Current Advances in Liver Transplantation

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Advances in the medical and surgical management of patients undergoing liver transplantation have made transplantation the method of choice for dealing with end-stage liver disease. With the availability of anti-viral agents such as interferon and ribavirin, pre and post transplant treatment of hepatitis C, the most common indication for liver transplantation, is now possible. The use of high dose hepatitis B immune globulin (HBIG) and lamivudine has decreased the incidence and severity of recurrence of hepatitis B after liver transplantation. Multimodal therapy including chemoembolization for hepatocellular carcinoma has made liver transplantation a viable option for selected patients with primary liver cancer. The development of more potent immunosuppressive agents has dramatically decreased the incidence of acute rejection, while the search for a solution to the problem of chronic rejection continues. Alcoholic liver disease remains a challenge for transplant physicians and surgeons; however, careful patient selection results in a relatively low rate of recidivism.

Surgical advances in liver transplantation have focused on eliminating associated morbidity and mortality as well as expanding the donor pool. Veno-venous bypass (VVB) and T-tube stenting, which were once considered essential techniques in liver transplantation, are now only rarely, if ever, necessary. Operative time, blood product usage, and time to extubation, as well as intensive care unit stay, have all been significantly reduced by elimination of VVB without associated morbidity. Elimination of T-tube usage has also effectively decreased morbidity. Donor expansion has become critical as the need for liver transplants exceeds donor availability. Use of marginal donors, including older donors, donors with up to 40% fat content, and donors with high pressor requirements, has proven to be a safe and effective means of increasing the donor pool. *In-situ* splitting of donors is the most promising technical advance in liver transplantation. This technique, along with living-related liver transplantation, is very important for providing donors to the pediatric population where donor availability is even more limited.

Part 1. Patient Selection for Liver Transplantation

Liver transplantation has become the treatment of choice for end-stage liver disease. As the indications for, and patient access to, liver transplantation have increased, the limiting factor for performing transplantation at the optimal time for maximal patient survival remains the donor organ shortage. While the 10%-20% death rate for those on the waiting list has remained relatively stable over the last several years, it represents an increasing number of patients as the United Network for Organ Sharing (UNOS) waiting list length for orthotopic liver transplantation (OLT) has doubled over the last 4 years. As an example, in January 1997, there were 7,000 waiting, but 12 months later, the number had increased to 9,500 (1, 2) (see Table 1).

The Mayo Clinic showed improved survival with transplantation earlier rather than later, and lower medical expenditures with earlier OLT (4). However, there has been a trend toward transplantation of patients who are more ill, since the current system of organ allocation favors patients who are sicker, and the length of the waiting list has grown faster than the size of the donor pool. The overall median waiting time from listing to liver transplantation for UNOS and for Ochsner is shown in Figure 1.

Several guidelines have been developed to assist the clinician in determining the appropriate time for referral of a patient for OLT. Some criteria are based on quality of life issues (5), some are disease-specific formulae (6,7), and others are based on severity of disease indicators such as laboratory data and physical examination (See Table 2).

There has been a recent move to institute minimal listing criteria such that similar patients in different geographic areas would have equal access to transplantation (see Tables 3 and 4). A meeting was held in February, 1997, among members of the transplant community to discuss ways to combat current inequities in the variable waiting times in different parts of the country, and to combat "waiting list inflation" where patients are listed early to ensure their priority, as there was no penalty for premature listing of patients at that time (3). Conceptually, the group felt patients should be listed when expected survival

Table 1. Candidates for Liver Transplantation Listed with UNOS at Year's End*

Year	# candidates	# recipients
1993	2,997	-
1994	4,059	-
1995	5,691	3,979
1996	7,467	4,098
1997	9,500	4,078

**Includes adults and children. From Lucey, Brown, et al (3) and Lake and Gourney (2), and the United Network for Organ Sharing (UNOS).*

Table 3. Minimal Listing Criteria (one of the following)

- A Child-Pugh score ≥ 7 (See Table 4)
- A less than 90% chance of surviving one year without liver transplantation
- An episode of spontaneous bacterial peritonitis
- The onset of stage 2 encephalopathy in a patient with acute liver failure
- An episode of portal hypertensive gastrointestinal bleeding

