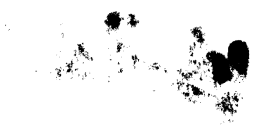# ORTHOTOPIC LIVER TRANSPLANTATION

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IMMUNOLOGY OF LIVER TRANSPLANTATION

Mechanisms of graft acceptance

Over a period of 33 years, it has become possible to successfully transplant individual intra-abdominal viscera or combinations of these organs. The consequences have been, first, new information about the metabolic interrelations that the visceral organs have in disease or health; second, the addition of several procedures to the treatment armamentarium of gastrointestinal diseases; and third, a more profound understanding of the means by which all whole organ grafts are "accepted". This last achievement has been the most fundamental and occurred in stages with long periods in between.

Clinical transplantation began as an empirical discipline. Although successes were achieved with increasing frequency, it was not understood how allografts were able, with the aid of immunosuppression, to weather the initial attack by the recipient immune system, and later to provide increasingly stable function for the host. Study of the gastrointestinal organs and their recipients have provided unique insights into these processes.[1-5] In 1969, when the liver became the first transplanted organ to be recognized as having a composite (chimeric) structure, it was noted that the Kuppfer cells and other tissue leukocytes became predominantly recipient phenotype within 100 days after transplantation while the hepatocytes permanently retained their donor specificity (figure 1). This transformation was assumed to be unique to the hepatic allograft.

However, 22 years later, first in rat models, and then in humans, it was realized that the same process occurred in all successfully transplanted intestines. The epithelium of the bowel remained that of the donor, whereas the lymphoid, dendritic and other leukocytes of recipient origin quickly invaded and became the dominant cells in the lamina propria, Peyer's patches, and mesenteric nodes. Subsequent studies of the kidney and thoracic organs made it obvious that all whole organ grafts underwent

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[2] Starzl TE, Demetris AJ, Trucco M, et al. Systemic chimerism in human female recipients of male livers. Lancet 340:876-877,1992.

[3] Starzl TE, Demetris AJ, Trucco M, et al. Chimerism after liver transplantation for Type IV glycogen storage disease and Type I Gaucher's Disease. N Engl J Med 328:745-749, 1993.

[4] Starzl TE, Demetris AJ, Murase N, Thomson AW, Trucco M, Ricordi C: Cell chimerism permitted by immunosuppressive drugs is the basis of organ transplant acceptance and tolerance. Immunol Today 14:326-332, 1993.

[5] Starzl TE, Demetris AJ,Trucco M, et al.: Cell migration and chimerism after whole organ transplantation: The basis of graft acceptance. Hepatology 17:1127-1152,1993.

similar changes, differing only quantitatively in the number of substituted tissue leukocytes which ranged from large in the case of the liver to small in organs like the kidney and heart.

What remained to be determined was the fate of the leukocytes vacating the grafts. The answers were provided by the longest survivors in the world after kidney transplantation (30 years) or after receiving a liver (23 years) who came to Pittsburgh in the spring and early summer of 1992 to be restudied.[1-5] Biopsies were obtained from each of these patients bearing someone else's liver or kidney, and also from more recently treated recipients of hearts, lungs, and intestines. The samples were taken from the transplanted organ as well as from the patient's own skin, lymph nodes, and other tissues.

Then, after special staining procedures (immunostaining or sex identification after fluorescence *in situ* hybridization [FISH]), the tissues were examined under the microscope to see if the individual cells that made them up had come from the organ donor, the recipient's own body, or both. Alternatively, the donor and recipient contributions to any specimen could be separated by polymerase chain reaction ("DNA Fingerprinting") techniques.

The answers that came from these analyses and from supporting laboratory experiments in animals showed that within minutes after restoring the blood supply of any transplant, myriads of sessile, but potentially migratory leukocytes that are part of the normal structure of all organs, left the graft and migrated all over the recipient. In the meanwhile, similar recipient cells took their place in the transplant without disturbing the highly specialized donor parenchymal cells. The relocated donor and recipient leukocytes learned to live in harmony, provided they were given sufficient protection during their nesting, by immunosuppressive drugs. In this new context, the drugs could be viewed as traffic directors, allowing movement of the white cells in both directions (to and from the graft) but preventing the immune destruction that is the normal purpose of this traffic.

It is not known yet how the two sets of white cells – a small population from the donated organ and a large one that is in essence the entire recipient immune system of the patient – reach a "truce". This is so complete in some cases that immunosuppression can be stopped, particularly after liver transplantation but less constantly with other organs. Such a stable biologic state can be induced more easily by the liver than by other transplanted organs because of the liver's higher content of the critical missionary leukocytes that apparently include pluri-potent stem cells.

While still incomplete, this much information already provides a tool with which to shape future strategies. The migratory cells can be purified from the bone marrow or spleen of a donor and then infused to improve the "acceptability" of various organs from that specific donor probably including those taken from an animal for use in humans as xenografts.

The cell migration and mixed chimerism phenomena make comprehensible the unexpected inability of donor-recipient HLA matching to accurately predict the outcome of whole organ transplantation; neither the new organ nor its new host remain the same as at the time of the matching tests.

Allograft rejection

Rejection is the most common non-technical complication after liver transplantation. Three major types of rejection have been described: hyperacute rejection, acute cellular rejection, and chronic rejection.

Hyperacute rejection

For many years, the liver was though to be resistant to antibody mediated hyperacute rejection and immediate graft failure was usually attributed to preservation failure or pre-existing ischemic graft damage rather than immunological phenomena. In contrast to renal transplantation, there was little evidence that the presence of preformed donor specific cytotoxic anti-lymphocyte (anti-HLA) antibodies was damaging to liver grafts.[6] In addition, successful kidney transplantation, in spite of a positive donor specific crossmatch, has been reported in patients who first receive a liver transplant from the same donor, but this protective effect of a

prior liver transplant cannot always be relied upon.[7-9]

Recent animal studies in rat, primate, and pig models, have demonstrated that hyperacute rejection of the liver can be produced in animals presensitized to a liver donor.[10-12] It is now recognized that the presence of preformed antibody can result in hyperacute rejection of a human liver allograft. The risk is greatest when a liver graft is placed in a recipient with an incompatible ABO blood type, but hyperacute

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[7] Fung J, Griffin M, Duquesnoy R, Shaw B, Starzl T. Successful sequential liver-kidney transplantation in a patient with preformed lymphocytotoxic antibodies. Transplant Proc 19:767-8, 1987.

[8] Dovoux D, Cherqui D, Shultz K, et al. Double liver-kidney transplantation in the presence of a positive T cross match. Presse Med 21:2015-6, 1992.

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[10] Knechtle SJ, Kolbech, Tsuchimoto S, et al. Hepatic transplantation into sensitized recipients. Demonstration of hyperacute rejection. Transplantation 43:8-12, 1987.

[11] Gubernatis G, Lauchart W, Jonker M, et al. Signs of hyperacute rejection of liver grafts in rhesus monkeys after donor-specific presensitization. Transplant Proc 19:1082-3, 1987.

[12] Merion RM, Colletti LM. Hyperacute rejection in porcine liver transplantation. I. Clinical characteristics, histopathology, and disappearance of donor-specific lymphocytotoxic antibody from serum. Transplantation 49:861-8, 1990.

rejection has also now been described in patients receiving ABO compatible grafts.[13-16] The usual morphological findings are a massive hemorrhagic necrosis evolving within hours or days of reperfusion of the graft. Deposits of immunoglobulin, the C-3 component of complement, properidin and fibrinogen are characteristic findings.[17] A necrotizing or neutrophilic arteritis is also seen. Because of the risk of hyperacute rejection, liver transplantation across incompatible ABO blood groups is hazardous and is contraindicated except in the most urgent circumstances.

Although the risk of antibody mediated hyperacute rejection in patients with preformed donor specific anti-HLA cytotoxic antibodies who receive ABO compatible graft remains

acceptably low, there is increasing evidence that the presence of preformed antibody increases the risk of late graft loss. Demetris et al reported a higher incidence of cellular rejection episodes and a higher rate of graft loss within 180 days of transplantation in recipients with preformed IgG lymphocytotoxic antibodies.[18] Although hyperacute rejection was not seen in these patients, platelet margination in central veins, acute cholangiolitis, centrilobular hepatocyte swelling similar to that seen in ischemic grafts, endothelial activation in arteries with medial changes, and recurring episodes of acute cellular rejection were commonly found. Perioperative administration of prostaglandin E1 (PGE1) may offer a protective advantage when grafting across a positive crossmatch.[19]

In a recent comparison of liver recipients maintained on an FK506 and prednisone protocol, antibody cross-match negative graft recipients had significantly better one year patient and graft survival rates (86% and 82%) than antibody cross-match positive recipients (68% and 56%).[20] In addition, cross-match

[13] Demetris AJ, Jaffe R, Tzakis A, et al. Antibody-mediated rejection of human orthotopic liver allografts. A study of liver transplantation across ABO blood group barriers. Am J Pathol 132:489-502, 1988.

[14] Rego J, Prevost F. Rumeau JL, et al. Hyperacute rejection after ABO incompatible orthotopic liver transplantation. Transplant Proc 19:4589-90, 1987.

[15] Cienfuegos JA, Pardo F, Hernández J, Camps J, Quiroga J, Pardo J. Hyperacute rejection in liver transplantation: morphological and clinical characteristics. Transplant Proc 24:141-2, 1992.

[16] Imagawa DK, Noguchi K, Iwaki Y, Busuttul RW. Hyperacute rejection following ABO-compatible orthotopic liver transplantation – a case report. Transplantation 54:114-7, 1992.

[17] Gubernatis G, Kemnitz J, Bornscheuer A, et al. Potential various appearances of hyperacute rejection in liver transplantation. Lagenbecks Arch Chir 374:20, 1989.

[18] Demetris AJ, Nakamura K, Yagihashi A, et al. A clinicopathological study of human liver allograft recipients harboring preformed IgG lymphocytotoxic antibodies. Hepatology 16:671-81, 1992.

[19] Takaya S, Iwaki Y, Starzl TE. Liver transplantation in positive cytotoxic crossmatch cases using FK 506, high dose steroids, and prostaglandin E1. Transplantation 54:927-9, 1992

[20] Takaya S, Bronsther O, Iwaki Y, et al. The adverse impact on liver transplantation of using

positive patients also required more blood products during surgery and had poorer initial graft function. The refractoriness of thrombocytopenic patients to platelet transfusions may be aggravated by anti-HLA antibodies.[21]

Acute cellular rejection

Acute cellular rejection may occur at any time after transplantation, but is most commonly seen clinically in the first 10 days to 2 months after transplantation. However, evidence of early rejection has been reported in 44% of protocol biopsies only 5 days after transplantation.[22] In those patients with early rejection on the day-5 biopsy, 67% ultimately required treatment with OKT3 for reversal, and recurrent rejection episodes were more common.

Klintmalm et al observed at least one episode of acute cellular rejection in 60.6% of 104 liver graft recipients treated with a baseline regimen of cyclosporine and prednisone. In this series, 42.3% of the patients had only one rejection episode. Of the 63 first episodes of rejection, 60 occurred within 21 days of

transplantation. Anti-rejection therapy with steroids or OKT3 was highly effective and only two patients eventually lost their grafts to rejection.[23]

The intrahepatic bile ducts and vascular endothelium, both of which express major histocompatibility (MHC) antigens and adhesion molecules, are the main targets of the immunological response. Liver biopsy remains the gold standard for diagnosis. Rejection must be differentiated from manifestations of vascular or biliary tract technical complications, preservation injury, opportunistic viral infection, drug toxicity, or any combination of the above.

Typical findings of acute cellular rejection include a lymphocytic infiltrate in the portal tracts with involvement of the bile ducts and endothelium of the portal veins. The central veins may also display a venulitis. The hepatic lobules are usually uninvolved except in severe cases when the mononuclear infiltrate may spill over the limiting plate and be associated with hepatocyte necrosis. This morphology is quite distinct from the piecemeal necrosis characteristic of hepatitis. Ominous findings on biopsy include paucity of bile ducts, arteritis, and hepatocellular ballooning with hepatocellular dropout. The degree of bile duct damage (as opposed to bile duct loss), the severity of the lymphocytic infiltrate, and the

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positive cytotoxic crossmatch donors. Transplantation 53: 400-6, 1992.

[21] Marino IR, Weber T, Kang YG, Esquivel CO, Starzl TE, Duquesnoy R. HLA alloimmunization in orthotopic liver transplantation. Transplant Proc 21:789, 1989.

[22] Brunt EM, Peters MG, Flye MW, Hanto DW. Day-5 protocol liver allograft biopsies document early rejection episodes and are predictive of recurrent rejection. Surgery 111:511-7, 1992.

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[23] Klintmalm GB, Nery JR, Husberg BS, Gonwa TA, Tillery GW. Rejection in liver transplantation. Hepatology 10:978-85, 1989.

mere presence of hepatocellular necrosis are not reliable predictors of outcome.[24]

Considerable effort has been devoted to finding markers of rejection that could be obtained by non-invasive means. Soluble interleukin-2 receptors (IL-2R) have been measured as a marker of lymphocyte activation in serum and bile. Both serum and bile levels of IL-2R are elevated 24 hours prior to the detection of acute rejection by other means and levels in bile are more specific and more sensitive than serum levels.[25] Hyaluronic acid (HA) and factor VIII related antigen (VIIIRAg), which detect endothelial damage, have also been measured. Elevated HA levels were found in patients with acute rejection and were highest in patients who went on to develop chronic rejection. VIIIRAg was elevated in all recipients and did not discriminate between rejection and other complications.[26]

The usual treatment of mild to moderate rejection is corticosteroids. More severe rejection or steroid-resistant rejection is treated

with monoclonal or polyclonal anti-lymphocyte antibody, as discussed below. In a recent study, eight patients with characteristic histological findings of rejection, including bile duct damage and endothelialitis, were observed to recover from rejection without additional immunosuppression.[27] This suggests that acute rejection is part of the adaptive process between host and graft that does not necessarily lead to permanent graft damage or graft loss. However, since it is difficult to tell in which patients rejection will resolve spontaneously, treatment is usually advisable if characteristic histological findings are present.

Acute rejection occurring more than six months after transplantation is less common, but usually responds well to steroid therapy. Many late rejections are associated with low levels of immunosuppression and compliance problems, but biliary tract complications should also be evaluated. The incidence of progression to chronic rejection is similar with early (7.0%) or late rejection (7.7%).[28]

Angiographic abnormalities may be found in patients with acute rejection, including varying degrees of intrahepatic arterial narrowing, stretching of the intrahepatic arterial

[24] Snover DC, Freese DK, Sharp HL, et al. An analysis of the use of biopsy in determining outcome of rejection. Am J Surg Pathol 11:1-10, 1987.

[25] Adams DH, Wang L, Hubscher SG, Elias E, Neuberger JM. Soluble interleukin-2 receptors in serum and bile of liver transplant recipients. Lancet 1:469-71, 1989.

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[27] Dousset B, Hubscher SG, Padbury RT, et al. Acute liver allograft rejection – is treatment always necessary? Transplantation 55:529-34, 1993.

[28] Mor E, Gonwa TA, Husberg BS, Goldstein RM, Klintmalm GB. Late-onset rejection in orthotopic liver transplantation. – associated risk factors and outcome. Transplantation 54:821-4, 1992.

tree, poor peripheral arterial filling, and a decrease in the number of intrahepatic arteries.[29] The increased resistance to flow in the rejecting graft may result in changes in the Doppler flow signal and be mistaken for hepatic arterial thrombosis.

Chronic rejection

Chronic allograft rejection develops in 10 to 15% of liver recipients. Its characteristic feature is a chronic obliterative arteriopathy leading to progressive loss of small bile ducts. Small portal arterioles less than 35 microns and bile ducts which should accompany arteries ranging from 35 to 74 microns in diameter are missing, with the greatest loss occurring amongst the smallest ducts. Histopathological evidence of large vessel arteriopathy is often absent.[30]

Other histological findings seen in chronic allograft rejection include centrilobular cholestasis and hepatocyte atrophy or ballooning, intrasinusoidal foam cells, spotty acidophilic necrosis, and perivenular sclerosis. All of these changes reflect a progressive ischemic injury.

Progressive cholestatic jaundice with elevated canalicular enzymes is the usual clinical presentation of chronic rejection. The diagnosis is established by liver biopsy and investigation to rule out other problems including viral hepatitis, hepatic artery or portal vein thrombosis, biliary obstruction, viral or toxic hepatitis, systemic infection, and recurrent disease. Chronic rejection is a relentless process that generally does not respond to additional immunosuppressive therapy. Although the early stages of chronic rejection may respond to conversion of patients from cyclosporine to FK 506, patients with well established chronic rejection eventually require retransplantation.[31]

Vanishing bile duct syndrome

An interesting variant of chronic rejection is the "vanishing bile duct syndrome" (VBDS) characterized by an obliterative cholangitis and ductopenia within 3 months of transplantation.[32] An increased incidence of VBDS has been associated with a positive lymphocytotoxic crossmatch, HLA mismatch, and CMV infection.[33, 34] It has been hypothesized that

[29] White RM, Zajko AB, Demetris AJ, et al. Liver transplant rejection: angiographic findings in 35 cases. Am J Roentgenol 148:2095-8, 1987.

[30] Oguma S, Belle S, Starzl TE, Demetris AJ. A histometric analysis of chronically rejected human liver allografts: insights into the mechanism of bile duct loss. Hepatology 9:204-9, 1989.

[31] Demetris AJ, Fung JJ, Todo S, et al. Conversion of liver allograft recipients from cyclosporine to FK 506 immunosuppressive therapy – a clinicopathologic study of 96 patients. Transplantation 53:1056-62, 1992.

[32] Ludwig J, Wiesner RH, Batts KP, Perkins JD, and Krom RA. The acute vanishing bile duct syndrome (acute irreversible rejection) after orthotopic liver transplantation. Hepatology 7:476-83, 1987.

[33] Batts KP, Moore SB, Perkins JD, et al. Influence of positive lymphocyte corssmatch and HLA

CMV infection, which augments expression of HLA antigens on bile duct epithelium, stimulates the immune response leading to destruction of small bile ducts and that cytokines produced in response to CMV infection may augment immune responses to the allograft. A more recent re-analysis by the Mayo Clinic group failed to confirm the association between HLA typing, CMV serology, or clinical CMV infection and VBDS.[35] However, the King's College group, using a more sensitive assay for viral DNA, was able to detect CMV DNA in 10 of 12 patients with VBDS, in all 18 patients studied with clinical CMV infection, and in none of 10 patients with neither infection nor VBDS.[36]

The relationship between CMV replication in the liver and VBDS requires further investigation. In the meantime, the incidence of

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mismatching on vanishing bile duct syndrome in human liver allografts. Transplantation 45:376-9, 1988.

[34] O'Grady JG, Alexander GJ, Sutherland S, Donaldson P, et al. Cytomegalovirus infection and donor recipient HLA antigens: interdependent cofactors in pathogenesis of vanishing bile-duct syndrome after liver transplantation. Lancet 2:302-5, 1988.

[35] Paya CV, Wiesner RH, Hermans PE, et al. Lack of association between cytomegalovirus infection, HLA matching and the vanishing bile duct syndrome after liver transplantation. Hepatology 16:66-70, 1992.

[36] Arnold JC, Portmann BC, O'Grady JG, et al. Cytomegalovirus infection persists in the liver graft in vanishing bile duct syndrome. Hepatology 16:494-6, 1992.

VBDS is declining, possibly as a result of better immunosuppression with triple drug regimens or FK 506, as well as improved management of CMV infection with prophylactic acyclovir and therapeutic ganciclovir.[37, 38]

Conventional immunosuppressive agents

Cyclosporine (Sandimmune®)

Cyclosporine, an 11-amino acid cyclic peptide, is a highly lipid soluble immunosuppressant which is extensively bound to plasma proteins. Cyclosporine blocks the production of IL-2, an important cytokine produced by activated T-lymphocytes, by disrupting calcium dependent activation pathways in the T-cell. Cyclosporine is metabolized by the liver and excreted in bile with only trace amounts excreted unchanged in the urine. At least ten metabolites have been identified, but are not well characterized. Absorption and dosage required to achieve adequate therapeutic blood levels are highly variable and necessitate careful monitoring of each patient.

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[37] Pirsch JD, Kalayoglu M, Hafez GR, et al. Evidence that the vanishing bile duct syndrome is vanishing. Transplantation 49:1015-7, 1990.

[38] Van Hoek B, Weisner RH, Ludwig J, et al. Combination immunosuppression with azathioprine reduces the incidence of ductopenic rejection and vanishing bile duct syndrome after liver transplantation. Transplant Proc 23:1403-5, 1991.

After liver transplantation, the drug is given as a continuous intravenous infusion at a dose of 3 to 5 mg/kg per day. Oral therapy at 10 to 12 mg/kg per day in two divided doses is begun as soon as gastrointestinal function permits, and is overlapped with intravenous therapy for several days until stable trough blood levels are obtained.

Cyclosporine is nephrotoxic and acutely produces a hyperkalemic renal tubular acidosis. Chronic cyclosporine nephrotoxicity is characterized by a progressive interstitial fibrosis. To avoid nephrotoxicity in the early postoperative period, cyclosporine may be withheld during the first 5 to 7 days after transplantation, during which time various combinations of azathioprine, prednisone, and polyclonal (ATGAM®, Upjohn) or monoclonal (Orthoclone OKT-3®, Ortho Pharmaceuticals) antilymphocyte antibody preparations are given. Oral cyclosporine is started when renal function has stabilized. Intravenous cyclosporine can also be avoided by giving cyclosporine via nasogastric tube, but absorption is highly variable early after transplantation and dependent upon both bowel function and bile production.

Other common manifestations of cyclosporine toxicity include hypertension, tremors, hypertrichosis, and gingival hyperplasia. Central nervous system abnormalities include fever, seizures, hallucinations and paranoid delusions, motor disorders and quadriplegia, speech disturbances,

cortical blindness, delirium and coma. Reversible changes in cerebral white matter may be seen on CT and magnetic resonance imaging studies. An association between CNS toxicity and low serum cholesterol has been suggested, but hypocholesterolemia is not present in all cases.[39, 40] Reduction in cyclosporine dosage usually results in improvement. Steroid toxicity, hypomagnesemia, low serum ionized calcium, and hypernatremia must also be considered in patients with suspected immunosuppression-associated neurotoxicity.

Cyclosporine elimination is dependent upon the hepatic cytochrome P-450 microsomal enzyme system. Other drugs which induce or inhibit this system will affect cyclosporine clearance. Enzyme inducing effects occur over several weeks and, when the inducing agent is withdrawn, the effect takes a similar time to reverse. Enzyme inhibition has a more rapid impact, as drug accumulation begins quickly and requires an early reduction of cyclosporine dosage.

Corticosteroids

Corticosteroids (prednisone and methylprednisolone) are used routinely as part

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[40] Truwit CL, Denaro CP, Lake JR, Demarco T. MR imaging of reversible cyclosporine A induced neurotoxicity. Am J Neuroradiol 12:651-9, 1991.

of the immunosuppression induction and maintenance protocols after liver transplantation. The 11-oxo group of prednisone is reduced in the liver to form the biologically active steroid prednisolone. An equilibrium between prednisone and prednisolone is established after oral administration and first pass through the liver. Even in patients with severe liver disease, interconversion of prednisone and prednisolone is not a limiting factor.[41]

For induction of immunosuppression, adult patients typically receive an intravenous bolus of one gram methylprednisolone intraoperatively, followed by a 5-day taper of high dose steroids, usually starting at 200 mg per day in four divided doses and reduced daily by 40 mg per day until a baseline of 20 mg per day is reached. As soon as gastrointestinal function permits, the patient is given oral prednisone. Pediatric patients (< 30 kg) receive a reduced dosage schedule, usually beginning at 100 mg on the first day and reduced by 20 mg per day to reach a baseline of 10 mg to 20 mg per day.

Corticosteroids also remain the first-line drug of choice for the treatment of mild or moderate acute cellular rejection. Typical treatment includes a repeat bolus of methylprednisolone followed by a repeat of the 5-day steroid taper.

Since the introduction of cyclosporine, it has been possible to taper steroid maintenance levels much more quickly that was possible under regimens based on azathioprine. There have also been several reported series of successful withdrawal of patients from prednisone within three to six months after transplantation.[42, 43] However, patients must be carefully monitored for acute rejection if withdrawal is attempted, and steroids should be promptly reinstituted in those cases in which acute rejection occurs.

Azathioprine

Azathioprine (Imuran®) is an analog of 6-mercaptopurine which, in combination with steroids, was the mainstay of clinical immunosuppression prior to the introduction of cyclosporine. It is a bone marrow suppressant and leukopenia is the usual dose limiting effect of the drug. Today, it is still used in moderate dosage as an adjunctive agent with cyclosporine and prednisone in patients unable to tolerate

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[41] Frey BM, Frey FJ. Clinical pharmakokinetics of prednisone and prednisolone. Clin Pharmakokinet 19:126-46, 1990.

[42] Margarit C, Martinez V, Inbanez V, Tormo R, Infante D, Iglesias H. Maintenance immunosuppression without steroids in pediatric liver transplantation. Transplant Proc 21:2230-1, 1989.

[43] Padbury RT, Gunbson BK, Dousset B, et al. Steroid withdrawal from long-term immunosuppression in liver allograft recipients. Transplantation 55:789-94, 1993.

usual dosages of cyclosporine, or to augment immunosuppression in patients with persistent or recurrent rejection.

Anti-lymphocyte antibody preparations

At the present time ATGAM® (Upjohn), a polyclonal antilymphocyte globulin and monoclonal Orthoclone OKT3® (monomurab-CD3, Ortho Pharmaceuticals) are the only antibody preparations in widespread use for the treatment of severe or steroid resistant acute cellular rejection. These agents are also used for their cyclosporine sparing effect in the early postoperative period.

OKT3 is an Ig2a murine monoclonal antibody which has been shown to be highly effective in reversing steroid resistant acute cellular rejection.[44, 45] It is supplied in 5 cc ampoules containing 5 mg of drug. The 5 cc dose is administered as an intravenous bolus in less than one minute daily for 10 to 14 days. OKT3 is active against the CD3 molecule in the T-cell membrane, a moiety associated with the antigen recognition structure and activation of signal transduction in T-lymphocytes. Binding results in both a rapid decrease in the number of circulating CD3 positive cells and a functional inactivation of the T-cell receptor. Activated T-cells release numerous cytokines. Premedication with methylprednisolone, acetaminophen, and antihistamine helps reduce the side effects of the cytokine release syndrome commonly experienced by patients during the first few days of administration.

OKT3 has also been advocated for prophylactic use in the first 7 to 14 days after transplantation to reduce the incidence of acute rejection and to avoid the nephrotoxic effects of cyclosporine. However, recent studies have failed to demonstrate any lasting benefit from prophylactic use of OKT3. Rather it is best reserved for treatment of steroid resistance acute cellular rejection or when cyclosporine must be withheld for a limited period.[46, 47]

Since OKT3 is a mouse protein, patients may develop anti-murine antibodies as a result of its use. Continued immunosuppression with steroids, azathioprine, or cyclosporine influences the titer, time course, and specificity of the anti-murine antibodies formed. Retreatment with OKT3 is usually ineffective in patients with significant titers of anti-murine

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[44] Cosimi AB, Cho SI, Delmonico FL, et al. A randomized clinical trial comparing OKT3 and steroids for treatment of hepatic allograft rejection. Transplantation 43:91-5, 1987.

