Progress in Liver Transplantation*

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Recent advances have resulted in dramatic improvements in both patient survival and quality of life after orthotopic liver transplantation. Almost 25

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years after the first human liver transplantation was performed in Denver, the procedure has finally gained acceptance as the preferred treatment for most forms of end-stage liver disease.[1]

Essential elements of an organ transplant program include organ procurement and preservation, organ implantation, immunosuppression and the management of allograft rejection, and the management of complications, including infection. In this review, advances in each of these areas as they apply to the recent progress in liver transplantation will be discussed.

Organ Procurement and Preservation

Organ Donation

The concept of brain death is now well established and accepted throughout the United States and Western Europe, but this was not easily accomplished and still remains a barrier to the development of organ transplantation in many other countries. In the United States, the public has also strongly supported a voluntary system of organ donation.

Organ donation has increased significantly in the past several years as a result of the extensive educational efforts of professional organizations and the media attention the field has received. Legislation at both state and federal levels has further encouraged organ donation and facilitated organ sharing and distribution. Nevertheless, organ preservation technology is still crude and storage times are limited, especially for livers and hearts. Frequent organ sharing across large distances is often difficult or impractical. Even if all the available donors in the country were utilized and organ sharing became a frequent and widespread practice, the need for organs would still exceed the available supply.

Some of the greatest resistance to organ donation has originated within the medical profession. Physicians of dying patients are often reluctant to explore the possibility of organ donation at what is always a sensitive and difficult time for both physician and family. Today much support is available to physicians, nurses, and donor families from the highly professional organ procurement agencies throughout the United States. Educational programs sponsored by local and regional procurement agencies, the North American Transplant Coordinators Organization (NATCO), and various medical societies and foundations have contributed greatly to public and professional awareness. "Required request" legislation mandating requests by hospitals for organ donation in appropriate circumstances has now been passed in many states. This legislation often includes mechanisms for state assistance for the development of organ donation programs by community hospitals.

Advances in Organ Procurement Surgery

Application of methods for the rapid core cooling of solid organs by aortic infusion of cold electrolyte- or colloid-containing solutions has resulted in effective and reliable methods for the retrieval of the liver and/or pancreas, kidneys, and heart or heart-lungs from a single brain-dead, heart-beating cadaver donor. Comprehensive descriptions of the methods for multiple organ retrieval developed at the University of Pittsburgh have been published and the reader is referred to these articles for technical details.[2, 3] Recently a significant modification in methodology has been developed that greatly shortens the time required to complete the organectomies, with no loss of graft quality.[4]

In the original description of the method for multiple organ retrieval, the most time-consuming and dangerous part of the procedure involved meticulous dissection of the hepatic hilum, including identification and preservation of the often anomalous arterial supply to the liver. Cold core cooling was not performed until this preliminary dissection, which often required 2 or more hours, was completed. Manipulation of the liver during this long period of dissection could interfere intermittently with either portal or hepatic artery blood flow, producing warm ischemic injury to the liver. Furthermore, many donors were unstable and could not tolerate such a long operative procedure.

In an effort to salvage unstable donors, the original procedure was modified by early cannulation and flushing of the distal aorta. Rapid core cooling of the abdominal organs was then possible, permitting prompt retrieval of the liver or pancreas and kidneys in a bloodless field.

This rapid method of organ retrieval has now become our standard method of organectomy. As soon as the thoracic procurement team surgeon is ready to arrest the heart, or if the donor spontaneously arrests, the upper abdominal aorta is crossclamped and cold core perfusion is immediately begun through cannulas in the inferior mesenteric vein and distal aorta. Once the heart is removed and the liver completely flushed, a rapid, bloodless dissection of the hepatic hilum is performed, with care taken to identify and preserve any anomalous vessels. In this manner, the donor hepatectomy can be completed by an experienced surgeon in approximately 30–45 minutes. The kidneys—undisturbed, completely flushed clear of blood, and cold—can then be rapidly removed en bloc.

The quality of the livers procured by this rapid technique has been superior to that of organs obtained by the conventional method. Peak transaminase levels within 48 hours of revascularization of the liver, which were often greater than 1,000 IU using the original methods, are now often less than 500 IU. The incidence of delayed renal graft function requiring dialysis within 1 week after transplantation has been lower than with other methods of kidney retrieval.

