Liver Transplantation: Current Status and Novel Approaches to Liver Replacement

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The major challenge currently facing liver transplantation is the performance of a greater number of liver transplants, which has been fueled by the large and growing disparity between the increasing number of qualified patients listed for transplantation and the relatively static number of available cadaver donor organs. In the past 2 years, approximately 4500 liver transplants have been performed annually, with 1-year survival rates in the 85%–90% range, while the waiting list has expanded as of November 2000 to more than 16,000 patients, resulting in an increasing death rate among listed patients. In the short term, there will continue to be a major focus on more effective use of available cadaver donor organs to balance the competing principles of justice (patients with most urgent need for transplant and lower probability of posttransplant survival) and medical utility (patients with less urgent need for transplant and higher odds of postoperative survival). Over the long term, there will be an increasing application of novel approaches to liver replacement including cadaver split liver transplantation and adult living donor liver transplantation and possibly, in the more distant future, xenotransplantation and hepatocyte transplantation. The treatment, and ideally the prevention, of recurrent disease after liver transplantation, particularly chronic hepatitis C—the most common indication for transplantation—is a major priority to optimize the use of liver grafts. Finally, improved immunosuppressive strategies, including movement toward minimal immunosuppression and steroid withdrawal and the development of safer and more effective drugs, is another important factor that has the potential to increase the success of liver transplantation.

Solid organ transplantation is a major achievement of modern medicine, and liver transplantation is established as the definitive treatment for a wide range of acute and chronic liver diseases. Over the past several decades, liver transplantation has evolved from an experimental procedure with limited success to a routine operation that provides excellent survival rates for patients who were previously doomed to death from irreversible acute liver failure or end-stage liver disease.

Development of Liver Transplantation

Early Experimental and Human Liver Transplantation

Selected events in the early history of liver transplantation are summarized in Table 1.[1,2] Although the first experimental attempts at liver transplantation were initiated by Welch in 1955[3] and Cannon in 1956,[4] the first attempts at human liver transplantation were by Starzl and colleagues in 1963.[1,5] Three patients underwent transplantation, with deaths occurring intraoperatively and on postoperative days 7 and 22, respectively. The first 1-year survival after human liver transplantation occurred in 1967 in a young child undergoing transplantation for hepatocellular carcinoma. Approximately one liver transplant per month was performed from 1968 to 1980 at the University of Colorado by Starzl et al., with a 1-year mortality rate >50% and a long-term survival of only 30%.[6] However, 30 (18%) of the first 170 consecutive patients undergoing liver transplantation at the University of Colorado from 1963 through 1979 lived more than 10 years.[1] The usual immunosuppressive regimen in this early experience was prednisone, azathioprine, and polyclonal antilymphocyte globulin.[6]

Development of Immunosuppression

The development of and evolution in the use of immunosuppressive agents was a critically important step in the growth of solid organ transplantation (Table 2). In animal experiments and during the early phase of cadaver kidney transplantation initiated before liver transplantation, the use of a combination of agents, i.e.,

Abbreviations used in this paper: IL, interleukin; OPO, organ procurement organization; UNOS, United Network for Organ Sharing.

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Table 1. Selected Events in the Early History of Liver Transplantation

Year	Event
1955	First experimental liver transplantation using an auxiliary technique (Welch)
1956	First experimental orthotopic liver transplantation (Cannon)
1963	Use of azathioprine and prednisone for immunosuppression
1963	First human liver transplantations (Starzl)
1966	Introduction of antilymphocyte globulin
1967	First 1-year survival after human liver transplantation (Starzl)
1980	Introduction of cyclosporine for immunosuppression
1983	National Institutes of Health Consensus Development Conference on liver transplantation
1987	Use of University of Wisconsin solution for improved organ preservation
1989	Introduction of tacrolimus for immunosuppression

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prednisone and azathioprine, facilitated successful renal transplantation by providing good control of rejection.[1,2,6] In this early experience, it was noted that large doses of parenteral corticosteroids were effective in reversing episodes of acute allograft rejection. These initial favorable experiences with prednisone and azathioprine led to the development of clinical kidney transplantation and set the stage for the development of liver transplantation.

The ultimate success of liver transplantation has been largely attributed to the development of cyclosporine, a calcineurin inhibitor. The effectiveness of cyclosporine in solid organ transplantation was initially demonstrated by Calne et al.[7–9] Cyclosporine was later shown to increase the survival rate after liver transplantation from approximately 30% to more than 70%.[10,11] These reported successes with liver transplantation using cyclosporine-based immunosuppression in the late 1970s and early 1980s led to the conclusion at a National Institutes of Health Consensus Development Conference in 1983 that liver transplantation was no longer experimental and deserved broader application in clinical practice.[12] This meeting initiated the modern era of liver transplantation and resulted in the establishment of liver transplant centers across the United States.

Other advances occurred in the use of immunosuppressive regimens. Initial use of tacrolimus, another calcineurin inhibitor, was associated with a yet further increase in 1-year graft and patient survival rates compared with the use of cyclosporine.[13] Later, direct comparison between the 2 agents in large, multicenter, controlled trials showed that cyclosporine and tacrolimus as the basis of a multiple drug immunosuppressive regimen achieved similar patient and graft survivals, but tacrolimus was associated with fewer episodes of acute cellular rejection and steroid-resistant rejection, less use of muromonab-CD3, and lower cumulative steroid exposure.[14–16]

Another advance in immunosuppression was the development of antilymphocyte antibody therapy, including the monoclonal antibody muromonab-CD3, which has been used as part of induction regimens to reduce the incidence and severity of acute allograft rejection and to treat steroid-resistant acute rejection.[17–19] Antibody therapy is occasionally used without cyclosporine or tacrolimus for induction of immunosuppression in the setting of renal insufficiency. After its licensure, muromonab-CD3 initially replaced the earlier antilymphocyte and antithymocyte globulin preparations that could never be standardized, but the availability of newer, alternative agents and the risk of Epstein–Barr virus infection, cytomegalovirus infection, and posttransplant lymphoproliferative disease associated with the use of muromonab-CD3 have led to less usage of this agent in recent years.

