Liver Transplantation

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[A] This is to acknowledge that Anne Larson MD has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Anne Larson will not be discussing off-label uses in her presentation.

Liver Transplantation – Then and Now

Chronic liver disease results in over one million outpatient physician visits and over 300,000 hospitalizations per year in the United States. While many patients with liver disease will not experience a reduced lifespan, over 27,000 patients annually progress to end-stage liver disease (ESLD), liver failure, and death (Tables 1 & 2).

TABLE 1. CHRONIC VIRAL HEPATITIS STATISTICS[1-3]

	Chronic Hepatitis B	Chronic Hepatitis C	Chronic Hepatitis D
Carriers (Worldwide)	>350 million 8-15% of population	>170 million 3% of population	~15 million
Carriers (US)	>1.25 million 0.2-0.9% of population	>2.7 million 1.8% of population	
Annual US Hospitalizations	11,000 – 17,000	32,000 (1996)	
Progression*	15-25%	10-20%	<5% co-infection 70-80% superinfection
Deaths Annually (US)	4,000 – 5,000	10,000 – 12,000	

*to cirrhosis/death; coinfection – acquired simultaneously with HBV; superinfection – acquired in the setting of chronic HBV

TABLE 2. CHRONIC LIVER DISEASE STATISTICS[1-3]

CHRONIC LIVER DISEASE & CIRRHOSIS	
• Mortality	• 27,257 deaths (2002)
• Hospitalizations	• 360,000 (2002)
• MD Office Visits	• 1 million (1985)
• Disability	• 112,000 people (1983-1987)
NUMBER OF US LIVER TRANSPLANTS	
• 2000	• 4,997
• 2001	• 5,195
• 2002	• 5,332
• 2003	• 5,673
• 2004	• 6,171
• 2005	• 6,444
• 2006	• 6,650
• 2007	• 6,494

http://digestive.niddk.nih.gov/statistics/statistics.htm
http://www.cdc.gov/nchs/fastats/liverdis.htm http://www.unos.org

Despite significant improvements in palliation of the complications of cirrhosis, patients still suffer reduced a quality of life and must confront the fact that their disease will often inexorably progress. Orthotopic liver transplantation (OLT) was developed as treatment for individuals dying of chronic end-stage liver disease and is a valid treatment option in this setting. Nevertheless, with the current shortage of organs, ~10% of patients listed for transplant die without receiving an organ.[4] There are also many patients who are not candidates for transplantation (i.e., due to comorbid illness, psychosocial contraindications, or financial issues).

In addition, some patients receive a transplant but succumb to complications of the transplant operation itself.

HISTORY

Orthotopic liver transplantation was first proposed by Cannon in 1956.[5] Experimentation with canine liver transplantation began in the late 1950s.[6-9] The first human OLT was attempted in 1963 – a 3-year-old boy with biliary atresia. The patient did not survive the operation.[10] The next 5 attempts at OLT in the US and Europe failed. The first "long term" survivor, a child with hepatoblastoma, was transplanted in 1967 but died due to metastasis 18 months following the operation.[11] Donors were those who had succumbed to their medical illnesses, but a new type of donor (brain dead donor) expanded the donor pool when the concept of brain death was accepted in 1968.[12] By the 1970s, overall 1-year survival following OLT was ~30%.[13] The most common causes of death were rejection, due to the use of nonselective (corticosteroids; azathioprine) immunosuppression with narrow therapeutic margins, and overwhelming infection. The introduction in 1979 of cyclosporine, which selectively targets T-cells and had a wider therapeutic margin, significantly improved long-term survival.

Throughout the 1980s, field rapidly expanded with refinement and standardization of donor organ procurement, refinement and standardization of transplantation techniques,[14] invention of veno-veno bypass,[15] introduction of further immunosuppressives (OKT3, tacrolimus), refinement of immunosuppressive regimens, and the introduction of better antibiotics and antivirals (acyclovir, ganciclovir).