Donor Assessment and Selection

It has been customary to evaluate the suitability of a potential liver donor based on traditional indicators of ischemic injury, including liver function tests, coagulation profile, oxygenation, blood pressure, level of pressor support, number and duration of cardiac arrests, and cause of death. However, these parameters of donor assessment can easily be applied too rigorously and may be much less reliable in predicting graft quality than has been assumed. In a retrospective analysis of 219 consecutive organ donors, we evaluated the reliability of liver function tests, arterial blood gas values, blood pressure, and cause of death in predicting early graft outcome and found that these parameters were difficult to rely on in predicting poor outcome.[5] If conservative criteria were applied for the evaluation of donor organs, a high degree of organ wastage would result. Furthermore, over half the donors rated as poor in fact gave livers with excellent early function. Since the need for organs far exceeds the available supply, restrictive criteria for donor acceptance that result in high levels of organ wastage are very damaging.

We continue to study this problem to develop a reliable model for the prediction of early graft outcome. In the meantime, we have liberalized our criteria for donor acceptance, without a discernible penalty.

Advances in Recipient Surgical Technique

Venovenous Bypass

A dangerous period during the operation in the recipient is the anhepatic phase when the native liver has been removed and the inferior vena cava and portal vein are occluded. During this period there is massive sequestration of blood volume in the peripheral venous circulation of the lower body and in the mesenteric venous circulation. The gastrointestinal tract becomes diffusely edematous, high renal vein pressure may result in deterioration of renal function, and bleeding from high pressure in the thin-walled venous collaterals found throughout the abdomen in patients with portal hypertension often increases. Volume preloading is required to maintain cardiac performance but can easily result in hypervolemia and pulmonary edema after revascularization of the liver. The high potassium and acid load returned to the systemic circulation after unclamping also poses a significant risk to the patient.

To reduce these risks and maintain physiologic stability during the anhepatic phase of surgery, a venovenous bypass technique is now routinely employed in most adults and selectively in children.[6–8] The inferior vena cava (through the saphenofemoral system) and portal vein are cannulated and blood is returned to the heart through a cannula in the axillary vein

(Fig 1). The patient is not given systemic heparin but the bypass tubing is heparin bonded and the system is primed with 350 ml of saline containing dilute heparin (2,000 IU/L). Using the bypass it is possible to maintain hemodynamic parameters at prehepatectomy levels without volume preloading. The intestinal tract remains uncongested except for a brief period during reconstruction of the portal vein. Renal venous hypertension is avoided, and as a result the incidence of renal failure requiring postoperative dialysis is less than 5%. Blood loss is reduced since use of the bypass provides time to oversew the large bare areas created by the hepatectomy and prevents the development of high pressure in venous collaterals.

Early placement of venous bypass facilitates completion of the recipient hepatectomy, especially dissection of the vena cava. With the portal vein mobilized and the surgeon free to lift the liver without compromising ve-

