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*Graft* 2003; 6; 68

DOI: 10.1177/1522162803256697

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# Liver Transplantation: An Overview

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The first human liver transplant was performed by Thomas Starzl in Denver in 1963. In the United States, the 5-year survival rate after liver transplantation is 75%, but many patients with liver disease die without ever having had transplantation because of a shortage of organs. Mortality rates are significantly higher in centers that perform 20 transplants or fewer annually. Liver transplantation is appropriate for almost all liver diseases. The decision to transplant is based on 1) assessment of the severity of liver failure; 2) the patient's prognosis on medical treatment; 3) quality of life; and 4) the potential of transplantation to restore patient health. The number of transplants is limited by the availability of donor organs. In 2000 in the United States, there were 17,000 patients on the waiting list; 4579 cadaveric and 371 living related transplants were performed. There were 1347 deaths on the waiting list.

**Keywords:** liver transplantation; split liver grafts; PERV; marginal donors; extended use organs

## History

Thomas Starzl carried out the first human liver transplant in 1963 in Denver. Initially the outcomes were very poor; however, the persistence of Starzl and his team was rewarded and in 1968 Calne set up the second transplant program in Cambridge. Patients were usually very sick at the time of transplant, and few survived the postoperative care. Over the next 2 decades, the numbers of patients grafted gradually increased and survival rates improved. There is no one reason for this improvement, but better selection, improved anesthetic and surgical techniques, the use of powerful and specific anti-microbials, and immunosuppressive agents all made significant contributions. In the 1980s, new programs developed primarily in North America and in Europe. Now liver transplantation has become a routine procedure for patients with end-stage liver disease.

The decision to consider liver transplantation is based on

1. An assessment of the severity of liver failure
2. The prognosis for the patient in response to current medical/surgical therapy

3. The quality of the patient's life (as a consequence of the liver disease)
4. The judgment on the potential for liver transplantation to restore the patient's health

The determination of suitability is independent of the underlying diagnosis, and for that reason the conditions for which liver transplantation may be an appropriate therapy constitute a list of almost all liver diseases.

## The Donor Organ Shortage

The source for donor livers in the Western world is almost exclusively from heart-beating brain dead donors. Sophisticated schemes are required to identify potential donors, retrieve their organs, and transport the organs to the location of the potential recipient. At the same time, the number of potential recipients awaiting liver transplant continues to grow at a furious pace, outstripping the modest increases in donor numbers. This has meant that there are many more recipients for every donor liver. Thus, in the United States in 2000, there were over 17,000 patients on the waiting list, only 4579 cadaveric transplants done and 371 living related

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 from *Liver Transplantation*, edited by  
 Michael R. Lucey, James Neuberger, and  
 Abraham Shaked.  
 DOI: 10.1177/1522162803256697

transplants. There were 1347 deaths on the waiting list. (See [www.unos.org](http://www.unos.org) for current data.)

The disparity between donor availability and recipient number has led to growing numbers of patients on the waiting list for liver transplant.

Innovative responses to the donor shortage have been introduced, but while these approaches may help relieve the situation, they are unlikely to ease the effects of the organ shortage:

1. Non-heart-beating donors. Non-heart-beating donors are uncommon, and the frequency of primary graft nonfunction and later, biliary strictures are greater in these allografts.
2. Split livers—the division of a cadaveric organ between two recipients. However, only some cadaveric donor livers are suitable for splitting.
3. Living donation—the harvesting of liver segments from living donors. Many recipients lack a family member or friend who is suitable or willing for living donation. Moreover, living segmental liver transplantation poses real risks of morbidity and even mortality (1% or more) for the donor.
4. Use of marginal donors and extended use donor organs.
  - Marginal donors: some donor livers are associated with a higher probability of primary nonfunction (the so-called marginal donor). Marginal organs include those from older or obese donors, or donors who are unstable prior to organ retrieval. Other marginal grafts include steatotic livers, in which histology demonstrates greater than 25% microvesicular or macrovesicular fat. These grafts are associated with a higher incidence of primary nonfunction of the allograft.
  - Extended-use organs from patients infected with present or past viral hepatitis B or C and those with extrahepatic malignancy or treated bacterial infection. Organs from virus-infected donors are matched to a recipient already infected by the same virus, albeit only after the recipient is apprised and has given consent. An example would be putting an anti-hepatitis C–positive

liver into an anti-hepatitis C–positive recipient, or an anti-HBcore-positive liver into an HBsAg-positive recipient.