The National Institutes of Health held its first Consensus Development Conference on OLT in 1983.[16] This group of experts declared that OLT was a valid, non-experimental, therapy for the irreversible and fatal complications of ESLD.[17] The National Organ Transplant Act of 1984 provided for a federally-funded network for organ procurement and transplantation.[18,19] This network is the United Network for Organ Sharing (UNOS), still in place today, which functions as a private, non-profit organization. In an attempt to equalize allocation of organs, regions were formed in 1986, dividing the country into roughly equal populations of approximately 22 million per region. UNOS raises awareness about organ donation, establishes equitable policies, maintains the National Transplant Waiting List, facilitates organ distribution and transplantation and monitors members for compliance with OPTN/UNOS policies. UNOS is also responsible for maintaining a scientific registry (the organ procurement and transplantation network [OPTN]; http://www.optn.org) on all transplants performed in the US. The first full year for which UNOS maintained the OPTN was 1988, and 1713 cadaveric liver transplants were performed that year. When a potential donor is identified, the local organ procurement organization (OPO) is informed. This independent group then approaches the family, obtains consent if the family

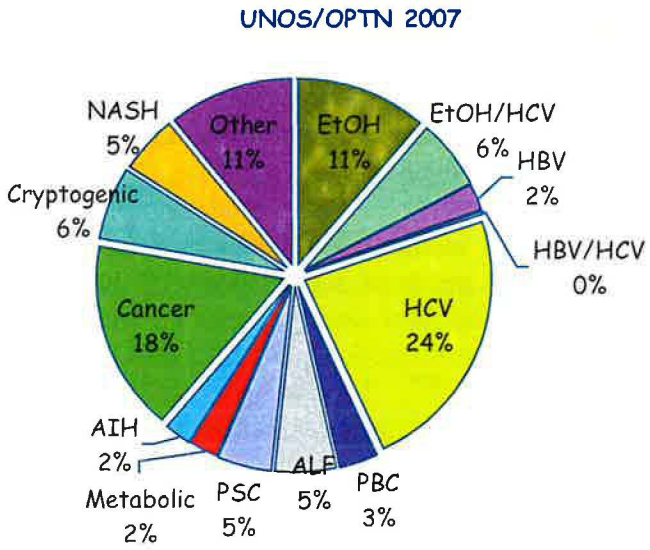
continues to desire donation, and manages the medical care of the donor. The OPO notifies UNOS, which identifies the next patient available for the organ. The Transplant Center is then notified that an organ is available for their patient.

WHY PERFORM LIVER TRANSPLANTS?

From an institutional perspective, a liver transplant program brings prestige, solid income, and is a magnet for referrals. From a clinical perspective, liver transplants are life-saving and lead to an extended survival with a good quality of life for most patients. For all these reasons, OLT has blossomed from 2 programs performing 62 transplants in 1982 to over 125 programs performing nearly 6,500 transplants in 2007. As medical expertise improves, the cost of performing transplant has improved significantly as well.

INDICATIONS[B]

Liver transplantation is indicated for acute or chronic liver failure from any cause. The most common indications for OLT in the US are noted in the figure to the right. Other causes of liver failure which benefit from transplantation include cystic fibrosis, Wilson disease, alpha-1 antitrypsin deficiency, biliary atresia, and Alagille syndrome.



Hepatocellular carcinoma (HCC), once considered to have a poor outcome, is now a common indication for OLT. Patients with HCC have comparable outcomes to those without HCC as long as the tumors are within predefined criteria (the "Milan criteria").[20,21] These criteria state that a single lesion can be no larger than 5 cm in diameter, and if multiple lesions are present, there can be no more than 3 lesions, each ≤3 cm in diameter. There must also be no evidence of vascular invasion or of metastasis. Other cancers which can be successfully treated with OLT include hepatoblastoma, epithelioid hemangioendothelioma, neuroendocrine tumors, and certain types of cholangiocarcinoma.

CONTRAINDICATIONS – who can we transplant?

There are contraindications to liver transplant which are considered relative. In this setting, the risk of these medical or other issues must be weighed against the benefit to the patient and the donor organ. Many currently relative contraindications were considered to be absolute contraindications as recently as 10 years ago. These include:

[B] EtOH – alcohol; HBV – hepatitis B virus infection; HCV – hepatitis C virus infection; PBC – primary biliary cirrhosis; PSC – primary sclerosing cholangitis; ALF – acute liver failure; AIH – autoimmune hepatitis; NASH – nonalcoholic steatohepatitis

1. advanced renal disease – patients can receive a combined liver/kidney transplant in the right setting
2. age >65 years – if otherwise healthy, these patients can do well; but overall survival is decreased compared to younger patients[22,23]
3. HIV – being evaluated under protocol[24-27]
4. severe hepatic hypoxemia – hepatopulmonary syndrome may actually be curable with transplant
5. recurrent disease – is risk of recurrence and subsequent sequelae worth taking?
6. severe malnutrition – survival decreases when BMI <19-20
7. other organ failure – will they survive the operation?
8. active ulcer disease – patients can bleed to death on the OR table
9. poor compliance