Other drugs, such as mycophenolate mofetil, sirolimus (rapamycin), and the 2 anti-interleukin (IL)-2 receptor antibodies, baxiliximab and daclizumab, which have been shown to be effective in kidney transplantation, are being tested in clinical trials to determine their role in liver transplantation.[20,21]

Additional Developments in Liver Transplantation

The early technical developments in liver transplantation and evolution to more effective and safer

Table 2. History of Immunosuppressive Drug Regimens

Year	Agent
1962	Azathioprine
1963	Azathioprine plus corticosteroids
1966	Polyclonal antibodies; antilymphocyte globulin as an adjunct
1970	Cyclophosphamide substituted for azathioprine
1978	Cyclosporine use in humans
1980	Cyclosporine plus corticosteroids
1981	Development of monoclonal antibodies
1989	Tacrolimus plus corticosteroids
1990s	Development of newer agents, e.g., mycophenolate mofetil, sirolimus (rapamycin), anti–IL-2 receptor antibodies—baxiliximab and daclizumab

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immunosuppressive drug schedules were associated with other important advances in the general care of the liver transplant recipient that resulted in the current 1-year patient survival rates of 85%–90%.[22] Improved timing with earlier performance of liver transplantation also facilitated better outcomes. Training of dedicated liver transplant anesthesiologists to manage hemodynamic and metabolic problems during surgery, the introduction of venovenous bypass, and improved surgical methods to control operative bleeding all led to improved outcomes in the early developmental phases of liver transplantation. Currently, use of blood during surgery is usually limited to fewer than 10 units, and up to 30% of liver transplantations can be performed without blood transfusion.[23] Venovenous bypass is seldom used currently, but in the initial experiences of many transplant surgeons, it was an effective technique to support hemodynamics during the anhepatic period of the operation. In the early experience with liver transplantation, up to half of the patients developed one or more biliary complications.[6] Evolution in techniques has now led to the use of a primary duct-to-duct anastomosis without T-tubes or stents, which has reduced the biliary complication rate to 5%–10%.[24] In addition, the use of radiologic and endoscopic diagnostic and therapeutic procedures facilitate the management of biliary complications with lower rates of morbidity.

Other important advances in modern liver transplantation are better diagnosis and treatment of acute and chronic rejection, use of steroid-free and low-dose immunosuppressive regimens for the long term, and improved prevention and treatment of infections that occur in the immunosuppressed transplant recipient.[25,26] Prophylactic regimens for bacterial, fungal, and viral infections after liver transplantation, including cytomegalovirus and late *Pneumocystis* infections, are now established and have reduced the incidence of these infections and their associated morbidity.

Current Status of Liver Transplantation

Indications and Selection Criteria

The general goals of liver transplantation are to prolong life and improve the quality of life while optimizing the use of available resources. Compilation of the cumulative experience with liver transplantation in adults in the United States demonstrates 1-year patient survival rates of 85%–90% for most liver diseases eventuating in transplantation (Table 3).[22] In addition, a recent meta-analysis of the English language literature confirms that liver transplantation does result in improved functional status of recipients.[27] Finally, the limited number of available cadaver donors relative to liver transplant candidates and the tightening of health care budgets are increasingly important factors influencing the selection and timing of transplantation to optimize resources and achieve the most cost-effective outcome without the need for retransplantation.[28–30]

Table 3. Survival After Adult Liver Transplantation by Diagnosis

Diagnosis	Survival (%)		
	1 yr	4 yr	7 yr
Primary sclerosing cholangitis	91	84	78
Primary biliary cirrhosis	89	84	79
Autoimmune hepatitis	86	81	78
Chronic hepatitis C	86	75	67
Alcoholic liver disease	85	76	63
Cryptogenic cirrhosis	84	76	67
Chronic hepatitis B	83	71	63
Malignancy	72	43	34

NOTE. UNOS Database 1987–1998; n = 24,900 patients.
Data from Seaberg et al.[22]

The selection of appropriate patients for liver transplantation to achieve these goals has become increasingly difficult in recent years. The specific indications and contraindications for liver transplantation, optimal timing of transplantation during the course of advanced chronic liver disease, and most appropriate use of scarce organs continue to evolve and be debated.[31,32] Liver transplantation is indicated for most causes of acute and chronic liver failure. The most common indications for liver transplantation in adults are chronic hepatitis C and alcoholic liver disease, and the most common indications for liver transplantation in pediatric patients are biliary atresia and α_1-antitrypsin deficiency.[22] Other common indications for adult liver transplantation include the chronic cholestatic disorders, primary biliary cirrhosis and primary sclerosing cholangitis, autoimmune hepatitis, chronic hepatitis B, metabolic diseases including hemochromatosis and Wilson disease, acute liver failure, and hepatocellular carcinoma (Table 4).[22]

Tables 5 and 6 list the general criteria that should be considered in the referral and selection of patients with end-stage liver disease and acute liver failure for liver transplantation.[31,33,34] The clinical, biochemical, psychosocial, and financial information available regarding any patient with acute or chronic liver failure is first reviewed to determine if these global selection criteria are met. This list of considerations can serve as an eligibility checklist for physicians considering referral of patients for evaluation of liver transplantation. The large and growing disparity between the availability of cadaver

Table 4. Liver Disease of Adult Transplant Recipients in the United States

Primary liver disease	Number	Percent
Chronic hepatitis C	5155	20.7
Alcoholic liver disease	4258	17.1
Alcoholic liver disease and hepatitis C	1106	4.4
Chronic hepatitis B	1368	5.5
Cryptogenic cirrhosis	2719	10.9
Primary biliary cirrhosis	2317	9.3
Primary sclerosing cholangitis	2178	8.7
Autoimmune hepatitis	1194	4.8
Acute liver failure	1555	6.2
Hepatic malignancy	951	3.8
Metabolic diseases	923	3.7
Other	1050	4.2
Unknown	126	0.5

NOTE. UNOS Database 1987–1998; n = 24,900 patients.
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donor livers and the number of qualified patients waiting for transplantation has led to increased pretransplant deaths and performance of transplantation in sicker patients. In general, patients should be referred early enough to facilitate a timely liver transplant before the onset of multiorgan failure, which significantly decreases survival and markedly increases the costs of transplantation. The prior long list of contraindications to liver transplantation has been trimmed, and the conditions noted in Table 7 are recognized by broad consensus as contraindications.