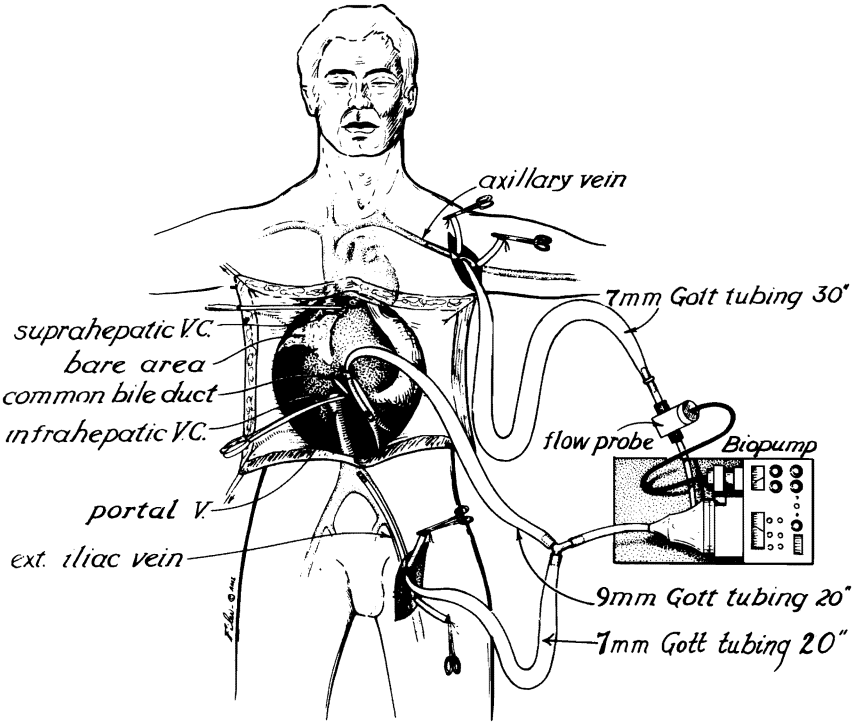

FIG 1.
Venovenous bypass during the anhepatic phase of liver transplantation. Outflow cannulas are placed in the iliofemoral system via the saphenous vein and in the portal vein. Return to the heart is obtained through a cannula placed in the axillary vein. The axillary vein is repaired after withdrawl of the bypass. (From Griffith BP, et al: Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. *Surg Gynecol Obstet* 1985; 160:270. Reproduced by permission.)

nous return, dissection of the infrahepatic and suprahepatic vena cava is simplified. Use of the bypass has enabled us to offer transplantation to higher risk patients such as older patients[9] and patients with poorly developed collateral channels who might not tolerate venous occlusion.

Technique of Vascular Anastomosis

Hepatic artery thrombosis is the second most common major technical complication after liver transplantation and has occurred in our experience in approximately 7% of cases.[10] The highest incidence (25%) has been in children under 1 year of age. The mortality associated with this complication is over 50%, and most patients require retransplantation.

Hepatic artery thrombosis manifests in one of three general patterns: frank hepatic gangrene, delayed biliary leak, or relapsing bacteremia.[11] The principal injury is ischemia of the bile duct system with bile duct or ductule necrosis and intrahepatic or extrahepatic bile extravasation. It must be suspected in all patients who suddenly become febrile after transplantation, who develop a biliary fistula, bile peritonitis or a bile abscess, or who have a blood culture positive for gram-negative organisms. Liver function tests may reflect massive hepatic necrosis or may show only mild or moderate changes similar to those seen with rejection. Doppler ultrasound is a useful screening modality, but arteriography is indicated for definitive diagnosis if hepatic artery pulsations are not clearly detected on the Doppler study.

Portal vein and vena cava stenosis or thrombosis are rare complications.[12] Sudden symptoms of portal hypertension such as variceal bleeding, coagulopathy, encephalopathy, and oliguria suggest portal vein thrombosis, and a venous phase arteriogram is indicated.

Our preferred method of vascular anastomosis for the vena cava, portal vein, and hepatic artery is end-to-end anastomosis with continuous nonabsorbable monofilament polypropylene suture. A potential hazard of this technique is suture line "purse-string" stenosis at the anastomosis resulting from continuous tension exerted on the suture during performance of the anastomosis. Furthermore, the hepatic artery is frequently in severe spasm during anastomosis and may not fully dilate until many hours after the completion of the surgery.

To prevent suture line stenosis, an "expansion factor" is provided (Fig 2).[13] The running suture is tied several millimeters or more from the wall of the blood vessel such that when the vessel distends under pressure or when vasospasm resolves, the suture can soak into the vessel and deformity at the anastomosis is prevented. A stay suture tied flush to the vessel immediately adjacent to the "expansion factor" prevents separation and leakage of the anastomosis at this critical point. We believe that use of this technique has greatly reduced the incidence of hepatic artery stenosis and thrombosis.