There are also many conditions that so severely affect peri-operative and post-transplant patient survival that transplantation is considered inappropriate. These absolute contraindications are:

1. severe cardiac pulmonary disease
2. severe pulmonary hypertension (mean PA >35 mmHg)
3. sepsis
4. extrahepatic cancer
5. extensive portal and mesenteric vein thrombosis
6. active alcohol or drug use
7. severe psychological disorders; or
8. inability to understand the procedure and the lifetime commitment it entails

As the field progresses and medical management of these conditions improves, they may no longer be considered contraindications at all. An example of an absolute contraindication which is now considered an indication is hepatitis B virus infection. Hepatitis B virus induced cirrhosis was once considered a poor indication for transplantation because of the rapid recurrence of aggressive and fatal disease – fibrosing cholestatic hepatitis B. Now, with the use of newer antiviral medications, it has one of the best outcomes.[28]

THE EVALUATION

Evaluation.[29] The pre-transplant evaluation for patients being considered for OLT must answer three fundamental questions:

- Are there other conditions that so severely affect patient survival that transplantation is inappropriate?
- Can the patient survive the operation and postoperative period?
- Can the patient comply with the complex medical regimen required after transplantation?

When the decision is made to proceed with transplantation, the patient undergoes many studies to detect medical contraindications to and urgency for transplantation (Table 3). Social, economic, and ethical factors are also included in the evaluation. The transplant team is large and includes the transplant hepatologist, transplant surgeon, transplant coordinator, anesthesiologist, diagnostic radiologist, interventional radiologist, transplant social worker,

dentist, psychologist and/or psychiatrist, and financial counselor. All participate in the decision regarding transplant. Other specialists may be consulting depending upon the need.

LISTING AND TIMING OF OLT

Listing. Once all the evaluations and studies are complete, the patient's case is presented to the "Transplant Selection Committee" – the entire team. If the patient meets all of the Transplant Center criteria and there are no contraindications to OLT, they are placed on the liver transplant waiting list ("activated"). If conditions are identified which require correction, these must be addressed prior to activation. If there are problems which are insurmountable, the patient may be turned down ("denied") for transplantation. In certain settings, patients or their physicians may appeal a denial.

TABLE 3. LIVER TRANSPLANT EVALUATION

Standard Blood Tests
CBC with differential
Basic Metabolic Panel
Hepatic Panel
–AST, ALT, ALP, bilirubin (total, direct), GGT, albumin
Calcium, Magnesium, phosphate
Prothrombin Time/INR
Viral Serologies
–HAV, HBV, HCV, CMV, EBV, HSV, HIV, VZV)
Blood type
Other Standard Testing
Chest X-ray, 4-phase abdominal CT, abdominal ultrasound with Doppler, EKG, echocardiogram, PPD, colonoscopy (age >50), cardiac stress test (age >50), PAP smear, mammogram, PSA
Potential Studies or Requirements
Coronary angiogram, pulmonary function tests, substance dependence rehabilitation

AST–aspartate aminotransferase; ALT–alanine aminotransferase, ALP–alkaline phosphatase, GGT–γ glutamyltranspeptidase, HAV–hepatitis A virus, HBV–hepatitis B virus, HCV–hepatitis C virus, CMV–cytomegalovirus, EBV–Epstein Barr virus, HSV–herpes simplex virus; HIV–human immunodeficiency virus; VZV–varicella zoster virus