Timing and Listing Criteria for Liver Transplantation

Patients with end-stage liver disease should not be placed on the transplant waiting list until their predicted 1-year survival based on the natural history of their underlying liver disease is less than 90%, the expected 1-year posttransplant survival. This recommendation was developed at a consensus conference, which was held at the National Institutes of Health and organized by the American Society of Transplantation and the American Association for the Study of Liver Diseases.[35] Uniform minimal listing criteria were developed for general application to patients with miscellaneous chronic liver diseases (Table 8).[35] Large natural history studies of patients with compensated cirrhosis due to miscellaneous causes[36,37] or chronic hepatitis C[38] have shown that survival is relatively good until decompensation of liver disease, when 5-year survival rates fall to approximately 50%. Thus, the Child–Turcotte–Pugh scoring system is now used routinely in the assessment of candidacy for liver transplantation; the time for listing is not simply the presence of cirrhosis, i.e., Child class A (Child–Turcotte–Pugh score of 5 or 6) without decompensation, but rather the development of decompensation, e.g., Child class B or C with a Child–Turcotte–Pugh score of 7 or greater (Table 9).[39,40]

Table 5. Patient Selection for Liver Transplantation

- Accepted indications for liver transplantation
  - Advanced chronic liver disease
  - Acute liver failure
  - Hepatocellular carcinoma
  - Miscellaneous liver diseases
- No alternative form of therapy
- No absolute contraindication to liver transplantation
- Willingness and ability to accept liver transplantation and comply with follow-up care
- Ability to provide for the costs of liver transplantation and posttransplant care

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Table 6. Criteria for Liver Transplantation in Fulminant Hepatic Failure

- Criteria of King's College, London
  - Acetaminophen patients
    - pH < 7.3, or
    - PT > 6.5 (INR) and serum creatinine > 3.4 mg/dL
  - Nonacetaminophen patients
    - Prothrombin time > 6.5 (INR), or
    - Any 3 of the following variables:
      - Age < 10 yr or >40 yr
      - Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reaction
      - Duration of jaundice before encephalopathy > 7 days
      - Prothrombin time > 3.5 (INR)
      - Serum bilirubin > 17.6 mg/dL
- Criteria of Hopital Paul-Brousse, Villejuif
  - Hepatic encephalopathy, and
  - Factor V level < 20% in patient < 30 yr, or
  - Factor V level < 30% in patient ≥ 30 yr

PT, prothrombin time; INR, international normalized ratio.
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Donor Shortage and Policies of the United Network for Organ Sharing

The number of liver transplant operations performed annually in the United States over the past 2 years has been relatively static at approximately 4500.[41]

Table 7. Contraindications to Liver Transplantation

- Compensated cirrhosis without complications (Child–Turcotte–Pugh score, 5–6)
- Extrahepatic malignancy
- Active untreated sepsis
- Advanced cardiopulmonary disease
- Active alcoholism or substance abuse
- Anatomic abnormality precluding liver transplantation

NOTE. In most but not all centers, cholangiocarcinoma and human immunodeficiency virus infection are also considered contraindications to liver transplantation.

Table 8. Non–Disease-Specific Minimal Listing Criteria

Immediate need for liver transplantation
Estimated 1-yr survival < 90%
Child–Turcotte–Pugh score ≥ 7 (Child class B or C)
Portal hypertensive bleeding, or a single episode of spontaneous bacterial peritonitis, irrespective of Child–Turcotte–Pugh score

Data from Lucey et al.[35]

There have been only minor increases in organ retrieval rates in recent years despite many approaches to increase donation. Although the number of donors and liver transplants increased 2.4-fold from 1988 to 1997, the number of patients on the liver transplant list increased 15.6-fold and the number of waiting list deaths increased 5.8-fold over the same period of time.[42] This trend has continued over the past 2 years (Figure 1), and, as of November 2000, there are more than 16,000 patients listed on the United Network for Organ Sharing (UNOS) waiting list in the United States.[41] In 1999, 6125 people in the United States died waiting for an organ transplant; 1753 of them were waiting for a liver.[41]

This growing discrepancy between the available donor organs and the need for transplantation has led to continued reevaluation of selection and listing criteria for liver transplantation as well as allocation and distribution policies for donor organs. Distribution determines over which geographic area livers will be allocated, and allocation determines which patients within a geographic area will receive the available livers.[43] The historical allocation scheme has dictated that the sickest patients who have waited the longest are transplanted first. In the recent past, there have been modifications and redefinition of UNOS status based on disease severity, but this same principle still holds (Table 10). In the current UNOS distribution scheme, patients at transplant programs served by a local organ procurement organization (OPO) have the first priority for livers obtained by that OPO, except for status 1 patients who may receive organs from anywhere in their UNOS region. This local primacy policy allows for a patient with chronic liver disease in one OPO not in immediate danger of dying, e.g., a patient listed as status 3, to receive a transplant ahead of a sicker patient in another nearby OPO, e.g., a patient in the intensive care unit and status 2A. This reality has led to discussions regarding widening the liver distribution area, but computer simulation modeling by UNOS showed that wider sharing, e.g., a single national waiting list, would allow justice (also termed "urgency") to prevail over medical utility. Utility factors focus on maximizing the overall benefits of transplantation to society, i.e., the practice of giving priority to the patient who maximizes the chances of a successful outcome by having the least risk of dying after a transplant. Justice, or urgency, recognizes the needs of the individual transplant patient, i.e. the practice of giving priority to the sickest patient, who has the greatest risk of dying before a transplant. The best organ allocation and distribution system to balance these factors remains elusive. Efforts are currently underway at UNOS to better define gradations of advanced Child C cirrhosis with liver failure and to focus allocation decisions more on disease severity than time listed and waiting.