Arterial revascularization in small children is demanding. Our preferred

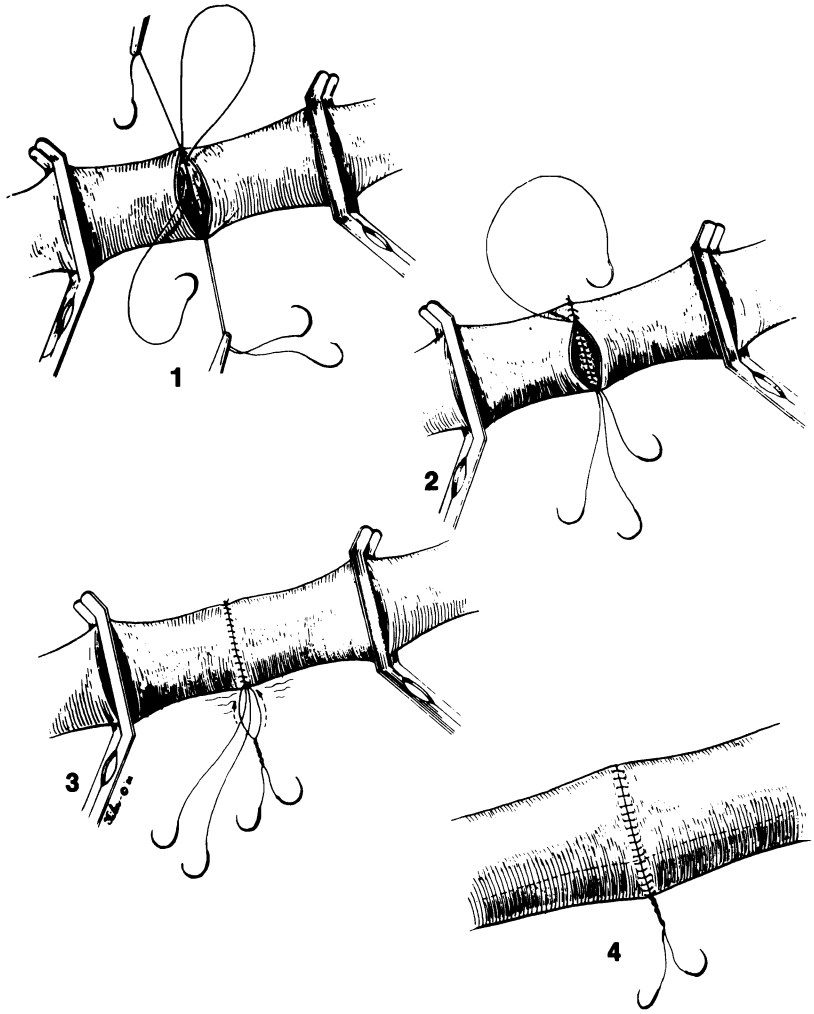

FIG 2.
Suture technique for venous and arterial anastomosis in liver transplantation. *1,* intraluminal performance of posterior wall anastomosis for vena caval or portal vein anastomosis after placement and tying of sutures. For arterial anastomosis, conventional extraluminal technique is used and the vessel is then rotated 180° to complete the opposite wall. *2,* the mate of one end suture is used to construct the other half of the circumference. *3,* the two ends are tied together away from the vessel wall. *4,* expansion and bulging of the suture line are evident as the extra polypropylene suture is taken up. (From Starzl TE, et al: A growth factor in fine vascular anastomoses. *Surg Gynecol Obstet* 1984; 159:164–165. Reproduced by permission.)

method is to anastomose the donor celiac artery to the proximal common hepatic artery at the level of the origin of the recipient splenic artery. The recipient splenic artery is ligated so that all flow is into the graft. The confluence of the recipient splenic and celiac arteries provides a larger orifice for anastomosis to the donor.

If direct revascularization is not possible, a free-standing graft of donor iliac artery is sewn to the recipient infrarenal aorta, passed through a tunnel posterior to the pancreas and duodenum, and then anastomosed to the donor celiac artery. Donor aortic conduits left in continuity with the donor hepatic arterial supply have largely been abandoned because of a high incidence of thrombosis.

Technique of Biliary Tract Reconstruction

Biliary tract leaks or obstructions are the most frequent technical complications after liver transplantation.[10] Fortunately, most of these, if recognized and dealt with promptly, can be successfully managed. Standardization of our methods for biliary tract reconstruction has significantly reduced the incidence of biliary tract complications.