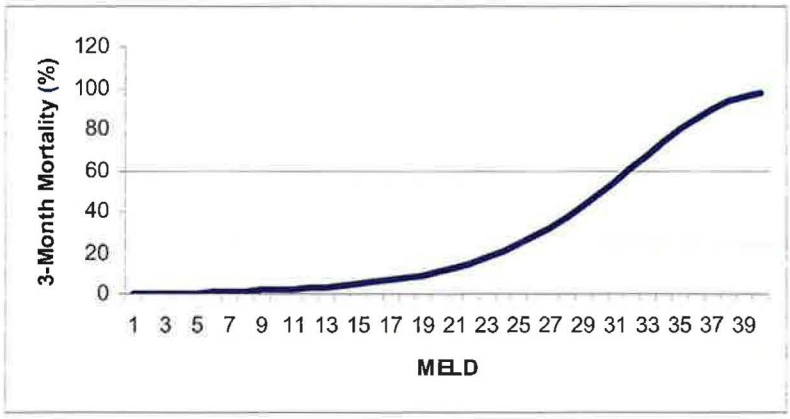
Timing. The timing of the liver transplant is critical to the success of the operation as well as patient and graft survival. Well compensated patients should not be transplanted. The 1-year mortality following liver transplantation is ~10%, therefore the risk of performing the operation must be worth taking. If the patient has a better predicted survival without transplantation, they should not undergo liver transplant.[30] Patients with a MELD score of ≤14 have a higher mortality with OLT than those of the same MELD (see below) who are not transplanted.[30] However, too great a delay in transplantation often results in pretransplant death, poor post-transplant survival and increased costs. Patients who are too sick to survive the operation should not be transplanted.

Listing for liver transplantation had traditionally been based upon waiting time. As OLT became more accepted and survival rates improved, the volume of patients seeking transplantation grew steadily and eventually outstripped the available donors. Thus, a system of listing which relied predominantly on waiting time ("first come first serve"), rather that disease severity ("sickest first"), led to a significant number of deaths while waiting for transplantation. Subsequently, listing was loosely stratified based upon the degree of patient illness (Child-Turcotte-Pugh or CTP Score).[31,32] The sickest patients (Child's Class C) were given priority. However, despite this, patients were transplanted based upon when they were listed for transplant; that is first come, first served. Patients went to the bottom of the list and had to "wait their turn." Thus, if the patient listed at #30 was sicker than the 29 already listed, there was no mechanism to transplant this patient sooner. In addition, two of the components in this system are subjective

(encephalopathy, ascites), and thus subject to intraobserver variability creating difficulties in accurately applying the scoring system.[33,34]

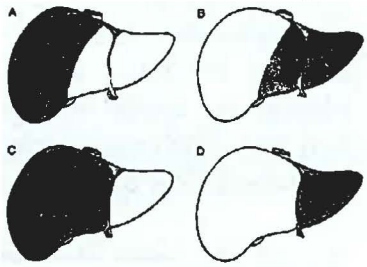
The need for a system which relied predominantly on disease severity led to the development of a predictive model based upon disease severity. In 1998, the Institute of Medicine instructed the transplant community to address this inequity. They set forth the guidelines that organs should be allocated in order of medical urgency, that the role of waiting times should be minimized, and that attempts should be made to avoid futile liver transplants and to promote the efficient use of scarce donor organs. Many models were evaluated, including the model for end-stage liver disease (MELD). Originally developed to predict 3-month survival following TIPS shunt placement in cirrhotics, the MELD score was validated to also accurately predict survival in various forms of chronic liver disease.[35-38] After a period of study, it was shown that with minor modifications, the MELD score accurately predicted 3-month mortality on the waiting list.[39,40] Therefore, UNOS adopted the MELD model and the liver transplant community began using it on February 27, 2002. This allowed for a more flexible listing system – sicker patients were given priority and time on the waiting list was minimized.[41] Following adoption of this listing system, there was an immediate reduction in the number of patients being added to the waiting list – healthier patients were no longer being listed to "accrue time."[40] Median waiting times for organs decreased during the MELD era and use of the MELD has made a significant contribution to the reduction in mortality while waiting for a liver transplant.[40,42-44]

MELD =
$9.57 \times \log_e$ creatinine (mg/dL) +
$3.78 \times \log_e$ bilirubin (md/dL) +
$1.120 \times \log_e$ INR] + 6.43



THE DONOR

In the past, the majority of donors were young people, usually under 40 years of age, who had died from traumatic brain injury. As the need for donor organs outstripped the volume of available organs, the transplant community has sought ways to expand the donor pool ("expanded criteria donors" or ECD). The age of an "acceptable" donor gradually increased. Currently, over a third of donors are over 50 years of age.[30] Other ECD livers include those with steatosis, livers from donors with certain types of malignancies, and the use of non-heart-beating donors (donation after cardiac death).