Table 4. Child-Pugh Score (9)

*Points	1	2	3
Encephalopathy	none	1 and 2	3 and 4
Ascites	absent or slight	moderate or controlled	uncontrolled
Bilirubin (mg/dL) (for non-biliary cirrhosis)	1-2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Protime (sec prolonged)	1-4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Biliary cirrhosis (PBC/PSC) Bilirubin (mg/dL)	1-4	4-10	>10

**Grading : A = 1-6, B=7-9, C=10-15*

Table 2. Guidelines for Determining Appropriate Referral Time for Liver Transplantation

QUALITY OF LIFE CRITERIA
(one or more of following symptoms)

• Cholestatic liver disease	intractable pruritus
	metabolic bone disease with fracture
	recurrent episodes of biliary sepsis
	xanthomatous neuropathy
• Chronic liver disease	intractable ascites
	hepatic encephalopathy
	variceal bleeding
	fatigue
• Metabolic liver disease	correction of nonhepatic manifestations

DISEASE SPECIFIC CRITERIA

- Primary biliary cirrhosis (PBC) – the Mayo scoring system for PBC is heavily based upon the patient's bilirubin and prothrombin time, as well as the presence of ascites, or edema (6, 7).
- Primary sclerosing cholangitis (PSC) – the Mayo scoring system for PSC is also based on bilirubin, albumin, ascites, and edema (6, 7).
- Alcoholic Liver Disease – 85% of transplant centers consider a period of abstinence, such as 6 months of sobriety, prior to listing for OLT as appropriate (8). Many also require active participation in a rehabilitation program prior to listing, as well as random urine testing for drug use.
- Hepatocellular carcinoma – if no evidence of extrahepatic or vascular spread.

DISEASE SEVERITY CRITERIA (one of the following)

• Chronic liver disease	hepatorenal syndrome
	recurrent spontaneous bacterial peritonitis
	serum albumin < 2.5 g/dL (25 g/L)
	serum bilirubin > 5 mg/dL
• Cholestatic liver disease	serum bilirubin > 10 mg/dL

for 1 year (the national average waiting time on the list) was ≤ 90%. The intention was to establish minimal listing criteria and to develop regional review boards that would approve cases which fell outside the minimal listing criteria. Patients with hepatocellular cancer may achieve a priority previously reserved for patients with decompensated cirrhosis or liver failure if they meet certain criteria, and are reviewed quarterly by regional review boards. These criteria include stage 1 or 2 hepatocellular carcinoma by TNM classification (one nodule ≤ 5 cm, or 2 or 3 nodules all < 3 cm). Patients with more advanced tumors may be listed at a lower priority on the waiting list (See Table 3).

Relative contraindications to liver transplantation include the presence of extrabiliary infection, active alcohol or illicit drug use, advanced age (defined as above 70), hepatopulmonary syndrome with pO_2< 50 mmHg which is unlikely to reverse after liver transplantation, hepatoma over 5 cm in diameter, more than 3 lesions, or vascular invasion by tumor. Absolute contraindications include extrahepatic malignancy, HIV positivity, or advanced cardiopulmonary disease, including severe pulmonary hypertension.

Controversies in Patient Selection

Hepatitis C infection is associated with recurrent hepatitis C after liver transplantation. However, long-term follow-up studies show patient survival after OLT for chronic hepatitis C compares favorably with that of patients transplanted for other liver diseases. The recurrent hepatitis tends to be milder than the pre-OLT hepatitis and may be favorably modified by immunosuppression. As well, hepatitis C may require 4 decades or more to cause liver failure in the new liver. Furthermore, donor livers from patients with hepatitis C infection are being used successfully at many centers for recipients with hepatitis C. These organs are carefully selected and evaluated with liver biopsy before being accepted for transplantation.