Duct to duct reconstruction over an external T-tube stent is our preferred method of reconstruction in patients without preexisting extrahepatic biliary tract disease and when there is no significant size discrepancy between the donor and recipient bile ducts. Advantages of this method include preservation of the sphincter of Oddi and availability of the T tube to monitor bile production, and for cholangiography. The T tube provides an important mold for the healing bile duct, and the upper limb of the T tube should reach to the hepatic duct bifurcation. The T tube is usually left in place for 6–8 weeks.

In many patients, preexisting disease of the extrahepatic biliary system or unfavorable anatomy precludes direct duct to duct repair. In these cases, anastomosis of the donor bile duct to the side of the distal portion of an 18-inch Roux-en-Y limb of proximal jejunum is used. The duct anastomosis is performed over a small polyethylene pediatric feeding tube catheter which eventually passes out spontaneously through the gastrointestinal tract. Roux-en-Y choledochojejunostomy is the safest method of biliary reconstruction, with a complication rate of less than 8%. Failures of duct to duct repair are usually best managed by conversion to this method of reconstruction.

Immunosuppression and the Management of Rejection

Cyclosporine

Between March 1, 1963, and February 1980, 170 patients received orthotopic liver transplants and conventional immunosuppression with aza-

thioprine and high-dose prednisone. Twenty-eight (16.5%) of these patients remain alive, including 15 patients now more than 10 years after transplantation. From March 1980 through August 1986, 720 patients received liver transplants and cyclosporine and low-dose prednisone for immunosuppression, and through October 1986, 494 (68.6%) were alive.

The patient survival curves for our accumulated experience with azathioprine and cyclosporine therapy are presented in Figure 3. These results emphasize that the principal benefit of cyclosporine therapy has been better control of acute rejection during the first 6 months after transplantation. Acute rejection has been less frequent and easier to treat in patients managed with cyclosporine than in patients managed with conventional therapy. In addition, late survival has been better in cyclosporine-treated patients, and this may be a benefit of the lower maintenance doses of steroids which can be used with cyclosporine, resulting in a reduced risk of life-threatening infectious complications.

Survival in Adults Treated With Cyclosporine

The five most common indications for transplantation in adults are cirrhosis (168 cases), primary biliary cirrhosis (122 cases), sclerosing cholangitis (58 cases), primary liver tumors (35 cases), and inborn errors of metabolism (25 cases). Survival rates after transplantation for these

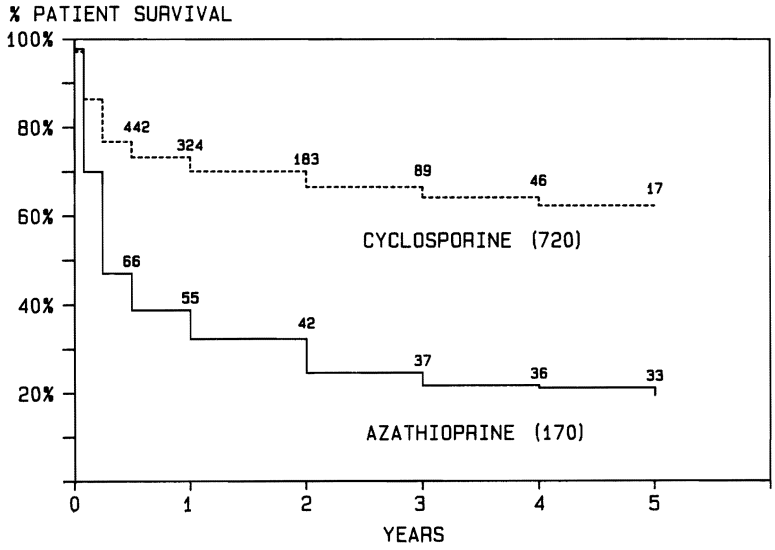

FIG 3.
Actuarial survival rates for 170 liver recipients treated between 1963 and 1980 with conventional azathioprine-prednisone immunosuppression and 720 liver recipients treated since 1980 with cyclosporine-prednisone therapy.