[45] Fung JJ, Demetris AJ, Porter KA, et al. Use of OKT3 with ciclosporine and steroids for reversal of acute kidney and liver allograft rejection. Nephron 46 (suppl 1):19-33, 1987.

[46] McDiarmid SV, Busuttil RW, Levy P, et al. The long term outcome of OKT3 compared with cyclosporine after liver transplantation. Transplantation 52:91-97, 1991.

[47] Höckerstedt K, Ericzon B-C, Bismuth H, et al. OKT3 prophylaxis in liver transplant patients: a European and Australian multicenter, prospective controlled trial. Transplant Proc 25:556-7, 1993.

antibody and sensitization should be suspected in patients with poor clearance of CD3 positive cells or low serum levels of OKT3.

New immunosuppressive agents

FK506 (Prograf®)

FK506, a 23-member ring macrolide lactone belonging to the same family of compounds as eythromycin, is a potent immunosuppressive agent. Although the chemical structure and cell receptor of FK506 are both different than those of cyclosporine, it has similar effects on T-cell function, including blocking of the antigen induced, calcium dependent signal transduction which leads to transcription of IL-2.[48, 49] Calcineurin, a Ca^{++}/calmodulin activated phosphatase, appears to be a common target when FK 506 and CsA are bound to their respective immunophilins, FK 506-binding protein (FKBP) and cyclophillin (CyP).[50, 51] There is also clinical experience

suggesting that FK 506 is an effective inhibitor of humoral mechanisms of rejection.[52]

In extensive clinical trials at the University of Pittsburgh and in recent multicenter trials in the United States, FK506 has been found to be compare favorably to cyclosporine for induction and maintenance immunosuppression after liver transplantation. It has also been used to rescue grafts from refractory rejection in patients treated initially with cyclosporine.[53-57]

FK 506 is not dependent upon bile for its absorption, but it is metabolized on first pass through the liver. Therefore, blood levels may

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[48] Kronke M, Leonard WJ, Depper JM, et al. Cyclosporine A inhibits T-cell growth factor gene expression at the level of mRNA transcription. Proc Nat Acad Sci 81:5214-8, 1984.

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activity of FK 506, related macrolactams, and cyclosporine. Transplant Proc 25: 644-6, 1993.

[52] Woodle E, Perdrizet GA, Brunt EM, et al. FK506: inhibition of humoral mechanisms of hepatic allograft rejection. Transplantation 54:377-81, 1992.

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[54] Todo S, Fung JJ, Starzl TE, et al. Liver, kidney, and thoracic organ transplantation under FK 506. Ann Surg 212:295-305, 1990.

[55] Fung JJ, Todo S, Jain A, et al. Conversion from cyclosporine to FK 506 in liver allograft recipients with cyclosporine related complications. Transplant Proc 22:6-12, 1990.

[56] US Multicenter FK506 Liver Study Group. Use of Prograf (FK 506) as rescue therapy for refractory rejection after liver transplantation. Transplant Proc 25:679-88, 1993.

[57] Jost U, Winkler M, Ringe B, Rodeck B, Pichlmayr R. FK 506 treatment of intractable rejection after liver transplantation. Transplant Proc 25:2666-7, 1993.

remain elevated in patients with poor graft function and close monitoring of blood or serum levels is important. Nephrotoxicity, as with cyclosporine, is the most common dose-limiting side effect.[58] Gastrointestinal side effects, including depression of appetite, nausea, and diarrhea, are common early in the course of treatment, and may in part be due to an antibiotic effect of the drug on the gut flora. Hypertension is less common with FK 506 than with cyclosporine and, when present, is often easier to control. Central nervous system toxicity is similar to that seen with cyclosporine. However, patients presenting with CNS toxicity on either cyclosporine or FK506 will usually improve when switched from one drug to the other, or if the dosage of the drug being used is reduced markedly.

RS-61443 (Mycophenolate mofetil)

RS-61443, the morphomonoethyl ester of mycophenolic acid (MPA), is a potent inhibitor of inosine monophosphate dehydrogenase. It interferes with the replication of DNA by inhibition of guanosine nucleotide formation. Since lymphocytes are dependent upon *de novo* synthesis of guanine nucleotides and lack the salvage pathway found in other rapidly dividing cell lines, MPA and RS-61443 have a preferential inhibitory effect on lymphocyte proliferation. Early clinical trials suggest that

RS-61443 is an effective immunosuppressant when used in combination with steroids for maintenance therapy and for rescue of rejecting liver allografts.[59, 60] Further trials are awaited with interest.

Rapamycin

Rapamycin is a lipophilic macrolide with a chemical structure closely resembling FK506. Despite the structural similarity to FK 506, rapamycin does not block IL-2 production and appears to act later in the lymphocyte activation cascade between the G1 and S phase of the cell cycle.[61-63] Thus, rapamycin can act to suppress an immune response after T-cell activation and can even act as an antagonist to FK 506. Rapamycin shows significant promise as an

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[58] Alessiani A, Cillo U, Fung JJ, et al. Adverse effects of FK 506 overdosage after liver transplantation. Transplant Proc 25:628-34, 1993.

[59] Klintmalm GB, Ascher NL, Busuttil RW, et al. RS-61443 for treatment-resistant human liver rejection. Transplant Proc 25:697, 1993.

[60] Friese CE, Hebert M, Osorio RW, et al. Maintenance immunosuppression with prednisone and RS-61443 alone following liver transplantation. Transplant Proc 25:1758-9, 1993.

[61] Dumont FJ, Staruch MJ, Koprak SL, Melino MR, Sigal NH. Distinct mechanisms of suppression of murine T-cell activation by the related macrolides FK-506 and rapamycin. J Immunol 144:251-8, 1990.

[62] Dumont FJ, Melino MR, Staruch MJ, Koprak SL, Fisher PA, Sigal NH. The immunosuppressive macrolides FK-506 and rapamycin act as reciprocal antagonists in murine T-cells. J Immunol 144:1418-24, 1990.

[63] Kay JE, Kromwel L, Doe SE, Denyer M. Inhibition of T and B lymphocyte proliferation by rapamycin. Immunology 72:544-9, 1991.

immunosuppressant in animal models. Because of its unique mechanism of action, clinical trials will be of great interest.

Brequinar sodium

Brequinar sodium is a substituted 5-quinolone carboxylic acid derivative that has broad anti-tumor activity in mice. It inhibits dihyrdoorotate acid dehydrogenase in the *de novo* pyrimidine biosynthesis pathway, resulting in depletion of precursors for necessary for RNA and DNA synthesis. It inhibits proliferation of murine lymphocytes activated by various mitogens and arrests T-cell and B-cell replication, but it does not interfere with early events in T-cell activation such as cytokine production.[64] It has been shown to be effective in prolonging heart, kidney, and liver allograft survival and has been used to induce tolerance to liver allografts in rats.[65] The clinical potential of this agent is yet to be determined.

Deoxyspergualin

15-deoxyspergualin (DSPG) is an analog of spergualin, an anti-tumor metabolite produced

by *Bacillus laterosporus*. It has been shown to have efficacy in clinical renal transplantation for treatment of acute rejection and for management of recipients of kidneys from ABO incompatible or preformed antibody positive donors.[66, 67] The drug has a selective effect on the differentiation pathway of B-lymphocytes and suppresses competent proliferating T-cells, such as cytotoxic T-cells. However, unlike cyclosporine and FK 506, DSPG does not affect IL-2 production or IL2-receptor expression.[68, 69]

It has recently been shown that DSPG binds to a heat shock protein, Hsp70.[70] Members of the heat shock protein 70 family are

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[64] Thomson AW, Woo J, Lemster B, Todo S, Fung JJ, Starzl TE. Potentiation of the antiproliferative activity of brequinar sodium for murine lymphocytes by exogenous cytidine. Transplant Proc 25:704-5, 1993.

[65] Knoop M, Cramer DV, Chapman FC, Makowka L. Brequinar sodium suppresses liver allograft rejection and induces permanent tolerance in the rat. Transplant Proc 25:706-7, 1993.

[66] Amemiya H, Suzuki S, Ota K, et al. A novel rescue drug, 15-deoxyspergualin. First clinical trials for recurrent graft rejection in renal recipients. Transplantation 49:337-43, 1990.

[67]Takahashi K, Tanabe K, Ocha S et al. Prophylactic use of a new immunosuppressive agent, deoxyspergualin, in patients with kidney transplantation for ABO-incompatible or preformed antibody positive donors. Transplant Proc 23:1078-82, 1991.

[68] Morikawa K, Oseko F, Morikawa S. The suppressive effect of deoxyspergualin on differentiation of human B-lymphocytes maturing into immunoglobulin producing cells. Transplantation 54:526-31, 1992.

[69] Fujii H, Nemoto K, Abe F, et al. Deoxyspergualin, a novel immunosuppressant, markedly inhibits mixed lymphocyte reaction and cytotoxic T-lymphocyte activity in vitro. Int J Immunopharamcol 14:731-7, 1992.

[70] Nadler SG, Tepper MA, Schacter B, Mazzucco CE. Interaction of the immunosuppressant dexoyspergualin with a member of the Hsp70 family of heat shock proteins. Science 258:484-6, 1992.

important to many cellular processes, including immune responses, and may represent a family of immunophilin binding proteins distinct from the *cis-trans* proline isomerases associated with the binding of cyclosporine and FK 506. This may explain the different mechanism of action of DSPG and the ability of this agent to act synergistically with cyclosporine or FK 506. The clinical efficacy of DSPG in liver transplantation remains to be established.

Other agents

So far, only a monoclonal antibody directed against the CD-3 determinant of the T-cell receptor has found widespread application as a clinical immunosuppressive agent, and most of the drugs that are used in clinical practice have been products of serendipitous discovery. Efforts to explore the clinical potential of other monoclonal antibodies directed against the CD4 determinant associated with helper T-cells, cytokine receptors, adhesion molecules, and "second signal" accessory molecules such as the CD28-B7 or CTLA4-B7 complexes continue. As our understanding of the signal transduction pathways activated by antigen-receptor binding and drug-immunophillin binding on the surface of the T-cell continue to evolve, other methods of aborting or redirecting the immune response mechanism will be developed and our understanding of how to achieve and control the accommodation between donor and host necessary to maintain graft acceptance will be increased.

INDICATIONS FOR LIVER TRANSPLANTATION

The liver diseases that can benefit from liver transplantation can be grouped into four major categories: chronic end stage liver disease, hepatic malignancies, fulminant hepatic failure and inborn errors of metabolism (Table 1). The evaluation of a potential liver transplant candidate varies markedly depending upon the specific disease indication for which liver transplantation is being considered. Thus, the initial goal in the evaluation process is to determine the correct diagnosis and etiology of the liver disease present in the candidate. This begins with a determination as to whether the patient has predominantly hepatocellular or cholestatic liver disease (Table 2). All patients who develop a complication of their liver disease should be referred to a transplant center for further evaluation and follow-up. The complications of interest include ascites, encephalopathy, coagulopathy, gastrointestinal bleeding, hypersplenism with clinically significant leucopenia and thrombocytopenia, severe fatigue, wasting or malnutrition, severe or disabling pruritus and liver associated bone disease (hepatic osteodystrophy). Once an individual has been identified as a potential liver transplant candidate, it is of paramount importance to stage the liver disease in order to define appropriately the timing of the procedure. The conventional criteria used to identify the

ideal candidate for a liver transplant, and the optimal timing for the procedure are reported in Table 3. Evaluation of these issues gives an estimate of the synthetic, excretory and metabolic function of the liver, as well an assessment of the life quality of the individual with end stage liver disease, and defines the transplant urgency.

Not only is it important to identify candidates for liver transplantation, but it is also mandatory to screen each candidate for the presence of any absolute or relative contraindications to the procedure (Table 4). The contraindications for liver transplantation have been reduced through the years as a consequence of steady improvements in surgical technique and intraoperative and postoperative care.

At present the only absolute contraindications include extrahepato-biliary sepsis, extrahepatic tumor or metastases, severe cardiopulmonary disease, and AIDS. The first of these is only a transient absolute contraindication. Once the sepsis is controlled, such patients can be given a transplant. In selected groups of patients, a careful screening for the presence of extrahepatic tumor is recommended: i.e., colon cancer in patients with primary sclerosing cholangitis (PSC), breast cancer in patients with primary biliary cirrhosis (PBC), head and neck cancer in subjects with a history of alcohol abuse.

All patients evaluated for liver transplantation require an accurate assessment of the function of their other organ systems, particularly of the heart, lungs and kidneys (Table 5). In older patients (> 50 years), even in the absence of clinical cardiac symptoms, a cardiac ultrasound and a MUGA scan are indicated to identify subclinical cases of heart disease. In selected cases, a coronary arteriogram or a left or right sided cardiac catheterization may be required. Younger potential liver transplant recipients with specific liver diseases known to be associated with an increased incidence of heart disease also need to undergo a thorough cardiopulmonary evaluation. These include candidates with a possible cardiomyopathy associated with alcoholism, hemochromatosis, Wilson's disease, and glycogen storage disease or pulmonary hypertension in individuals with autoimmune or chronic cholestatic liver disease, alpha-1 antitrypsin deficiency, or chronic active hepatitis C.

The presence of pre-existing renal disease adversely effects transplant survival and often becomes a major postoperative problem. Thus, an accurate assessment of an individual's renal function prior to transplantation is mandatory. In cases with advanced renal disease, a combined liver-kidney transplant may be considered in selected cases.[71, 72]

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[71] Margreiter R, Kramar R, Huber C, et al. Combined liver and kidney transplantation (letter). Lancet 1: 1077-1078, 1984.

[72] Toussaint C, De Pauw L, Vienne A, et al. Radiological and histological improvement of

Specific Disease Indications

Primary Biliary Cirrhosis (PBC)

PBC represents an ideal indication for liver transplantation because of its slow and progressive evolution, which allows for a sufficiently accurate prediction of the ideal timing for surgery.[73] In general, once the serum bilirubin level exceeds 10 mg/dl in symptomatic patients, survival averages less than 50% at two years. A more accurate index can be obtained by the evaluation of six readily available clinical parameters which can be used to produce a risk score that can be used to estimate the median survival of patients: These parameters include the patient's age, serum bilirubin level, serum albumin level, the presence of cirrhosis, the presence or absence of central lobular cholestasis and a history of prior treatment with azathioprine.[74]

The general policy is to consider a patient ready for transplantation when the estimated life expectancy of the patient is predicted to be less than one year, unless complications of their liver disease such as uncontrollable variceal bleeding, intractable itching or bone demineralization are adversely affecting the individual's quality of life and necessitate earlier transplantation. The current one-year survival rate for patients hospitalized for PBC at most centers ranges between 70% and 85%.[75,76]

Primary Sclerosing Cholangitis (PSC)

This disease shares many clinical similarities with PBC, particularly its slow progressive course with a late onset of the major complications of cirrhosis. The condition of patients with this disease is generally well-maintained until very late in its course.[77] For this reason individuals with PSC are usually considered excellent candidates for liver transplantation.[78] Intractable itching, disabling pruritus, recurrent cholangitis, ascites, osteoporosis, and encephalopathy are the typical indications for transplantation.

oxalate osteopathy after combined liver-kidney transplantation in primary hyperoxaluria type 1. Am J Kidney Dis 21:54-63, 1993.

[73] Esquivel CO, Benardos A, Demetris AJ, et al. Liver transplantation for primary biliary cirrhosis in 76 patients during the cyclosporine era. Gastroenterology 94:1207-1216, 1988.

[74] Neuberger J, Altman DG, Christensen E, Tygstrup N, Williams R. Use of a prognostic index in evaluation of liver transplantation for primary biliary cirrhosis. Transplantation 41:713-6, 1986.

[75] Starzl TE, Demetris AJ, and Van Thiel DH. Medical progress: Liver transplantation (Part II). N Engl J Med 321:1092-1099, 1989

[76] Starzl TE, Demetris AJ and Van Thiel DH. Medical progress: Liver transplantation (Part I). N Engl J Med 321:1014-1022, 1989.

[77] LaRusso NF, Wiesner RH, Ludwig J, et al. Primary sclerosing cholangitis. N Engl J Med 310:899-903, 1984.

[78] Marsh JW Jr, Iwatsuki S, Makowka L, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. Ann Surg 207:21-28, 1988.

An important association exists between PSC and ulcerative colitis.[77] Therefore, a colonoscopic examination is mandatory prior to transplantation in order to exclude the presence of a colon cancer, which is known to occur more frequently in patients with ulcerative colitis. PSC is also strongly associated with an increased risk for cholangiocarcinoma (CCa).[77] Multiple (at least 3) percutaneous or endoscopic brushings of the biliary tree in an attempt to identify an occult cholangiocarcinoma in such cases are required prior to transplantation. Unfortunately, even with the use of combined radiologic and cytologic techniques, the identification of a CCa in cases of PSC is very difficult, and the diagnosis is often made only after a pathologic examination of the removed liver has been performed.

Once an individual with PSC is identified as a potential liver transplant recipient, invasive surgical procedures such as various biliary reconstructions and partial or total colectomy should be avoided because they may increase the technical difficulty of the transplant procedure.

The current one-year survival rate for patients transplanted for PSC ranges between 70% and 80% in patients without previous surgery, as compared to a value of 50-60% in patients with a history of prior biliary tract procedure.[75, 76, 78]

Autoimmune Chronic Active Hepatitis (ACAH)

This unpredictable liver disease is characterized by an extremely variable course, complicated by multiple recurrent episodes of "active hepatitis" which eventually lead to cirrhosis and all of its complications. Even in cases where an early diagnosis and treatment is instituted with a powerful immunosuppressive agent, cirrhosis and hepatic decompensation is likely to occur. Thus, liver transplantation represents the therapy of choice for advanced ACAH.

However, the unique behavior of this disease, which is characterized by exacerbations and remissions, makes the timing of the transplant procedure rather difficult. In many cases, the long-term use of immunosuppressive agents creates untoward effects such as bone demineralization, recurrent infections, steroid-induced myopathy and obesity that become the impetus for transplantation.

The current one-year survival for patients transplanted for ACAH ranges between 60% and 90%.[75, 76, 79]

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[79] Sanchez UL, Czaja AJ, van Hoek B, Krom RA. Prognostic features and role of liver transplantation in severe corticosteroid treated autoimmune chronic active hepatitis. Hepatology 15:215-21, 1992.

Alcoholic Liver Disease

Alcohol abuse is the etiologic factor responsible for most of the liver disease in Western societies. Individuals with either Laennec's cirrhosis or alcoholic hepatitis are the largest group of potential candidates for liver transplantation at most transplant centers. Unfortunately, the scarcity of donor organs has caused many transplant centers to redefine their indications and contraindications for liver transplantation such that individuals with alcoholic liver disease are relatively disenfranchised as potential liver allograft recipients.[80-84] Concerns about alcohol abuse recidivism and the potential for a lack of compliance with the post-transplant management, together with social prejudice and the adverse publicity associated with giving an alcoholic a donor organ in preference to a less ill

non-alcoholic, have been raised and continue to be raised such that alcohol abuse has become a relative contraindication for liver transplantation.[83]

However, when acceptance of alcohol abuse as the etiology of the liver disease can be documented, with abstinence for more than 3 months, recidivism and non-compliance are unusual. Moreover, the survival rate for individuals transplanted for alcoholic liver disease does not differ from that reported for patients transplanted for non-alcoholic end-stage liver disease. A recent study has reported that alcohol use after liver transplantation is less common in patients transplanted for alcoholic liver disease than it is for patients transplanted for other disease indications.[85] The recidivism rate is less than 15% in cases transplanted for end stage liver disease. Unfortunately, the recidivism rate is as high as 50% in the few transplanted for life-threatening alcoholic hepatitis.

When an individual with alcoholic liver disease is evaluated for liver transplantation, the presence of specific, unique, alcohol-related contraindications, such as cerebral or cerebellar atrophy, cardiomyopathy and chronic pancreatitis, must be carefully assessed. These conditions can both increase the peri-operative

[80] Atterbury CE: The alcoholic in the lifeboat. Should drinkers be candidates for liver transplantation? J Clin Gastroenterol 8:1-4, 1986.

[81] Gasbarrini A, Fagiuoli S, Gavaler JS, Azzarone S, Francavilla A, Van ThielDH. Orthotopic liver transplantation for alcoholic liver disease. Alcologia 4:19-21, 1992.

[82] Killeen TK. Alcoholism and liver transplantation: ethical and nursing implications. Perspectives in Psychiatric Care 29:7-12, 1993.

[83] Knechtle SJ, Fleming MF, Barry KL, et al. Liver transplantation for alcoholic liver disease. Surgery 112:694-701,1992.

[84] Osorio RW, Freise CE, Ascher NL, et al. Orthotopic liver transplantation for end-stage alcoholic liver disease. Transplant Proc 25:1133-4, 1993.

[85] Bonet H, Gavaler JS, Wright HI, Fagiuoli S, Gurakar H, Van Thiel DH. The effect of continued alcohol use on allograft rejection following liver transplantation for alcoholic liver disease. Gastroenterology 104:878, 1993.

risk and reduce the likelihood of a significant improvement in life quality following an otherwise successful transplant.

The one-year survival rate of individuals transplanted for alcohol-related liver disease at most centers ranges between 75% and 85%.[75, 76, 83-85]

Virus-Related End-Stage Liver Disease

End-stage liver disease occurring as a consequence of viral infection (HBV, HBV/Delta, HCV, and non-A, non-B, non-C) is the most common indication for liver transplantation worldwide. It is estimated that more than 30% of the world's liver transplant candidates have a disease which is related directly to a hepatotrophic viral infection.

In assessing patients with hepatitis B for a liver transplant, it is mandatory to determine the replicative status of the virus. In the absence of active viral replication (HBeAg- / HBVDNA-), liver transplantation is generally successful and disease recurrence is unusual; on the other hand, for those who have evidence of active viral replication (HBeAg+/HBVDNA+), a 100% recurrence rate is to be expected. Worse yet, the graft liver disease progresses at a rate much faster than the original infection. For these reasons, active HBV infection currently represents a relative contraindication for liver transplantation. The one-year survival rate for individuals transplanted for active HBV disease ranges between 45-55%, compared to a figure of

70-80% in patients without evidence of active viral replication.

Peri- and post-transplant therapy either with hyperimmune gammaglobulins, interferon and HBV vaccine, or a combination of these agents, delays the onset of recurrent disease and may prevent recurrence of the infection in the allograft if continued indefinitely.[86-89] Treatment with alpha interferon (IFN) prior to transplantation, in an attempt to arrest HBV replication, has not influenced the rate of HBV reinfection after transplantation when compared to the rate observed in patients treated with anti-HBs immunoglobulin alone.[90] Continuous passive immunoprophylaxis after transplantation with an anti-HBs immunoglobulin (Ig) has reduced the 2-year actuarial rate of recurrence of

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[86] Blumhardt G, Neuhaus P, Bechstein WO et al. Liver transplantation in HBsAg positive patients. Transplant Proc 22: 1517-1518, 1990.

[87] Gugenheim J, Crafa F, Fabiani P, et al. Long-term passive immunoprophylaxis of B virus recurrence after liver transplantation in HBs antigen-positive patients. Transplant Proc 25:1349-50, 1993.

[88] Lauchart W, Muller R, Pichlmayr R. Long term immunoprophylaxis of hepatitis B virus reinfection in recipients of human liver allografs. Transplant Proc 19: 4051-4053,1987.

[89] Mora NP, Klintmalm GB, Poplawski SS, et al. Recurrence of hepatitis B after liver transplantation: Does hepatitis-B-immunoglobulin modify the recurrent disease? Transplant. Proceed 22:1549-1550, 1990.

[90] Bismuth H, Azoulay D, Dennison A. Recent developments in liver transplantation. Transplant Proc 25:2191-94, 1993.

HBsAg in serum to less than 30% and can indefinitely maintain HBsAg seronegativity and HBVDNA negativity in graft biopsy specimens. *In situ* hybridization assays of liver biopsies may detect HBV genoma before the reappearance of HBsAg.[91] However, even in Ig treated patients who remain seronegative for HBsAg and negative for HBVDNA negative in liver biopsies, HBVDNA is often detectable by PCR in peripheral blood mononuclear cells.[92]

In normal non-immunosuppressed individuals either co-infection or superinfection of HBV hepatitis with HDV is characterized by a more rapid progression to cirrhosis and/or liver failure than is seen in individuals with HBV infection alone. This appears not to be the case in liver transplant recipients.[93] HDV infection recurs early after liver transplantation before any evidence for recurrent HBV infection or clinical/biochemical hepatitis is present. In general, recurrent HDV infection is subclinical.

HDV infection in both non-immunosuppressed individuals and in immunosuppressed liver allograft recipients appears to suppress HBV replication. Interestingly, following liver transplantation, HDV infection only becomes clinically evident after recurrent HBV disease becomes evident; this rather strongly suggests that the delta virus cannot by itself be pathogenic, that it is able to replicate in the absence of HBV and that for HDV disease to occur clinically, clinically active HBV infection is required.[94]

The mean survival of liver allograft recipients transplanted for HBV/HDV co-infection has been reported to be as high as 75%, which compares favorably to a figure of 45-55% in HBVDNA positive/HDV negative recipients.[75, 76, 93]

Hepatitis C virus disease accounts for even a greater number of transplants than does HBV disease. With new methods to detect HCV infection, the incidence of HCV disease in individuals otherwise thought to have alcoholic, autoimmune or cryptogenic disease has been shown to range between 30%-70%. HCV disease, like HBV infection, can recur, but does so at a rate different than HBV disease. It must be remembered that infection and disease are not synonymous. The available data suggest that

[91] Reynès M, Tricottet V, Samuel D, et al. Allograft biopsies in situ hybridization HBVDNA detection of serum HBsAg-repositive patients treated with anti-HBV immunoprophylaxis after liver transplantation for HBV cirrhosis. Transplant Proc 25:1347-48, 1993.

[92] Feray C, Zignego AL, Samuel D, et al. Persistent hepatitis B virus infection on mononuclear blood cells without concomitant liver infection. The liver transplantation model. Transplantation 49:1155-8, 1990.

[93] Ottobrelli A, Marzano A, Smedile A, Recchia S, Salizzoni M, et al. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. Gastroenterology 101:1649-1655, 1991.

[94] Grendele M, Colledan M, Gridelli B et al. Does the experience with liver transplantation suggest that hepatitis delta virus is not cytopathic? Transplant Proc 22:1551-1553, 1990.

almost 100% of HCV+ recipients will experience a recurrent infection. Nonetheless, both graft and patient survival are good, ranging between 87% and 100% at two years in several different series. In contrast to a non-universal reinfection rate, on average only 1 out of 3 HCV+ recipients will experience a clinical, biochemical, or histologic recurrent disease; moreover, when such occurs, it tends to be mild to moderate in severity.[95, 96] Recent evidence suggests that severe or multiple rejections episodes, especially those requiring treatment with antilymphocyte antibody, may result in a higher and earlier incidence of recurrent hepatitis C.[97]

Fulminant Hepatic Failure

Fulminant hepatic failure is a medical emergency and thus represents an urgent indication for liver transplantation.[98, 99] The

survival of a patient transplanted for FHF depends upon the ability of the medical team to stabilize the patient while simultaneously establishing the correct diagnosis.