Solutions to the Organ Shortage

The current approaches to the organ shortage include increased efforts to achieve higher rates of new organ procurement and expanded use of current donors, including implantation of livers from "marginal donors" and older donors. Effective treatment, or prevention, of recurrent disease after liver transplantation, particularly chronic hepatitis C—the most common indication for transplantation—is also important to optimize the use of liver grafts. In addition, novel surgical alternatives to standard liver transplantation are being applied more frequently to increase access to transplanation, including cadaver split liver and adult living donor liver transplantation.[44] Xenotransplantation and hepatocyte transplantation remain potential options in the future but are not expected to play an important role over the next several years.

Organ Donation

There have been escalating national efforts to increase organ donation, and in 1998 there was a 5.6% increase in cadaver donors in the United States, the first substantial increase since 1995.[41] The organ do-

Table 9. Child–Turcotte–Pugh Classification

	1 Point	2 Points	3 Points
Bilirubin (*mg/dL*)	<2	2–3	>3
PBC and PSC patients	<4	4–10	>10
Albumin (*g/dL*)	>3.5	2.8–3.5	<2.8
PT prolonged (*s*)	1–3	4–6	>6
INR	<1.7	1.8–2.3	>2.3
Ascites	None	Slight, or controlled medically	Moderate, or severe
Encephalopathy	None	1–2	3–4

NOTE. Child–Pugh class and score: A, 5–6 points; B, 7–9 points; and C, 10–15 points.
PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PT, prothrombin time; INR, international normalized ratio.
Data from Child and Turcotte[39] and Pugh et al.[40]

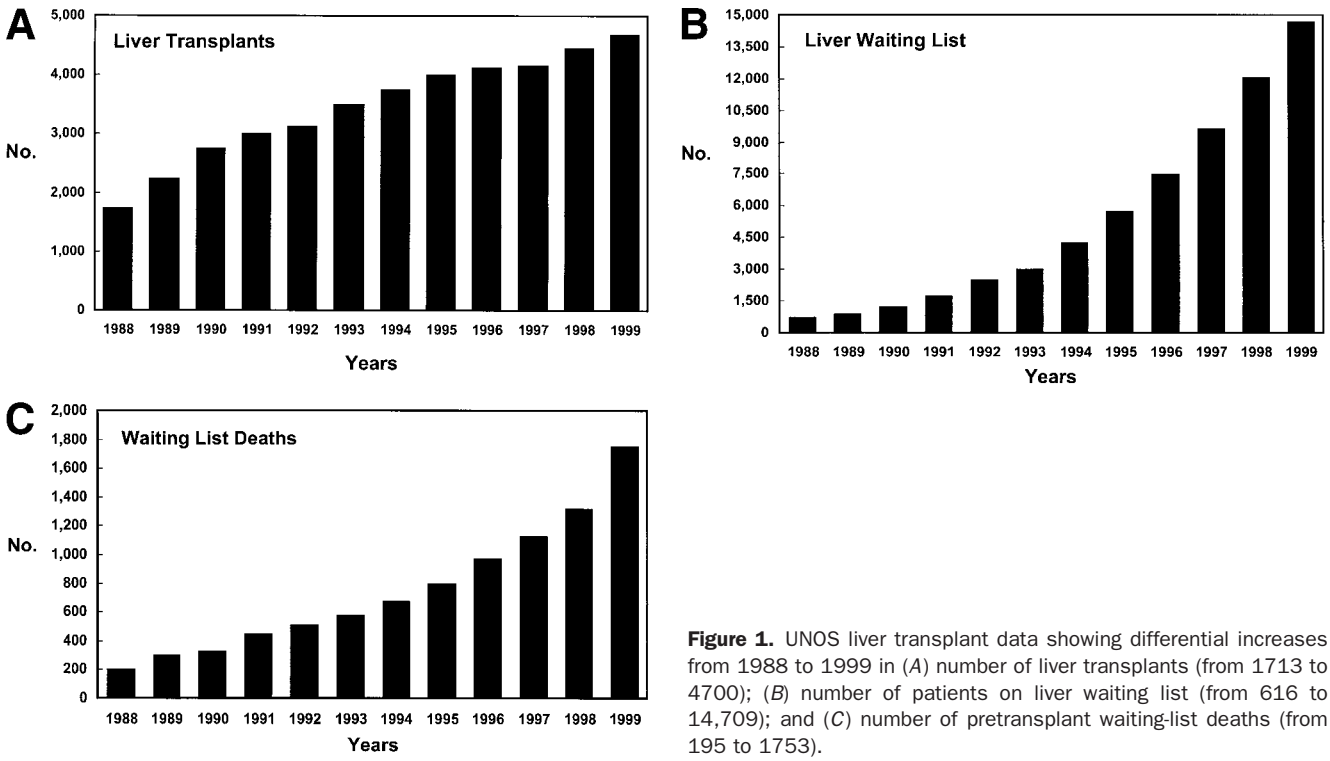


Figure 1. UNOS liver transplant data showing differential increases from 1988 to 1999 in (*A*) number of liver transplants (from 1713 to 4700); (*B*) number of patients on liver waiting list (from 616 to 14,709); and (*C*) number of pretransplant waiting-list deaths (from 195 to 1753).

nation rate in the United States is approximately 20 per million population, which is reasonably good and comparable to that in Spain, the leading country, with donor rates of 25 per million, vs. Italy, the worst country, with a rate of less than 10 per million.

Table 10. UNOS Liver Status for Patients ≥18 Years of Age According to Disease Severity

Status 1	Fulminant liver failure with life expectancy <7 days, including fulminant hepatic failure, primary graft nonfunction, hepatic artery thrombosis, and acute decompensated Wilson disease
Status 2A	Hospitalized in intensive care unit for chronic liver failure with life expectancy <7 days, with a Child–Pugh score of ≥10, and 1 of the following: unresponsive active variceal hemorrhage, hepatorenal syndrome, refractory ascites/hepatic hydrothorax, or stage 3 or 4 hepatic encephalopathy
Status 2B	Requiring continuous medical care, with a Child–Pugh score of ≥10, or a Child–Pugh score ≥7, and 1 of the following: unresponsive active variceal hemorrhage, hepatorenal syndrome, spontaneous bacterial peritonitis, or refractory ascites/hepatic hydrothorax Presence of a hepatocellular carcinoma
Status 3	Requiring continuous medical care, with a Child–Pugh score of ≥7, but not meeting criteria for status 2B
Status 7	Temporarily inactive

Data from UNOS: implemented July 1997; modified January 1998 and August 1998.