Transplantation in patients with hepatitis B has historically been less successful than that in patients with other causes for liver disease. Fortunately, new antiviral agents, such as lamivudine and hepatitis B immunoglobulin, have been used prophylactically to reduce recurrent hepatitis B to low levels. Survival for patients with hepatitis B who receive prophylactic antiviral therapy is becoming similar to that for liver recipients who are not infected with hepatitis B.

Transplantation in patients with alcoholic liver disease is complicated by the risk that patients will return to alcohol use after liver transplantation. The risk of recidivism after OLT remains somewhere between 10% and 40%, with recidivism defined as any consumption of alcohol. The number with graft loss from alcohol use is unknown but believed to be quite small. The University of Michigan Alcoholism Prognosis Scale (UMAPS) for Organ Transplant Candidates, which scores the risk of recidivism for a patient, is based upon patient and family acceptance of alcoholism, the presence of social support and substitute activities for alcohol use, and social stability such as a steady job and home (8, 10). The value of the UMAPS score in predicting recidivism has not yet been prospectively assessed in transplant recipients. Although 23% of the liver recipients in the UNOS registry for 1994 had alcohol-related liver disease, this figure represents fewer than 10% of Americans dying every year from alcoholic liver disease.

Part 2. Transplantation Techniques

Liver transplantation is still performed in much the same way as the first liver transplant performed by Starzl in 1963 (11). However, newer techniques and aggressive use of marginal donors have made liver transplantation more accessible to the ever-increasing list of patients in need. In addition, elimination of some procedures previously considered standard may help decrease operative time, blood product usage, and morbidity and allow for earlier extubation and shorter intensive care unit (ICU) stay. Even the standard Mercedes-style incision is usually unnecessary. This incision may increase wound complications and pain with no benefit in exposure over a modified chevron-style incision.

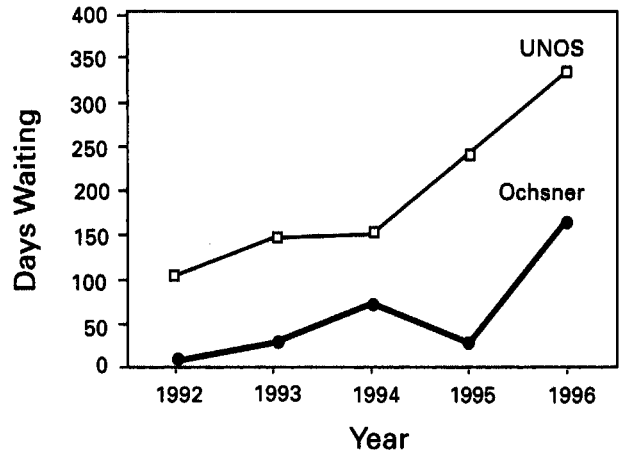

Figure 1. Median waiting times for liver transplant recipients have steadily increased over the last 7 years. Ochsner versus UNOS Registry Report 1996.

Elimination of Veno-venous Bypass

Veno-venous bypass became a standard part of OLT in 1984 as a method of improving hemodynamic stability, reducing blood product requirements and preventing renal dysfunction (12). However, after much debate over the necessity of VVB, many centers have adopted a policy of selective VVB based on hemodynamic stability upon cross-clamping the vena cava (13, 14). Other surgeons have chosen piggyback techniques with incomplete caval occlusion with or without portal caval shunting (15, 16). In the experience of one author (JOE) in an ongoing series of 116 consecutive adult liver transplants performed without VVB and with caval cross-clamping and removal, operative time could be significantly reduced to a median of 4.6 hours with decreased blood product usage and no greater severity in renal dysfunction than that seen in 32 recipients with VVB. In this series, anhepatic hemodynamic parameters, blood product usage, pressor usage, and postoperative renal function on postoperative days 0, 1, 3, and 10 were all recorded prospectively in the No-VVB group and compared with retrospective data in a group of 32 previous patients who underwent transplantation using VVB. The only statistically significant difference identified between the 2 groups was in operative time. One-year patient and graft survivals were 81% and 78%, respectively, in the VVB group and 84 % and 80%, respectively, in the No-VVB group. There was a trend toward decreased blood product usage in the No-VVB group with median red blood cell (RBC) and fresh frozen plasma (FFP) requirements of 9 units and 17 units, respectively, compared with 13 RBC and 20 FFP in the VVB group. Fourteen patients in the No-VVB group required no blood products. Median time to extubation in the No-VVB group was 8 hours with a median ICU stay of 24 hours. The incidence of renal dysfunction was no different between the two groups, while there was a trend toward earlier improvement in renal function in the No-VVB group (Figure 2). Complications related to a bypass catheter, which occurred in 20% of VVB patients, were of course eliminated in the No-VVB group. In conclusion, elimination of VVB in OLT decreases operative time, which in turn allows for earlier extubation and shorter ICU stays. Elimination of VVB may also decrease blood product usage and improve survival with a more rapid improvement in renal function posttransplant.