Other techniques employed to expand the donor pool include splitting a donor organ into a right and left graft–two potential transplants from one organ–and living donor liver transplantation (LDLT).[45-47] Partial liver grafts, however, perform worse than whole liver grafts.[47] While the use of ECD organs has expanded the donor pool somewhat, it has

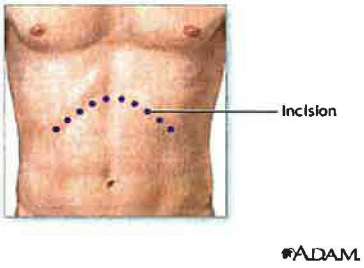
resulted in variable success and is accompanied by increased rates of complications (i.e., early graft failure, biliary complications, and need for retransplantation).[48-50] Thus, use of these grafts could have a negative influence on recipient outcome and care must be taken to match donor and recipient characteristics as best as possible.[51]

The use of living donors remains controversial.[52,53] LDLT can be considered in the appropriate setting – the risk to the donor must be worth taking in conjunction with the benefit to the recipient.[54] There is a 0.3% risk of donor death, ~30% post-operative morbidity, pain and discomfort, potential future liver failure (and they may not be a candidate for living donor liver themselves), a long recovery of 1-3 months, and potential problems with future insurability.

There are certain situations in which the donor liver can no longer be considered usable. These situations include the setting of significant abdominal trauma (which can damage the liver), prolonged cardiac arrest or hypotension (ischemic injury to the donor liver), donor illness (cancer, infection, hepatitis), hypoxemia (hypoxic injury to the liver), and potentially "older" donors. The recipient also carries greater risk. As noted above, partial grafts do less well, and these grafts have an increased incidence of vascular and biliary complications, as well as occasionally being too small ("small for size").

THE TRANSPLANT

A full treatise on the transplant operation is beyond the scope of this review. The operation has been significantly refined over the years. The liver is removed (explanted) via a subcostal incision. The new liver is implanted via anastomosis to the inferior vena cava, portal vein, common bile duct, and hepatic artery. The entire operation takes approximately 4-6 hours. While in the past, significant volumes of blood products were necessary – at times over 50-100 units – most transplants are now done fairly bloodlessly. The ideal hospital course is generally rather short. Most patients remain in the intensive care unit only 1-2 days, followed by another 4-8 days on the regular hospital ward, being discharged by postoperative day 7-10. The hospital course is one of increasing ambulation, discharge planning and patient education, ensuring adequate nutrition, pain control, and patient safety at home.



OUTCOMES

The outcome of all patients who undergo OLT in the US and Europe is continuously tracked via comprehensive databases – the OPTN/UNOS database in the US and the European Transplant Registry (ELTR). Using outcome measures from these databases, models are available to address the issues of organ allocation and to track the efficacy of both cadaveric OLT and LDLT.[55] The large increase in OLT over the last 20 years in the US has had a favorable impact on chronic liver disease mortality.[56]

Overall, the 1-year survival post-OLT is ~90%. The 7–10-year survival rate for OLT is 60-80%, depending upon the etiology of the underlying liver disease.[57] The MELD score appears also to be useful in predicting survival following OLT.[58-61]

12-MONTH SURVIVAL FOLLOWING PRIMARY OLT [60,61]

MELD	<15	15-24	>25		p-value
12-Month Survival	89%	85%	76%		0.002
MELD	**<10**	**19-24**	**25-35**	**>36**	
12-Month Survival	90%	89%	79%	69%	<0.001

Retransplantation

Retransplantation accounts for approximately 10% of all OLTs in the US. The most common indications for reOLT are primary graft nonfunction, hepatic artery thrombosis, allograft rejection, and recurrent disease. Patients who undergo retransplantation have a higher mortality following OLT than those undergoing primary OLT, with 1-, 3-, and 5-year survival rates ~20% lower than for primary OLT (http://www.optn.org). The difference in survival is the greatest in patients with MELD >25.[62] Those who undergo reOLT also have significantly longer hospital and ICU stays with associated higher total hospital charges compared with those who receive only one transplant.[63-65] Retransplantation for liver failure secondary to recurrent hepatitis C virus infection has been associated with a particularly poor survival.[66]

CONCLUSIONS

Orthotopic liver transplantation is currently treatment available for individuals dying of chronic end-stage liver disease or of acute liver failure. Significant progress has been made over the last two decades with regard to allograft and patient survival. Currently, the 7–10-year survival rate for OLT of 60–80%, is a dramatic improvement over the essentially zero 7–10 year survival of patients with ESLD without transplantation.

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