The prognosis is greatly influenced by the etiology of the FHF. Patients with acetaminophen intoxication have a mortality rate of 20-30%, compared to a rate of 45-50% for those with HAV- or HBV-induced liver failure or a rate as high as 80% or more in cases of HCV, nonA, nonB, nonC hepatitis, halothane hepatitis, or fulminant Wilson's disease.[100] Thus, there is no reason to temporarily delay a transplant procedure for an individual having one of these diseases.

A grade III coma, a Factor V less than 20%, a serum creatinine greater than 10 mg/dl, a serum bilirubin level greater than 20 mg/dl, and an age greater than 10 years are each indicators of a poor prognosis without liver transplantation.[101, 102] With each additional

[95] Wright TL, Donegan E, Hsu HH, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology 103:317-22, 1992.

[96] Shah G, Demetris AJ, Gavaler JS, Lewis JH, Todo S, Van Thiel DH. Incidence, prevalence, and clinical course of hepatitis C following liver transplantation. Gastroenterology 103:323-9, 1992.

[97] Sheiner P, Eytan M, Kishikawa K, et al. Severe or multiple rejection episodes increase the incidence of early recurrent hepatitis [abstract]. Second Congress of the International Liver Transplantation Society, Toronto, Canada, October 7, 1993.

[98] Mutimer DJ, Elias E. Liver transplantation for fulminant hepatic failure. Prog in Liver Dis 10:349-67, 1992.

[99] Pauwels A, Mostefa-Kara N, Florent C, et al. Emergency liver transplantation for acute liver failure. Evaluation of London and Clichy criteria. J Hepatology 17:124-7,1993.

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[101] O'Grady JG, Alexander GJM, Hayllan KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 97:439-445, 1989.

[102] Van Thiel DH. When should a decision to proceed with transplantation actually be made in cases of fulminant or subfulminant hepatic failure:

factor, the prognosis worsens and the requirement for transplantation increases. The current 1-year survival rate following liver transplantation for FHF ranges between 55% and 75%.[99, 101]

Hepatic Malignancies

The indications for liver transplantation for individuals with hepatocellular carcinoma have decreased over the last 10 years as a result of the high rate of disease recurrence. From a surgical standpoint, individuals with hepatocellular carcinoma (HCC) are excellent candidates because of their age and their well-maintained hepatic function. As a consequence, their perioperative mortality and morbidity are low.

Small, incidental tumors discovered after the removal of a cirrhotic liver rarely recur. However, HCC found prior to transplantation recurs in up to 80% of cases and does so as early as 3 months post-transplant; the average interval to detectable recurrent tumor is 12-18 months (median 8 months).[103] A fall in alpha-fetoprotein is commonly seen after total hepatectomy and transplantation, but unfortunately does not predict that tumor will not recur. A bilobar distribution of tumor, the presence of cirrhosis, an infiltrative type of tumor, macroscopic vascular invasion and

lymph node metastases are factors that independently predict tumor recurrence and, therefore, survival after transplantation for hepatic malignancy.[104]

Tumor size and multifocality are the most important determinants of outcome and are mot useful in patient selection. Single lesions less than 3-5 cm have the best prognosis. The Cambridge group has observed no recurrences in patients who received a transplant for single dominant lesions measuring less than 4 cm.[105] In Bismuth's experience, 3- year survival in patients with one or two small lesions measuring less than 3 cm was 83% after transplantation compared to 41% for patients treated with subtotal resection.[90] The superior results with transplantation suggests that subtotal resection may miss small multifocal cancers that can be cured by total hepatectomy and transplantation.

A combination of pre- and post-transplant intraarterial chemotherapy appears to increase the survival of patients transplanted for HCC.

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at admission to hospital or when a donor organ is made available? J Hepatology 17:1-2.1993.

[103] Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 202:401-407, 1985.

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[104] Esquivel CO, Iwatsuki S, Marino IR, Markus BH, Van Thiel DH and Starzl TE. Liver transplantation for hepatocellular carcinoma and other primary hepatic malignancies. In: *Trends in Gastroenterology*. Sugahara K (ed.), Japan, 323-332, 1989.

[105] McPeake JR, O'Grady JG, Zaman S, et al. Liver transplantation for primary hepatocellular carcinoma: tumor ize and number determine outcome. J Hepatol 18:226-34, 1993.

Current survival rates are 63% at 1 year, 42% at 3 years, and 40% at 5 years.[106, 107]

The fibrolamellar variant of HCC usually occurs in a non- cirrhotic liver and in a young adult. It is also characterized by a slow rate of disease progression. Nonetheless, the rate of disease recurrence following liver transplantation ranges between 30% and 50%.[75, 76, 108]

The results with cholangiocarcinoma are even worse than those for individuals transplanted for HCC. Cholangiocarcinoma invariably recurs with a recurrence rate of 70% at 8 months, even when the tumor is well localized in a peripheral rather than a central location. The prognosis is even worse for hilar tumors, which recur within 3 months in 100% of cases.[75, 76, 104]

Liver transplantation may prolong overall survival in patients with either primary or metastatic neuroendocrine tumors of the pancreas or small bowel. Tumor recurrence,

when it recurs, is usually evident within a year of the transplant procedure.[109]

Patients with hepatic sarcomas have an almost universal rate of tumor recurrence within months of the transplant procedure; the only exception to this is epitheliod hemangioendothelioma, which can have a long disease-free interval following liver transplantation.[110]

Liver transplantation has been performed rarely on patients with metastatic colorectal or breast cancer.[111, 112] In both cases, the results have been universally unsatisfactory.

Biliary Atresia

Biliary atresia represents the most common indication for liver transplantation in children,

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[106] Carr BI, Selby R, Madariaga J, et al. Prolonged survival after liver transplantation and cancer chemotherapy for advanced-stage hepatocellular carcinoma. Transplant Proc 25:1128-9, 1993.

[107] Stone MJ, Klintmalm G, Polter D, Husberg B, Egorin MJ. Neoadjuvant chemotherapy and orthotopic liver transplantation for hepatocellular carcinoma. Transplantation 48:344-7, 1989.

[108] Starzl TE, Iwatsuki S, Shaw BW Jr, et al. Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obstet 162:145-148, 1986.

[109] Makowka L, Tzakis AG, Mazzaferro V, et al. Transplantation for the liver for metastatic endocrine tumors of the intestine and pancreas. Surg Gynecol Obstet 168:107-11, 1989.

[110] Marino IR, Todo S, Tzakis AG, et al. Treatment of hepatic epithelioid hemangioendothelioma with liver transplantation. Cancer 62:2079-84, 1988.

[111] Huber C. Niederwieser D, Schonitzer D, Gratwohl A, Buckner D, Margreiter R. Liver transplantation followed by high-dose cyclophosphamide, total-body irradiation, and autologous bone marrow transplantation for treatment of metastatic breast cancer: a case report. Transplantation 37:311-2, 1984.

[112] Mazzaferro V, Dindzans V, Makowka L, Van Thiel DH. Approach to hepatic metastases from colorectal adenocarcinoma. Sem Liv Dis 8:247-253, 1988.

accounting for more than half the transplant procedures which are performed in children.[113] In the pre-transplant era the prognosis for children with biliary atresia was grim, having a survival rate of only 5% at 2 years. The introduction of the Kasai procedure has improved dramatically the short term prognosis. Unfortunately it is not a cure and many if not all surviving children develop cirrhosis with portal hypertension usually by the age of 5 years.

Currently, liver transplantation represents only cure for biliary atresia. It remains somewhat controversial whether any surgical procedure, particularly those involving the biliary tree such as the Kasai procedure, should be done prior to a liver transplant in children with biliary atresia because of the high risk for cholangitis and technical complications. Because it is difficult to obtain a small size liver suitable for an infant, the Kasai procedure continues to be a bridge operation performed in order to allow the infant to grow large enough to undergo a safe transplant procedure. Living-related donations, reduced size and split livers remain additional options. The survival of children with biliary atresia following liver transplantation is more than 80% at one year, with a 5-years survival rate greater than 75%.[75, 76, 113]

Budd Chiari Syndrome

This syndrome is characterized by hepatic vein thrombosis occurring as either a primary disease condition or secondarily as a consequence of a systemic hypercoagulative disorder, usually a myeloproliferative disease. The clinical course of the Budd Chiari Syndrome is usually slow, with a gradual progression to liver failure occurring over several months to years. In rare cases, a rapid onset followed by a steady downhill course is observed. Acute Budd-Chiari syndrome may be managed by side-to-side portocaval or mesoatrial shunting. The presence of cirrhosis, intractable ascites and refractory gastrointestinal bleeding constitute indications for liver transplantation. The establishment of a correct etiologic diagnosis of the hepatic vein thrombosis is of paramount importance in the clinical management of the patient after transplantation, since conditions such as polycythemia vera, essential thrombocytosis or any of the other myeloproliferative diseases require life-long anticoagulation and or myelotoxic therapy.[114]

Inborn Errors of Metabolism

Inborn errors account for 25% of the liver transplants performed in children and an

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[113] Iwatsuki S, Shaw Bw Jr, Starzl TE: Liver transplantation for biliary atresia. World J Surg 8:51-56, 1984.

[114] Campbell DA Jr, Rolles K, Jamienson N, et al. Hepatic transplantation with perioperative and long term anticoagulation as treatment for Budd-Chiari syndrome. Surg Gynecol Obstet 166:551-558, 1988.

occasional liver transplant in adults.[115, 116] The indication for liver transplantation in an individual with an inborn error of metabolism can be either : 1) a chronic hepatopathy occurring as a direct result of the metabolic defect, 2) a hepatopathy occurring as part of a systemic disease or, 3) failure of an organ other than the liver as a consequence of a metabolic defect peculiar to the liver that spares the liver but causes extrahepatic organ dysfunction.

In the first case, the metabolic defect is corrected by the liver transplant alone. Examples are protein C and S deficiency, antithrombin III deficiency, Wilson's disease, tyrosinemia, galactosemia, and glycogen storage disease types I and IV.[76, 117, 118] In the second case, the liver transplant will not eliminate the metabolic defect which is present also in other organs (i.e., protoporphyria, Gaucher's disease, hemochromatosis), and a specific therapy should

be continued after transplantation.[119-121] Finally, in the last case, even if the hepatic disease is virtually absent and the metabolic defect affects other vital organs, liver transplant may reduce disease acceleration and is occasionally a clinical cure. Examples are familial hypercholesterolemia types I and IV, alpha 1-antitrypsin deficiency, urea-cycle deficiencies, and oxalosis.[72, 122-124]

Survival rates for these conditions are among the highest for any disease indication following liver transplantation.[115, 116]

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[115] Esquivel CO, Marino IR, Fioravanti V, Van Thiel DH. Liver transplantation for metabolic disease of the liver. Gastroenterology Clin N Am 17:167-175, 1988.

[116] Starzl TE. Surgery for metabolic liver desease. In: *Surgery of the liver*. McDermott WV Jr, ed. Oxford: Blackwell Scientific, 127-36, 1989.

[117] Mieles LA, Esquivel CO, Koneru B, Makowka L, Van Thiel DH, Tzakis AG, Starzl TE. Liver transplantation for tyrosinemia. A review of 10 cases from the University of Pittsburgh. Dig Dis Sci 35:153-157, 1990.

[118] Sternlieb I. Wilson's disease: Indications for liver transplant. Hepatology 4:155-175, 1984.

[119] Pillay P, Tzoracloeftherakis E, Tzakis AG, Kakizoe S, Van Thiel DH, Starzl TE. Orthotopic liver transplantation for hemochromatosis. Transplant Proc 23:1888-1889, 1991.

[120] Powell LW. Does transplantation of the liver cure genetic hemochromatosis? J Hepatol 16:259-61, 1992.

[121] Smanik EJ, Tavill AS, Jacobs GH, et al. Orthotopic liver transplantation in two adults with Niemann-Pick and Gaucher's Disease: Implications for the treatment of inherited disease. Hepatology, 17: 42-49, 1993.

[122] Hoeg JM, Starzl TE, Brewer HB: Liver transplantation for treatment of cardiovascular disease: Comparison with medication and plasma exchange in homozygous familiar hypercholesterolemia. Am J Cardiol 59:705-707, 1987.

[123] Sokal EM, Ulla L, Harvengt C, et al. Liver transplantation for familial hypercholesterolemia before the onset of cardiovascular complications. Transplantation 55:432-3, 1993.

[124] Van Thiel DH, Starzl TE. α-1-antitrypsin deficiency and liver transplantation. In: *Alpha 1-antitrypsin Deficiency*. Lenfant C (ed), NIH Monograph, Bethesda, MD, 1992.

PRE-TRANSPLANT ASSESSMENT AND PROGNOSTIC PARAMETERS

Several parameters which indicate deterioration or decompensation of end stage liver disease require continued reassessment during the pretransplant follow-up of a liver transplant candidate. A change in any of these parameters constitutes disease progression and an increased need for transplantation. The specific parameters to be followed in such cases are: 1) hepatic and renal function, 2) coagulation status, 3) the individual's metabolic and nutritional status, 4) the patient's microbiologic and immunologic status, 5) the candidate's neurologic status and 6) other peculiar problems.

Hepatic and Renal Function

An increase in either the serum bilirubin or the serum creatinine level associated with the onset of ascites and/or encephalopathy represents significant disease progression and enhances the risk of perioperative mortality. The serum electrolytes and particularly the serum sodium level are an important prognostic parameter; a serum sodium level less than 125 mmol/L should be corrected prior to a liver transplant procedure. It is important to note that a rapid correction of hyponatremia can produce central pontine myelinolysis. Hepatorenal syndrome (HRS) is reversible after liver transplantation and patient survival is comparable in patients with and without HRS before operation. However, renal function in the first 12 weeks after surgery may be worse in patients with HRS.[125]

Coagulopathy

During the preoperative period, a coagulopathy, particularly when associated with portal hypertension, constitutes a serious risk for gastrointestinal bleeding. As a result, coagulation parameters should be monitored closely, and the candidates awaiting liver transplantation may require intermittent infusions of fresh frozen plasma rich in coagulation factors.

Metabolic and Nutritional Status

Malnutrition in the cirrhotic patient is multifactorial and occurs as a consequence of asthenia, malabsorption, reduced hepatic protein synthesis, recurrent hospitalization and infectious episodes. Every patient included on a liver transplant candidate list should be evaluated for nutritional deficits and have such deficits treated. A determination of how to provide the proper amount of protein and calories is important. Thus, the serum albumin, prealbumin, TIBG (Total Iron Binding Globulin), liposoluble vitamins (A, D, E and K)

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[125] Seu P, Wilkinson AH, Shaked A, Busuttil RW. The hepatorenal syndrome in liver transplant patients. Amer Surgeon 57:806-9, 1991.

and trace elements levels should be monitored periodically.

Immunity and Microbiologic Function

The hypergammaglobulinemia typical of the cirrhotic state occurs as a result of an increase in the stimulation of B cells with portal systemic shunting and impaired Kupffer cell removal of portal venous antigens. Despite the apparent hypergammaglobulinemia, B cell function is often reduced and specific immune globulin levels, such as those against HBV, may be reduced, in part as a result of a defect in T cell-mediated immune regulation. Moreover, the complement system, the number and function of circulatory phagocytes, and the fixed reticuloendothelial system of the liver are all compromised. Malnutrition further aggravates these immune problems. ·

As a consequence, the cirrhotic patient is at increased risk for bacterial, fungal and viral infections. During the perioperative period, liver transplant candidates and recipients should have surveillance cultures of the pharynx, urinary, and gastrointestinal tracts, ascitic fluid and female genital tract. Serologic tests for cytomegalovirus, the herpes viruses, herpes zoster, Epstein-Barr virus, toxoplasmosis, *Treponema pallidum,* and various fungal infections (*Aspergillus fumigatus,* candida, chlamydia, histoplasma) should be monitored as well. A tuberculin test and appropriate control skin tests are also recommended.

Vaccination against HBV and pneumococcus should be performed as a routine in all candidates. During the fall months the use of an influenza vaccine is recommended.

Neurologic Status

All liver transplant candidates should undergo a careful neurologic evaluation and follow-up examination to include both clinical (physical examination and ammonia levels) and instrumental assessment. EEG, visual and auditory evoked potentials and, in selected cases, CT scanning of the head should be performed. During the preoperative period, episodes of hepatic encephalopathy need to be treated aggressively with intestinal decontamination and laxatives (neomycin, paromomycin, lactulose) and a reduction in dietary protein intake.

Other Peculiar Problems

In older patients (> 50 years), even in the absence of clinically evident cardiac symptoms, a cardiac ultrasound and a MUGA test should be performed routinely. Cardiomyopathies, often not detected clinically without specific testing, are known to occur frequently in patients with chronic cholestasis and in individuals with alcoholic and familial (Wilson's disease, hemochromatosis, glycogen storage disease) disorders of the liver. In such cases, special attention to the cardiac evaluation is warranted.

Certain liver diseases, such as alpha-1-antitrypsin deficiency, cystic fibrosis,

autoimmune chronic active hepatitis, HCV and HBV hepatitis, have a higher incidence of pulmonary disease than present in the general population consisting of a spectrum of obstructive, restrictive and vascular diseases which necessitate preoperative evaluation. Obviously all pulmonary infections must be treated and must be resolving, if not cured, prior to transplantation.

The presence of pulmonary hypertension with a right ventricular pressure above 50 mmHg is associated with a poor intra-operative prognosis and requires special attention on the part of the anesthesiologist prior to and during the transplant operation.[126-128] Intrapulmonic shunts which develop in cirrhotic patients are reversible, but the patient may require prolonged postoperative ventilatory support.[129, 130]

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[126] Plevak D, Krowka M, Rettke S, Dunn W, Southorn P. Successful liver transplantation in patients with mild to moderate pulmonary hypertension. Transplant Proc 25:1840, 1993.

[127] Prager MC, Cauldwell CA, Ascher NL, Roberts JP, Wolfe CL. Pulmonary hypertension associated with liver disease is not reversible after liver transplantation. Anesthesiology 77:3754-8, 1992.

[128] Scott V, De Wolf A, Kang Y, et al. Reversibility of pulmonary hypertension after liver transplantation: a case report. Transplant Proc 25:1789-90, 1993.

[129] Erikson LS, Söderman C, Ericzon B-G, Eleborg L, Wahren J, Hedenstierna G. Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. Hepatology 12:1350-57, 1990.

Management Of Chronic Hepatic Disease Complications Prior To Liver Transplantation

Encephalopathy

A moderate protein diet consisting of 0.75 to 1.0 g protein/kg/day body weight is recommended for most patients. Salt restriction is required for most also. Water restriction is required for those with hyponatremia with serum sodium levels less than 130 mEq/L.

Lactulose or a milk containing diet in those with lactose intolerance is used most widely. The goal with either is to obtain 2-4 soft bowel movements per day. Larger doses can produce dehydration, acidosis and various electrolyte abnormalities.

Recently, oral prostaglandin E1 has been used to enhance intestinal transit and increase renal blood flow, both of which reduce the nitrogenous substrate loads that contribute to the syndrome of hepatic encephalopathy.

Esophageal/Gastric Varices

Large varices of the esophagus (grade 3 or 4) or of the stomach are at risk for bleeding while patients wait for a donor organ. Patients with a history of prior bleeding or those with signs of an increased risk of bleeding, such as

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[130] Scott V, Miro A, Kang Y, et al. Reversibility of the hepatopulmonary syndrome by orthotopic liver transplantation. Transplant Proc 25:1787-88, 1993.

hemocytic spots, red spots and whale lines, can be treated either with esophageal sclerotherapy or varix banding. The latter method is preferred if the varices are not actively bleeding. Sclerotherapy is reserved to control active bleeding because of its increased risk of producing a focus of infection in or about the esophagus, either high in the abdomen or in the inferior mediastinum.

Patients with bleeding that cannot be controlled easily with sclerotherapy, or individuals who cannot be maintained free of recurrent bleeding, can be treated successfully with a transjugular intrahepatic shunt (TIPS), a useful bridge to transplantation in patients with variceal hemorrhage or refractory ascites.[131-133] Distal spleno-renal and mesocaval shunts, which avoid the hepatic hilum, are preferred to conventional portacaval shunts when surgery to control variceal hemorrhage is necessary. In general, shunt procedures should be reserved for patients who have good hepatic reserve and who are not expected to require transplantation in the

foreseeable future. Esophago-gastric devascularization procedures may produce severe scarring in the upper abdomen and should be avoided in potential transplant candidates.

All patients who bleed should be placed on either omeprazole or an H_2 blocker and receive oral antibiotics in an effort to limit mucosal injury and prevent the development of either a gram negative bacteremia or spontaneous bacterial peritonitis as a result of bacterial translocation.

Ascites

Minor and moderate grades of ascites do not specifically require treatment. Large volume or massive ascites is treated with large doses of spironolactone and a loop diuretic such as furosemide. In severe cases, particularly those with rapidly recurring ascites or those with a prior history of spontaneous bacterial peritonitis, serial large volume peritoneocentesis or a transjugular intrahepatic portasystemic shunt (TIPS) procedure can be used to manage the ascites.

Renal Dysfunction

Individuals with advanced liver disease occasionally have co-existent renal disease and many have functional renal dysfunction related to their underlying liver disease. The best methods to prevent functional renal impairment are the avoidance of non-steroidal anti-inflammatory agents for pain, the maintenance of an adequate vascular volume with albumin

[131] Richter GM, Noeldge G, Palmasz JC, and Roessle M. The transjugular intrahepatic portosystemic stent-shunt (TIPS): result of pilot study. Cardiovascular and Interventional Radiology 13:200, 1990.

[132] Woodle ES, Darcy M, White HM, et al. Intrahepatic portosystemic vascular stents: a bridge to hepatic transplantation. Surgery 113:344-51, 1993.

[133] LaBerge JM, Ring E, Gordon RL. Creation of transjugular intrahepatic portosystemic shunts with the wallstent endoprosthesis: results in 100 patients. Radiology 187:413-20, 1993.

and/or other colloid infusions and, if necessary, the use of dopamine infusions. The latter is often complicated by the production of hypotension. In such cases, the combined use of dopamine plus an α-adrenergic vasoconstrictor such as noradrenaline may be required.

Dialysis should be considered if the serum creatinine exceeds 2.5 mg/dl and may be necessary if the serum creatinine level exceeds 2.0 mg/dl if hepatic encephalopathy is also a problem.

ORGAN DONATION AND PRESERVATION

Donor availability and selection

The dramatic improvement in results after liver transplantation and an expanded list of indications for the procedure has created a significant increase in the demand for organ donors. Estimates of the available supply of donor organs ranges from 6,900 to 9,600 per year. In 1991, 3,182 livers were procured, an estimated procurement efficiency of 33% to 61%.[134]

Over the past several years, the rate of organ donation has remained level (Figure 2). Although the donor pool has been expanded by more liberal criteria for donor selection, by improvements in organ preservation, and by use of reduced size grafts, at the same time improved care of trauma victims and effective road safety programs (Figure 3), including increased use of seat belts (Figure 4), have had an opposite impact. As a result median waiting

time of candidates for liver transplantation has increased (Figure 5), but this has not yet resulted in a significant increase in the rate of death of patients on the waiting list (Figure 6).

Donor and recipient matching for liver transplantation is mainly based on ABO compatibility and estimated liver size. Height and weight are usually used to match a donor with a recipient, with appropriate allowances for abnormal liver size in the recipient as determined preoperatively by imaging studies. Thoracic circumference is also a indicator of liver size and is used by some centers in estimating donor liver volume.

Immunological criteria

Except for ABO compatibility, immunological criteria have not been applied to the selection of liver donors. As previously discussed, the traditional donor-specific antibody crossmatch that is a prohibitive barrier in renal transplantation is not used for liver donor-selection.

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[134] Orlans CE, Evans RW, Ascher NL. Estimates of organ-specific donor availability for the United States. Transplant Proc 25:1541-2, 1993.

Early studies suggested that HLA-matching had either no impact on survival or a paradoxical beneficial effect on liver grafts, with slightly better survival seen in those patients who received an HLA-mismatched graft.[135, 136] More recent studies have suggested a slight survival advantage for HLA-A and HLA-B matched grafts, but no effect has been found for DR matching.[137, 138] The highly effective immunosuppression used in liver transplantation, together with improvements in non-immunological factors, including surgical technique and patient management, have contributed to improved patient survival in recent years and may mask the lesser effects of HLA matching, reducing its importance to overall outcome.

Cytomegalovirus

Cytomegalovirus infection is a common complication in immunosuppressed patients, but the mortality of CMV infection has been dramatically reduced since the introduction of ganciclovir (see discussion below). Although there is an increased risk for development of CMV infection with grafts from CMV seropositive donors, no significant adverse effect of CMV infection on patient or graft survival is seen. Therefore, given the current organ donor shortage, CMV serologic matching of donors and recipients is neither practical nor worthwhile.[139]

Viral hepatitis

More difficult questions concern the use of liver donors with a history of exposure to hepatitis viruses. In the case of hepatitis B, patients positive for hepatitis B surface antigen should not be used. It is probably also wise to avoid patients with elevated IgM titers of hepatitis B core antibody.

Whether or not it is reasonable to use livers from donors with measurable IgG core antibody remains to be determined. Some organs from such donors may be used preferentially in HBV DNA positive recipients, or in individuals known to be "immune" to hepatitis B as manifested by high titers of anti-HBsAg antibody. Some small risk of HBV DNA transfer with organs from such donors does exist

[135] Adler M, Gavaler JS, Duquesnoy RJ, et al. Relationship between the diagnosis, preoperative evaluation, and prognosis after liver transplantation. Ann Surg 208:196-202, 1988.

[136] Markus BH, Duqesnoy RJ, Gordon RD, et al. Histocompatibility and liver transplant outcome. Does HLA exert a dualistic effect? Transplantation 46:372-7, 1988.

[137] Yagihashi A, Kobyashi M, Noguchi K, et al. HLA matching effect in liver transplantation. Transplant Proc 24:2432-33, 1992.

[138] Kobayashi M, Yagihasi A, Noguci K, et al. HLA-DR matching effect in in orthotopic liver transplantation under FK 506. Transplant Proc 25:228-9, 1993.

[139] Stratta RJ, Wood RP, Langnas AN, et al. Donor selection for orthotopic liver transplantation: lack of an effect of gender or cytomegalovirus (CMV) status. Transplant Proc 22:410-13, 1990.

and could result in a disease exacerbation, possibly due to a strain of virus contained in the donor organ different from that previously experienced by the recipient.

Considerable controversy exits concerning the use of liver grafts from patients with significant titers of antibody to hepatitis C virus (HCV). The prevalence of hepatitis C seropositivity among organ donors is reported to be 2%.[140] The first generation ELISA assay used to detect hepatitis C antibody has a high false positive rate. As a result, efforts to determine the actual rate of transmission of hepatitis C through organ donation based on results of this assay may underestimate the risk. Second and third generation tests have higher specificity.