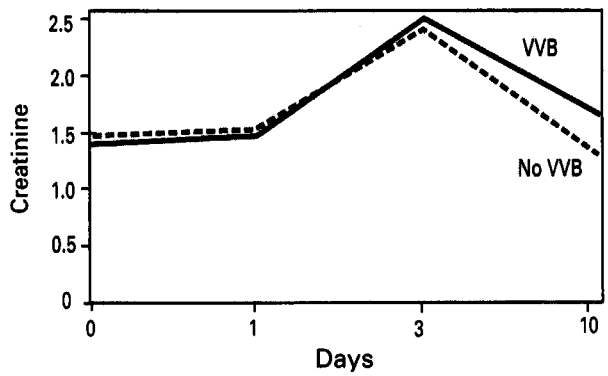

Figure 2. Comparison of serum creatinine in veno-venous bypass (VVB) vs. no veno-venous bypass (No VVB) on days 1, 3, 10. There is a trend toward earlier improvement in renal function in the No VVB group.

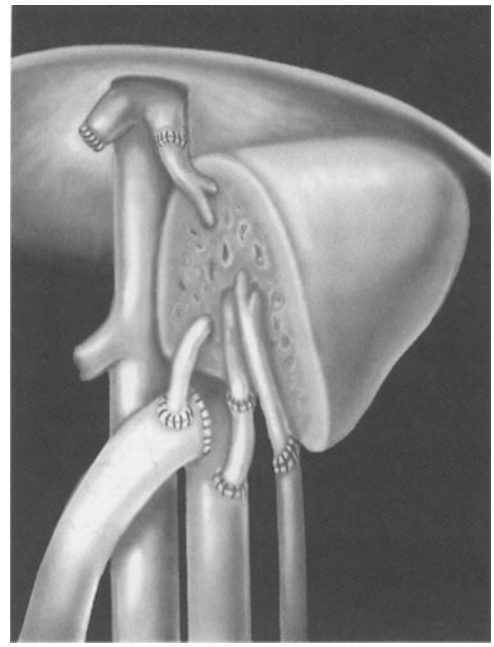

Figure 3. Technique of transplantation of left lateral segment used in living-donor and split liver transplantation.

Elimination of T-tubes

The use of T-tube stenting of the chole-dochocholedochostomy (CDD) in OLT has been an integral part of the operation since its inception until recently. T-tubes have been considered necessary to prevent biliary leaks and strictures, and monitoring of the bile drainage has been considered essential in determining quality of liver function in the postoperative period (17). OLT without T-tube stenting was first reported in 1990 and has subsequently been used selectively by several centers (18, 19). CDD has been performed without T-tube draining in 75 consecutive adult OLT performed by the author in the ongoing series previously mentioned. Operative biliary complications occurred in 8% of these patients compared with 9.4% in 60 patients who underwent OLT with T-tube stenting ($p > .05$). All of the biliary complications in the group without T-tubes were detected by HIDA scan except one leak which was identified by endoscopic retrograde cholangiopancreatography. Peritonitis requiring hospitalization after T-tube removal is reported to occur in 19-25% of patients with T-tubes, with up to one half of these

requiring operative or endoscopic intervention (20). Obviously, this complication is eliminated through avoidance of T-tubes. Evaluation of liver function can be accurately assessed by determination of transaminase levels and prothrombin times and does not require direct visualization of bile. In conclusion, T-tube stenting adds significant risk of subsequent morbidity without decreasing biliary complications or improving assessment of liver function. In addition, routine T-tube cholangiograms added significant expense to the cost of liver transplantation.

