Survival	
		<u>Functioning</u>	<u>ReTx</u>	<u>Died</u>	<u>Graft</u>	<u>Patient</u>
1	119	57 (47.9%)	38 (31.9%)	24 (20.2%)	49.4%	62.4%
2	110	79 (71.8%)	17 (15.5%)	14 (12.7%)	74.3%	82.2%
3	21	10 (47.6%)	8 (38.1%)	3 (14.3%)	71.4%	87.5%
1-3	250	146 (58.4%)	63 (25.2%)	41 (16.4%)	62.0%	73.4%
No OKT3*	362	181 (50.0%)	90 (24.9%)	91 (25.1%)	53.3%	71.8%

*For comparative purposes data for all liver transplant recipients not receiving OKT3 from August 1983 to June 1986 are added.¹

Table 4. Orders for Postoperative Care of Adult Liver Transplant Patients

-
- Diagnosis: S/P orthotopic liver transplant
 - Condition: Critical
 - Vital Signs: Q15 min until stable, then hourly
Hourly CVP, I & O
 - NPO
 - Bedrest until tracheal extubation, then up as tolerated
 - Respiratory care per ICU
 - Foley catheter to closed gravity drainage
 - Jackson-Pratt drains to closed bulb suction
 - T-tube to closed drainage
 - NG tube to low continuous suction-irrigate with 30 ml normal saline Q1H
 - Riopan 5 ml Q2H per NG tube clamp for 15 min
Double dose if gastric pH < 5
 - Turn Q2H, endotracheal suctioning Q4H, postural drainage and clapping
Q4H
 - D5 1/2 NS at 125 ml/hr
 - Cyclosporine 2 mg/kg iv Q12H at 10 a.m. and 10 p.m. daily
 - Methylprednisolone: 50 mg iv Q6H X 4, then
40 mg iv Q6H X 4, then
30 mg iv Q6H X 4, then
20 mg iv Q6H X 4, then
20 mg iv Q12H X 2, then
20 mg iv QD
 - Cyclosporine trough level from 9:30 p.m. blood

Table 4. (cont.)

- Ampicillin 1.0 gm iv Q6H X 5d
 - Cefotaxime 1.0 gm iv Q6H X 5d
 - Mycostatin 5 ml swish and swallow QID once NG tube is out (and myostatin vaginal suppository TID to female patients)
 - CRX now and daily
 - STAT, then Q6H X 4: CBC, PT, PTT, platelets
 - Q6H X 4 electrolytes, BUN, creatinine, glucose, amylose
 - Daily labs: CBC, diff, PT, PTT, platelets, electrolytes, Ca, P, Mg, BUN, creatinine, bilirubin (T/D), SGOT, SGPT, alk phos, GTP, total protein, albumin, and amylase
 - Keep 4 units packed red cells on hold
-

Table 5. Criteria for Weaning from Mechanical Ventilation and Tracheal Extubation

-
- Hemodynamically stable patient
 - Alert patient able to defend airway
 - $\text{PaO}_2 > 60$ torr on an $\text{F}_I\text{O}_2 \leq 0.4$ and ≤ 5 cm H_2O PEEP
 - Maximum inspiratory force > 20 cm H_2O
 - Vital capacity ≥ 10 ml/kg
-

Table 6. Clinical Presentations of Hepatic Artery Thrombosis

1. Fulminant hepatic necrosis

Frank hepatic gangrene

Rapid rise in serum transaminasis

Rapid clinical deterioration

2. Delayed biliary leak

Ischemic necrosis of the bile ducts with subhepatic fluid
collection

Drainage of bile through abdominal tubes

Frank bile peritonitis

Bacteremia

Changes in the liver chemistry profile similar to those
seen with rejection.

3. Relapsing bacteremia

Indolent clinical course

Usually only minor abnormalities in

liver chemistry profile

Table 7. Protocol for Administration of OKT-3

I. Evaluation before administration

A. Determined within 24 hours of first dose:

1. Physical examination recorded in chart
2. Chest X-ray reviewed by house officer
3. Hct, WBC, diff, platelets PT, PTT, lytes, BUN, creat, Ca^{++} , PO_4 , glucose, SGOT, SGPT, alk phos, GGTP, bili T/D, total protein, albumin.
4. Weight recorded on chart.