Even using the relatively non-specific first generation ELISA assay, the incidence of seropositivity for hepatitis C in a large population of voluntary blood donors in Spain was only 1.2%, but among these seropositive patients, 70% were confirmed to be seropositive by a second generation RIBA assay. Among 105 confirmed seropositive donors for whom liver biopsy was available, 21% had persistent

chronic hepatitis, 45% had chronic active hepatitis, and 7% had active cirrhosis.[141]

A similar report from Italy also found a high incidence of abnormal histological findings in the livers of voluntary blood donors confirmed to be hepatitis C antibody positive by a second generation RIBA assay.[142] Furthermore, the New England Organ Bank has reported a high incidence of positive PCR for HCV RNA in organ donors with a positive first-generation ELISA for anti-HCV, and high incidence of conversion from negative to positive PCR in recipients of an organ from an HCV PCR positive donor.[140] However, the Miami transplant group has reported a low incidence of mortality and morbidity from liver disease in kidney recipients who received organs from confirmed hepatitis C positive donors.[143]

Since the overall incidence of hepatitis C in the organ donor population is small and there is increasing evidence that many seropositive donors are infectious, it is prudent to avoid use of liver grafts from hepatitis C seropositive

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[140] Pereira BJG, Milford EL, Kirkman RL, et al. Evidence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. N Engl J Med 327:910-475, 1992.

[141] Esteban JI, López-Talavera JC, Genescà J, et al. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. Ann Int Med 115:443-9, 1992.

[142] Alberti A, Chemello L, Cavaletto D, et al. Antibody to hepatitis C virus and liver disease in volunteer blood donors. Ann Int Med 114:1010-1012, 1991.

[143] Roth D, Fernandez JA, Babischkin S, et al. Detection of hepatitis. C virus infection among cadaver organ donors: evidence for low transmission of disease. Ann Int Med 117:470-475, 1992.

donors except in urgent circumstances. The antibodies detected with current assay techniques are not neutralizing antibodies and have no protective effect. Furthermore, there is good experimental evidence demonstrating that there are multiple strains of hepatitis C virus and that prior infection with one strain does not necessarily protect against infection by another strain, or even reinfection by the same strain.[144]

Assessment of organ viability

At the present time, there is no single, convenient test that is relied upon to predict donor organ quality or graft viability prior to implantation. The conversion of lidocaine to monoethylglycinexlide (MEGX) by the liver has been shown to correlate with conventional tests of hepatic function and can be measured quickly and inexpensively.[145] The sensitivity of the MEGX values has been reported to be only 65% and therefore the test is less reliable at determining that a liver should be discarded when the MEGX level is low.[146] Grafts from donors with a MEGX less than 50 ng/mL should be considered to be at high risk of poor function

and correlation should be sought with other selection criteria, including liver biopsy.[146, 147]

ICG clearance, arterial ketone body ratio (AKBR), and hyaluronic acid levels in the venous effluent of the graft have all shown some significant correlation with postoperative graft function.[148-150] Pre-transplant biopsy is also important, but is not infallible, since irreversible subcellular damage is easily missed with conventional histology. Significant fatty infiltration with macrovesicular steatosis, hydropic degeneration of hepatocytes, and pericentral or panlobular individual hepatocyte necrosis are indicative of increased risk of poor

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[147] Tesi RJ, Elkhammas EA, Davies EA, et al. Safe use of liver donors with MEGX values less than 90 ng/mL. Transplant Proc 25:1655-56, 1993.

[148] Osaki N, Ringe B, Bunzendahl H, et al. Postoperative recovery of mitochondrial function of the human liver graft procured and preserved with University of Wisconsin solution. Transplant Int 3:128-32, 1990.

[149] Yamaoka Y, Washida M, Manaka D, et al. Arterial ketone body ratio as a predictor of donor liver viability in human liver transplantation. Transplantation 55:92-5, 1993.

[150] Rao PN, Bronsther O, Pinna A, et al. Prediction of early graft function by effluent levels of hyaluronic acid in clinical liver transplantation. Transplant Proc 25:2141-2, 1993.

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[144] Farci P, Alter HJ, Govindarajan S, et al. Lack of protective immunity against reinfection with hepatitis C virus. Science 258:135-140, 1992.

[145] Ollerich M, Burdelski M, Ringle B, et al. Lignocaine metabolite formation as a measure of pre-transplant liver function. Lancet 1:640, 1989.

[146] Adam R, Azoulay D, Astarcioglu I, et al. Limits of the MEGX test in selection of liver grafts for transplantation. Transplant Proc 25:1653-4, 1993.

graft function.[151-153] Fatty change is frequently associated with obesity, alcohol ingestion, diabetes, nutritional disorders, drug use, and advanced age, but often without significant abnormalities of conventional liver function tests. However, fatty livers do not appear to tolerate the preservation process well and are at high risk of severe dysfunction and failure after transplantation.

Transplantation of a liver from a donor with a prolonged stay in an intensive care unit prior to organ donation has also been associated with poor graft function. This may be related to depletion of glycogen stores in the graft as a result of nutritional depletion and additional depletion of glycogen by anaerobic metabolism in grafts with a long preservation time. Whether or not deliberate repletion of glycogen prior to preservation and transplantation can ameliorate this phenomenon needs further study.[154]

Exclusion criteria

The age range of organ donors has expanded in recent years and is generally term newborn to 65 years of age with acceptable results.[155, 156] However, fatty infiltration is more common in older donors and MEGX values tend to be lower. Therefore, organs obtained from older donors should be carefully evaluated for abnormal histology and the preservation times of organs from such donors should be kept as short as possible.[157] Impaired early graft function and cholestasis are often seen with livers from older donors; these transient problems, however, are not associated with increased long term graft loss.[158, 159]

Other donor selection criteria include:

[151] Todo S, Demetris A, Makowka L, et al. Primary nonfunction of hepatic allografts with preexisting fatty infiltration. Transplantation 47:903, 1989.

[152] D'Alessandro A, Kalayoglu M, Sollinger HW, et al. The predictive value of donor liver biopsies for the development of primary nonfunction after liver transplantation. Transplantation 51:157-63, 1991.

[153] Markin RS, Wood RP, Stratta RJ, et al. Predictive value of intraoperative biopsies of donor organs in patients undergoing orthotopic liver transplantation. Transplant Proc 22:418-9, 1990.

[154] Adam R, Reynes M, Bao YM, et al. Impact of glycogen content of the donor liver in clinical liver transplantation. Transplant Proc 25:1536-7, 1993.

[155] Adam R, Astarcioglu I, Azoulay D, et al. Age greater than 50 years is not a contraindication for liver donation. Transplant Proc 23:2602-3, 1991.

[156] Wall WJ, Mimeault R, Grant DR, Bloch M. The use of older donor livers for hepatic transplantation. Transplantation 49:377-81, 1990.

[157] Adam R, Astarcioglu D, Azooulay D, et al. Liver transplantation from elderly donors. Transplant Proc 25:1556-57, 1993.

[158] Adam R, Astarcioglu D, Azoulay D, et al. Liver transplantation from elderly donors. Transplant Proc 25:1556-57, 1993.

[159] Buckel E, Sanchez-Urdazpal J, Steers J, et al. Impaired initial function in liver grafts from donors > 50 years of age. Transplant Proc 25:1558-59, 1993.

- Absence of sepsis, or any transmissible disease
- No malignancy (except for minor skin cancers)
- No history of intravenous drug abuse
- Known cause of death
- No preexisting hepatic disease
- No significant trauma to the liver
- Normal or near normal (and preferably improving) liver function tests (PT, PTT, SGOT, SGPT, bilirubin – the outer limits of acceptability depend upon clinical profile of the donor and urgency of the potential recipient).

In donors who have sustained a severe ischemic episode, the kidneys are usually more sensitive to ischemia than is the liver. If the kidneys are still producing urine, the liver is usually viable. A transient rise in liver aminotransferase enzymes is often found and is acceptable if repeat values show improvement. Severe hypernatremia (serum sodium > 160 mEq/L) is not well tolerated by the liver and may be found in donors who have been severely dehydrated for management of brain swelling.

Ideally, every cadaver donor should have an autopsy to determine the presence of conditions, especially malignancies, that might be transmitted by an organ graft to the recipient. However, in practice, permission for such an examination is often denied or the examination cannot be performed expeditiously enough to be

of clinical use.[160] Choriocarcinoma has been transmitted from a single donor to both a liver and two kidney recipients.[161] Based on this report, it is worthwhile to test female donors of childbearing age who have a history of irregular menstruation or a recent pregnancy or spontaneous abortion for HCG levels to rule out this possibility.

It is common practice to accept organs from donors with cerebral neoplasms, unless a ventriculoperitoneal shunt has been placed, as these lesions typically kill by their intracranial mass effect rather than by metastatic spread. Nonetheless, transmission of an intracerebral neoplasms from a donor to an organ graft recipient has been reported.[162, 163] For this reason ,we do not routinely recommend the use of livers obtained from donors with malignant intracerebral neoplasms, unless an autopsy can establish that the lesion is confined to the brain.

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[160] Penn I. Malignancy in transplanted organs. Transplant Int 6:1-3, 1993.

[161] Marsh JW, Esquivel CO, Makowka L, et al. Accidental transmission of malignant tumor from a donor to multiple recipients. Transplantation 44:449-50, 1987.

[162] Lefrancois N, Touraine JL, Cantarovich D, et al. Transmission of medulloblastoma from cadaver donor to organ transplant recipients. Transplant Proc 19:2242, 1987.

[163] Morse JH, Turcotte JG, Merion RM, et al. Development of a malignant tumor in a liver transplant graft procured from a donor with a cerebral neoplasm. Transplantation 50:875-77, 1990.

Alcohol abuse

Donors with a history of alcohol abuse and elevated blood alcohol levels are acceptable for organ donation if liver function is good and liver histology is normal. There is no correlation between an elevated blood alcohol level and subsequent initial graft function or 30-day graft survival.[164]

Organ procurement and preservation

The basic techniques of organ procurement and graft implantation were developed over a twenty-five year period at the University of Colorado and later at the University of Pittsburgh. Procurement of a whole liver graft from a brain dead, heart beating cadaver donor remains the main source of organs. This is usually performed as part of a multiple organ procurement in which the kidneys, heart, lungs, and pancreas are all removed for transplantation. However in recent years, in addition to reduced size and split liver grafts from heart beating, brain dead donors, liver segments from living related donors are being used to compensate for the demand for organs for infants and small children. The surgical techniques of organ retrieval are well described.[165-167]

Belzer and associates in 1987 introduced a new preservation solution, the University of Wisconsin (UW) solution, which has permitted a significant prolongation of the cold storage time for cadaver liver grafts.[168,169] UW solution differs from Euro-Collins in that it contains adenosine, allopurinol, raffinose, hydroxyethyl starch, and lactobionate. UW solution offers better protection of the microvasculature of the liver from reperfusion injury. It contains no glucose and does not support continued anaerobic glucose metabolism during cold storage of the liver. Its osmotic properties reduce the graft swelling that is seen after preservation in Euro-Collins.

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[164] Hassanein TI, Gavalier JS, Fishkin D, Gordon R, Starzl TE, Van Thiel DH. Does the presence of a measurable blood alcohol level in a potential organ donor affect the outcome of liver transplantation? Alcohol Clin Exp Res 15:300-3, 1991.

[165] Starzl TE, Hakala TR, Shaw BW Jr, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158:223, 1984.

[166] Starzl TE, Miller C, Broznik B, and Makowka L. An improved technique for multiple organ harvesting. Surg Gynecol Obstet 165: 343-8, 1987.

[167] Casavilla A, Gordon RD, and Starzl TE. Techniques of Liver Transplantiation. In: *Surgery of the Liver and Biliary Tract.* Blumgart LH, ed. Churchill Livingston, London, in press.

[168] Kalayoglu M, Sollinger HW, Stratta RJ, et al. Extended preservation of the human liver for clinical transplantation. Lancet 1:616, 1988.

[169] Belzer FO, D'Allesandro AM, Hoffman RM, et al. The use of UW solution in clinical transplantation. A 4-year experience. Ann Surg 215:579-83, 1992.

Extension of the safe cold storage time for liver grafts has many practical logistic advantages, including more time for recipients to get to the transplant center, for transport of grafts from distant centers, for preparation of reduced liver grafts, and for switching to a "back-up" recipient if the first intended recipient is found to be unsuitable, as well as for semi-elective scheduling of cases during regular working hours.

Although successful preservations have been obtained after as much as 30 hours of cold storage in UW solution, it is now apparent that there are risks to extending the cold ischemia time beyond 12 to 18 hours. The incidence of graft loss in the Pittsburgh experience was found to increase significantly when organ preservation was extended beyond 18 hours.[170] Bismuth has reported better initial graft function and long term outcome in patients whose liver grafts were preserved in UW solution for less than 12 hours.[171] The Mayo Clinic group reported a correlation between the incidence of nonanastomotic biliary strictures and the length of the cold ischemia time for livers preserved in either Euro-Collins or UW solution. This observation has been confirmed in subsequent studies.[172, 173] Thus, it is important to minimize cold storage time.

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[170] Furukawa H, Todo S, Imventarza O, et al. Effect of cold ischemia time on the early outcome of human hepatic allografts preserved with UW solution. Transplantation 51:1000-4, 1991.

[171] Adam R, Bismuth H, Diamond T, et al. Effect of extended cold ischemia with UW solution on graft function after liver transplantation. Lancet 340:1373-6, 1992.

[172] Sanchez UL, Gores GJ, Ward EM, et al. Ischemic type biliary complications after orthotopic liver transplantiation. Hepatology 16:49-53, 1992.

[173] Kadmon M, Bleyl J, Kuppers B, Otto G, and Herfarth C. Biliary complications after prolonged University of Wisconsin solution preservation of liver allografts. Transplant Proc 25:1651-2, 1993.

SURGICAL TECHNIQUE

The recipient operation consists of the removal of the native liver, vascular anastomosis of the veins and arteries of the graft to the recipient vessels (anhepatic phase), hemostasis, and biliary reconstruction. In patients with previous upper abdominal surgery or multiple prior episodes of spontaneous bacterial peritonitis, highly vascularized adhesions may make the recipient hepatectomy very difficult. For this reason, operations in the upper abdomen should be avoided, whenever possible, in potential liver transplant candidates.

A complete description of operative technique is beyond the scope of this chapter and has been provided elsewhere.[167] The following will highlight the essential features of the operation.

Abdominal incision and exposure

Orthotopic liver transplantation is most commonly performed through a bilateral subcostal incision with an upper midline extension. In infants and small children, the upper midline extension is usually not needed. In patients with extensive prior surgery or multiple adhesions, in patients requiring exposure of the infrarenal aorta for reconstruction of the hepatic arterial supply, and in tumor patients in whom an extended dissection is to be performed, a lower midline extension may be added. Thoracic extensions are rarely needed.

In pediatric patients and in many adults, a "hockey stick" approach using an upper midline incision with lateral extension at a level just above the umbilicus to just beyond the right mid-axillary line may be used. This approach provides better access to the infrarenal aorta when exposure is needed for reconstruction of the hepatic artery and is less disfiguring than the standard bilateral subcostal incision. However, in patients with a massively enlarged liver or a large left lobe, extensive prior abdominal surgery, or in those requiring concomitant splenectomy, the incision may need to be extended to the left.

The approach to remove the native liver is determined by the conditions encountered at surgery. In most cases, a hilar dissection is performed first, followed by mobilization of the hepatic lobes and exposure of the suprahepatic and infrahepatic portions of the inferior vena cava.

Veno-venous bypass

The most critical stage of the recipient operation is the anhepatic phase, during which removal of the diseased liver is completed and the vascular reconstruction of the graft is performed. Interruption of the portal vein and vena cava results in complete blockage of the

venous outflow from the splanchnic bed and lower body. Without a bypass, severe renal, splanchnic and systemic venous hypertension and congestion can occur with sequestration of venous blood, reduced cardiac filling pressure, swelling of the intestines, renal dysfunction, and increased bleeding from congested venous collaterals.

A partial veno-venous bypass was developed in Pittsburgh to prevent the physiological trauma of the anhepatic phase (Figure 7).[174] With this technique, outflow cannulas are inserted into the portal and the femoral veins allowing both splanchnic and systemic blood to return to the heart by way of an inflow cannula placed in the axillary vein. A centrifugal-force pump is used to maintain flow rates of 1.5 to 3.5 L/min. Flows of at least 3.0 to 3.5 L/min may be necessary to maintain a renal perfusion pressure of 50 mm Hg or higher.[175, 176] Veno-venous bypass is used routinely for adult patients. Infants and small children

weighing less than 15 kg tolerate venous occlusion reasonably well. The risks of low rates of blood flow through the bypass and of pulmonary emboli outweigh the benefits of bypass in the majority of pediatric cases.

With the traditional approach, the infrahepatic portion of the inferior vena cava is removed with the native liver. However, an alternative approach is to dissect the liver off the vena cava, leaving the native vena cava with a cuff of hepatic veins behind for anastomosis to the suprahepatic vena cava of the graft (Figure 8).[177] In some cases, this "piggyback" technique can avoid the need for venous bypass, as the recipient vena cava remains intact. However, this method requires a more difficult caval dissection.

The vascular anastomoses

Once the native liver has been removed and hemostasis has been obtained in the exposed retroperitoneal bare area, the implantation of the graft begins with anastomosis of the suprahepatic vena cava (Figure 9). This is followed by anastomosis of the infrahepatic vena cava. The portal vein is flushed with cold electrolyte or colloid solution as the infrahepatic vena cava is sewn to flush the potassium rich preservation solution out of the graft and to

[174] Denmark SW, Shaw BW Jr, Griffith BP, Starzl TE. Venous-venous bypass without systemic anticoagulation in canine and human liver transplantation. Surg Forum 34:380, 1983.

[175] Scherer R, Giebler R, Schmutzler M, Erhard J, Lange R, Kox WJ. Shuntflow vs renal perfusion pressure during venovenous bypass in human orthotopic liver transplantation. Transplant Proc 25:2590, 1993.

[176] Scherer R, Giebler R, Schmutzler M, Erhard J, Lange R, Kox WJ. Effect of high shuntflows during portofemoro-subclavian venovenous bypass in human orthotopic liver transplantation. Transplant Proc 25:2591, 1993.

[177] Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 210:649-52, 1989.

remove air from the vena cava prior to revascularization.

In the conventional approach to reconstruction, the portal vein reconstruction is performed next, after which venous inflow and outflow is restored to the graft. However, an experienced surgeon may elect to proceed first with reanastomosis of the hepatic artery, as the field is often relatively dry at this point, facilitating exposure of this most demanding part of the vascular reconstruction. The most common method of hepatic arterial revascularization is an end-to-end anastomosis of the donor celiac trunk to the recipient common hepatic artery at the level of the gastroduodenal artery takeoff.

Extra-anatomic arterial reconstructions, usually involving a conduit of donor iliac artery from the infrarenal or supraceliac aorta, are often used for infants and small children and for adults with unsuitable native vessels. The usual origination of such a graft is an end-to-side anastomosis to the infrarenal aorta (Figure 10). The graft is then tunneled through the transverse mesocolon and passed in the avascular plane anterior to the pancreas and posterior to the stomach to reach the hepatic hilum for an end--to-end anastomosis to the donor hepatic artery.[178] Alternative sites for the origin of the arterial graft are the supraceliac aorta and the

right iliac artery. Patency rates for these extra-anatomic reconstructions, when used in primary transplantations, are comparable to conventional hepatic artery reconstruction and are superior when used for retransplantations.[179]

Long standing portal hypertension results in pathological changes in the wall of the portal vein that eventually may progress to thrombosis.[180] Organized thrombosis, atrophy, friability or cavernous transformation of the portal vein may make the main portal vein unusable. In some cases, declotting of the portal vein may be attempted. If this not feasible and the confluence of the mesenteric and splenic veins is patent, an interposition vein graft (usually iliac vein from the liver donor) may be used to bridge the gap between the donor and recipient portal veins.

If neither the native portal vein nor its confluence can be used, a mesoportal "jump graft" of donor iliac vein is used to create a new portal vein (Figure 11).[181, 182] The graft is

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[178] Tzakis AG, Todo S, Starzl TE. The anterior route for arterial graft conduits in liver transplantation. Transplant Int 2:121, 1989.

[179] Hennein HA, Mendeloff EN, Turcotte JG, et al. Aortic revascularization of orthotopic liver allografts: indications and long-term follow-up. Surgery 113:279-85, 1993.

[180] Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. Ann-Surg. 213:199, 1991.

[181] Sheil AGR, Thompson JF, Stevens MS, et al. Mesoportal graft for thrombosed portal vein in liver transplantation. Clin Transplantation 1:18-9, 1987.

[182] Tzakis A, Todo S, Stieber A, Starzl TE. Venous jump grafts for liver transplantation in patients with

anastomosed end-to-side to the superior mesenteric vein and tunneled through the transverse mesocolon and the avascular plane between the stomach and pancreas to reach the hepatic hilum. The graft is then joined end-to-end to the donor portal vein.

Biliary reconstruction

Most patients with end stage cirrhosis have some degree of coagulopathy with thrombocytopenia, prolonged prothrombin time, and low fibrinogen levels prior to transplantation. A low grade fibrinolysis is also common, but hyperfibrinolysis is most often encountered after reperfusion of the liver graft. This has been attributed both to increased endothelial release of tissue type plasminogen activator (t-PA) and decreased hepatic clearance of endogenous t-PA during the anhepatic phase of surgery.[183] Terpstra has reported that the increase in fibrinolysis seen during orthotopic liver transplantation, is not seen with heterotopic grafting.[184] This suggests that reduced clearance of t-PA during the anhepatic phase is a major contributor to hyperfibrinolysis.

Careful intraoperative monitoring of coagulation, either by use of the thromboelastogram (TEG) or specific coagulation factor assays, and component specific replacement of clotting factors (fresh frozen plasma, cryoprecipitate, factor VIII concentrate, and platelet transfusions) is essential.[185] Administration of antifibrinolytic agents (aprotinin or episilon-aminocaproic acid) may be required to correct hyperfibrinolysis. Neuhaus has demonstrated an advantage to giving aprotinin as a continuous infusion during surgery.[186]

In difficult cases, especially in patients with severe portal hypertension or extensive prior surgery, hours of tedious work may be required to obtain hemostasis. Once hemostasis is achieved, the biliary reconstruction is performed. Two methods are commonly used: duct-to-duct reconstruction over a T-tube stent and end-to-side anastomosis of the donor duct to a Roux-en-Y limb of proximal jejunum (Figure 12).

The donor gallbladder is removed. T-tubes across a duct-to-duct anastomosis are left in place for two to three months following surgery,

portal vein thrombosis. Transplantation 48:530, 1989.

[183] Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. Blood 71:1090-5, 1988.

[184] Bakker CM, Metselaar HJ, Groenland TN, et al. Increased tissue-type plasminogen activator activity in orthotopic but not heterotopic liver transplantation: the role of the anhepatic period. Hepatology 16:404-8, 1992.

[185] Kang YG, MArtin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anesth Analg 64:888, 1985.

[186] Himmelreich G, Muser M, Neuhaus P, et al. Different aprotinin applications influencing hemostatic changes in orthotopic liver transplantation. Transplantation 53:132-6, 1992.

but are usually clamped within seven to ten days of operation to improve bile flow into the intestine. An internal silastic biliary stent is usually placed across a choledochojejunostomy and will eventually pass spontaneously through the GI tract.

A third method, use of the donor gallbladder as a conduit between donor and recipient ducts, is an alternative when a Roux-en-Y choledochojejunostomy cannot be done because of previous intestinal resection or prohibitive adhesions. However, biliary stone and sludge formation are common after this method of reconstruction and it is rarely used.[187]

Reduced size liver transplantation

The concept of *ex vivo* hepatic resection to produce a size compatible graft was initially developed at the University of Colorado in 1975 when a 23 month old boy was given the left lateral segment of an adult liver. More recently, at centers in Brussels, Chicago, Hanover and Paris, the method has been reintroduced and shown to produce results approaching those achievable with whole liver transplantation.[188-]

[191] Reduced liver grafts are usually implanted using the piggyback method described previously.

Transplantation of two liver fragments from a single donor to separate recipients was first used successfully in Australia, but has since been used at other centers in the United States, Europe, and Japan.[192-195] The "split liver" graft is a very demanding technique and it remains to be established whether the incidence of technical complications and the durability of both fragments justifies this approach. So far, one-

[187] Halff G, Todo S, Hall R. Late complications with gallbladder conduit biliary reconstruction after liver transplantation. Transplantation 48:537, 1989.

[188] Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 95:267-70, 1984.

[189] Broelsch CE, Emond JC, Thistlethwaite JR, et al. Liver transplantation with reduced-sized organs. Transplantation 45:519, 1988.

[190] Otte JB, Ville de Coyet J, Sokal E, et al. Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. Ann Surg 211:146, 1990.

[191] Strong R, Ong TH, Pillway P, et al. A new method of segmental orthotopic liver transplantation in children. Surgery 104:104-7, 1988.

[192] Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Succsessful liver transplantation from a living donor to her son. N Engl J Med 24:322:1505-7, 1990.

[193] Broelsch CE, Emond JC, Whitington PF, et al. Application of reduced size liver transplants as split grafts, auxilary orthotopic grafts, and living related segmental transplants. Ann Surg 212:368-75, 1990.

[194] Moreno Gonzales G, Gomez SR, Garcia GI, et al. Utilization of split liver grafts in orthotopic liver transplantation. Hepatogastroenterology 40:17-20, 1993.

[195] Otte JB, Ville de Goyet, Alberti D, et al. The concept and technique of the split liver in clinical transplantation. Surgery 107:605-12, 1990.

year patient survival with split liver grafting is about 50%, which unfavorably compares with the results obtained with whole organ grafting.[90]

Recently the technique of reduced size liver grafting has been extended to the use of a liver segment from a living related donor in an effort to further extend the pool of available organs for pediatric recipients.[196, 197] Although the limited results available with this technique so far are good, the concept of jeopardizing the life of a healthy donor for the benefit of a diseased recipient is controversial. There has been one death of a living related liver donor as a result of a postoperative pulmonary embolus.

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[196] Broelsch CE, Edmond JC, Whitington PF, et al. Application of reduced-size liver transplants as split grafts, auxilary orthotopic grafts, and living segmental transplants. Ann Surg 212:368-75, 1990.

[197] Ozawa K, Uemoto S, Tanaka K, et al. An appraisal of pediatric liver transplants from living relatives. Initial clinical experience in 20 pediatric liver transplantations. Ann Surg 216:547-53, 1992.

POSTOPERATIVE MANAGEMENT

Early postoperative recovery

The postoperative course is dependent upon the preoperative condition of the patient, the difficulty of the operative procedure, and the function of the graft. Patients who go to operation in good nutritional status, who have an uneventful operation with minimal or moderate blood loss, and those whose graft functions well can be expected to recover quickly and to require only 24 to 48 hours of postoperative intensive care. Patients with advanced muscle wasting, a prolonged operation with high blood loss, intrapulmonic shunts (hepatopulmonary syndrome), severe renal insufficiency, or poor early graft function predictably have a more protracted recovery.