Expanded Use of Donors

The expanded use of donors in recent years has included implanting donor livers from older individuals, use of grafts with substantial fatty change, and engrafting donor grafts from patients with transmissible diseases. Donor livers from patients with chronic hepatitis C have been transplanted into hepatitis C recipients, and livers from patients with a positive hepatitis B core antibody have been transplanted into hepatitis B, and occasionally other, recipients. The latter experience is too limited to know the long-term outcome compared with that in patients receiving grafts from uninfected donors; however, positive hepatitis B core antibody–positive grafts frequently transmit hepatitis B virus (HBV), and recipients without HBV infection are thus at risk and should receive prophylaxis, most likely lamivudine rather than hepatitis B immune globulin.[45] On the other hand, the short-term and medium-term outcome of transplanting hepatitis C virus (HCV)-positive grafts into patients with chronic hepatitis C seems to be good.[46]

Although increasing donor age is associated with poor graft function, the organ shortage seems to justify use of these grafts, and the overall percent of donors over age 50 has increased substantially.[47] It seems that the judgment of the harvesting surgeon about the likelihood of function of the donor liver is also an important factor affecting graft survival. In one study, there was a significantly

lower survival of grafts judged to be "fair" or "poor" vs. "good" from donors ≥50 years of age (61% vs. 92%).[48] Even the use of donor livers from individuals older than age 70 or 80 years of age have been used successfully.[49,50]

Recurrence of Disease After Liver Transplantation

Chronic hepatitis C has become the most common cause of end-stage liver disease requiring liver transplantation, accounting for 25%–40% of all transplant procedures in individual centers.[41] In addition, HCV infection may be present in patients with alcoholic liver disease as well as those classified as having cryptogenic cirrhosis undergoing liver transplantation. A compilation of liver transplants in the United States from 1994 to 1998 showed that 23% of transplantations were performed for chronic hepatitis C and 7% for both alcoholic cirrhosis and hepatitis C.[22] Most patients have had HCV infection for several decades before the onset of liver failure.

After liver transplantation, HCV reinfection occurs in nearly all patients, with the majority developing recurrent hepatitis of varying severity and rates of progression to fibrosis and cirrhosis.[51,52] Fortunately, the infection seems to be benign in 80%–85% of patients on short-term and medium-term follow-up, and survival rates are comparable with those of patients transplanted for nonviral chronic liver diseases. However, a small subset of hepatitis C transplant recipients develop fibrosing cholestatic hepatitis, often associated with very high viral loads or progression of HCV quasispecies, and progress rapidly to liver failure.[53–55] It has been shown that patients with recurrent hepatitis C have a poorer quality of life, more frequent depression, and higher psychological distress than other patients without recurrent HCV infection.[56] Whether or not progression to cirrhosis will occur in the majority of patients with longer follow-up remains uncertain but is certainly a possibility.

Numerous host and viral factors have been implicated in the development of severe recurrent hepatitis C, suggesting that the process is multifactorial. In general, HCV causes liver damage via direct cytotoxicity and indirectly by eliciting host immune responses against infected hepatocytes. Among the potential risk factors predisposing to more severe HCV recurrence (Table 11),[57] the most important seem to be high HCV RNA levels before transplantation and early after transplantation, genotype 1b in some but not all studies, certain HLA genes or sharing of class I and class II HLA antigens between donor and recipient, and the occurrence of rejection with the need for increased levels of immunosuppression or use of certain agents such as muromonab-CD3. Distinguishing recurrent hepatitis C from acute allograft rejection may be difficult. Symptoms are similar, as is the pattern of liver chemistry abnormalities. Rejection typically occurs in the first 3 months after transplantation, whereas recurrent hepatitis C is more likely thereafter. The histologic features of recurrent HCV infection and allograft rejection also overlap and include portal mononuclear cell infiltrates, swollen hepatocytes with necrosis, and bile duct damage, making distinction between these 2 entities difficult at times.[51] However, endotheliitis is unique to rejection, and a predominant lobular hepatitis suggests hepatitis C.

Table 11. Factors Associated With More Severe Recurrence of HCV After Liver Transplantation

Viral
Genotype 1b
High (>1 × 10^6 Eq/mL) pretransplant HCV RNA levels
High early posttransplant HCV RNA levels
Cytomegalovirus infection
Absence of pretransplant HBV coinfection
Allograft recipient
HLA matching
Age >49 yr
Nonwhites
Early posttransplant histologic injury
Immunosuppression
High level of immunosuppression
Episodes of rejection
OKT3 use
Methylprednisone boluses and high cumulative doses

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There is no ideal prophylaxis against recurrent hepatitis C. More rapid reduction in the level of immunosuppression early after transplantation and earlier tapering and discontinuation of prednisone are commonly used. However, avoidance of rejection with the need for increased doses of immunosuppressive drugs or use of muromonab-CD3 is important. Studies are in progress to determine if prophylactic therapy with interferon and ribavirin early after liver transplantation will alter the posttransplant infection rate or severity of recurrent hepatitis C. The treatment of recurrent HCV infection with antiviral therapy after liver transplantation and the timing of the initiation of such therapy remain uncertain. It seems that either interferon or ribavirin alone are not beneficial,[58] but the combination of both agents shows promise.[59] In one study, 18 of 21 patients tolerated therapy, and there was a virologic sustained response in 24% of patients with improved aminotransferase levels and liver biopsy histologic scores.[59] Whether or not maintenance therapy can be discontinued in patients who have a sustained virologic response remains unknown.