5. Xenotransplants: the use of genetically modified animals, such as pigs or primates, is still a very long way from clinical use. While some of the problems of hyperacute rejection may be overcome, problems, such as chronic rejection, freedom from introducing infection (such as the porcine endogenous retrovirus PERVs), as well as physiological concerns make it unlikely that this approach will provide a solution to the organ shortage in the next decade.
6. Increasing organ donation: there are wide variations in the rates of organ donation—between 8 and 37 donors per million. Attempts to increase organ donation by education have largely failed: the most successful model in Spain is dependent on provision of a well-organized system of donor coordinators and acceptance of older donors.
7. Future approaches may include stem cell transplantation and hepatocyte transplantation.

Thus it is unlikely that these methods will meet the needs of all potential recipients.

### Outcome of Liver Transplantation

Liver transplantation has become the treatment of choice for many forms of life-threatening liver disease because of the continuing lack of less radical therapies and the gradual improvement in survival and quality of life after liver transplantation. Five-year survival in excess of 75% is expected for most patients, and patients who have survived more than 10 years after transplantation are commonplace in long established programs. The success of liver transplantation has occurred despite unacceptably high early mortality and morbidity in a subset of recipients. In addition, we now have to learn the best ways of managing the unwanted consequences of long-term immunosuppression and recurrence of the original disease in the long-term survivor.

The outcome of liver transplantation is dependent on donor organ and recipient factors (see Table 1). Donor factors, which reduce graft success, include donor age and transplantation of a liver allograft

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#### SPLIT LIVER GRAFTS

The division of a cadaveric organ between two recipients.

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#### PERV

Porcine endogenous retrovirus.

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#### MARGINAL DONORS

Donors associated with a high probability of primary nonfunction.

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#### EXTENDED USE ORGANS

Organs from patients infected with present or past hepatitis B or C and those with extrahepatic malignancy or treated bacterial infection.

Table 1 | FACTORS INFLUENCING THE OUTCOME OF ORTHOTOPIC LIVER TRANSPLANTATION

<b>Donor Factors:</b>
Donor age: older donors are less successful
Donor gender: significantly worse results when a female liver is given to a male recipient
Donor liver fat content: > 25% fat at increased risk of primary allograft nonfunction
<b>Recipient Factors:</b>
Acutely ill: requiring ICU care before transplantation
Acute renal failure
Recipient Diagnosis: (see Table 2)
<b>Factors Independent of Donor or Recipient:</b>
Center activity—small centers have been linked to poor outcome. This is a controversial observation

Table 2 | OUTCOME OF LIVER TRANSPLANTATION IN THE UNITED STATES

PRIMARY DIAGNOSIS	N (94-95)	1 YEAR	STD ERR	N	5 YEAR	STD ERR
Survival %		Survival %		Survival %		
Noncholestatic cirrhosis	3520	86.2	0.6	10734	70.1	0.6
Cholestatic liver disease	939	89.4	1.1	3477	80.7	0.8
Biliary atresia	337	91.9	1.6	1549	82.1	1.2
Acute hepatic necrosis	392	77.5	2.2	1367	67.1	1.5
Metabolic disease	274	88.7	2	978	79.9	1.5
Malignant neoplasms	151	76.3	3.9	796	35.4	2.2
Overall	6271	87	0.5	20063	72.3	0.4

Based on The U.S. Scientific Registry of Transplant Recipients and The Organ Procurement and Transplantation Network. Transplant Data 1988-1996. Reference 1.

from a female donor into a male recipient. It is widely held that the fat content of the donor liver influences early graft function, perhaps by facilitating the generation of reactive oxidative species.

Although the etiology of liver disease usually does not preclude liver transplantation, nevertheless, the cause of the underlying liver disease significantly affects the outcome after liver transplantation.

The best outcomes are observed in patients with chronic cholestatic disorders and in chronic liver failure from cirrhosis of many causes.

The outcome is worse among patients transplanted for fulminant liver failure and significantly worse in patients with malignant disease of the liver.

Retransplantation carries a poorer outcome than primary grafting.

The outcome of liver transplantation is influenced by the severity of illness of the recipient prior to surgery. Patient and graft survival are significantly impaired in recipients requiring intensive-care-unit management or among patients with multisystem

failure, prior to transplant. The allocation system currently in use in the United States, Spain, and Germany ensures that donor livers are offered preferentially to such high-risk candidates. Finally, center characteristics influence outcome after liver transplantation, at least in the United States where it has been shown that mortality rates are significantly higher in centers that perform 20 transplants or fewer per annum, compared to centers that perform more than 20 annually.

#### SUGGESTED READING

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