Most patients arrive in the recovery unit with significant excess fluid volume, but oliguria is common in the initial 24 to 48 hours after surgery. As a result, diuretics and colloid infusions (fresh frozen plasma or albumin) are often needed. As mentioned above, some centers use antilymphocyte preparations for induction immunosuppression in the early postoperative period to avoid the use of nephrotoxic immunosuppressive agents, such as cyclosporine or FK 506. Crystalloids should be limited to maintenance fluids to avoid pulmonary edema. Narcotic and sleep medications should be avoided until good graft function is established and the patient is alert.

Hypertension is a serious management problem in the early postoperative period when patients are still in a coagulopathic state, are often thrombocytopenic, and are at increased risk of intracerebral bleeding. It should be treated aggressively. Nifedipine, β-blockers (labetolol, propanolol), and hydralazine are first line drugs. Nitroglycerine or nitroprusside infusions are used in more severe cases.

Continued bleeding after surgery must be treated promptly. Coagulation is monitored closely after surgery including platelet count, prothrombin time, fibrinogen levels, factor VIII, and D-dimers or euglobulin lysis time. Appropriate measures should be taken to correct disturbances if the patient is bleeding. Re-exploration is advocated for all patients who bleed after surgery if the abdomen is distended or imaging studies show an abdomen containing a significant volume of clotted blood. All vascular anastomoses should be carefully examined and all clot should be evacuated from the abdomen during such explorations.

In a stable patient, a restrained approach to the correction of coagulopathy is recommended. A prothrombin time within 15 seconds of control and platelet counts as low as $30,000/mm^3$ are acceptable. Overcorrection of a moderate coagulopathy and overtransfusion in a stable patient may contribute to thrombosis of

the hepatic artery.[198] In small children, who are at higher risk of hepatic artery complications, anticoagulation with Dextran 40 and aspirin and persantine is recommended. Patients who receive a transplant for Budd-Chiari syndrome should be started on an antithrombosis protocol as soon as they are stable and graft function is ensured.

Primary graft failure

Good liver function after surgery is indicated by spontaneous correction of coagulopathy, stable blood glucose, declining serum lactate levels, improving urine output, and improving mental status. If a T-tube is present, the quantity and quality of bile production can also be monitored. Deteriorating mental status, hyperkalemia, alkalosis, and hypoglycemia indicate severe graft failure. Low levels of coagulation factors V and VII are commonly found in patients with graft failure.[199] If poor graft function is suspected, a Doppler ultrasound study of the hepatic vessels should be obtained to assess patency of the portal vein and hepatic artery. Potassium infusions should be avoided and 10% dextrose in water should be administered. Continuous

intravenous infusion of prostaglandin E1 (PGE1), which may have beneficial effects in fulminant hepatic failure and graft preservation, has been reported to be useful in the treatment of primary graft dysfunction.[200, 201] However, one recent prospective randomized trial failed to demonstrate a beneficial effect of perioperative PGE1 infusions on reperfusion injury.[202]

Ultimately, only urgent retransplantation can save the patient with irreversible ischemic injury from sepsis or irreversible brain swelling. In extreme circumstances, removal of a necrotic graft with the creation of a temporary portocaval shunt may stabilize the patient briefly until a new graft can be implanted, typically within 48 hours.[203, 204]

[198] Buckels JA, Tisone G, Gunson BK, McMaster P. Low haematocrit reduces hepatic artery thrombosis after liver transplantation. Transplant Proc 21:2460-1, 1989.

[199] Bilik R, Superine RA, Poon AO. Coagulation plasma factor levels are early indicators of graft nonfunction following liver transplantation. J Pediat Surg 27:302-6, 1992.

[200] Greig PD, Woolf GM, Abecassis M, et al. Treatment of primary liver graft nonfunction with prostaglandin E1. Transplantation 48:447-53, 1989.

[201] Isai H, Sheil AG, McCaughan G, Dolan P, Waugh R. Successful reversal of primary graft non-function in a liver transplant patient treated with prostaglandin E1. Aust N Z J Surg 62:314-6, 1992.

[202] Alevizacos P, Belchstein WO, Roussaint R, Neuhais P. Failure of PGE1 to prevent liver allograft reperfusion injury in a prospective randomized trial. Transplant Proc 25:2545-6, 1993.

[203] Ringe B, Pichlmayr R, Lubbe N, Bornscheuer A, Kuse E. Total hepatectomy as a temporary approach to acute hepatic or primary graft failure. Transplant Proc 21:3822-41, 1989.

[204] So SKS, Barteau JA, Perdrizet GA, Marsh JW. Successful retransplantation after a 48-hour anhepatic state. Transplant Proc 25:1962-3, 1993.

Prior to the introduction of UW solution for liver preservation, primary graft failure was a precipitous event occurring within the first week after surgery. Postperfusion biopsies may show zonal or severe focal necrosis. A neutrophilic exudate may be present and suggests the possibility of hyperacute rejection. The results of the donor specific antibody crossmatch should be assessed if such findings are observed.

A more insidious form of primary graft failure with persistent cholestatic jaundice and eventual fibrosis of the portal tracts has been seen in recent years. Typically, these patients show evidence of severe hepatocellular injury with high aminotransferase levels in the first few days after surgery. However, despite a rapid fall in aminotransferase activity, cholestatic jaundice persists and gradually worsens in the ensuing weeks. Biopsies typically show no evidence of rejection, but expansion of the portal tracts with increasing fibrosis and areas of centrilobular necrosis are seen.

COMPLICATIONS

Technical complications

Technical complications, especially biliary tract and vascular complications, remain a significant problem and are responsible for 10% of graft losses and 8% of the patient mortality seen after liver transplantation.[205] Mortality at 6 months after transplantation is 32% in patients who suffer a surgical complication, compared to 11% in patients without such complications.[206]

Vascular

Hepatic artery. Thrombosis of the hepatic artery is the most common vascular complication seen after liver transplantation. In the two largest reported series from Pittsburgh and from Omaha, the incidence of hepatic artery thrombosis was 6.7% and 6.3%, respectively.[205, 207] The highest risk of arterial thrombosis is associated with a recipient or donor weight of less than 15 kg and a long cold ischemic

time.[208, 207] Causes include technical failures, preservation injury, overly aggressive correction of coagulopathy, a high hematocrit, post-transplant hypercoagulability, severe allograft rejection, and postoperative pancreatitis.[198, 209-212]

Graft arterial thrombosis has three general patterns of presentation: 1) fulminant hepatic gangrene; 2) delayed biliary leak with or without bile abscess; 3) relapsing bacteremia with minimal, if any, liver dysfunction.[213] It should be suspected in any patient with a

[205] Lerut J, Gordon RD, Iwatsuki S, Starzl TE. Surgical complications in human orthotopic liver transplantation. Acta Chir Belg 87:193-204, 1987.

[206] Lebeau G, Yanaga K, Marsh J, et al. Analysis of surgical complications after 397 hepatic transplantations. Surg Gynecol Obstet 170:317-22, 1990.

[207] Langnas AN, Marujo W, Stratta RJ, Wood RP, Shaw BW Jr. Vascular complications after orthotopic liver transplantation. Am J Surg 161:76-82, 1991.

[208] Tan K, Yandza T, de Hemptinne B, Clapuyt P, Claus D, Otte JB. Hepatic artery thrombosis in pediatric liver transplantation. J Pediat Surg 23:927-30, 1988.

[209] Yanaga K, Makowka L, Starzl TE. Is hepatic artery thrombosis after liver transplantation really a surgical complication? Transplant Proc 21:3511-3, 1989.

[210] Stahl RL, Duncan A, Hooks MA, et al. A hypercoagulable state follows orthotopic liver transplantation. Hepatology 12:553-8, 1990.

[211] Mazzaferro V, Esquivel CO, Makowka L, et al. Hepatic artery thrombosis after pediatric liver transplantation – a medical or surgical event? Transplantation 47:971-7, 1989.

[212] Badger I, Buckels JA. Hepatic artery thrombosis due to acute pancreatitis following liver transplantation. Transplantation 48:526-7, 1989.

[213] Tzakis AG, Gordon RD, Shaw BW Jr, Iwatsuki S, Starzl TE: Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. Transplantation 40:667-71, 1985.

postoperative fever and elevation of liver function tests. Blood cultures which grow enteric organisms such as Klebsiella species, *Escherichia coli*, or enterococci are almost pathognomonic.

Doppler ultrasound is an effective screening device. However, arteriography should be obtained whenever the diagnosis of hepatic artery thrombosis is strongly suspected on clinical grounds, even if the Doppler study is reported to show arterial flow, since hepatopedal arterial collaterals may develop and result in a misinterpretation of the Doppler study.[214, 215] A reversed or absent diastolic Doppler flow signal may be found early after transplantation and is not a reliable predictor of subsequent hepatic artery thrombosis.[216] Also, in patients such as children with very small vessels, both Doppler flow studies and arteriography may give false-positive findings. Rollins et al have described four pediatric recipients less than 26 months of age with Doppler flow and angiographic studies

suggesting hepatic artery thrombosis who were found to have patent vessels at autopsy.[217]

Treatment of hepatic artery thrombosis depends upon both the etiology and the clinical presentation. Stable patients without persistent sepsis, bile leak, or bile abscess can often be maintained on an oral antibiotic for a prolonged period of time. Intrahepatic biliomas resulting from hepatic artery thrombosis can be initially managed with percutaneous drainage. Although progression of multiple ischemic biliary strictures may eventually necessitate retransplantation, patients treated by interventional radiology and medical therapy often avoid retransplantation for several years.[218, 219]

If massive liver injury has not occurred, early technical failures can sometimes be salvaged by immediate surgical correction or by fibrinolytic therapy followed by transluminal angioplasty for correction of an underlying

[214]Flint E, Sumkin JH, Zajko AB, Bowen A. Duplex sonography of hepatic arterial thrombosis after liver transplantation. Am J Roentgenol 151:481-3, 1988.

[215]Hall TR, McDiarmid SV, Grant SV, Boechat MI, Busuttil RW. False negative duplex Doppler studies in children with hepatic artery thrombosis after liver transplantation. Am J Roentgenol 154:573-5, 1990.

[216] Propeck PA, Scanlan KA. Reversed or absent hepatic arterial diastolic flow in liver transplants shown by duplex sonography: a poor predictor of subsequent hepatic artery thrmbosis. Am J Roentgenol 159:1199-201, 1992.

[217] Rollins NK, Timmons C, Superina RA, Andrews WS. Hepatic artery thrombosis in children with liver transplants: false-positive findings at Doppler sonography and arteriography in four patients. Am J Roengenol 160:291-4, 1993.

[218] Hoffer FA, Teele RL, Lillihei CW, Vacanti JP. Infected biliomas and hepatic artery thrombosis in infant recipients of liver transplants. Interventional radiology and medical therapy as an alternative to retransplantation. Radiology 169:435-8, 1988.

[219] Kaplan SB, Zajko AB, Koneru B. Hepatic biliomas due to hepatic artery thrombosis in liver transplant recipients: percutaneous drainage and clinical outcome. Radiology 174:1031-5, 1990.

arterial stricture.[220, 221] Fulminant hepatic necrosis requires retransplantation. In severe cases, such as those resulting in gas gangrene of the liver, it may be necessary to remove the liver and sustain the patient with a temporary veno-venous bypass or portacaval shunt in expectation that another donor can be found quickly.[222]

Hepatic artery strictures without thrombosis cause ischemic graft injury. Percutaneous transluminal angioplasty has been used to manage these lesions.[223, 224] Direct surgical repair is difficult and rarely successful.

Aneurysms of the hepatic artery are rare after transplantation and are usually anastomotic

pseudoaneurysms caused by a combination of technical flaws and infection. The diagnosis in many cases can be made by CT scan or duplex sonography, but angiography is required for a definitive diagnosis.[225] These lesions may present with intra-abdominal or gastrointestinal bleeding, but typically they are asymptomatic and are detected on screening examinations conducted for other purposes. Management options include embolization, excision with ligation, direct repair or reconstruction with an arterial conduit, and retransplantation. Patients who present with infected pseudoaneurysms from biliary leakage are more likely to require retransplantation for successful management than patients who present with bleeding without associated bile leakage.[226]

An important consideration in the differential diagnosis of sudden hemorrhage is splenic artery aneurysm, which has been shown to have a significant propensity to rupture after liver transplantation.[227, 228] Preoperative

[220] Yanakga K, Lebeau G, Marsh JW, et al. Hepatic artery reconstruction for hepatic artery thrombosis after orthotopic liver transplantation. Arch Surg 125:628-31, 1990.

[221] Hidalgo EG, Abad J, Canterero JM, et al. High dose intra-arterial urokinase for the treatment of of hepatic artery thrombosis in liver transplantation. Hepatogastroenterology 36:529-32, 1989.

[222] Shaked A, McDiarmid SV, Harrison RE, Gelebert H, Colonna JO, Busuttil RW. Hepatic artery thrombosis resulting in gas gangrene of the transplanted liver. Surgery 111:462-5, 1992.

[223] Abad J, Hidlago EG, Cantarero J, Parga G, et al. Hepatic artery anastomotic stenosis after transplantation: treatment with percutaneous transluminal angioplasty. Radiology 171:661-2, 1989.

[224] Castaneda F, So S, Hunter DW, et al. Reversible hepatic transplant ischemia: case report and review of literature. Cardiovasc Intervent Radiol 13:88-90, 1990.

[225] Tobben PJ, Zajko ABm Sumkin JH, et al. Pseudoaneurysms complicating organ transplantation: roles of CT, duplex sonography, and angiography. Radiology 169:65-70, 1988.

[226] Madriaga J, tzakis A, Zajko A, et al. Hepatic artery pseudoaneurysm ligation after orthotopic liver transplantation. Transplantation 54:824-8, 1992.

[227] Ayalon A, Weisner RH, Perkins JD, Tominaga S, Hayes D, Krom RA. Splenic artery aneurysms in liver transplant patients. Transplantation 45:386-9, 1988.

[228] Breams JJ, Hiatt JR, Klein AS, Colonna JO, Busuttil RW. Splenic artery aneurysm rupture

imaging studies should be examined and the superior aspect of the pancreas should be palpated during surgery to look for these lesions, which should be ligated if identified.

Portal vein. Postoperative portal vein thrombosis or stenosis are infrequent complications that can present with acute hepatic necrosis, esophageal variceal hemorrhage, or refractory ascites. In some patients, mild disturbances of liver function tests and prothrombin time and enlarging, but nonbleeding, esophageal varices, may be the presenting signs.[229]

As with arterial thrombosis, management depends upon presentation. If liver function is well preserved, retransplantation may be avoided in favor of nonoperative therapy, direct repair, or conventional management of the complications of portal hypertension. Percutaneous transhepatic portal vein angioplasty with intraluminal stenting has been used to treat portal vein stenosis.[230] Splenorenal shunts have been used to manage patients whose

principal presentation is esophageal variceal hemorrhage.[231, 232]

Inferior vena cava. Obstruction of the venous outflow from the graft at the suprahepatic caval anastomosis is rare, but can occur with end to end anastomosis of the hepatic veins in reduced size liver grafts.[233] It presents as a Budd-Chiari syndrome and should be considered in any patient with an enlarged graft and persistent ascites. Liver biopsy may show persistent centrilobular congestion. Doppler ultrasound examination of the hepatic veins shows loss of normal hepatic vein and inferior vena cava periodicity and may show distension of the hepatic veins and vena cava with high velocity jetstreaming at the anastomotic site.[234] However, perioperative ischemia and acute rejection may also produce abrupt dampening of

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following orthotopic liver transplantation. Transplantation 45:1136-7, 1988.

[229] Burke GW, Ascher NL, Hunter D, Najarian JS. Orthotopic liver transplantation: nonoperative management of early acute portal vein thrombosis. Surgery 104:924-8, 1988.

[230] Olcott EW, Ring EJ, Roberts JP, Ascher NL, Lake JR, Gordon RL. Percutaneous portal vein angioplasty and stent placement after liver transplantation. J Vasc Intervent Radiol 1:17-22, 1990

[231] Rouch DA, Emond JC, Ferrari M, Yousefzadeh D, Whitington P, Broelsch CE. The successful management of portal vein thrombosis after hepatic transplantation with a splenorenal shunt. Surg Gynecol Obstet 166:311-6, 1988.

[232] Marino IR, Esquivel CO, Zajko AB, et al. Distal splenorenal shunt for portal vein thrombosis after liver transplantation. Am J Gastroenterol 84:67-70, 1989.

[233] Emond JC, Heffron TG, Whitington PF, Broelsch C. Reconstruction of the hepatic vein in reduced size liver transplantation. Surg Gynecol Obstet 176:11-17, 1993.

[234] Rossi AR, Pozniak MA, Zarvan NP. Upper inferior vena caval anastomotic stenosis in liver transplant recipients: Doppler US diagnosis. Radiology 187:387-9, 1993.

the pulsatile waveform present in the hepatic veins.[235, 236]

Biliary tract

In the most recent analysis of technical complications after liver transplantation in 323 patients at the University of Pittsburgh, biliary obstruction or leakage occurred in 18% of patients.[206] In a series of 226 patients at the University of Nebraska, the incidence of biliary tract complications was similar (19.1%) and necessitated reoperation in 13.4%.[237]

In the Pittsburgh series, the incidence of obstruction after duct-to-duct reconstruction (18%) was significantly higher than the incidence after reconstruction by Roux-en-Y choledochojejunostomy (3%). However, the incidence of biliary leakage was higher after choledochojejunostomy (9% vs. 2%). In both the Omaha and Pittsburgh experience, complications after choledochojejunostomy tended to occur earlier and require more operative intervention than complications after duct-to-duct reconstruction.

Both radionucleid imaging and sonography have been useful in the diagnosis of biliary tract complications, but contrast cholangiography remains the most reliable diagnostic method.[238, 239] Doppler ultrasound screening to evaluate the status of the hepatic artery and portal vein, however, is an important component of the evaluation of any biliary fistula or stricture.

The T-tube exit site is the most common place that biliary leaks occur after duct-to-duct reconstruction. Small leaks discovered in an asymptomatic patient on routine contrast studies usually do not require treatment. Many minor symptomatic leaks, such as those occurring after T-tube removal, can be managed expectantly or by endoscopic placement of a nasobiliary stent.[240] Few patients require laparotomy for suture repair of the T-tube exit site.

[235] Coulden RA, Britton PD, Farman P, Nobel JG, Wight DG. Preliminary report: hepatic vein Doppler in the early diagnosis of acute liver transplant rejection. Lancet 336:273-5, 1990.

[236] Britton PD, Lomas DJ, Coulden RA, Farman P, Revell S. The role of hepatic vein Doppler in diagnosing acute rejection following paediatric liver transplantation. Clin Radiol 45:228-32, 1992.

[237] Stratta RJ, Wood RP, Langnas AN, et al. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. Surgery 106:675-83, 1989.

[238] Anselmi M, Lancberg S, Deakin M, et al. Assessment of biliary tract after liver transplantation: T-tube cholangiography or IODIDA scanning. Br J Surg 77:1233-7, 1990.

[239] Zemel G, Zajko AB, Skolnick ML, Bron KM. The role of sonography and transhepatic cholangiography in the diagnosis of biliary tract complications after liver transplantation. Am J Roentgenol 151:943-6, 1988.

[240] Ostroff JW, Roberts JP, Gordon RL, Ring EJ, Ascher NL. The management of T-tube leaks in orthotopic liver transplant recipients with endoscopically placed nasobiliary catheters. Transplantation 49:922-4, 1990.

Anastomotic leaks are more serious and usually require operative intervention. The status of the hepatic artery must be determined before repair is attempted. Direct repair of a leak from a duct-to-duct anastomosis is hazardous; it is usually prudent to convert the reconstruction to a Roux-en-Y choledochojejunostomy. Leakage from a choledochojejunostomy is usually associated with intestinal soilage which may prohibit immediate repair. A fresh anastomosis to a segment of healthy bowel should be performed when feasible. High anastomosis of jejunal mucosa to the hepatic capsule and parenchyma (intrahepatic cholangiojejunostomy) has been used successfully in patients with infection and destruction of the extrahepatic biliary tree.[241]

Numerous studies have demonstrated an association between the development of biliary strictures after liver transplantation and graft ischemic injury. Risk factors for the development of biliary strictures include prolonged graft preservation time in either Euro-Collins or UW solutions, high dose pressor support of the donor prior to procurement of the liver, ABO incompatibility between the donor and the recipient, and occult hepatic artery thrombosis.[242-245]

Percutaneous biliary dilatation of biliary strictures has a reported success rate ranging from 40% to 90%.[246] The Mayo Clinic reports achieving long term patency in 88% of patients treated with biliary stents and repeated biliary dilatations. However, one year graft survival in patients with ischemic biliary strictures is 69% compared to 88% in patients without such complications.[247]

Several studies have reported an increased incidence of non-anastomotic biliary strictures

[241] Langnas AN, Stratta RJ, Wood RP, Ozaki CF, Bynon JS, Shaw BW. The role of intrahepatic cholangiojejunostomy in liver transplant recipients after extensive destruction of the extrahepaticbiliary system. Surgery 112:712-7, 1992.

[242] Li S, Stratta RJ, Langnas AN, Wood RP, Marujo W, Shaw BW Jr. Diffuse biliary tract injury after orthotopic liver transplantation. Am J Surg 164:536-40, 1992.

[243] Colonna JO, Shaked A, Gomes AS, et al. Biliary strictures complicating liver transplantation. Incidence, pathogenesis, and outcome. Ann Surg 216:344-50, 1992.

[244] Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Ischemic type biliary complications after orthotopic liver transplantation. Hepatology 16:49-53, 1992.

[245] Sankary HN, McChesney L, Hart M, Foster P, Williams J. Identification of donor and recipient risk factors associated with nonanastomotic biliary strictures in human hepatic allografts. Transplant Proc 25:1964-67, 1993.

[246] Morrison MC, Lee MJ, Sani S, Brink JA, Mueller PR. Percutaneous balloon dilatation of benign biliary strictures. Radiol Clin North Am 28:1191-201, 1990.

[247] Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Diagnostic features and clinical outcome of ischemic-type biliary complications after liver transplantation. Hepatology 17:605-9, 1993.

in patients who received a transplant for primary sclerosing cholangitis (PSC).[245, 248] In a review of the cholangiograms obtained in 643 recipients of 687 liver grafts at the University of Pittsburgh, intrahepatic biliary strictures were identified in 105 (15%) allografts, anastomotic strictures in 105 allografts(15%), and non-anastomotic extrahepatic biliary strictures in 17 allografts (2%). The incidence of intrahepatic biliary strictures was significantly higher in patients who received a transplant for PSC (27%) compared to those who underwent transplantation for other reasons (13%). Non-anastomotic extrahepatic biliary strictures were also more common in the PSC group (6% versus 2%). Whether the increased incidence of non-anastomotic structures after liver transplantation for PSC is a manifestation of the original disease, or a complication more likely to occur in patients with a choledochojejunostomy, is not known. So far, there has been no demonstrated increased incidence of non-anastomotic strictures in patients reconstructed with choledochojejunostomy after liver transplantation for diseases other than PSC.

A "biliary cast syndrome" with the accumulation and concretion of sludge in the biliary tree in the absence of an anastomotic stricture is a reported complication after liver transplantation. A combination of medical therapy with choliuretic drugs, interventional radiology to manage intrahepatic strictures, and surgical revision of the biliary reconstruction have been used to avoid retransplantation in such cases.[249]

A modest dilatation of the biliary tree is commonly seen after liver transplantation and is of no clinical significance.[250] A functional obstruction of the biliary tree with progressive dilatation of the extrahepatic and intrahepatic bile ducts in the absence of any strictures may occur after duct-to-duct reconstruction. This "ampullary dysfunction syndrome" may be the result of denervation of the ampulla of Vater during the hilar dissection necessary to remove the native liver and expose the hepatic artery. Although it has been rarely discussed in the literature, this syndrome is well known to liver transplant surgeons. It usually requires endoscopic papillotomy or surgical revision to a choledochojejunostomy.

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[248] Sheng R, Zajko AB, Campbell WL, Abu-Elmagd K. Biliary strictures in hepatic transplants: prevalence and types in patients with primary sclerosing cholangitis. Am J Roentgenol 161:297-300, 1993.

[249] Chen CL, Wang KL, Chuang JH, Lin JN, Chu MF, Chang CH. Biliary sludge-cast formation following liver transplantation. Hepatogastroenterology 35:22-4, 1988.

[250] Campbell WL, Foster RG, Miller JW, Lecky JW, Zajko AB, Lee KY. Changes in extrahepatic bile duct caliber in liver recipients without evidence of biliary obstruction. Am J Roentgenol 158:997-1000, 1992.

Gastrointestinal and other systemic complications

Intestinal obstruction is an infrequent complication after liver transplantation, since most adhesions are confined to the supracolic portion of the abdomen. If a Roux-en-Y limb has been used for biliary reconstruction, small bowel may herniate under the mesentery of the Roux-Y limb if it has not been tacked to the peritoneum. Pseudo-obstruction of the colon also occurs, but it is less common than after kidney transplantation.

The jejunojejunostomy performed to construct a Roux-en-Y limb is often the site of an intestinal fistula or of occult gastrointestinal bleeding when these complications occur after liver transplantation. Anastomotic leaks have been more frequent in children. An enteric leak or fistula should be suspected whenever there is evidence of intra-abdominal polymicrobial or candida infection. Late bowel perforations are most often caused by diverticulitis, appendicitis, cytomegalovirus enteritis, or lymphoproliferative lesions.

Esophageal, gastric, intestinal, colonic and rectal ulcerations, with or without hemorrhage, may result from opportunistic infection as seen in cytomegalovirus gastroenteritis and colitis and Clostridium difficile colitis. Management includes appropriate antibiotic therapy (ganciclovir, metronidazole), blood replacement, and reduction in immunosuppression. In unusually severe cases, surgical resection may be necessary.

Ascites often persists for weeks to several months after transplantation and should be managed in the usual manner with salt restriction, spironolactone, and loop diuretics. Large volume paracentesis with colloid replacement (25% salt poor albumin) is used for severe cases. If the portal vein is patent and venous outflow is unobstructed, the ascites will eventually resolve. Peritoneovenous shunting is rarely indicated. Late recurrence of ascites suggests recurrent liver disease, including chronic rejection, hepatitis, or recurrent primary disease.

The etiology of pancreatitis after liver transplantation is not certain and often is multifactorial. Manipulation of the gland during dissection, congestion of the pancreas during the anhepatic phase of surgery, ischemic damage from ligation of the gastroduodenal artery, and use of high dose steroids for induction immunosuppression are possible contributing factors. A mild amylasemia is common early after liver transplantation and usually resolves in a few days. Persistent amylasemia and elevated serum lipase with edema of the pancreas on CT scan or ultrasound are more ominous and often herald pancreatic abscess, pseudocyst or hemorrhagic pancreatitis. Significant clinical pancreatitis is most common after liver transplantation in patients with active viral hepatitis at the time of transplantation, especially if acute hepatitis B is present.[251] The

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[251] Alexander J, Demetris AJ, Gavaler JS, Makowka L, Starzl TE, Van Thiel DH. Pancreatitis following

morbidity and mortality of major pancreatic complications after liver transplantation are high.