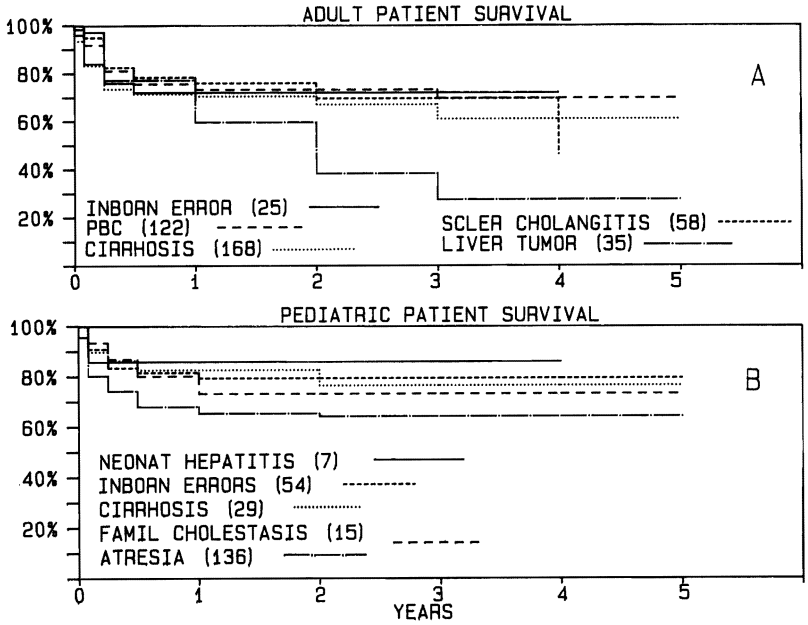

FIG 4.
A, actuarial survival rates for adult liver recipients who underwent transplantation for cirrhosis (mostly chronic aggressive hepatitis), primary biliary cirrhosis, sclerosing cholangitis, primary liver tumors, and inborn errors of metabolism. **B,** actuarial survival rates for pediatric liver recipients who underwent transplantation for biliary atresia, inborn errors of metabolism, cirrhosis, familial cholestasis, and neonatal (giant cell) hepatitis.

indications in adults are shown in Figure 4,A and all are similar except for survival after transplantation for primary liver malignancy and for patients with surface antigen–positive hepatitis.

Our experience with transplantation for primary liver malignancy has been disappointing.[14] Early survival after transplantation for cancer has been excellent, but long-term survival has been poor because of a very high incidence of recurrent disease, usually within 1 year of transplantation. There are some notable exceptions. Patients with the fibrolamellar variant of hepatocellular carcinoma have also had a high recurrence rate but palliation has often been achieved for more than 1 year. Patients with epitheloid hemangioepithelioma of the liver have usually enjoyed long-term survival.

There are 14 patients in our experience who were discovered to have incidental hepatic cancers confined to the liver at the time of transplantation for other diseases such as postnecrotic cirrhosis. All 14 patients have survived without recurrence of cancer. This observation suggests that most

patients with hepatic tumors too extensive for conventional resection have disease that is not curable by transplantation, but that survival after transplantation in patients with early malignant disease truly confined to the liver is possible.

Patients positive for hepatitis B surface antigen (HBsAg) are at high risk of recurrence of hepatitis after transplantation. Hyperimmune globulin has not been effective in preventing recurrence. A trial of interferon therapy is presently under way.

Survival in Children Treated With Cyclosporine

Survival rates for patients 18 years of age or less at the time of liver transplantation is presented in Figure 4,B. Biliary atresia accounted for approximately half of the cases, and survival was excellent except for infants (less than 1 year old), in whom a high incidence of technical complications, especially hepatic artery thrombosis, limited early survival to only 60% and necessitated retransplantation in approximately 25% of the patients. Postnecrotic cirrhosis, inborn errors of metabolism, familial cholestasis, and neonatal (giant cell) hepatitis accounted for most of the other pediatric cases, and survival has been good for all of these indications.

Complications of Cyclosporine Therapy

Hypertension is a common side effect of cyclosporine therapy and most patients require additional drugs to control it. In the acute postoperative recovery period, intravenous control with intermittent doses of apresoline or labetalol or continuous infusion of nitroglycerin or labetalol may be required. Later, oral therapy with hydralazine and a β-adrenergic blocker is often effective. Recently we have had favorable experience with calcium channel–blocking drugs (nifedipine, Vasotec) or labetalol.