B. Patient should receive special consideration if:

1. Obviously in respiratory distress
2. Obviously fluid overloaded
3. Neutropenia (WBC < 3000)

II. During administration

- A. High risk patients and all pediatric patients should be transferred to an ICU to receive the first two doses
- B. All patients must have a functioning IV line in place and an infusion pump should be available
- C. All patients will have O_2 available
- D. A crash cart with intubation equipment will be available
- E. All patients will have a cardiac monitor
- F. Epinephrine should be available at bedside in doses appropriate for the patient
- G. One gram of solu-cortef should be available

Table 7. (cont.)

III. Medications

A. All patients receive one hour before OKT-3:

1. Solucortef 1 gm IV if > 30 kg 1st day
500 mg to 1 gm IV if < 30 kg 1st day
250 mg IV if > 30 kg 2nd day
125 mg IV if < 30 kg 2nd day
2. Benadryl 15-25 mg IV/25-50 mg po
3. Tylenol 325-650 mg po or 650 mg pr

B. Administration of OKT-3

1. Must be given by physician
2. > 30 kg 5 ml over 5 min by IV push
< 30 kg 2.5 to 5 ml over 5 min by IV push

IV. Nursing - write "VS per OKT-3 protocol", which equals:

A. Days 1 and 2

VS baseline preadministration temp, pulse, respiratory rate,
and blood pressure, then

q 15 min X 2 hours

q 30 min X 2 hours

q 1 hour X 2 hours

then q 2 h

B. Days 3 through 14

1. VS baseline as day 1 and 2

q 30 min X 1 hour

Table 7. (cont)

q 2 hours until stable

then q 4 hours

2. Observe for:

- a. fever (most patients will have some)
- b. chills (most patients will have some)
- c. diarrhea
- d. nausea and vomiting
- e. chest pain or respiratory distress

3. Call house office for:

- a. temp > 39
- b. fall in systolic BP > 20 mmHg
- c. respiratory rate > 35
- d. any chest pain
- e. any respiratory distress

V. Treatment of anaphylactic reactions

- 1. STAT arterial blood gases
- 2. Start O₂ by nasal cannula 2-4 liters/min
- 3. Solucortef 200-400 mg IV push if no relief or respiratory distress, then
- 4. Epinephrine 1:1000 solution, give 0.01 mg/kg (maximum dose: 0.3 ml) SC. Repeat q 5-15 min to a maximum of 3 doses depending upon response.
- 5. Start epinephrine infusion at 0.1 ug/kg/ml up to a maximum of 1 mg/kg/min (1:100 vial 15 mg/250 cc D5W).

Table 7. (cont.)

6. Failure to respond at any point is indication for prompt intubation and transfer to the ICU.
 7. Serial ABGs should be obtained by house officer until symptoms resolve.
-

Table 8. Side Effects of Cyclosporine

Nephrotoxicity (reversible)

Hypertension

Hyperkalemia

Hepatotoxicity

Hirsutism

Gingival hyperplasia

Tremor/Seizures

Regional flushing

Vague abdominal discomfort

Breast fibroadenoma in women

Lymphoproliferative disease

Table 9. Initial Evaluation for Postoperative Fever

Physical examination

Chest and abdominal radiographs

Sputum gram stain, culture, and sensitivity

Culture/sensitivity - drains, tubes, open wounds

Culture/sensitivity - long term indwelling lines

Arterial and venous blood cultures

Urine for cytomegalovirus

Throat swabs for cytomegalovirus

LEGENDS

Figure 1 Total United States experience with extra-renal transplants through 1985.

Figure 2 Number of liver transplants performed in Pittsburgh since 1980.

Figure 3 Indications for 720 liver transplants performed in Pittsburgh.

Figure 4 Acturial data describing the relation between number of HLA-A loci mismatches and graft survival following liver transplantation. Although not significant ($p = 0.054$), survival tends to be better as the number of HLA-A loci mismatches increases.