There is a significant incidence of hepatitis associated aplastic anemia developing one to seven weeks after liver transplantation performed for acute non-A, non-B hepatitis. Mortality has been high, but marrow recovery has occurred in some patients followed for more than a year.[252] A recent study suggests that the aplastic anemia in these cases is due to a non-A, non-B, non-C hepatitis virus.[253]

Infection

Decreased reliance on azathioprine and steroids has made bacterial infection less of an problem in organ transplantation, but infections, especially opportunistic viral and fungal infections, are associated still with much of the morbidity and mortality after liver

transplantation.[254-256][257] Over 80% of liver recipients have one or more episodes of infection and two-thirds of these infections are serious. Seventy percent of infections occur in the first 60 days after transplantation. In the first month, bacterial and fungal infections predominate. Bacterial sepsis is often associated with ischemic graft injury, severe rejection, or cholangitis. After the first month, viral infections are more common. In the reported experience from the University of Pittsburgh, the overall incidence of viral infection was 59% for cytomegalovirus (CMV), 35% for herpes simplex (HSV), 25% for Epstein-Barr virus (EBV), and 7% for varicella-zoster (VZV).[258]

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liver transplantation. Transplantation 45:1062-6, 1988.

[252] Tzakis AG, Arditis M, Whitington PF, et al. Aplastic anemia complicating orthotopic liver transplantation for non-A, non-B hepatitis. N Engl J Med 319:393-6, 1988.

[253] Hibbs JR, Frickhofen N, Rosenfeld SJ, et al. Aplastic anemia and viral hepatitis. Non-A, non-B, Non-C? JAMA 267:2051-4, 1992.

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[254] Kusne S, Dummer J, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine 67:132-43, 1988.

[255] Markin RS, Stratta RJ, Woods GL. Infection after liver transplantation. Am J Surg 14:64-78, 1990.

[256] Paya CV, Hermans PE, Washington JA, et al. Incidence, distribution, and outcome of episodes of infection in 100 orthotopic liver transplantations. Mayo Clin Proc 64:555-64,1989.

[257] Barkholt L, Ericzon BG, Tollemar J, et al. Infections in human liver recipients: different patterns early and late after transplantation. Transplant Int 6:77-84, 1993.

[258] Singh N, Dummer JS, Kusne S, et al. Infections with cytomegalovirus and other herpes viruses in 121 liver transplant recipients: transmission by donated organ and the effect of OKT3 antibodies. J Infect Dis 158:124-31, 1988.

Bacterial pneumonia occurs in 17% of liver recipients.[259] In the first three months after transplantation gram-negative bacilli and *Staphylococcus aureus* have predominated. Prophylaxis with single strength trimethoprim-sulfamethoxasole has proven to be highly effective in preventing *Pnemocystis carinii* pneumonia, once a major cause of mortality after solid organ transplantation. It has also made Legionella pneumonia a rarity. This prophylaxis should be continued indefinitely, since pneuomocystis pneumonia can occur if patients are withdrawn from antibiotic prophylaxis even years after transplantation. For patients with an allergy to sulfa drugs, monthly inhalation therapy with Pentamidine is also effective.[260] Bronchoalveolar lavage is quite helpful in the early diagnosis of pulmonary infections in immunosuppressed patients.

Cytomegalovirus (CMV) infections are the most common viral infections encountered in liver transplant recipients and can present with esophagitis, gastroenteritis, proctocolitis, hepatitis, pneumonitis, or retinitis. Cytomegalovirus infections may also involve the skin and be mistaken for herpes simplex infections.[261, 262] Seronegative recipients of organs from seropositive recipients are at the highest risk, but patients treated with heavy immunosuppression, especially antilymphocyte therapy, or requiring retransplantation, are also at increased risk.[263-266]

Prophylaxis with CMV immune globulin or acyclovir has been advocated for high risk patients. A recent meta-analysis of 18 clinical trials of immune globulin prophylaxis in bone marrow and solid organ transplant recipients confirmed a beneficial effect of either

[259] Mermel LA, Maki DG. Bacterial pneumonia in solid organ transplantation. Semin Respir Infect 5:10-29, 1990.

[260] Hirschel B, Lazzarin A, Chopard P, et al. A controlled study of inhaled pentamidine for primary prevention of *Pneumocystis carinii* pneumonia. N Engl J Med 324:1079-83, 1991.

[261] Lee JY. Cytomegalovirus infection involving the skin in immunocompromised hosts, a clinicopathological study. Am J Clin Pathol 91:96-100, 1989.

[262] Patterson JW, Broeker AH, Kornstein MJ, Mills As. Cutaneous cytomegalovirus infection in a liver transplant recipient. Diagnosis by in situ DNA hybridization. Am J Dermatopathol 10:524-30, 1988.

[263]Gorensek MJ, Carey WD, Vogt D, Goormastic M. A multivariate analysis of risk factors for cytomegalovirus infection in liver transplant recipients. Gastroenterology 98:1326-32, 1990.

[264] Hooks MA, Perlino CA, Henderson JM, Millikan WJ, Kutner MH. Prevalence of invasive cytomegalovirus disease with administration of muromonab CD-3 in patients undergoing orthotopic liver transplantation. Ann Pharamcother 26:617-20, 1992.

[265] Pillay D, Charman H, Burroughs AK, Smith M, Rolles K, Griffiths PD. Surveillance for CMV infection in orthotopic liver transplant recipients. Transplantation 53:1261-5, 1992.

[266] Stratta R, Scheefer MS, Mirkin RS, et al. Clinical patterns of cytomegalovirus disease after liver transplantation. Arch Surg 124:1443-9, 1989.

hyperimmune or the less expensive polyvalent immune globulin.[267] High dose acyclovir therapy has shown efficacy for CMV prophylaxis in a randomized placebo-controlled trial in renal allograft recipients.[268] A more recent trial using a similar protocol showed a reduction in the incidence of CMV infection and disease in seropositive recipients, but had no effect on the incidence or mortality of CMV pneumonia, and had no demonstrable benefit for seronegative recipients.[269]

Bismuth has reported a significant decrease in the incidence of CMV infection and disease, especially in CMV seropositive recipients, with high dose acyclovir given for the first three months after liver transplantation.[270] The Omaha group has shown a significant reduction in the incidence of herpetic and Epstein-Barr virus infections, but no difference in the incidence of cytomegalovirus infections, in a randomized prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients who had received OKT3.[271]

Since the upper gastrointestinal tract and the allograft liver are the organ systems most commonly involved with significant CMV disease, biopsy specimens obtained from these tissues are especially helpful in establishing a diagnosis. In studies comparing conventional light microscopy, immunoperoxidase staining with monoclonal or polyclonal antibody, in situ DNA hydridization, and inoculation of cell cultures, immunostaining with monoclonal antibody has been shown to be the most expedient and the most reliable method for early detection of CMV infection in tissue specimens.[272-274] In situ DNA hybridization

[267] Glowaki LS, Smail FM. Meta-analysis of immune globulin prophylaxis in transplant recipients for the prevention of symptomatic cytomegalovirus disease. Transplant Proc 25:1408-10, 1993.

[268] Balfour HH, Chace BA, Stapelton JT, Simmons RL, Fryd DS. A randomized placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N Engl J Med 320:1381-7, 1989.

[269] Legendre C, Ducloux D, Ferroni A, et al. Acyclovir in preventing cytomeglaovirus infection in kidney transplant recipients. Transplant Proc 25:1431-33, 1993.

[270] Saliba F, Eyraud D, Samuel MF, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. Transplant Proc 25:1444-45, 1993.

[271] Stratta RJ, Schaefer MS, Cushing KA, et al. A randomized prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients receiving OKT3 therapy. Arch Surg 127:55-63, 1992.

[272] Paya CV, Holley KE, Wiesner RH, et al. Early diagnosis of cytomegalovirus hepatitis in liver transplant recipients: role of immunostaining, DNA hybridization and culture of hepatic tissue. Hepatology 12:119-26, 1990.

[273] Theise ND, Conn M, Thung SN. Localization of cytomegalovirus antigens in liver allografts over time. Hum Pathol 24:103-8, 1993.

[274] Rabah R, Jaffe R. Early detection of cytomegalovirus in the allograft liver biopsy: a comparison of methods. Pediatr Pathol 7:5549-56, 1987.

shows high sensitivity, but lacks specificity.[275] A significant number of patients with CMV detected by polymerase chain reaction never develop clinically significant disease.[276]

The treatment of choice for cytomegalovirus infection is intravenous ganciclovir, 9-(1,3-dihydroxy-2-propoxymethyl) guanine.[277-280] Usually a minimum of 14 days of therapy is required. Foscarnet is an alternative drug for the exceptional patient whose infection is resistant to ganciclovir.

Herpes simplex infections in transplant recipients are usually oral or genital reactivations, but HSV can cause a severe hepatitis or pneumonitis.[258, 281] HSV reactivation infections are more common in patients treated with antilymphocyte therapy. Acyclovir is effective treatment and low dose prophylaxis with acyclovir is recommended for at least six months after transplantation.

Disseminated varicella-zoster infections in immunosuppressed patients require high dose therapy with acyclovir and have a high morbidity and mortality. Patients seronegative for varicella-zoster should receive a course of VZV immune globulin (VZIG) within 72 hours of exposure to an actively infected individual. In high risk exposures, such as a family member with chicken pox, it is also prudent to give VZIG to a seropositive patient and to administer acyclovir to seronegative patients, since clinical disease has been reported in susceptible individuals even after a course of VZIG.[282]

Epstein-Barr virus is a ubiquitous DNA virus. EBV infections after liver transplantation are discussed below with post-transplant lymphoproliferative disorders.

[275] Masih AS, Linder J, Shaw BW, Wood RP. Rapid identification of cytomegalovirus in liver allograft biopsies by in situ hybridization. Am J Surg Pathol 12:362-7, 1988.

[276] Delgado R, Lumreras C, Alba C, et al. Low predictive value of polymerase chain reaction for diagnosis of cytomegalovirus disease in liver transplant recipients. J Clin Microbiol 30:1876-8, 1992.

[277] Harbison MA, De Girolami PC, Jenkins RL, Hammer SM. Ganciclovir therapy of severe cytomegalovirus infection in solid-organ transplant recipients. Transplantation 46:82-8, 1988.

[278] Paya CV, Hermans OE, Smith TF, et al. Efficacy of ganciclovir in liver and kidney transplant recipients with severe cytomegalovirus infection. Transplantation 46:229-34, 1988.

[279] DAlessandro AM, Pirsch JD, Stratta RJ, Sollinger HW, Kalayoglu M, Belzer FO. Successful treatment of severe cytomeglaovirus infections with ganciclovir and CMV immune globulin in liver transplant recipients. Transplant Proc 21:3560-1, 1989.

[280] deHemptine B, Lamy ME, Salizzoni M, et al. Successful treatment of cytomegalovirus disease with 9-(1,3-dihydroxy-2-propoxymethyl guanine). Transplant Proc 20:652-5, 1988.

[281] Kusne S, Schwartz M, Breinig MK, et al. Herpes simplex virus infections after solid organ transplantation. J Infect Disease 163:1001-, 1991.

[282] McGregor RS, Zitelli BJ, Urbach AH, et al. Varicella in orthotopic liver transplant recipients. Pediatrics 83:256-61, 1989.

The most common fungal pathogens encountered in immunosuppressed patients are candida species. These are most often non-invasive overgrowths in the oropharyngeal, esophageal, and vaginal cavities and respond to topical therapy. Invasive candidiasis requires systemic therapy with amphotericin B or fluconazole. Although preoperative selective decontamination of the gut has been shown to reduce the incidence of gram negative bacterial and candida infections, there are practical limitations to its use and it has not been shown to affect patient mortality.[283, 284]

Aspergillus infections may present in the upper and lower respiratory tracts, skin, soft tissues, or central nervous system. A diffuse pneumonia with patchy infiltrates is a common presentation. Blood vessel invasion occurs early and may lead to insidious development of brain abscesses which are difficult to cure. A long course of systemic antifungal therapy is required.

Cryptococcal infection should be suspected in any immunocompromised patient with headache or meningismus. Appropriate tests for cryptococcal antigens, and India ink stain and fungal cultures of spinal fluid should be obtained. Invasive infections with Mucor or Rizopus species are rare, but do produce lethal CNS and soft tissue infections. Treatment includes reduction of immunosuppression, excision of localized lesions, and a long course of systemic antifungal therapy.

De novo malignancies after liver transplantation

Approximately 6% of organ transplant recipients develop de novo neoplasms. Mortality from these cancers is only 1%. The cancers most common in organ transplant recipients include skin and lip cancers (especially squamous cell cancers), non-Hodgkin's lymphomas, Kaposi's sarcoma, vulvar and perineal carcinomas, and in-situ uterine cervical carcinomas.[285]

Post-transplant lymphoproliferative disorders (PTLD)

Epstein-Barr virus (EBV) infection is common in organ transplant recipients. In a review of 51 consecutive pediatric liver recipients at the University of Pittsburgh, the incidence of primary and reactivation EBV infection was 68% and 48% respectively, rates similar to those seen in adults.[286] Most clinical

[283] Weisner RH, Hermans PE, Rekela J, et al. Selective bowel decontamination to decrease gram-negative aerobic bacterial and candida colonization and prevent infection after orthotopic liver transplantation. Transplantation 45:570-4, 1988.

[284] Badger IL, Crosby HA, Kong KL, et al. Is selective decontamination of the digestive tract beneficial in liver transplant patients? Interim results of a prospective randomized trial. Transplant Proc 23:1460-1, 1991.

[285] Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients. Clin Transplantation 4:53-62, 1990.

[286] Breinig MK, Zitelli B, Starzl TE, Ho M. Epstein-Barr virus, cytomegalovirus, and other viral

infections with EBV result in a systemic viral syndrome resembling infectious mononucleosis or present in atypical form with jaw pain, arthralgias, joint space effusions, diarrhea, encephalitis, pneumonitis, mediastinal lymphadenopathy, or ascites. Findings in the liver graft may include a mixed mononuclear portal and sinusoidal infiltrate with atypical large, noncleaved cells and immunoblasts, but with minimal damage to bile ducts, and an associated lobular hepatitis.[287]

EBV has been associated clinically with two B-cell malignancies, Burkitt's lymphoma and B-cell lymphomas in immunosuppressed hosts. Among the non-Hodgkin's lymphomas occurring after organ transplantation, 86% are of B-cell origin, 14% are of T-cell origin, and less than 1% are null cell in origin. Extranodal involvement is common (69%). Involvement of the central nervous system, which is rare in the general population, is usually confined to the brain and is found in 28% of affected patients.[285]

The reported incidence of lymphoproliferative disorders after liver transplantation is 1.7% to 2.5%.[288-290] The B-

cell lesions range from a polymorphic B-cell hyperplasia to a variety of frank polyclonal or monoclonal B-cell lymphomas including immunoblastic tumors and plasmacytomas.[291]

The liver allograft is involved in over one-third of cases, but the tonsils, gastrointestinal tract, and kidneys are also frequently affected.[292] Localized lesions in the gastrointestinal tract may obstruct or perforate and when found need to be excised. Lesions in the oropharynx, especially in children, may produce respiratory obstruction and require surgical excision.[293] Biopsy of involved tonsils can be hazardous. Lesions occurring early after transplantation (within 3 months) are most common in patients with early, aggressive rejection treated with

infections in children after liver transplantation. J Infect Dis 156:273-9, 1987.

[287] Randhawa PS, Markin RS, Starzl TE, Demetris AJ. Epstein-Barr virus-associated syndromes in immunosuppressed liver transplant recipients. Am J Surg Path 14:538-47, 1990.

[288] Nalesnik MA, Makowka L, Starzl TE. The diagnosis and treatment of posttransplant

lymphoproliferative disorders. Curr Prob Surg 25:367-42, 1988.

[289]McAlister V, Grant D, Roy A, Vilmaz Z, Ghent C, Wall W. Posttransplant lymphoproliferative disorders in liver recipients treated with OKT3 or ALG induction immunosuppression. Transplant Proc 25:1400-1, 1993.

[290] Levy M, Bachman B, Husberg B, et al. De novo maligancy following liver transplantaiton: a single-center study. Transplant Proc 25:1397-1399, 1993.

[291] Ferry JA, Jacobson JO, Conti D, Delmonico F, Harris NL. Lymphoproliferative disorders and hematologic malignancies following organ transplantation. Mod Pathol 2:583-92, 1989.

[292] Cohen JI. Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. Medicine 70:137-60, 1991.

[293]Sculerati N, Arriaga M. Otolaryngologic management of posttransplant lymphoproliferative disease in children. Ann Otol Rhinol Laryngol 99:445-50, 1990.

heavy immunosuppression, especially monoclonal or polyclonal antibody therapy. Patients who receive multiple courses of anti-lymphocyte antibody therapy for rejection are at highest risk for a PTLD.[289, 294]

Treatment consists of withdrawal of immunosuppression, administration of high dose acyclovir, and resection of troublesome localized lesions. When allograft graft rejection occurs, it is anticipated that the immune system will have recovered enough to control the lymphoproliferative process and that immunosuppression can be cautiously resumed. Survival has been highest in patients with the least number of organ systems involved and with polyclonal rather than monoclonal lesions.[292] Aggressive malignant lesions which fail to respond to reduction of immunosuppression may require treatment with systemic chemotherapy or radiotherapy, but mortality for these lesions is high.

Genetic probing techniques have been used in an effort to identify patients at greatest risk of developing EBV-related lymphoproliferative lesions and to assist in making a distinction between the lymphocytic infiltrates seen in allograft rejection and the lymphoid hyperplasia seen in EBV-related syndromes. Tissue specimens from transplant recipients with PTLD, and from those without PTLD but with a

past history of EBV infection, have been compared using an *in situ* hybridization (ISH) technique with a synthetic oligonucleotide DNA probe from a tandem repeat region (NotI) that is abundantly transcribed during productive EBV infection. Tissue from all patients with PTLD examined by ISH showed nuclear staining for EBV in the lymphoid infiltrates. However, allograft biopsies from patients with acute cellular rejection and serological evidence of past EBV infection were negative. Thus, ISH with an appropriate probe can distinguish the atypical lymphoid infiltrate of EBV-associated PTLD from the infiltrate of acute cellular rejection.[295]

Also using INH with an oligonucleotide probe, Randhawa et al studied the tissue expression of a small RNA transcribed by the EBER-1 gene during latent EBV infection to identify patients at risk of developing PTLD. EBER-1 gene expression was studied in specimens from 24 liver recipients that had been obtained 2 days to 22 months before development of PTLD. In 17 of the 23 patients, 1% to 40% of mononuclear cells were positive for EBER-1 gene expression. In all 24 cases, EBER-1 positive cells were identified in the lymphoproliferative lesions that ultimately developed. Only 2 of 20 control specimens

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[294] Solomon H, Gonwa TA, Mor E, et al. OKT3 rescue for steroid-resistant rejection in adult liver transplantation. Transplantation 55:87-91, 1993.

[295] Montone KT, Friedman H, Hodinka RL, Hocks DG, Kant JA, Tmaszewski JE. In situ hybridization for Epstein-Barr virus NotI repeats in posttransplant lymphoproliferative disorder. Mod Pathol 5:292-302, 1992.

taken from patients with preservation injury of the graft, acute rejection, or viral hepatitis, but in whom PTLD had not developed within 9 to 71 months after biopsy, showed EBER-1 positive cells and these were few in number. Thus, expression of the EBER-1 gene may be a useful as a marker for the subsequent development of PTLD and for making appropriate adjustments in immunosuppressive therapy in patients who are found to be at risk.[296]

Kaposi's sarcoma

Kaposi's sarcoma, which has a negligible incidence in the general population, was an obscure tumor until its occurrence was associated with patients with acquired immunodeficiency syndrome. The incidence in organ transplant recipients is 6%. The lesions may be confined to the skin, conjunctiva, or oropharynx, but visceral involvement, usually of the lungs or gastrointestinal tract, has been observed in 41% of transplant patients.[285] The lesions may regress with reduction or temporary withdrawal of immunosuppression. The highest incidence in liver transplant recipients has been in males of Mediterranean origin. There is an association between Kaposi's sarcoma and CMV disease. The reported mortality of Kaposi's sarcoma in liver transplant recipients is 45%.[297]

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[296] Randhawa PS, Jaffe R, Demetris AJ, et al. Expression of Epstein-Barr virus-encoded small RNA (by the EBER-1 gene) in liver specimens from transplant recipients with post-transplant lymphoproliferative disease. N Engl J Med 327:1710, 1992.

[297] Bismuth H, Samuel D, Venancie G, menouar G, Szekely AM. Development of Kaposi's sarcoma in liver transplant recipients: characteristics, management, and outcome. Transplant Proc 23:1438-39, 1991.

SURVIVAL AFTER LIVER TRANSPLANTATION

The number of organ transplantations performed in the United States has increased steadily for nearly 10 years (figure 13). Since cyclosporine became available for general use in the United States in 1984, patient and graft survival rates after liver transplantation have improved dramatically. Similar improvement in survival rates has been experienced in Europe also. By the end of the 1980s, nearly 9,100 liver transplantations had been performed at 133 transplant centers on the two continents with one-year survival rates exceeding 75% and two-year survival rates exceeding 65% for most indications.[298]

Results in the United States

A summary of the liver transplantation experience for the United States during the period from 1988-1990 was published by the UNOS Liver Transplant Registry in 1992.[299] By 1990 there were 75 liver transplant centers in 33 states and the District of Columbia. Only 15 centers performed 100 or more transplantations during the period from 1988 to 1990, and only 6

centers (7.5%) were performing more than 100 transplantations per year. Twelve or less transplants were performed by 25 (31%) of the centers.

The indications for liver transplants performed between 1988 and 1990 are summarized in table 6. The most significant change has been the increase in the proportion of patients undergoing liver transplantation for alcoholic cirrhosis, which has grown from 9.1% in 1988 to 17.8% in 1990.

The age of liver transplant recipients in the United States has been increasing with a median recipient age of 39 years in 1988, 42 years in 1988, and 43 years in 1990. This has probably been encouraged by reports of successful transplantation of older recipients with survival rates comparable to younger adults.[300, 301] The national registry 6 month, 1-year and 3-year survival rates, stratified by age groups, for liver transplant recipients in 1988-1990 are summarized in Table 11.

Patient survival rates for the major indications for liver transplantation in adults and

[298] Gordon RD and Bismuth H. Liver transplant registry report. Transplant Proc 23:58-60, 1991.

[299] Belle SH, Beringer K, Murphy J, et al. Liver Transplantation in the United States: 1988-1990. In: *Clinical Transplants 1991*. Teraski P, Cecka JM, eds. Los Angeles,UCLA Tissue Typing Laboratory, 13-29, 1992.

[300] Starzl TE, Todo S, Gordon RD. Liver transplantation in older patients [letter]. N Engl J Med 316:484, 1987.

[301] Stieber AC, Gordon RD, Todo S. Liver transplantation in patients over 60 years of age. Transplantation 51:271-84, 1991.

children are summarized in Tables 8 and 9. Among adults with primary biliary cirrhosis and sclerosing cholangitis, survival at 6-months after transplantation is high (86% and 88%, respectively) with high survival maintained out to three years of follow-up (78% and 79%, respectively). Survival rates after transplantation for chronic active hepatitis B and non-A, non-B are also good at 6 months (77% and 80%, respectively), but there is a greater attrition of patients, especially for hepatitis B, such that survival at 3-years is 54% and 68%, respectively. Survival of patients with alcoholic cirrhosis compares favorably to other patients with postnecrotic cirrhosis. The poorest long term survival is seen with patients receiving transplants for malignant neoplasms.

In children, biliary atresia is by far the most common indication for liver transplantation, and accounts for more than 50% of the cases in most reported series. Survival for this condition at 6-months is 82% with good survival being maintained out to 3 years (75%).

Patient survival stratified according to the UNOS classification system for patient condition at the time of transplantation is summarized in Table 10. These results show a decreased survival as the level of hospital care required by the patient at the time of surgery increases. Only 61% of patients on life support immediately prior to transplantation survive one year, compared to 75% of patients hospitalized, but not in an intensive care unit, and 81% of patients disabled at home.

Finally, confirming of what has already been reported in single center studies, there is a significant patient and graft loss associated with transplantation across ABO blood groups. Results stratified according to donor and recipient ABO blood groups are presented in table 11. The poorer results with ABO mismatched grafts probably reflect both the biological disadvantages of crossing the ABO blood groups and, perhaps more importantly, the use of ABO mismatched grafts for more urgent patients.

Results at the University of Pittsburgh

The largest and oldest liver transplant program in the United States is located at the University of Pittsburgh. The results of liver transplantation at this center for the period from 1984 to 1990 have been presented in detail elsewhere and will be summarized here.[302] During the period from 1984 through September, 1987 liver transplantation was performed using Euro-Collins solution for graft preservation, cyclosporine and prednisone (with or without supplemental azathioprine) for maintenance immunosuppression, and OKT3 monoclonal antibody for treatment of steroid resistant rejection. During this period, 787

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[302] Gordon RD, Fung J, Tzakis AG, et al. Liver transplantation at the University of Pittsburgh, 1984 to 1990. In: *Clinical Transplants 1991*. Teraski P, Cecka JM, eds. Los Angeles, UCLA Tissue Typing Laboratory, 1992; 105-17.

patients received a liver transplant with an actual 12-month patient survival of 78.9% and first graft survival of 62.4%. Of the original 787 patients, 214 (27.2%) patients ultimately required retransplantation of at least one more graft.

The Pittsburgh team switched to UW solution for graft preservation starting in October, 1987 with a modest increase in patient and graft survival rates. Experimental trials with FK506 began in 1989, and from January 1989 through December 1990, 822 patients received a liver transplant, including 399 who were treated primarily with FK506 instead of cyclosporine, and 103 patients who were switched from cyclosporine to FK506 as part of a graft rescue protocol. During this period, observed patient survival improved at one year to 83.1% and one-year graft survival improved to 73.5%. Only 16.8% of these patients required a second graft.

· ·A breakdown of the indications for liver transplantation during the two periods of observation is shown in table 12. Postnecrotic cirrhosis, including chronic active hepatitis B, autoimmune hepatitis, and cryptogenic cirrhosis (which includes most patients with chronic active hepatitis C) remains the most common indication for liver transplantation. As in the nationwide experience, there has been a significant increase in the number of transplantations performed for alcoholic cirrhosis.

Patient and graft survival rates for liver transplantation are shown in table 13.

Significant improvement in survival rates are seen for patients with fulminant hepatic failure, biliary atresia, primary sclerosing cholangitis, and chronic active hepatitis B. Earlier referral of patients and aggressive protocols for preoperative management, including intracerebral blood flow monitoring and methods for prevention of excess intracranial pressure, may have contributed to the improvement seen in patients with fulminant hepatic failure.

Earlier patient referral, more experience in performing transplantation in patients with previous biliary surgery, and restraint in the use of invasive surgical procedures may have contributed to the improvements seen for primary sclerosing cholangitis and biliary atresia. Technical· improvements in methods for arterial reconstruction and use of reduced liver grafts for small children may also be important factors in the improved results for biliary atresia.