Retransplantation for recurrent HCV infection, particularly with the rapidly growing waiting list for primary transplants, is controversial, because the results have been variable and often quite poor although early retransplantation may achieve better results.[60]

Other diseases can recur after liver transplantation, including HBV infection, alcoholic liver disease, hepatocellular malignancy, and the immunologic liver diseases primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis.[61,62] The strategies to diagnose and/or prevent these entities are better established than the approach to recurrent hepatitis C. In the early 1990s, the prophylactic use of high-dose, intravenous hepatitis B immune globulin was shown to be effective in the prevention of recurrent hepatitis B after liver transplantation.[63] The best current prophylactic regimen seems to be various combinations of both hepatitis B immune globulin, possibly in lower doses via the intramuscular route, to bind hepatitis B surface antigen and lamivudine to suppress viral replication.[64,65]

Although an average of 15% of patients undergoing liver transplantation for alcoholic cirrhosis consume some amount of alcohol after transplantation, return to alcohol abuse or dependency and the development of recurrent alcoholic liver disease in the allograft is uncommon.[66,67]

The risk of recurrent hepatocellular carcinoma after liver transplantation is substantial but can be kept to a minimum by strict adherence to pretransplant selection criteria.[68] The generally accepted criteria for transplanting patients with hepatocellular carcinoma are the Milan criteria of no lesion >5 cm in diameter or no more than 3 lesions of >3 cm in diameter.[69] Cholangiocarcinoma has a very high risk of recurrence and is usually considered a contraindication to liver transplantation, except in special circumstances evaluating new multimodal therapies.[70,71]

Recurrent primary biliary cirrhosis is usually a benign histologic finding and not clinically important,[72] but recurrent primary sclerosing cholangitis can lead to biliary strictures and occasionally allograft failure.[72,73] It has also been recognized that autoimmune hepatitis recurs commonly after liver transplantation and that these patients should be maintained on somewhat higher levels of immunosuppression long-term, including maintenance prednisone to prevent recurrence.[72,74]

Evolving Immunosuppression Strategies

Immunosuppression strategies in current use are typically classified into induction regimens, maintenance immunosuppression, and more aggressive therapy to treat acute allograft rejection.[20,21] The initial induction immunosuppressive regimen in the early posttransplant period, when the risk of allograft rejection is the highest, includes high-dose intravenous corticosteroid therapy with rapid tapering to oral doses of 20 mg/day by the end of the first week. The calcineurin inhibitors, cyclosporine and tacrolimus, are the basis for the majority of maintenance immunosuppression protocols and are initiated at the time of transplantation. Both agents have substantial toxicity, including hypertension, nephrotoxicity, neurotoxicity, and gastrointestinal symptoms. Hyperglycemia is more common with tacrolimus, and gingival hyperplasia and hypertrichosis with cyclosporine. Azathioprine has often been used as part of a triple-drug induction regimen with prednisone and cyclosporine, but the greater potency of tacrolimus and lower incidence of acute rejection has led in some centers to the use of a two-drug regimen of tacrolimus and prednisone. In the early weeks to months after transplantation, trough tacrolimus levels are maintained between 8 and 12 ng/mL, whereas trough levels of 5–7 ng/mL are satisfactory for long-term maintenance immunosuppression. Mycophenolate mofetil is a new immunosuppressive agent that exerts its effect by reversible inhibition of inosine monophosphate dehydrogenase and may have an advantage over azathioprine based on more specific enzyme inhibition. The usual dosage of mycophenolate mofetil is 2 g/day in divided doses, and the most common side effects are gastrointestinal symptoms and leukopenia. Mycophenolate mofetil has been used in place of azathioprine as part of multidrug induction regimens to facilitate use of lower doses of cyclosporine or tacrolimus, to allow reduced prednisone usage, and to treat resistant-acute and chronic rejection.

In patients with pretransplant renal insufficiency, the potent murine monoclonal antibody muromonab-CD3 was used in the past as a substitute for the nephrotoxic calcineurin inhibitors during induction of immunosuppression, but the high incidence of posttransplant cytomegalovirus and Epstein–Barr virus infection as well as posttransplant lymphoproliferative disease has led more recently to limited use of this agent.

An evolving alternative agent that has recently become available and may play a role in immunosuppressive regimens in patients with poor renal function is sirolimus (also known as rapamycin).[21,22] Sirolimus is structurally similar to tacrolimus, but acts by a different mechanism and is not nephrotoxic. Its most frequent side effects include hyperlipidemia, thrombocytopenia, and leukopenia. Early experience is encouraging with the use of sirolimus in combination with either cyclosporine or

tacrolimus after liver transplantation.[75,76] With both regimens, it is possible to use lower doses of cylosporine and tacrolimus and possibly spare the use of corticosteroids.

The two anti–IL-2 receptor antibodies, baxiliximab and daclizumab, which are effective in kidney transplantation, are being tested in clinical trials to determine their role in liver transplantation.[20,21] Both agents have no major side effects and may play a future role in induction immunosuppresion in patients at risk of calcineurin-induced side effects.

The transition from induction to maintenance immunosuppression begins early after transplantation and is gradual over several months. The ultimate level of maintenance immunosuppression is adjusted according to the underlying liver disease, e.g., lower in patients receiving transplants for chronic hepatitis B or C and higher in patients with pretransplant diagnoses of autoimmune hepatitis and possibly primary biliary cirrhosis, whether or not the patient experienced acute rejection, and the philosophy and experience of transplant teams with different regimens. The common side effects of drugs used for maintenance immunosuppression, as well as treatment of episodes of acute rejection, have had a negative impact on liver transplant recipients. In particular, the side effects of long-term prednisone, including diabetes, hypertension, hypercholesterolemia, osteopenia, and growth retardation in children, have led to efforts to withdraw steroids.[77] The availability of potent primary immunosuppressive agents, such as tacrolimus, or use of combinations of agents including mycophenolate or potentially sirolimus, has made it possible to discontinue prednisone often without breakthrough rejection in the majority of patients. Only patients who are beyond 4–6 months posttransplantation, have undergone transplantation for conditions other than autoimmune hepatitis and possibly primary biliary cirrhosis, have normal liver function, and have not experienced recent rejection are candidates for slow withdrawal of prednisone with close monitoring.[77]

The classic treatment of acute allograft rejection is intravenous corticosteroids, usually methylprednisolone at a dose of 1000 mg, given for 1 or 2 injections and sometimes followed by a 6-day taper of oral prednisone from 200 to 20 mg/day. If rejection does not respond or another episode occurs over a short interval, the patient is designated as having steroid-resistant rejection. Treatment strategies for this more serious problem vary but may include one or more of the following options: increased corticosteroids, addition of mycophenolate mofetil, increased dosage of tacrolimus, switch from cyclosporine to tacrolimus, course of muromonab-CD3, and retransplantation.