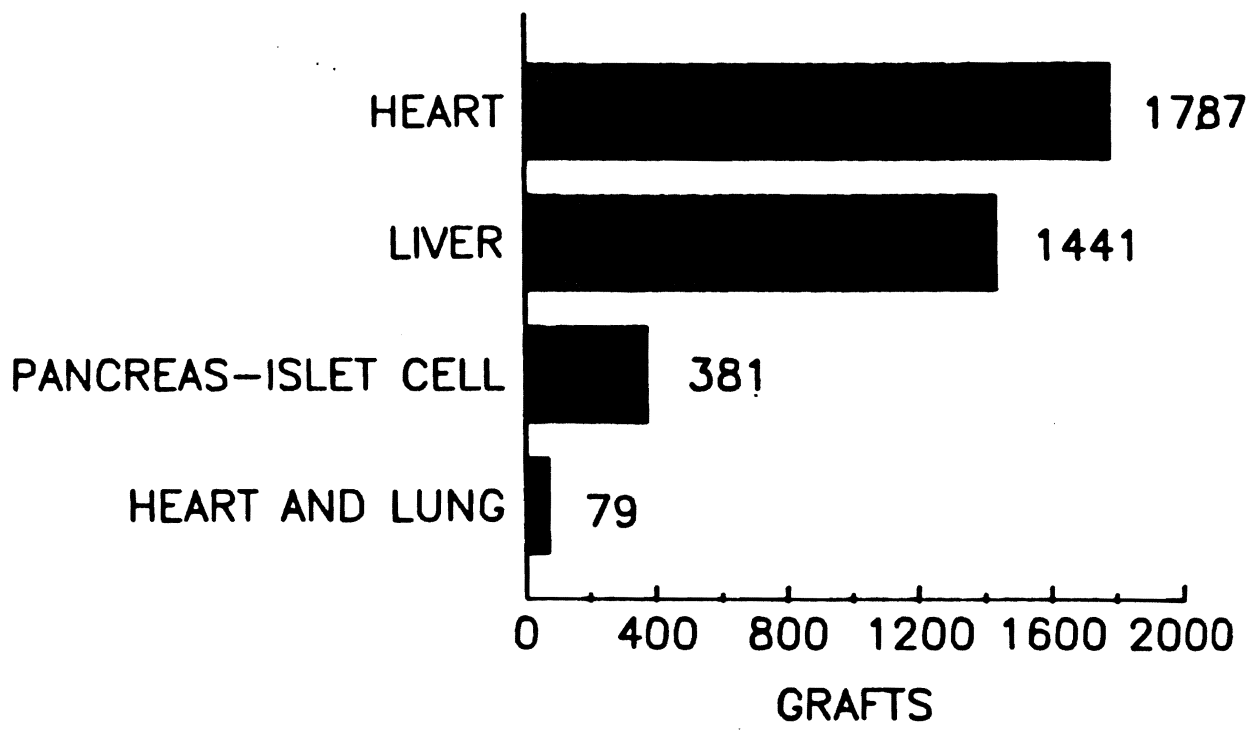
Figure 5 Acturial data describing the relation between number of HLA-DL loci mismatches and graft survival following liver transplantation. HLA-DR mismatches do not significantly affect graft survival.

Figure 6 Relation between patient age and survival following liver transplantation.

Figure 7 Illustrations of the final biliary reconstruction following liver transplantation using either choledocho-choledochostomy with T-tube start (left) or choledocho-jejunostomy to a Roux-en-Y limb of jejunum (right).

Figure 8 Comparison of patient survival rates following liver transplantation with either cyclosporine (dashed line) or azathioprine (solid line) are used for immunosuppression.