Exclusion of patients with hepatitis B early antigen (HBeAg) or high titers of HBV DNA from transplantation and routine use of immunoprophylaxis with immune globulin after transplantation may explain the improved survival seen for patients with chronic active hepatitis B. Nonetheless, the long term prognosis for these patients remains guarded.

Survival after transplantation for cryptogenic cirrhosis, which includes most patients with chronic active hepatitis C, remains favorable, but the true risks associated with hepatitis C can only be assessed as the newer

techniques for characterizing this virus are applied to the liver transplant population. Preliminary evidence indicates that greater than 90% of patients remain HCV positive after transplantation, but the implications for the subsequent development of cirrhosis in the graft are not yet clear.[90]

Overall, the results of liver transplantation for cancer have been disappointing. Some slow growing sarcomatous tumors, such as epitheloid hemangioendotheliomas, have a favorable prognosis with liver transplantation.[303] Although most metastatic tumors are not suitable for liver transplantation, the neuroendocrine tumors are an exception.[304, 305]

Efforts to improve the prognosis of patients with hepatocellular and biliary tract cancers must continue. At the present time, the best results are seen with patients with small (< 3 cm), uni- or binodular tumors. Patients with large or multiple tumors have a high recurrence rate after transplantation.[90] Some encouraging

improvements in patient survival are being reported after preoperative intra-arterial chemotherapy for patients with advanced-stage hepatoma, but longer follow-up of more patients is needed.[306] Given the current shortage of organs, liver transplantation for hepatobiliary cancers should probably be restricted to centers with well delineated protocols designed to test new approaches to this vexing problem.

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[303] Makowka L, Tzakis AG, Mazzaferro V, et al. Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. Surg Gynecol Obstet 168:107-11, 1989.

[304] Kelleher MB, Iwatsuki S, Sheahan DG. Epitheloid hemangioendothelioma of liver. Clinicalpathological correlation of 10 cases treated by liver transplantation. Am J Surg Pathol 13:999-1008, 1989.

[305] Alsina AE, Bartus S, Hull D, Rosson R, Schwizer R. Liver transplantation for metastatic neuroendocrine tumor. J Clin Gastroenterol 12:533-7, 1990.

[306] Carr BI, Selby R, Madariaga J, Iwatsuki S, Starzl TE. Prolonged survival after liver transplantation for advanced-stage hepatocellular carcinoma. Transplant Proc 25:1128-9, 1993.

Table 1. Indications for Liver Transplantation

1. Advanced Chronic Liver Disease
- *Cholestatic Liver Disease*
  - Primary Biliary Cirrhosis (PBC)
  - Primary Sclerosing Cholangitis (PSC)
  - Secondary Biliary Cirrhosis
  - Biliary Atresia
  - Bile Duct Paucity Syndrome
  - Familial Cholestatic Syndromes
- *Hepatocellular Disease*
  - Chronic Viral-induced Liver Disease
  - Chronic Drug-Induced Liver Disease
  - Alcoholic Liver Disease
  - Chronic Autoimmune Liver Disease
- *Vascular Disease*
  - Budd-Chiari Syndrome
  - Veno-occlusive Disease

2. Hepatic Malignancies
- Hepatocellular Carcinoma (HCC)
- Cholangiocarcinoma
- Sarcomas of the liver
- Isolated Metastatic Disease
  - Neuroendocrine Tumor
  - Colo-Rectal Cancer
  - Others

3. Fulminant Hepatic Failure
- Viral Hepatitis
  - A, B, C, D,
  - nonA-nonB-nonC, EBV
- Acute Alcoholic Hepatitis
- Drug-Induced/Toxic Acute Liver Disease
  - Halothane
  - Acetaminophen
  - Gold
  - Disulfiram
  - Amanita phalloides
  - Others
- Metabolic Liver Disease
  - Wilson's Disease
  - Reye's Syndrome
  - Organic Acidurias

Table 1 (con't). Indications for Liver Transplantation

4. Metabolic Liver Disease
- Alpha-1-antitrypsin Deficiency
- Wilson's Disease
- Tyrosinemia
- Galactosemia
- Hemochromatosis
- Crigler-Najjar Syndrome Type II
- Erythropoietic Protoporphyria
- Urea-Cycle Deficiencies
- Glycogen-Storage Disease Type I & IV
- Homozygous Type IIa hypercholesterolemia
- Gaucher's Disease
- Oxalosis
- Protein C Deficiency
- Protein S Deficiency
- Antithrombin III Deficiency
- Type A and B Hemophilia

Table 2. Complications of End-Stage Liver Diseases

HEPATOCELLULAR DISEASE	COMPLICATIONS	CHOLESTATIC DISEASE
	Synthetic Failure	
Typical	Hypoalbuminemia	Late
Typical	Coagulopathy	Late
	Cholestasis	
Present	Hyperbilirubinemia	Typical/Important
Usually absent	Xanthelasma	Usually present
Usually absent	Hypercholesterolemia	Usually present
	Portal Hypertension	
Present	Ascites	Present (late)
Present	Variceal bleeding	Late
Present	Hepatic encephalopathy	Late
Early phase only	**Hepatomegaly**	Present
	Hypersplenism	
Present	Anemia	Present (late)
Present	Thrombocytopenia	Present (late)
Present	Leucopenia	Present (late)
Uncommon	**Osteodystrophy**	Common
Present	**Hepatocellular Carcinoma**	Exceptionally rare
Exceptionally rare	**Cholangiocarcinoma**	Present

**Table 3.   Clinical and Biochemical Indications to Assess the Timing
          for Liver Transplantation**

1. Acute Liver Failure

Bilirubin > 10-20 mg/dl and increasing
Prothrombin time > 10 sec. above normal and increasing
Encephalopathy (Grade 3 and progressing)

2. Chronic Liver disease

• *Cholestatic Liver Disease*
    Bilirubin > 15 mg/dl
    Intractable Pruritus
    Severe Bone Disease

• *Hepatocellular Liver Disease*
    Albumin < 2.5 g/dL
    Hepatic encephalopathy
    Prothrombin Time > 5 sec. above normal

• *Factors Common to Both Types of Liver Disease*
    Hepato-renal syndrome
    Recurrent Spontaneous Bacterial Peritonitis
    Intractable Ascites
    Recurrent Variceal Bleeding
    Recurrent Episodes of Biliary Sepsis
    Development of liver malignancy

Table 4 - Contraindications to Liver Transplantation

Absolute

Extra hepato-biliary sepsis

Hepato-biliary malignancy with extra-hepatic
metastases

Severe cardio-pulmonary disease

AIDS

Relative

Portal vein thrombosis

HBV ESLD with active viral replication

HIV positivity

Marked obesity

Previous major abdominal surgery

Poor compliance

Table 5 - Other organ systems and End-Stage Liver Disease

I. THE HEART
A) Atherosclerotic Heart Disease
- older age > 50 years
- familial hypercholesterolism
- diabetes mellitus

B) Cardiomyopathy
- alcohol
- Wilson's disease
- hemochromatosis
- glycogen storage disease

C) Right Heart Function
Autoimmune Hepatitis
- pulmonary hypertension
- pulmonary fibrosis

cystic fibrosis

alpha-1 antitrypsin deficiency

II. THE LUNGS
A) Obstructive Disease without Infection
- a1 antitrypsin deficiency
- IgA deficiency with bronchitis
- cystic fibrosis

B) Restrictive Disease
-chronic autoimmune hepatitis

C) Vascular Disease
- chronic active hepatitis (HCV)
- a1 antitrypsin deficiency
- hypercoagulable status
  - Budd Chiari
  - polycythemia rubra vera
  - paroxysmal nocturnal hemoglobinuria
  - protein C or S deficiency
  - antithrombin III deficiency

D) Hepatopulmonary Syndrome
- pan lobular lung disease
- focal lung disease

III. RENAL FUNCTION
A) Glomerulopathy
- chronic hepatitis B, ? C

B) IgA Nephropathy
- alcoholism

C) Interstitial nephritis
- chronic autoimmune hepatitis
- drug-induced liver disease

D) Glomerulonephritis
- chronic autoimmune hepatitis

E) Renal Calculi
- metabolic disease
- PSC with IBD

F) Hypertension/Atherosclerosis
- older patients

Table 6. Most common indications for liver replacement in the United States, 1988-1990

	1988	1989	1990
Patients	1,489	1,861	2,308
Fulminant failure	**7.7%**	**7.2%**	**8.2%**
Hepatitis A	0.6%	0.5%	0.5%
Hepatitis B	1.1%	2.0%	1.3%
Hepatitis, non-A, non-B	3.0%	2.1%	3.5%
Drug/toxin	1.3%	1.2%	1.0%
Other or unspecified	1.6%	1.5%	2.7%
Postnecrotic cirrhosis	**40.8%**	**47.2%**	**51.5%**
Autoimmune hepatitis	4.0%	3.0%	3.5%
Chronic active hepatitis B	5.8%	6.0%	6.2%
Chronic active hepatitis, non-A, non-B	10.8%	12.5%	17.1%
Cirrhosis, other or unspecified	11.0%	11.3%	11.1%
Alcoholic cirrhosis	9.1%	15.1%	17.8%
Cholestatic liver disease	**36.4%**	**34.3%**	**27.8%**
Primary biliary cirrhosis	12.9%	9.1%	8.5%
Primary sclerosing cholangitis	9.4%	9.4%	7.8%
Secondary biliary cirrhosis	0.9%	0.8%	0.8%
Biliary atresia	13.1%	11.4%	9.5%
Other	0.1%	0.1%	0.2%
Metabolic disorders	**6.0%**	**5.3%**	**5.6%**
Alpha-1-antitrypsin deficiency	2.4%	2.6%	2.2%
Wilson's disease	1.6%	0.9%	1.1%
Hemochromatosis	0.6%	0.8%	1.2%
Other	1.3%	1.0%	1.2%
Benign neoplsms	**0.7%**	**0.4%**	**0.3%**
Polycystic liver disease	0.5%	0.3%	0.2%
Other	0.2%	0.1%	0.1%
Malignant neoplasms	**5.1%**	**5.7%**	**4.9%**
Hepatocellular carcinoma	3.1%	2.9%	2.7%
Cholangiocarcinoma	0.7%	1.1%	0.6%
Hemangio-endothelioma	0.1%	0.2%	0.3%
Miscellaneous	**16.4%**	**14.9%**	**12.2%**
Budd-Chiari	1.5%	1.0%	0.7%
Congenital hepatic fibrosis	0.4%	0.4%	0.4%
Cystic fibrosis	0.5%	0.1%	0.3%

Adapted from Belle et al.[299]

Table 7. Patient survival rates in the United States after liver transplantation based on recipient age, 1988-1990

	6 month	1-year	3 years
< 3 years	77%	75%	67%
3-17 years	83%	81%	75%
18-29 years	79%	76%	65%
30-39 years	84%	79%	72%
40-49 years	82%	78%	67%
50-59 years	77%	73%	63%
≥ 60 years	75%	71%	61%

Adapted from Bell et al.[299] There were 5,658 patients at risk at one month, 4,928 at 6 months, 3,978 at 12 months, and 1,172 at 36 months.

Table 8. Adult (≥ 18 years) patient survival rates in the United States after liver transplantation, 1988-1990

	6 month	1-year	3 years
Fulminant hepatic failure	68%	65%	60%
Chronic active hepatitis, non-A, non-B	80%	77%	68%
Chronic active hepatitis B	77%	69%	54%
Alcoholic cirrhosis	81%	79%	65%
Primary biliary cirrhosis	86%	84%	78%
Primary sclerosing cholangitis	88%	85%	79%
Metabolic disorders	79%	74%	67%
Malignant neoplasms	71%	60%	28%

Adapted from Bell et al.[299]

Table 9. Pediatric (< 18 years) patient survival rates in the United States after liver transplantation, 1988-1990

	6 month	1-year	3 years
Fulminant hepatic failure	65%	64%	*62%
Biliary atresia	82%	80%	75%
Cholestatic cirrhosis	83%	83%	83%
Other cirrhosis	84%	77%	67%
Metabolic disorders	88%	87%	75%
Malignant neoplasms	69%	69%	*41%

Adapted from Bell et al.[299]

*Figures shown are 2-year survival rates since 3-year results were not available for these indications.

Table 10. Patient survival rates in the United States after liver transplantation stratified according to patient status at the time of surgery, 1988-1990

	6 month	1-year	3 years
Working full time/ attending school	85%	75%	75%
Partially disabled/subnormal growth	85%	77%	75%
Homebound/failing to thrive	86%	77%	72%
Hospitalized	79%	70%	64%
Intensive care	78%	69%	67%
On life support	64%	57%	54%

Adapted from Bell et al.[299]

Table 11. Patient survival rates in the United States after liver transplantation stratified by donor-recipient ABO compatibility, 1988-1990

	6 month	1-year	3 years
ABO identical	81%	78%	68%
ABO mismatched, compatible	72%	67%	62%
ABO mismatched, incompatible	69%	66%	54%

Adapted from Bell et al.[299]

Table 12. Most common indications for liver replacement at the University of Pittsburgh

	Jan 1984-Sep 1987	Jan 1989- Dec 1990
Fulminant hepatic failure	36 (4.6%)	24 (2.9%)
Postnecrotic cirrhosis	222 (28.2%)	280 (34.1%)
Cryptogenic cirrhosis	166 (21.1%)	177 (21.5%)
HBsAg+ cirrhosis	27 (3.4%)	53 (6.4%)
Autoimmune CAH	17 (5.0%)	25 (3.0%)
Alcoholic cirrhosis	39 (5.0%)	167 (20.3%)
Biliary atresia	152 (19.3%)	81 (9.9%)
Primay biliary cirrhosis	123 (15.6%)	66 (8.0%)
Sclerosing cholangitis	55 (7.0%)	55 (6.8%)
Genetic disorders	72 (9.1%)	33 (4.0%)
Alpha-1-antitrypsin deficiency	40 (5.1%)	18 (2.2%)
Wilson's disease	13 (1.7%)	5 (0.6%)
Primary liver cancer	20 (3.2%)	58 (7.1%)

Adapted from Gordon et al.[302]

Table 13. Observed 12-month patient and graft survival rates for common indications for liver transplantation at the University of Pittsburgh

	Jan 1984-Sep 1987		Jan 1989- Dec 1990	
	Patient Survival	Graft Survival	Patient Survival	Graft Survival
Fulminant hepatic failure	61.1%	36.1%	79.2%	58.3%
Postnecrotic cirrhosis	76.1%	65.3%	82.1%	73.9%
Cryptogenic cirrhosis	78.9%	67.5%	81.4%	73.5%
HBsAg+ cirrhosis	59.3%	51.9%	86.6%	81.1%
Autoimmune CAH	82.4%	70.6%	84.0%	72.0%
Alcoholic cirrhosis	76.9%	71.8%	82.6%	75.4%
Biliary atresia	65.1%	50.7%	88.9%	77.8%
Primay biliary cirrhosis	75.6%	65.9%	81.8%	69.7%
Sclerosing cholangitis	83.6%	76.4%	98.2%	80.0%
Genetic disorders	76.4%	75.0%	84.8%	81.8%
Alpha-1-antitrypsin deficiency	80.0%	80.0%	77.8%	77.8%
Wilson's disease	76.9%	69.2%	100,0%	80.0%
Primary liver cancer	50.0%	50.0%	70.7%	63.8%

Adapted from Gordon et al.[302] All patients were followed for at least one year and there were no patients lost to follow-up. The survival rates are actual, observed survival rates, not actuarial estimates.
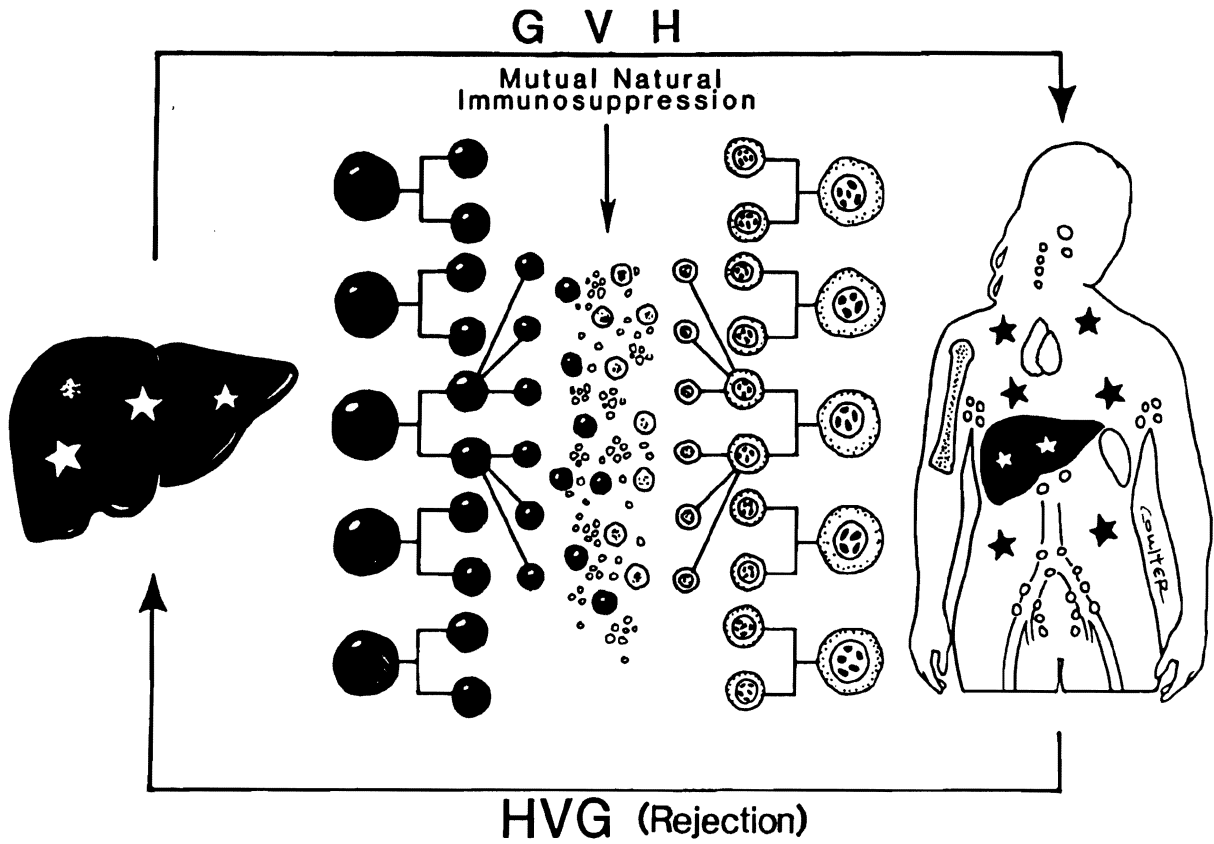
LEGENDS

Figure 1: The phenomenon of cell migration (with repopulation and chimerism) which is postulated to be the basis of graft acceptance. Note the interaction at the site of donor-recipient mutual cell engagement. This is thought to be the first step toward donor specific non-reactivity (tolerance) by a mechanism of peripheral clonal "silencing".

Figure 2: Cadaveric organ donors in the United States, 1990-1992.

Figure 3: Highway fatalities per 100 vehicular million miles traveled.

Figure 4: Seatbelt usage by United States motor vehicle operators.

Figure 5: Median waiting time of candidates for a liver transplant in the United States

Figure 6 Death rate for patients waiting for liver transplantation in the United States.

Figure 7: The pump driven veno-venous bypass is used to decompress the systemic and splanchnic venous beds during the anhepatic phase of the operation. Outflow lines to the pump are placed in the iliofemoral system via a cutdown on the saphenous vein and a return cannula is placed in the axillary vein. *From Casavilla A, et al., with permission.*[167]

Figure 8: The "piggyback" method of graft implantation. **(A)** The recipient vena cava is left intact and a clamp is applied across the origin of the major hepatic veins. **(B)** 33A cuff is prepared by joining the origins of the middle and left hepatic veins. The right hepatic vein (not shown here) is usually tied off. **(C)** The suprahepatic vena cava of the graft is sewn to the funnel of the hepatic veins and the infrahepatic cava of the graft is simply tied off. The liver rests on top of the recipient vena cava. *From Casavilla A, et al., with permission.*[167]

Figure 9: Steps in the implantation of an orthotopic liver graft. **(A)** Completion of the suprahepatic vena cava anastomosis. **(B)** Completion of the infrahepatic vena cava anastomosis. The portal vein is flushed with cold albumin or electrolyte solution to wash out the high potassium containing preservation fluid and to eliminate air in the vena cava. **(C)** The portal vein bypass cannula is removed and the portal vein anastomosis is completed. *From Casavilla A, et al., with permission.*[167]

Figure 10:   Use of a jump graft of donor iliac artery for extranatomic reconstruction of the hepatic arterial supply. The graft is passed through the transverse mesocolon, anterior to the pancreas, and posterior to the distal stomach to emerge at the hepatic hilum anterior and medial to the portal vein. Alternative sites for the origination of an arterial jump graft include the right iliac artery and the supraceliac aorta (not shown). *From Casavilla A, et al., with permission.*[167]

Figure 11:   Use of a jump graft of donor iliac vein from the superior mesenteric vein to the donor portal vein. The graft is tunneled through the transverse mesocolon, anterior to the pancreas, and posterior to the stomach to reach the hepatic hilum. *From Casavilla A, et al., with permission.*[167]

Figure 12:   The biliary reconstruction. If the recipient duct is normal and closely matches the donor duct in caliber, an end-to-end reconstruction over a T-tube is performed using interrupted 5-0 or 6-0 polyglycolic acid suture. In cases in which the anatomy is not favorable for a this technique, an eighteen inch Roux-en-Y limb of jejunum is created and an end-to-side choledochojejunostomy over an internal silastic stent is performed using running 5-0 or 6-0 polyglycolic acid suture (inset). *From Casavilla A, et al., with permission.*[167]

Figure 13:   Liver transplantations per year in the United States, 1983-1992.

Figure 1.   The phenomenon of cell migration (with repopulation and chimerism) which is postulated to be the basis of graft acceptance. Note the interaction at the site of donor-recipient mutual cell engagement. This is thought to be the first step toward donor specific non-reactivity (tolerance) by a mechanism of peripheral clonal "silencing".
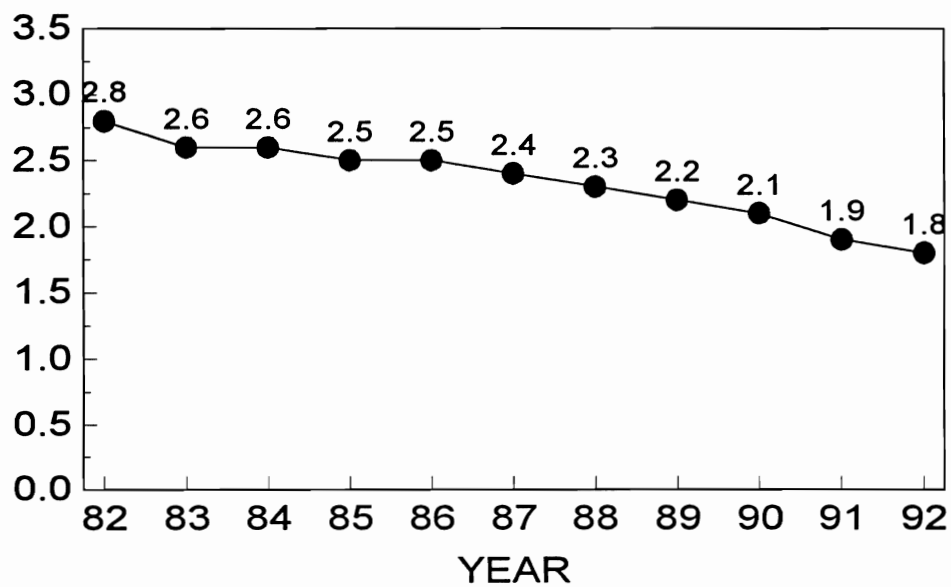
Number of donors
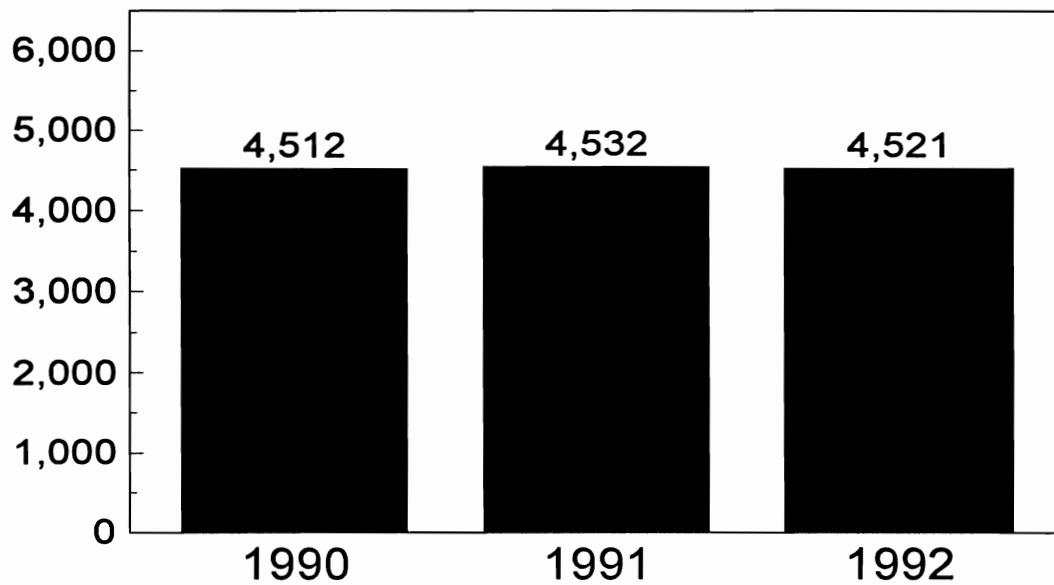
Source: United Network for Organ Sharing
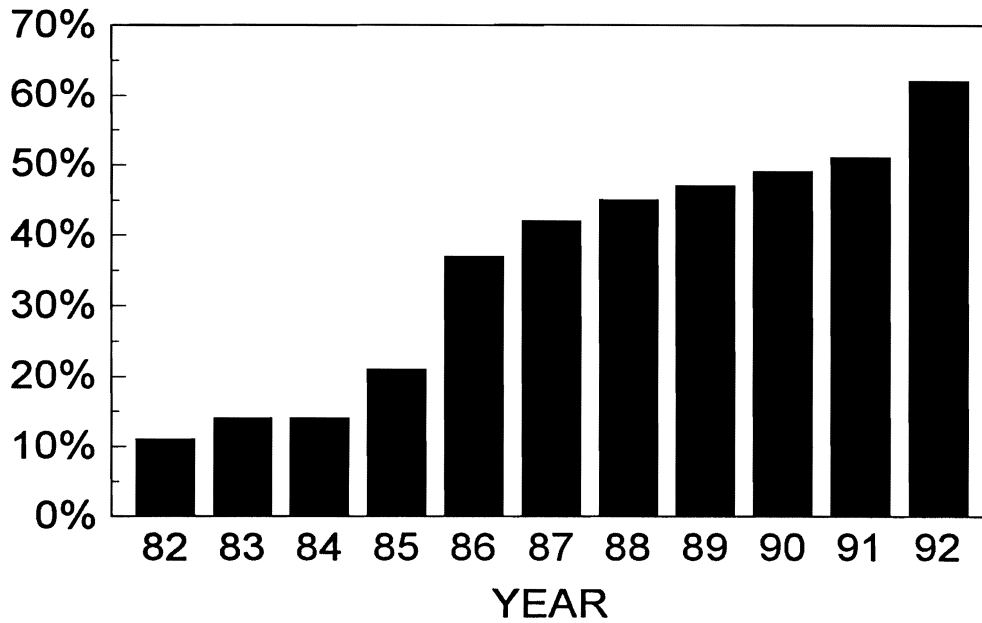
Figure 2.   Cadaveric organ donors in the United States, 1990-1992.