Expanded Donor Techniques

Marginal Donors. Currently over 11,000 patients await liver transplantation, while only around 4,000 donor livers are available each year. The rate of increase in the number of donors available each year is remaining relatively stable while the number of patients awaiting transplantation is rapidly increasing. The inequity of donors available to waiting recipients requires innovative and aggressive measures to expand the donor pool, including use of marginal or extended donors. Marginal donors include older donors, donors with some fatty infiltration, and use of hepatis C antibody positive donors for hepatitis C recipients and hepatitis B core antibody positive donors for recipients with hepatitis B. Donors with high pressor requirements or a period of ischemia can be safely used as well, as long as the transaminase levels are not rising and biopsy does not reveal necrosis (21). Livers with fatty infiltration up to 40% can be safely transplanted with a low risk of non-function as long as the donor is otherwise stable (22, 23). Older donors up to 75 years of age can also be safely used; however, the 5-year survival for recipients of these donors may be lower. It is important to use these donors based on patient need and consideration of older donors for older recipients. Donors with positive serology for hepatitis C or B should be biopsied to determine whether or not there is active hepatitis.

***In-Situ* Splitting.** *In-situ* splitting of cadaveric donor livers was first reported in 1996 as a method to expand the donor pool without increasing cold ischemic times, which is a problem with back-table splitting. *In-situ* splitting uses the exact same method as procurement of the left lateral segment of a living donor (24, 25) (Figure 3). Initial results of *in-situ* splitting have shown survival rates similar to those of recipients of whole liver allografts (24). Split-liver transplantation and reduced-size transplantation are essential methods to increase organ availability to the pediatric population where size of the donor is an important limitation. Split-liver transplantation should be instituted whenever possible, however, because two recipients can benefit, in that the left lateral segment can be transplanted into a child while the right lobe can be used in an adult. Presently, the right lobe is allocated by UNOS as deemed "medically appropriate" allowing for patients to receive transplants who may not be able to survive the usual waiting time, such as patients with hepatocellular carcinoma. In addition, *in-situ* splitting offers every advantage of living donor liver transplantation without the concern for causing harm to a living donor.

Living Donor Liver Transplantation. The first successful living-related liver transplant using the left lateral segment of a mother's liver into her child was first reported in 1990 in Australia (26). Broelsch reported an experience of 20 living-related liver recipients in 1992 from the University of Chicago with 1-year patient survival of 80% (25). Since that time, over 1,000 living donor liver transplants have been performed with the technique now being expanded into adult recipients. Emotionally, but not genetically, related donors are being used with increasing frequency as well. Even the use of right lobes from living donors has been reported. The usual maximum weight for a recipient to be considered for a left lateral segment donor is approximately 30 kg. The overall survival of living donor recipients according to the International Living Donor Liver Transplant Registry is 73%, while the survival is 80-90% in elective recipients. Living donor liver transplantation is an essential technique for any center performing pediatric liver transplantation and should be considered for any child who is at considerable risk of dying while on the waiting list.

Conclusions

New advances in medical management and surgical techniques have made liver transplantation a viable option for most patients with end stage liver disease. Antiviral therapy for hepatitis patients has improved their survival with liver transplantation to that of most other diagnoses. Appropriate patient selection has also given patients with alcoholic cirrhosis a chance for a new life through liver transplantation. Multimodal therapy, including liver transplantation for select patients with unresectable hepatocellular carcinoma, has demonstrated much improved survival compared with that previously achieved.

Operative time, blood product usage, and intensive care unit stay can be decreased through the elimination of venovenous bypass. Liver transplantation without T-tubes may decrease morbidity and the number of radiographic procedures required. Donor availability remains the primary obstacle to the future success of liver transplantation. Split-liver transplantation, living donor liver transplantation, and use of marginal donors are important methods to further expand the donor pool.

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