Figure 1



SOURCE: OFFICE OF HEALTH TECHNOLOGY ASSESSMENT

Figure 2

NUMBER OF PATIENTS

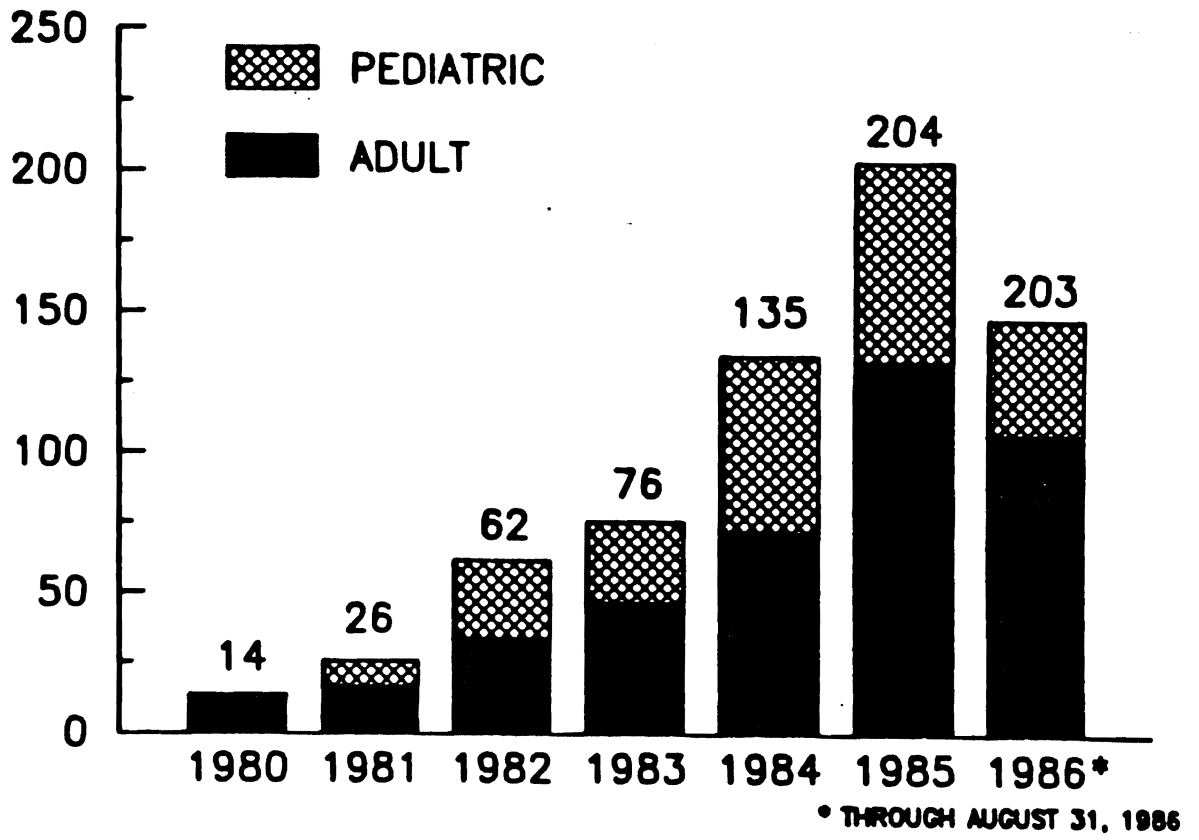


Figure 3

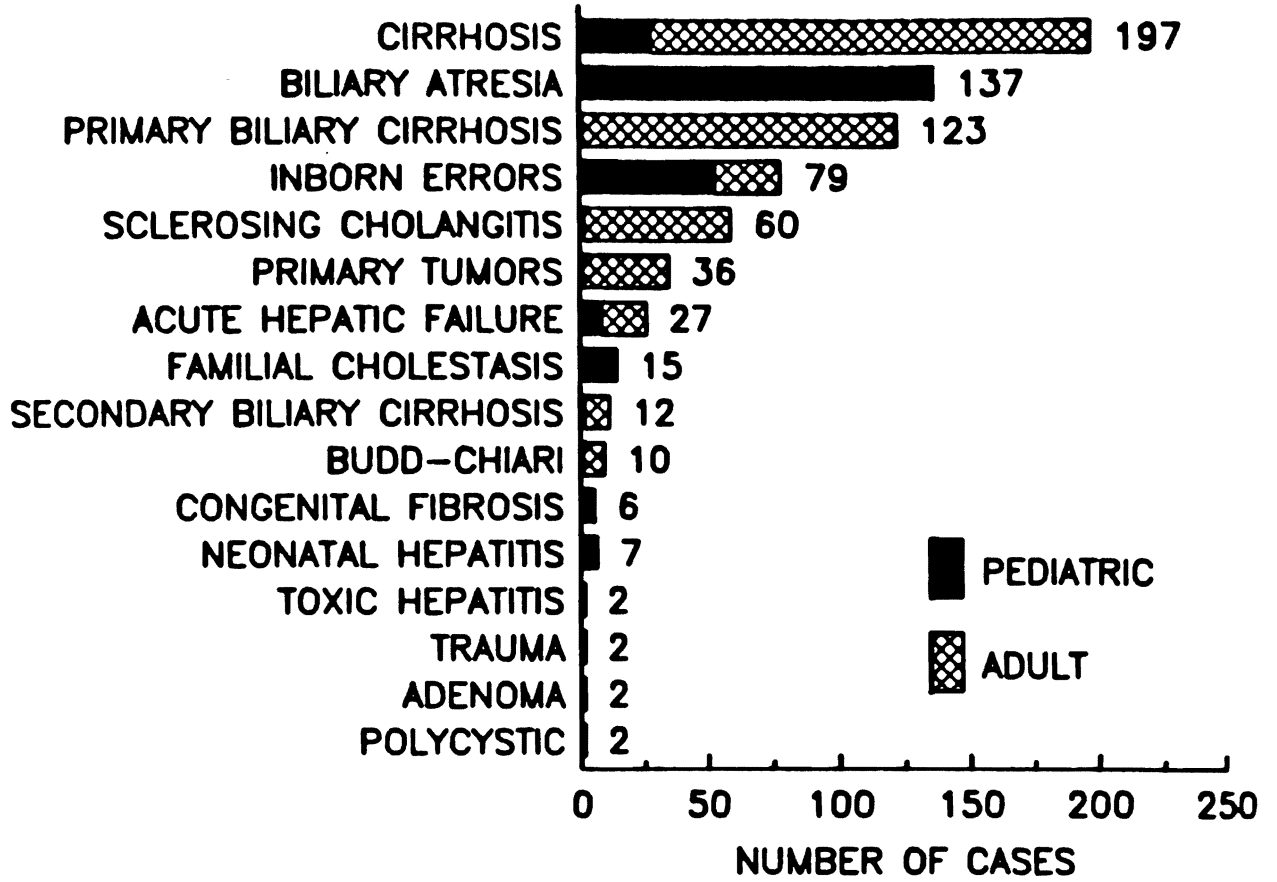