Newer and Novel Approaches to Liver Replacement

Split Liver Transplantation

Split liver transplantation, after initial unsatisfactory results, has undergone a resurgence over the past 3–4 years.[78] This procedure essentially achieves liver transplantation in 2 recipients from a single cadaver liver, usually a right lobe implanted into an adult recipient and left lobe or left lateral segment transplanted into a child. The segmental anatomy of the liver, which is the basis of dissection for both split liver transplantation and living donor liver transplantation, is shown in Figure 2. Split liver transplantation can be used between 2 institutions as well as at a single transplant center. Split liver transplantation was a logical extension of reduced-size liver transplantation in children, in which the left lateral segment (segments 2 and 3) or left lobe (segments 2, 3, and 4) was taken from an adult cadaver organ for implantation into a child, and the remaining right lobe was

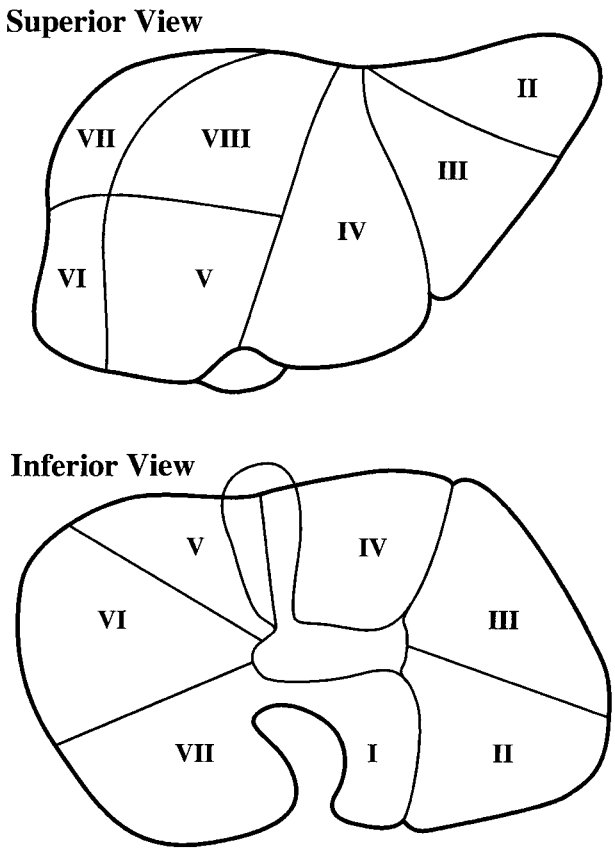


Figure 2. Segmental anatomy of the liver in the superior and inferior views. Segment VIII is visible only on the superior view, and segment I (caudate lobe) is visible only on the inferior view.

discarded. Although complications were more common than with whole organ transplantation, the initial experience with reduced-size liver transplantation overall was reasonably good.[79–81] This technique increased the number of donor organs for pediatric patients but did not increase the total number of organs available overall for liver transplantation and placed adults waiting for a cadaver graft at a disadvantage.

In split liver transplantation, the whole cadaver adult liver is divided into 2 functioning grafts, i.e., segments 2 and 3 (left lateral segment) for a child, and segments 4–8 (right trisegment) for an adult. Split liver transplantation not only increases the total number of donor organs, but also avoids the drawbacks of reduced-size liver transplantation with disposal of the right trisegment and of living donor liver transplantation with operative risk to the donor. Two techniques have been used for split liver transplantation, i.e., ex vivo, splitting the liver on the bench after removal from the cadaver, and in vivo (in situ), division of the liver in the cadaver before procurement. The first split liver transplantation was reported by Pichlmayr et al. in 1988,[82] and the first expanded series of 30 patients was reported by Broelsch et al.[83] In this early experience using the ex vivo technique, results were poor with only 67% of adults and 20% of children surviving, and there was a high rate of complications, particularly biliary, and reoperations. In a report from the European Split Liver Registry by DeVille et al.[84] of 50 donors yielding 100 grafts, the adult graft and patient survival rates were 72% and 80%, respectively, in elective UNOS status 2B and 3 patients and 56% and 68%, respectively, in urgent UNOS status 1 or 2A patients. In a representative more recent series reported by Mela et al.[85] at Kings College Hospital, graft and patient survival rates were improved, i.e., 88% and 90%, respectively. Although the data remain limited, recent reports suggest that in vivo split liver transplantation may be superior to the ex vivo technique in terms of graft and patient survival rates as well as technical complications. In a series of 102 pediatric and adult patients who received 110 in vivo split grafts at the University of California at Los Angeles, the overall graft and patient survival rates were similar to rates achieved with standard whole organ transplantation.[86] Split liver transplantation is an important option for expanding the cadaveric liver donor pool and has the potential to provide grafts to the majority of listed pediatric patients and to substantially decrease the adult waiting times as well.

Living Donor Liver Transplantation

Living donor liver transplantation was first reported in children in 1988 by Raia et al.[87] and in adults in 1994 by Hashikura et al.[88] Adult-to-pediatric living donor living transplantation was associated with a 1-year survival of 82% in the initial experience with 149 cases from Kyoto University,[89] and these excellent results have been duplicated in many other centers that achieve survival rates no different from those observed using cadaver donors. The theoretical advantage of increased histocompatibility with the use of a liver from a parent has not resulted in lower rates of rejection. In children, living donor liver transplantation using segments 2 and 3 from an adult donor has become the standard of care in many centers. The risk to the adult donor from a left lateral segmentectomy is quite low.