Fatality Rates

Source: National Highway Traffic Safety Administration

Figure 3.   Highway fatalities per 100 million vehicular miles
traveled.

Percent Use

Source: National Highway Traffic Safety Administration

Figure 4.   Seatbelt usage by United States motor vehicle operators.

Median Wait (days)
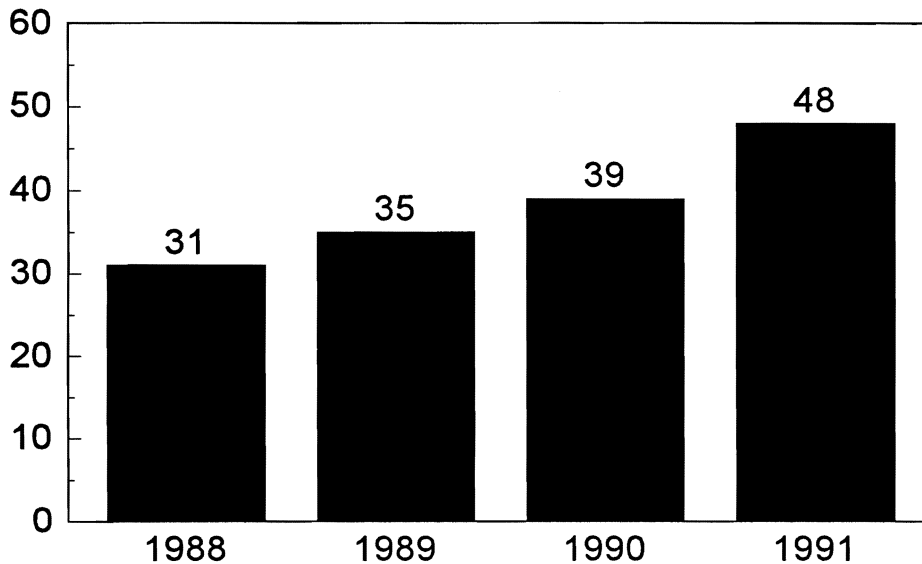
Source: United Network for Organ Sharing

Figure 5.   Median waiting time of candidates for a liver transplant in the
United States
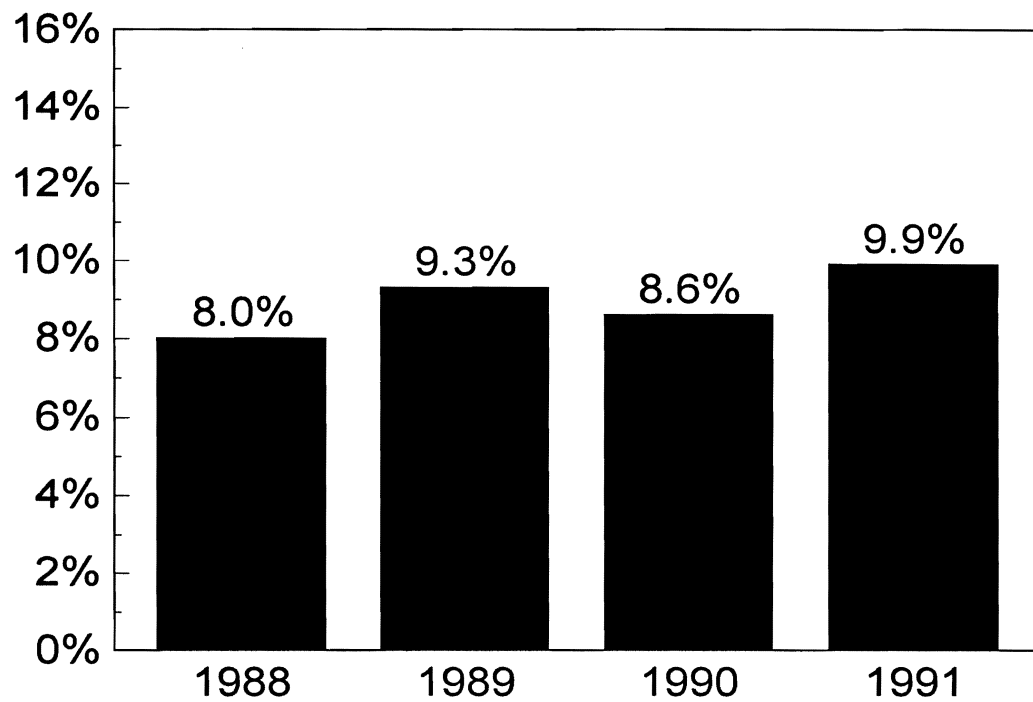
Source: United Network for Organ Sharing

Figure 6.   Death rate for patients waiting for liver transplantation in the
United States.
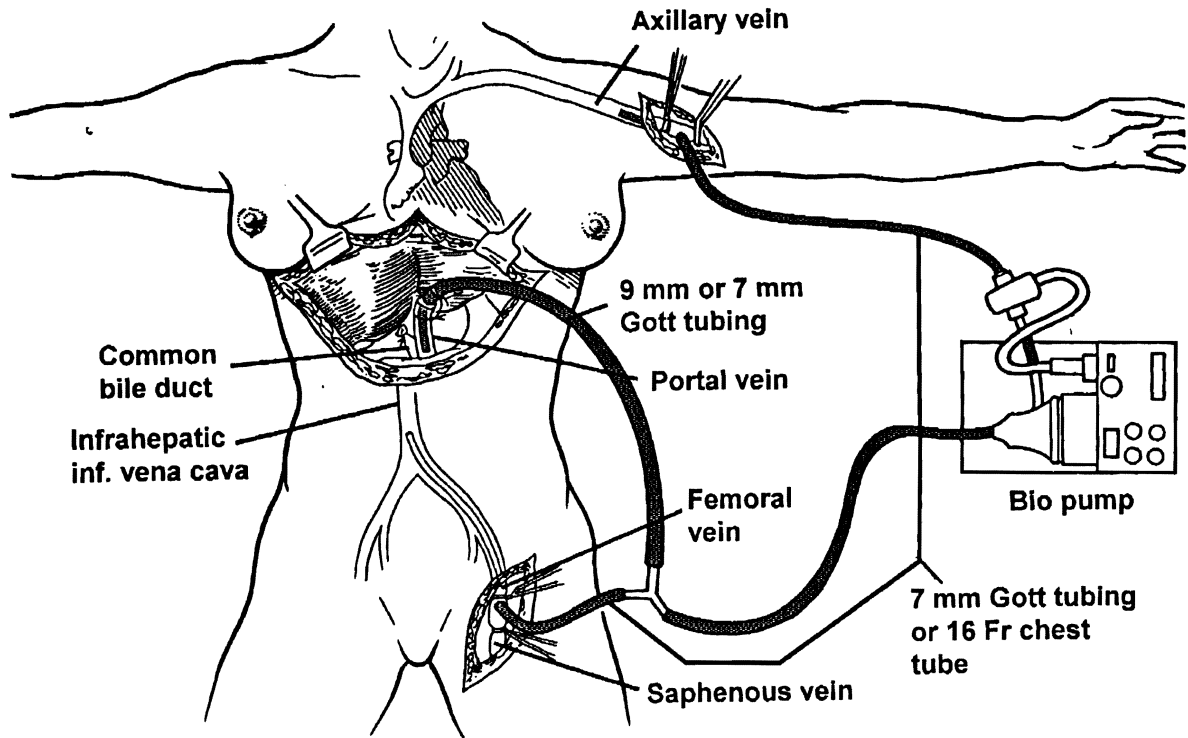
Figure 7. The pump driven veno-venous bypass is used to decompress the systemic and splanchnic venous beds during the anhepatic phase of the operation. Outflow lines to the pump are placed in the iliofemoral system via a cutdown on the saphenous vein and a return cannula is placed in the axillary vein.
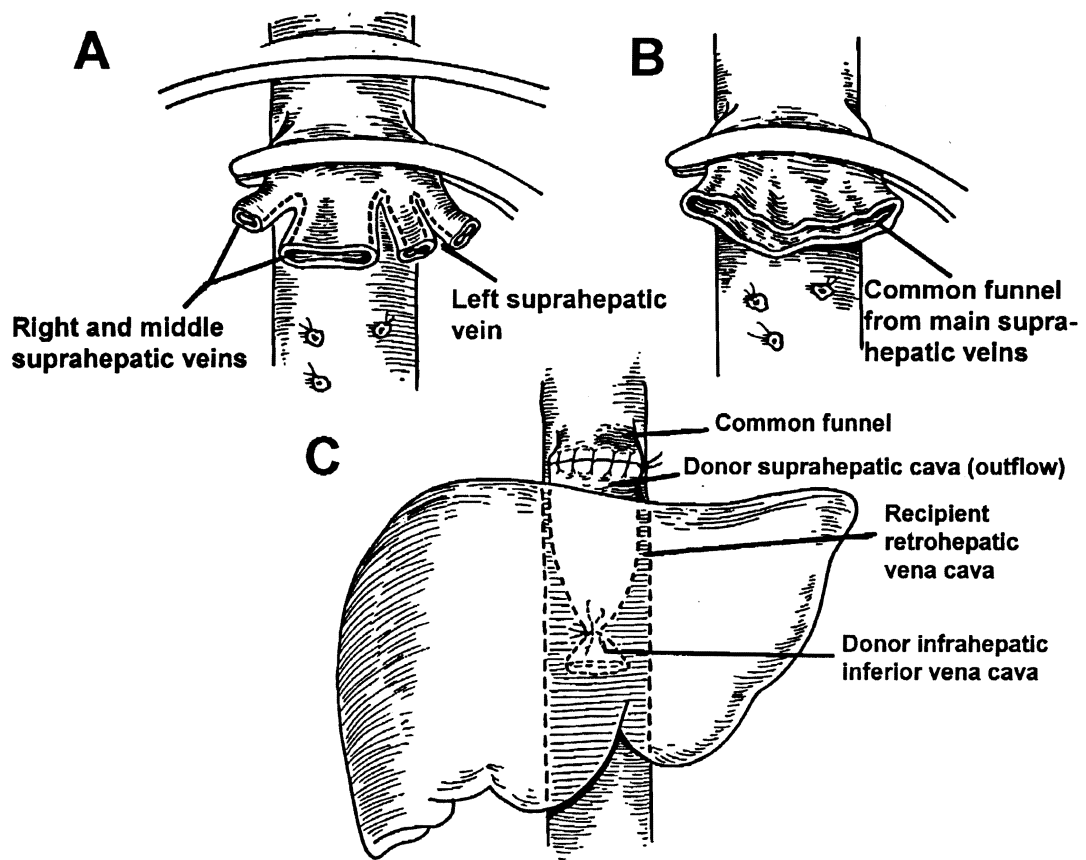
A

Right and middle
suprahepatic veins

Left suprahepatic
vein

B

Common funnel
from main supra-
hepatic veins

C

Common funnel

Donor suprahepatic cava (outflow)

Recipient
retrohepatic
vena cava

Donor infrahepatic
inferior vena cava

Figure 8.   The "piggyback" method of graft implantation. **(A)** The recipient
vena cava is left intact and a clamp is applied across the origin of
the major hepatic veins. **(B)** A cuff is prepared by joining the
origins of the middle and left hepatic veins. The right hepatic vein
(not shown here) is usually tied off. **(C)** The suprahepatic vena
cava of the graft is sewn to the funnel of the hepatic veins and the
infrahepatic cava of the graft is simply tied off. The liver rests on
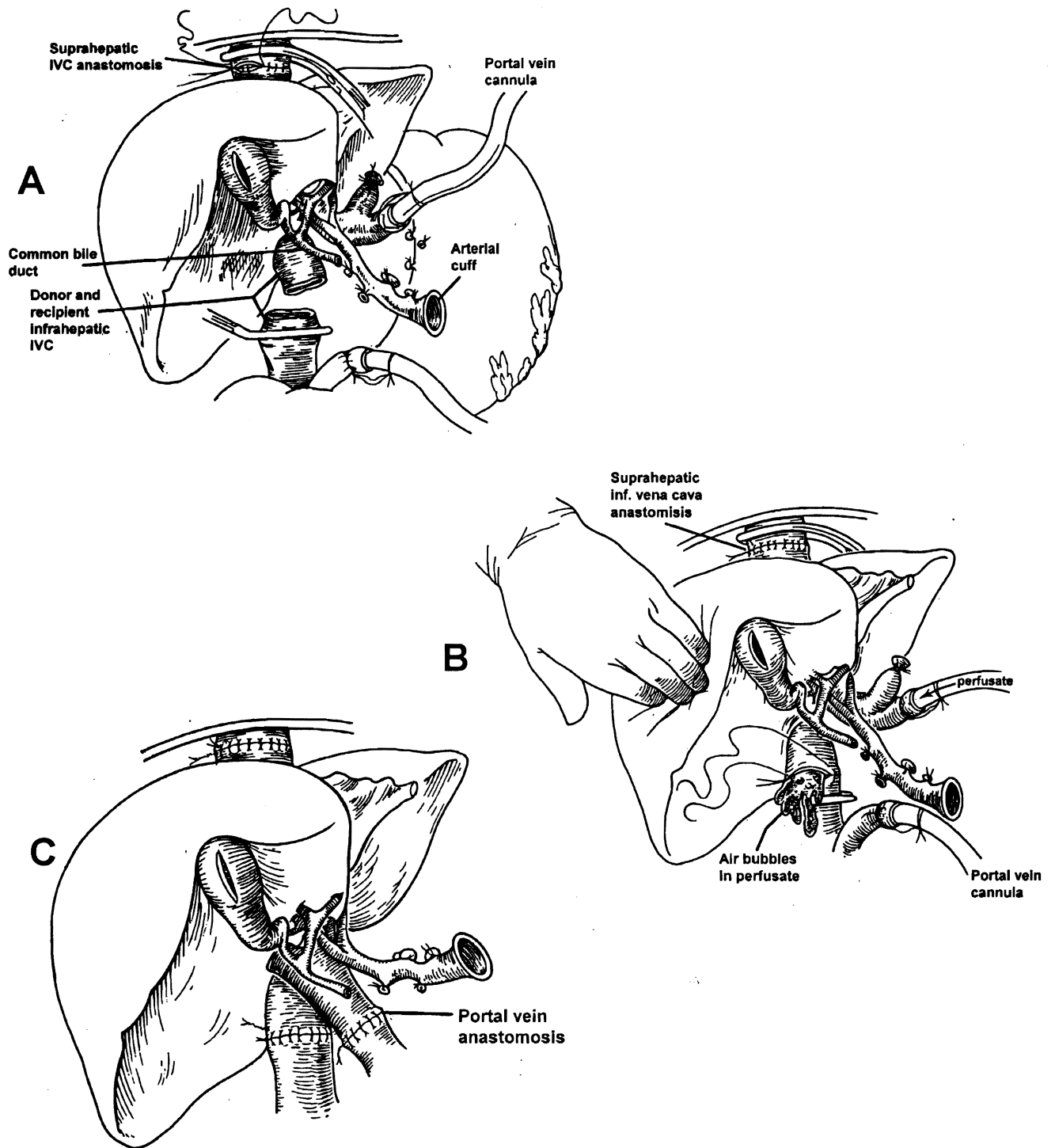top of the recipient vena cava.

Figure 9.   Steps in the implantation of an orthotopic liver graft. **(A)** Completion of the suprahepatic vena cava anastomosis. **(B)** Completion of the infrahepatic vena cava anastomosis. The portal vein is flushed with cold albumin or electrolyte solution to wash out the high potassium containing preservation fluid and to eliminate air in the vena cava. **(C)** The portal vein bypass cannula is removed and the portal vein anastomosis is completed.
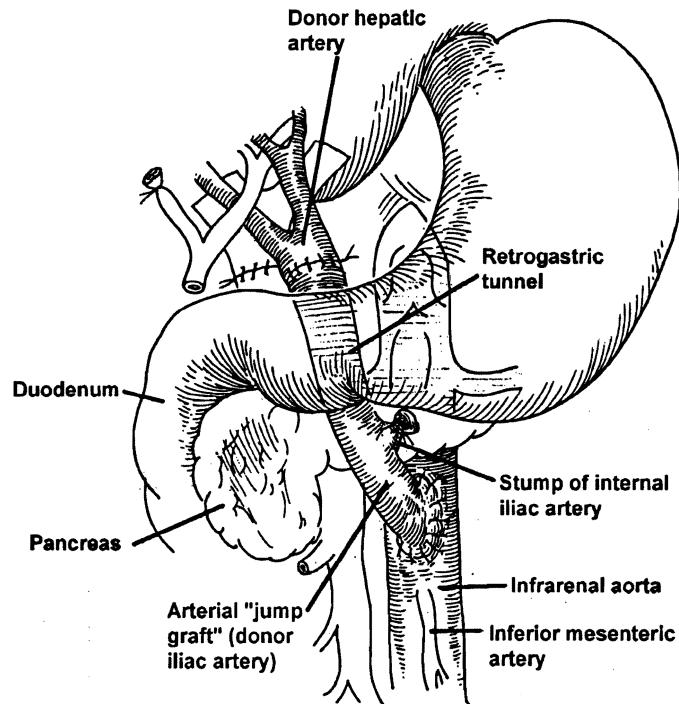
Donor hepatic
artery

Retrogastric
tunnel

Duodenum

Stump of internal
iliac artery

Pancreas

Infrarenal aorta

Arterial "jump
graft" (donor
iliac artery)

Inferior mesenteric
artery

Figure 10. Use of a jump graft of donor iliac artery for extranatomic recon-
struction of the hepatic arterial supply. The graft is passed
through the transverse mesocolon, anterior to the pancreas,
and posterior to the distal stomach to emerge at the hepatic
hilum anterior and medial to the portal vein. Alternative sites
for the origination of an arterial jump graft include the right iliac
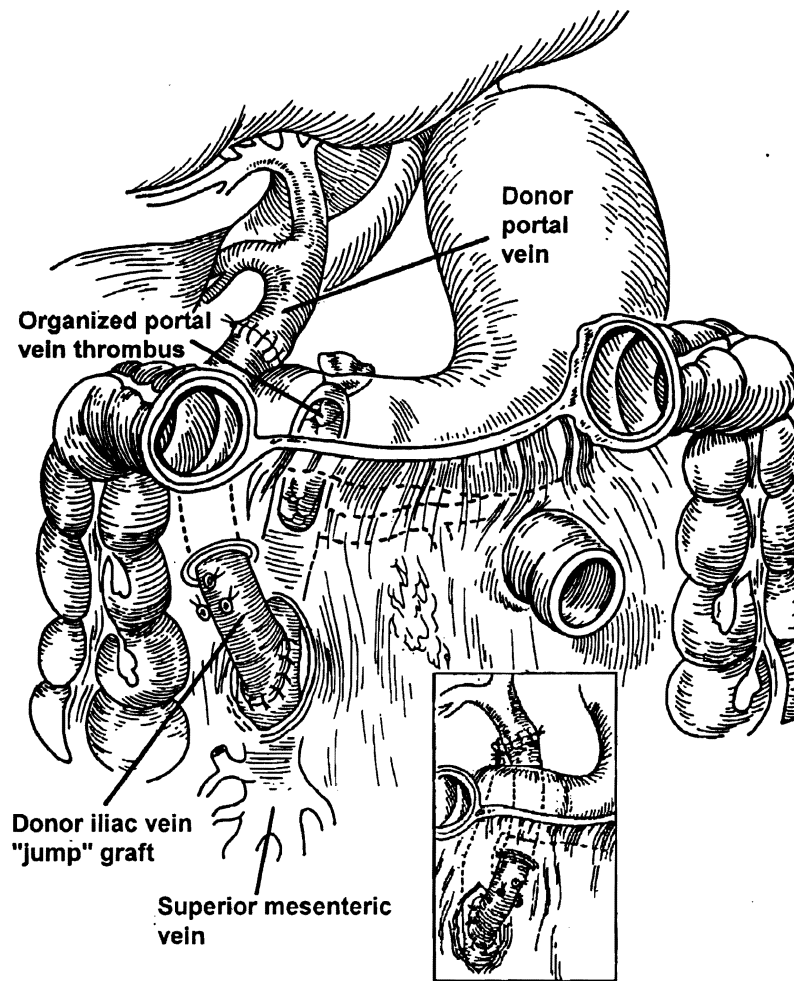artery and the supraceliac aorta (not shown).

Figure 11.   Use of a jump graft of donor iliac vein from the superior mesenteric vein to the donor portal vein. The graft is tunneled through the transverse mesocolon, anterior to the pancreas, and posterior to the stomach to reach the hepatic hilum.
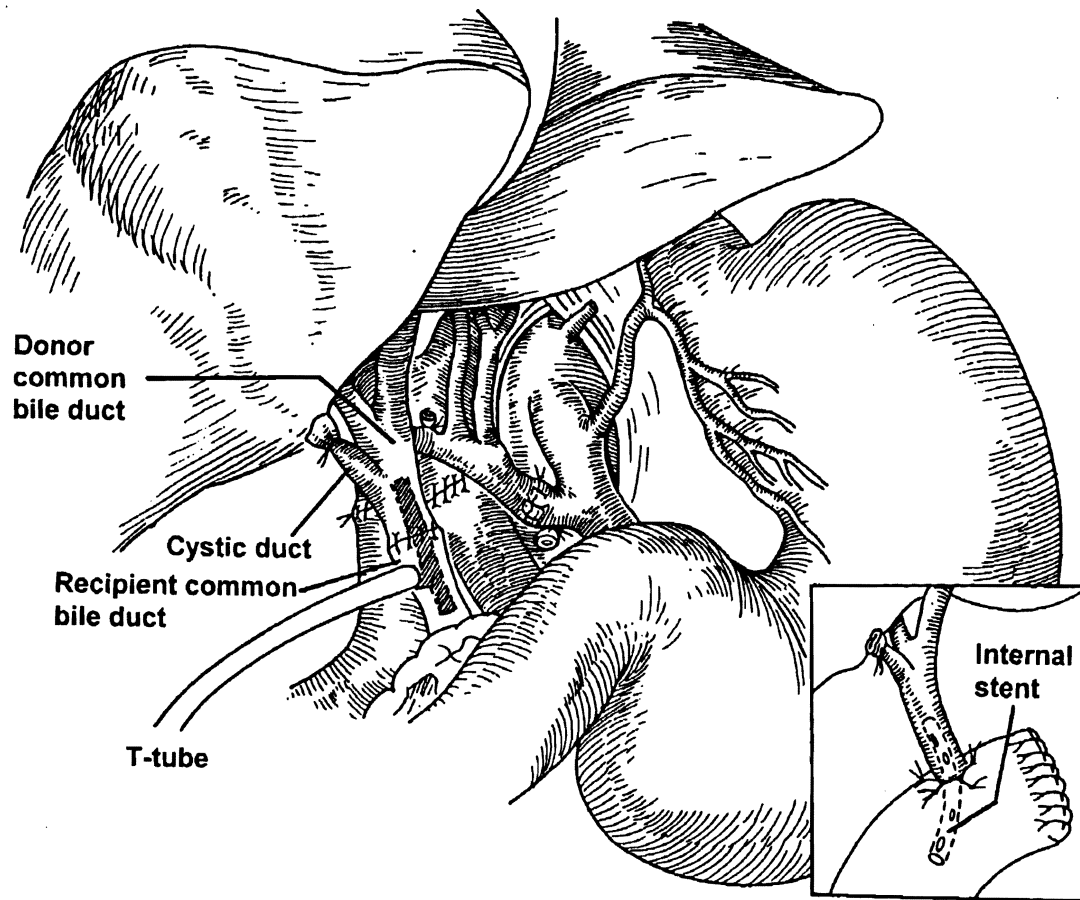
Figure 12. The biliary reconstruction. If the recipient duct is normal and closely matches the donor duct in caliber, an end-to-end reconstruction over a T-tube is performed using interrupted 5-0 or 6-0 polyglycolic acid suture. In cases in which the anatomy is not favorable for a this technique, an eighteen inch Roux-en-Y limb of jejunum is created and an end-to-side choledochojejunostomy over an internal silastic stent is performed using running 5-0 or 6-0 polyglycolic acid suture (inset)

Number of transplants
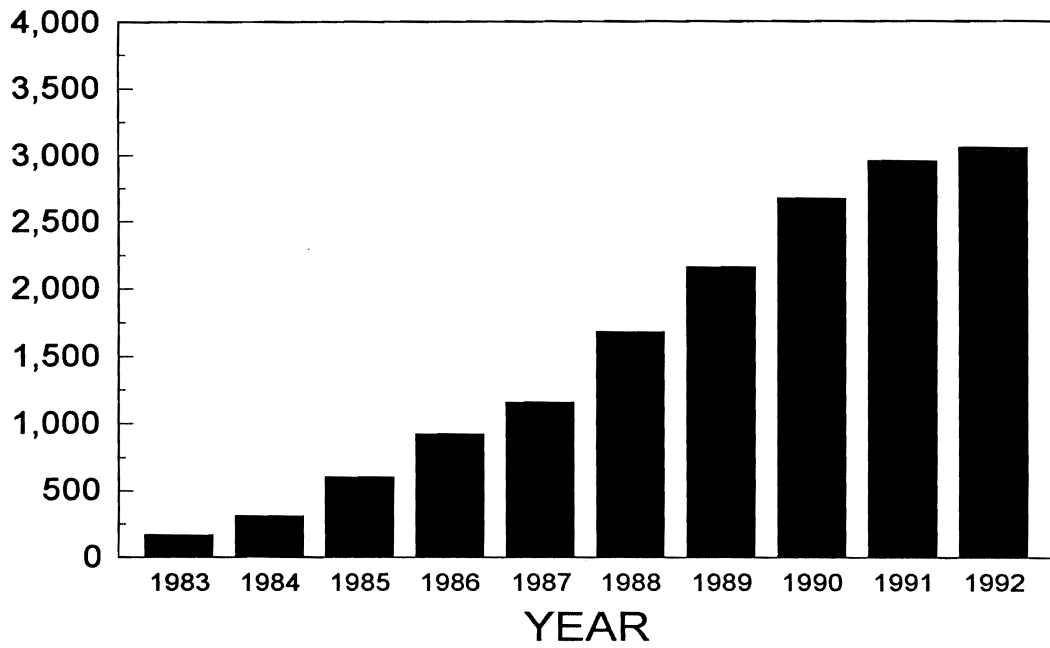
Source: United Network for Organ Sharing

Figure 13.   Liver transplantations per year in the United States, 1983-1992.