Figure 4

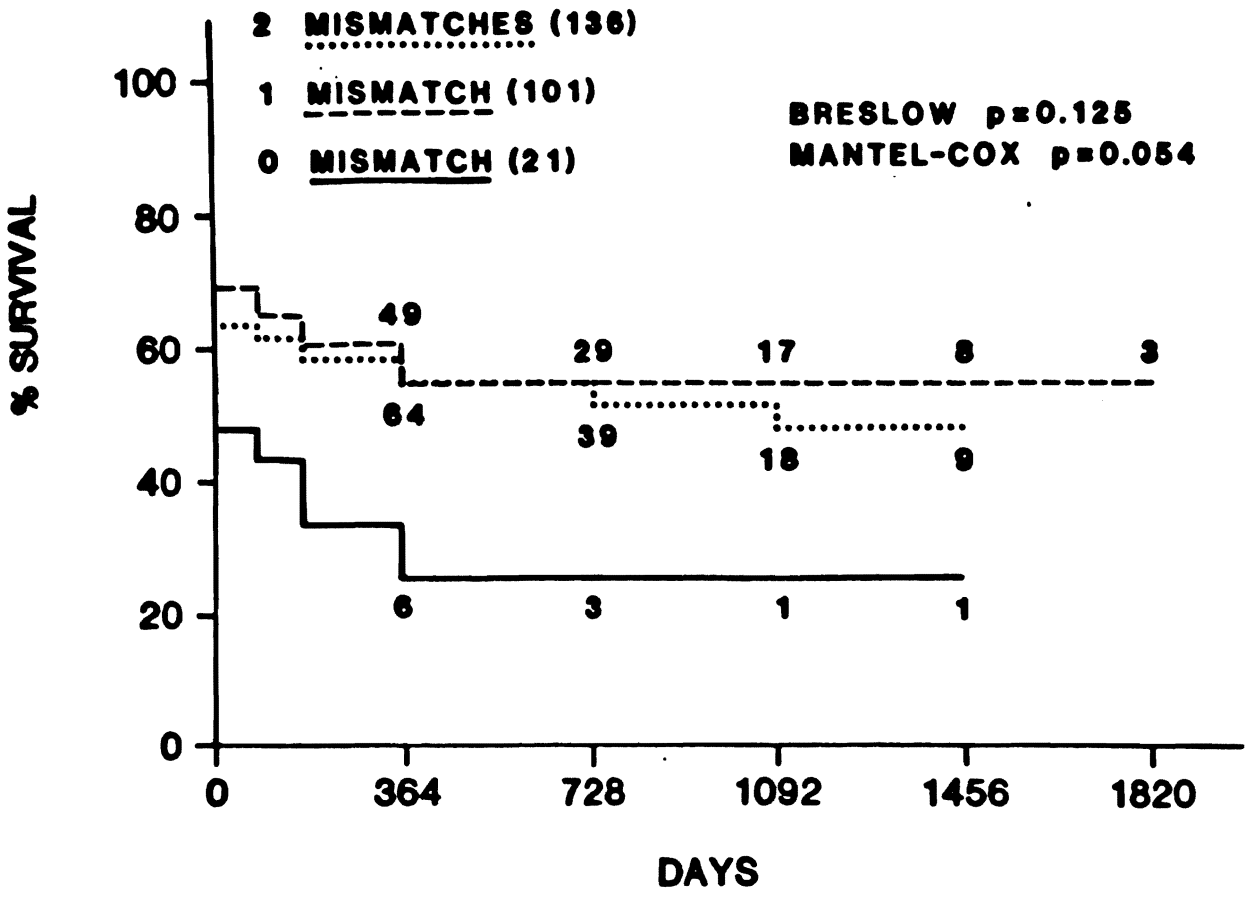


Figure 5