Many bacterial infections are better tolerated with cyclosporine than with azathioprine. In part this may be due to the selective mechanism of action of cyclosporine on T lymphocytes and in part to the lower doses of prednisone required to prevent rejection. However, opportunistic infections such as *Pneumocystis* and *Legionnella pneumoniae* and systemic viral infections, especially with herpes simplex or zoster, varicella, Epstein-Barr virus, and cytomegalovirus, are a serious threat. We currently treat all our liver recipients with oral Bactrim (trimethoprim-sulfamethoxazole) prophylaxis (one single strength tablet each day) for *Pneumocystis* for 6 months after transplantation.

Localized herpetic lesions in the oral and genital areas are common and can be treated by topical or oral acyclovir therapy. Disseminated infection is treated with reduction of immunosuppression and the intravenous administration of acyclovir. Although there are experimental antiviral agents for treatment of other viral infections, for the most part these can only be managed by reduction or withdrawal of immunosuppressive agents.

Epstein-Barr virus infection in patients taking cyclosporine is associated with the development of lymphomatous lesions. Involvement of mesenteric and retroperitoneal lymph nodes may produce abdominal pain and intestinal obstruction or perforation. Lesions in the head and neck region are also common and may result in oropharyngeal or airway obstruction. The lesions will usually regress with withdrawal of cyclosporine. Radiation therapy or chemotherapy is rarely indicated.[15]

Cyclosporine is a nephrotoxic drug, and elevated blood urea nitrogen (BUN) and serum creatinine levels are common in patients taking this immunosuppressive agent in therapeutic doses. Fortunately, irreversible renal injury severe enough to require dialysis has been uncommon. However, patients with a difficult early postoperative course may require sparing of cyclosporine to preserve renal function. Alternative therapy with conventional immunosuppression or antilymphocyte globulin can be used for this purpose.

Antilymphocyte Therapy

OKT3 (Orthoclone), Ortho Pharmaceuticals, Raritan, N. J.) is a mouse antihuman monoclonal T lymphocyte antibody preparation. It is an effective agent for the control of steroid-resistant acute cellular allograft rejection. Its mechanism of action is probably complex and may include both physical removal of antibody-coated cells by the reticuloendothelial system and functional inactivation of the T cell antigen receptor.

In over 2 years' experience with this agent we have found it to be particularly helpful in the management of acute cellular rejection during the period from 10 to 90 days after transplantation. It is also valuable in the first week after transplantation for patients unable to tolerate therapeutic doses of cyclosporine.[16]

OKT3 is administered as a single daily intravenous 5-mg bolus (1.0–2.5 mg in small children). Side effects including malaise, nausea, myalgias arthralgias, and headaches are common but rarely severe enough to require withdrawal of therapy, and usually diminish with succeeding doses. Premedication with steroids and antihistamine is used for the first several days. No deaths immediately attributable to administration of OKT3 have occurred in our experience.

Retransplantation

In our first 500 liver transplants done with cyclosporine, 22.7% of the patients required retransplantation. Allograft rejection necessitated 53.1% of the retransplants. Fortunately, survival after retransplantation for allograft rejection is nearly 60%, almost as good as survival after primary transplantation.

Technical failure, mainly hepatic artery thrombosis, was responsible for 27.9% of the retransplants. More retransplants were required for hepatic

artery thrombosis in children (39.8%) than in adults (16.2%). One-year survival after retransplantation for loss of a primary graft from technical complications is only 43.1%.

Primary graft failure results in an immediate life-threatening crisis. These patients rapidly develop coagulopathy, oliguria, and severe acid-base and electrolyte abnormalities, and frequently become septic. Urgent retransplantation is the only hope, and survival even then only has been 27.4%. As discussed earlier, prediction of poor early graft function based on donor assessment by traditional parameters is not very reliable except in extreme cases.

Long-Term Morbidity and Mortality

The rehabilitation of patients after successful liver transplantation is excellent, and most enjoy a quality of life comparable to that enjoyed before the onset of liver disease. The risk of death beyond the first year after transplantation is less than 3%.[17] The most frequent cause of death beyond a year after transplantation is graft failure from rejection. It is important to continue to monitor graft function and maintain adequate immunosuppression indefinitely.