Living donor liver transplantation in adults using a right hepatic lobe has expanded in recent years, with good results reported from centers in the United States[90,91] and Japan.[92] Right lobes (segment 5–8) have been most commonly used, although extended right lobes or trisegments (segments 4–8) have been used for larger recipients to ensure adequate hepatic volume and left lobes (segments 2–4) have been used for smaller recipients. This operation is usually performed electively, but the Japanese have also applied living donor liver transplantation to high-urgency patients with good outcomes.[93] Adult living donor liver transplantation is an obvious technique to shorten the waiting time and better select the ideal timing for transplantation before progressive deterioration that might reduce the chance of a favorable outcome. A graft obtained from a living donor who is carefully evaluated and in excellent health should be more ideal than a graft from a brain-dead cadaver that may have suffered ischemic and other metabolic insults during a terminal event. In addition, living donor liver transplantation permits the immediate transplantation of the donated portion of liver and thus limits the ischemic injury associated with longer extracorporeal preservation times typically experienced in cadaver liver transplantation. However, only a relatively small percent of potential donors are satisfactory candidates after undergoing complete evaluation, and thus adult living donor liver transplantation is only a partial solution to the long waiting times and donor shortage for adult liver transplantation. In one institution study, 100 potential living donor recipients were considered, with 51 rejected based on recipient characteristics; of the remaining 49 patients, 26 living donors were evaluated yielding 15 donor-recipient pairs who underwent living donor liver transplantation.[94]

The evaluation of potential living donors is stepwise and typically takes several weeks to months. Patients first undergo a complete history and physical examination with screening blood studies including blood type and viral serology followed by a careful social and psychiatric assessment. Many patients are excluded at this step because of an incompatible blood type or the detection of previously unrecognized medical or psychosocial problems. Radiologic studies including computed tomography or magnetic resonance imaging are performed, followed by visceral angiography if imaging abnormalities are identified. A liver biopsy may be performed to exclude steatosis, with up to 10%–30% used as the cutoff for exclusion. The potential recipient is typically listed as UNOS status 3 or 2B, but not 2A, i.e., undergoing rapid deterioration. Transplantation of a right lobe graft from a living donor is a technically complex procedure, and every effort must be directed at maintaining the health of the altruistic donor. The morbidity and mortality to the donor is probably 10% and 0.5%, thus making the donor operation quite formidable and necessitating careful informed consent. Any large operation such as resection of the right lobe of the liver has the usual risks of pulmonary embolus and pneumonia as well as specific risks of this operation such as bleeding, bile leak, and need for reoperation.

Today, because of long waiting times, many patients become untransplantable as a result of multiorgan failure or infectious complications. Living donor liver transplantation provides an opportunity to transplant patients before the onset of sepsis, renal failure, or other complications that preclude transplantation. In addition, patients with small hepatocellular carcinomas who are likely to be curable by liver transplantation if performed in a timely fashion and patients with primary sclerosing cholangitis at increased risk of cholangiocarcinoma are excellent candidates for a timely living donor liver transplantation.

Xenotransplantation

Humans are obviously the ideal source of organs for transplantation, but the increased need for liver transplantation disproportionate to the availability of cadaver or living donors has led to increased interest in the use of animals as a source of organs. If xenotransplantation can be developed to be safe and affordable, it has the potential to increase access to liver transplantation. Xenotransplantation is the engraftment of organs obtained from one species into another species. Most investigators are now focusing on the pig as a potential donor based on appropriate size, unlimited supply, ability to be genetically engineered, and more easily controlled risk of infection by an agent carried by the graft.[95,96] The advantages of genetic engineering of donor animals is that these organs might be resistant to tissue injury and rejection by modulation of endothelial cell activation. The immunologic hurdles to xenotransplantation are hyperacute rejection and acute vascular rejection as well as cellular rejection. Recent approaches to prevent the activation of the recipient's complement system on the endothelial lining of blood vessels in the newly transplanted organ can effectively prevent hyperacute rejection. Another important hurdle in xenotransplantation is zoonosis, i.e., the potential transmission of infectious agents from the graft to the recipient. On the other hand, a xenograft might be used to prevent reinfection that would inevitably occur if a human organ were used. This philosophy led to the initial unsuccessful attempts to transplant the liver of baboons, known to be resistant to HBV infection, into a recipient with end-stage liver disease secondary to chronic hepatitis B.[97] It has been suggested that the movement to xenotransplantation will occur in a step-by-step process, beginning with limited clinical trials, using xenotransplantation initially as a bridge to human cadaver transplantation, then implanting porcine xenografts in patients who cannot receive a human graft, and finally using xenotransplantation as an alternative to allotransplantation.[95,96] Before this sequence can unfold, a number of critical ethical and regulatory issues will need to be studied and addressed.[98,99]

Hepatocyte Transplantation

The major goals of hepatocyte transplantation are to treat inherited metabolic disorders, acute liver failure, and complications of chronic liver failure such as hepatic encephalopathy.[100,101] Numerous studies in animals have demonstrated the feasibility of liver cell transplantation. Hepatocytes can be isolated from a number of species, including humans, and then either cultured or cryopreserved for future use. Viable hepatocytes can be harvested from livers considered unsuitable for liver transplantation, and cells harvested from a single liver can be used for multiple recipients. Transplanting liver cells through transcatheter techniques is relatively simple. Cultured cells can be transplanted directly from allogeneic donors, which requires immunosuppression. Alternatively, hepatocytes can be transplanted back into an individual after harvesting and transduction in culture with a therapeutic gene for either a defective or absent protein, in which case immunosuppression is not required.[100] In metabolic disorders, transplantation of a relatively small hepatocyte mass should theoretically be adequate. However, attempts to correct Crigler–Najjar syndrome with hepato-

cyte transplantation yielded only modest success.[102] Transplantation of hepatocytes in acute liver failure has the potential to replace lost hepatocytes and either serve as a bridge to orthotopic liver transplantation or prolong survival long enough to allow recovery and regeneration of the injured liver. The role of hepatocyte transplantation in chronic liver disease is less certain, but hepatic encephalopathy has shown improvement in preliminary animal and human studies.[103,104] The future potential for clinical hepatocyte transplantation is good based on recent progress.

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