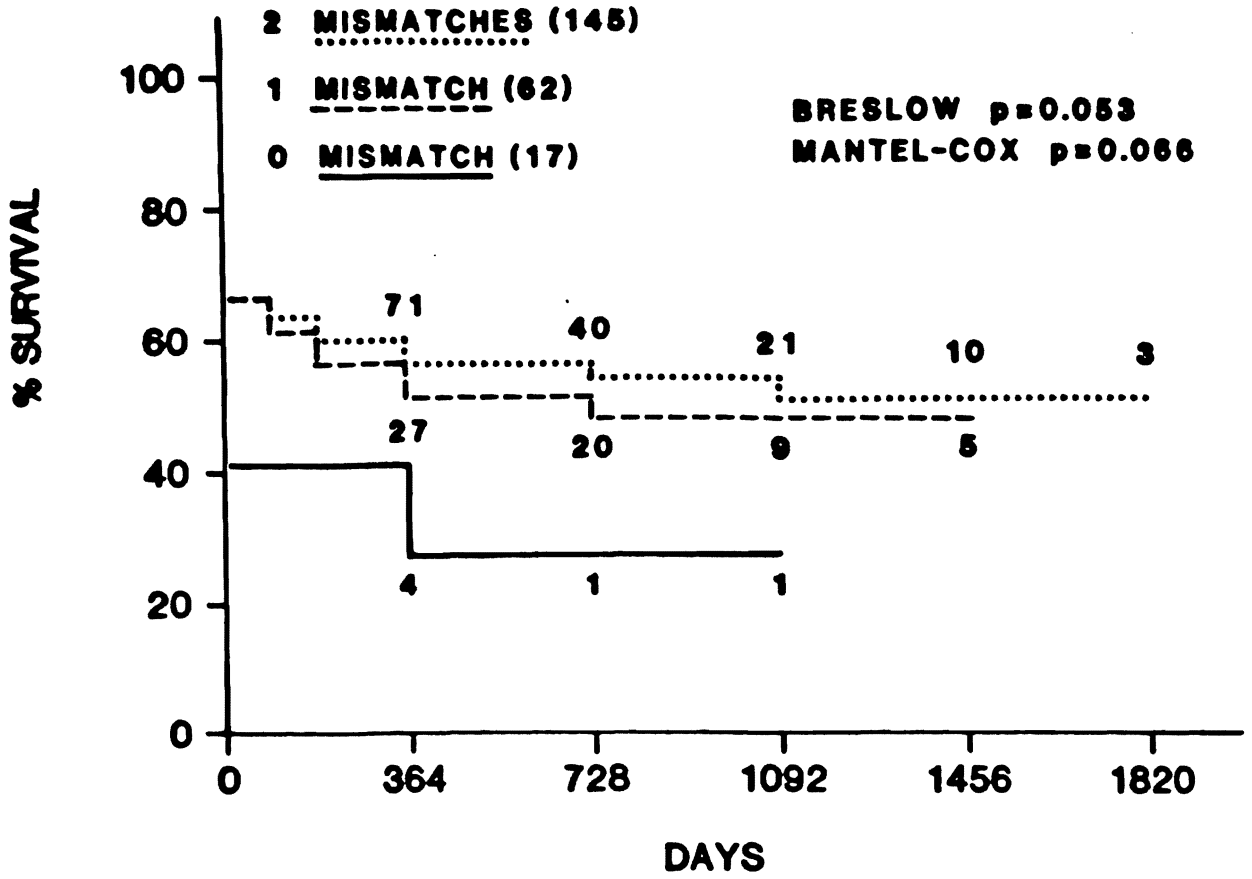


Figure 6

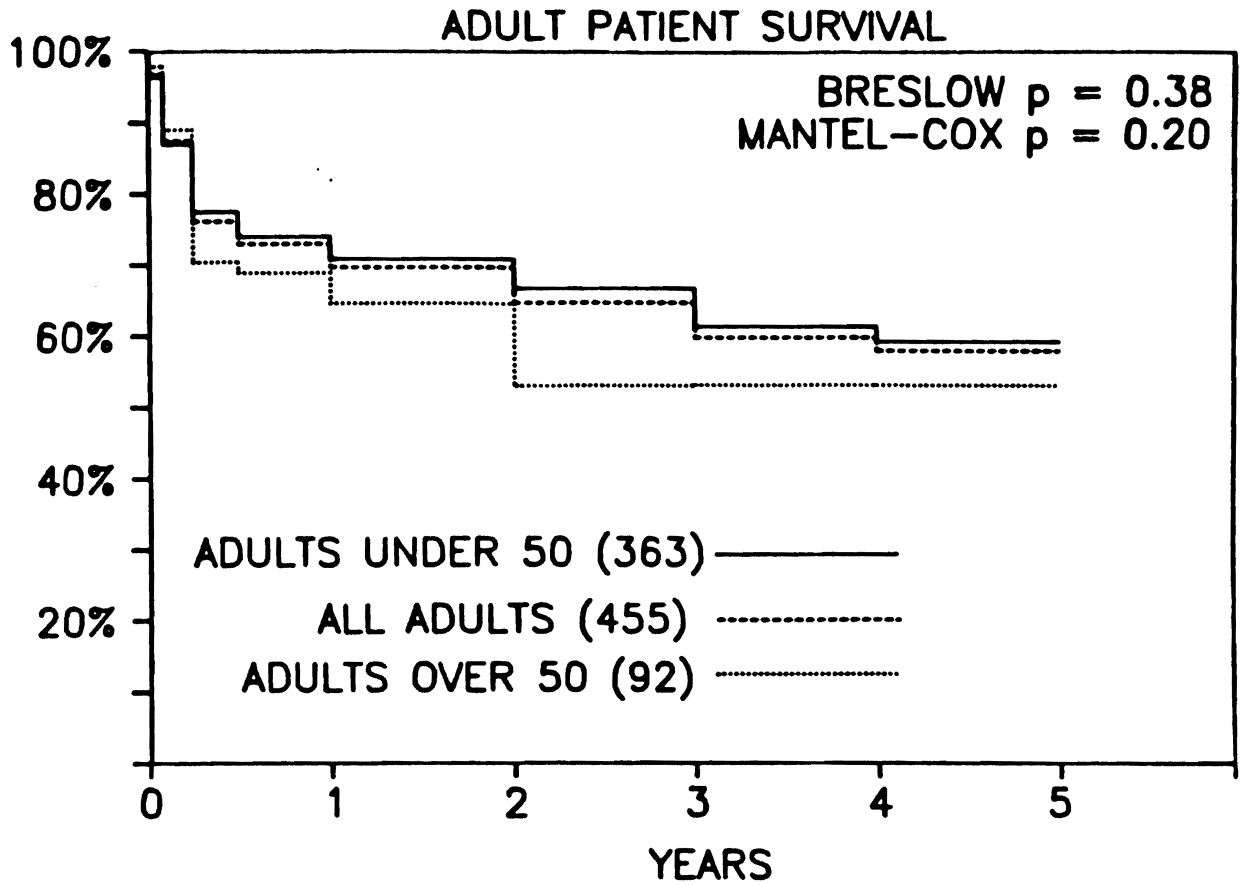


Figure 8