The second most common cause of late death after liver transplantation is recurrent liver malignancy. The vast majority of patients who underwent transplantation because of liver tumors that could not be treated by conventional resection have died within 2 years of transplantation with recurrent disease.[12] De novo malignancies after liver transplantation have been rare, and five of the six lesions seen in our series have been cyclosporine-dependent lymphomatous lesions associated with Epstein-Barr virus infections. As discussed previously, these lesions will usually regress with reduction or withdrawal of immunosuppression.[15]

Most technical complications occur within the first few months after transplantation, but bile duct strictures may present at any time. Liver function abnormalities often resemble those seen in rejection. Ultrasound and even liver biopsy are often unreliable since low-grade rejection may remain undetected. Direct visualization of the biliary tree by endoscopic or transhepatic cholangiography is required for accurate diagnosis. The etiology of late strictures is not known but it may in some cases result from injury caused by episodes of graft rejection.

Chronic nephrotoxicity from cyclosporine is common but only two patients have had to be switched to alternative therapy. Chronic dialysis has not been required in any of our patients maintained on cyclosporine for 2–5 years after transplantation. We recommend conversion to conventional therapy with azathioprine and prednisone only in extraordinary circumstances when cyclosporine cannot be tolerated. We have, however, used combination therapy with moderate-dose azathioprine (50–100 mg/day) and reduced cyclosporine for patients unable to tolerate therapeutic levels of cyclosporine.

Multiple Organ Transplants

In 1984 a 6-year-old girl with end-stage heart disease from homozygous familial hypercholesterolemia became the first successful recipient of a simultaneous heart and liver transplant.[18, 19] The liver transplant was performed to correct the genetic defect in hepatic metabolism responsible for her heart disease. Follow-up studies have demonstrated successful correction of the metabolic defect.[20] The child has returned to school and is growing well. Two subsequent combined heart-liver transplants were attempted but failed for technical reasons.

Combined liver and kidney failure has led us to perform simultaneous liver and kidney transplants in 10 patients. In most of these cases, combined transplantation was done for severe renal failure occurring as a complication of end-stage liver disease. In one case polycystic disease of both liver and kidneys and in another case polycystic kidneys and congenital hepatic fibrosis necessitated a double transplant. All were patients in whom recovery of renal function was thought unlikely or whose function was so impaired that they would be unable to tolerate cyclosporine immunosuppression.

In all cases except one, the liver and kidney were obtained from the same donor, and in all cases but one the kidney was transplanted immediately after completion of the liver transplant. Eight of the latter kidneys were transplanted within 24 hours of harvest and functioned promptly. The only exception was in a patient with a positive crossmatch whose liver functioned. In general, kidneys transplanted in combination with a liver have functioned well, and patients have tolerated the higher doses of cyclosporine required for liver transplantation. Eight of the ten liver-kidney recipients are surviving and in seven, both grafts are functioning.

Conclusion

Survival after liver transplantation has improved dramatically for both adults and children since the introduction of cyclosporine. Technical improvements, including use of a venovenous bypass and standardized methods of biliary tract reconstruction, have also contributed to reduced morbidity and mortality.

Liver transplantation is the treatment of choice for most patients with end-stage liver disease and offers better long-term survival and quality of life for patients with cirrhosis complicated by esophageal varices, intractable ascites, or encephalopathy than does sclerotherapy or peritoneal-venous or portosystemic shunting.

Portoenterostomy for biliary atresia must be reassessed in view of the advantages of successful liver transplantation and the potential difficulties created by futile repeated surgical forays into the hepatic hilum. Survival

of infants after liver transplantation is not as good as in older children, and there is a perpetual severe shortage of donors for small children. A successful portoenterostomy provides a grace period, allowing for additional growth and development and later transplantation. However, attempts at revision of failed operations and creation of stomas makes liver transplantation more difficult if not impossible.

Liver replacement for primary hepatic malignancy has been disappointing for most types of cancer. Additional methods of treatment must be developed to improve the prognosis for these patients.

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