Special Article

Liver Transplantation: Current Indications and Patient Selection for Adult Patients with Chronic Liver Disease

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Liver transplantation is a life saving procedure for patients with a variety of irreversible acute and chronic liver diseases for which no other therapy is available. To date, success of transplantation has been significantly improved with 1-year graft and patient survival rates of approximately 90%. As new information becomes available the indications for individual diseases have been changed somewhat. This review will provide a general basis for patient selection and timing of liver transplantation for adult patients with chronic liver disease.

Keywords: *Liver transplant, Chronic liver disease, Patient selection, Timing, Current indications*

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Over the life-span of many physicians and surgeons, liver transplantation has evolved from an experimental procedure to its current acceptance as an effective therapeutic modality for a variety of end stage acute and chronic liver diseases for which no other satisfactory treatment is available. The first attempt at liver transplantation by Dr. Thomas Starzl occurred in 1963 but was unsuccessful. Five years, later however, the first successful human liver transplant was performed, again by Dr. Starzl. Since then liver transplantation is now a routinely successful operation. The high success rate is due to the many advances that have occurred since early days of transplantation. Current survival rates 1, 3, and 5 years after liver transplantation in the United States and Canada are 88%, 80%, and 75%, respectively Not only can people live a long life after a liver transplant, but the quality of life is typically excellent. Most people can return to their regular job and daily routines without limitations.

Although occasionally, liver transplantation is performed in patients for metabolic disease, as a form of macroscopic gene replacement therapy, the largest patient group comprises patients with end stage decompensated liver disease. Decompensation is defined as the presence of cirrhosis and one or more of the following: jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or bleeding esophageal varices. Other complications associated with end stage liver disease such as severe itching and profound fatigue are also indications for liver transplant. The present review will provide a general basis for patient selection and timing of liver transplantation for adult patients with chronic liver disease.

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End stage liver disease

Patients with end stage liver disease comprise the majority of patients undergoing liver transplantation. Owing to regional variances in the criteria for placing an individual on the waiting list for liver transplantation, in 2005 the American Association for the Study of Liver Diseases[1] published recommendations regarding the minimum criteria that an adult should meet to be put on this list. These guidelines recommend that an individual placed on the waiting list should be ready to proceed with transplantation immediately should an organ become available. On the basis of

Table 1. MELD/PELD calculator

MELD score =	0.957 x Loge (creatinine mg/dl)
	+ 0.378 x Loge (bilirubin mg/dl)
	+ 1.120 x Loge (INR)
	+ 0.643

Abbreviations: INR = international normalized ratio; MELD = model of end-stage liver disease

published data, individuals with a Child-Pugh score of seven or more, MELD (Model for End-stage Liver Disease, Table 1) score of ten or more or those with their first major complication (ascites, spontaneous bacterial peritonitis, variceal bleeding, or hepatic encephalopathy), meet these criteria and should be evaluated and listed for transplantation. The timing of transplantation involves determining when an individual will derive the maximum benefit from receiving a new liver. The goal is to avoid both premature transplants when liver disease is not advanced and futile transplants when individuals are too sick. On the one hand, if the transplant is performed before liver failure develops, then the morbidity and mortality of the transplant operation will outweigh the benefits.

Chronic hepatitis B

Chronic infection with hepatitis B virus (HBV) is one of the most common causes of cirrhosis of the liver and hepatocellular carcinoma worldwide, frequently requiring liver transplantation.

Previously HBV infection was considered a relative contraindication to liver transplantation, due to high rates of recurrence associated with progressive liver disease[2,3]. In the absence of therapy, HBV re-infection occurred in approximately 75% of cases overall and was greatest in patients with high levels of viral replication pretransplantation[4].

Significant improvements in both patient and graft survival in HBV liver transplant recipients have been made during the past 15 years. The first major therapeutic advance was the use of long-term hepatitis B immune globulin (HBIG) to prevent reinfection[5]. The second major advance came with the availability of highly effective and well-tolerated antiviral agents against HBV, such as lamivudine and adefovir dipivoxil, which improved the outcomes of both patients with decompensated cirrhosis awaiting transplantation[6-8] as well as those transplant recipients who had recurrent HBV disease[8-10]. Finally, with the use of HBIG in combination with antivirals (lamivudine and adefovir), the risk of reinfection has been reduced to 10% or less during the first two years following transplantation[11-15].

As a result of these therapies, the outcomes of patients with acute and chronic HBV-related liver disease undergoing liver transplantation are now similar to or better than those of patients undergoing transplantation for non-HBV indications[16,17].

Cost of HBIG administration is a major drawback especially in many Asian developing countries. Long-term low dose intramuscular prophylaxis with less cost and good result has been proposed[18]. The optimal duration of HBIG in patients receiving combination therapy with a nucleoside analogue has not been established. Terrault et al reported no incidence of recurrent HBV in patients those received lamivudine alone after the combination of HBIG and lamivudine for 6 months post-transplantation. The results of these studies suggest that HBIG may be discontinued after a period of combination therapy, at least in patients who have low levels of viral replication pre-transplantation. Lastly, in order to induce natural anti-HBS production and permit HBIG termination, vaccination with recombinant HBV vaccines after transplantation has been attempted with controversial results[19,20].

Chronic hepatitis C

Hepatitis C is the most common indication for orthotopic liver transplantation in western countries. Unfortunately, liver transplantation is not a cure for hepatitis C. Viral recurrence is universal and damage to the new liver occurs routinely. Recurrent HCV infection is among the leading causes of graft loss and the need for retransplantation. Thus, the challenges in liver transplantation as a treatment for hepatitis C include accessing adequate numbers of liver grafts and controlling the virus before and after transplantation to mitigate recurrent disease.

Pre-liver transplant treatment with interferon and ribavirin can be quite effective in some patients with relatively well-compensated cirrhosis, particularly those with genotype 2 and 3 infection. Furthermore, successful treatment before transplantation usually prevents postoperative HCV infection[21]. A decision to treat patients with clinical manifestations of cirrhosis must be made cautiously as decompensated disease is considered a contra-indication by many expert hepatologists.

In patients with hepatitis C who develop recurrent cirrhosis after transplantation, rapid decompensation is common. Up to 42% of individuals with

HCV-related cirrhosis after transplantation have been reported to develop decompensation, manifested as ascites, encephalopathy or hepatic hydrothorax, and less than 50% of individuals survive for one year after they develop decompensation[22]. Thus, data indicate that the progression of hepatitis C is accelerated after orthotopic liver transplantation compared with non-transplanted individuals.

Several factors have been associated with the increased severity of recurrent HCV and the decreased recipient survival such as donor liver over 60 years, high HCV viral load before transplant, advanced recipient age, hyperbilirubinmia, treatment of acute rejection (use of steroid pulses or anti-lymphocyte therapies such as OKT3), prolong INR, pre-liver transplant cytomegalovirus (CMV) status and CMV infection[23-25]. Other factors such as obesity or alcohol use accelerate histological progression after transplantation have not been well studied, but their effects are likely to be similar to those in the non-transplant setting.

Antiviral treatment after transplantation often is poorly tolerated and has limited efficacy. The combination of interferon and ribavirin has been associated with a sustained virologic response rate of approximately only 20%[26-28] and perhaps increasing to approximately 30% with the combination of peg-interferon and ribavirin[29-31]. However, adverse effects, including rejection of the transplant, are a major concern[32,33].

Phase II clinical trials of post transplantation HCV prophylaxis with hepatitis C immunoglobulin (HCIG) therapy have been completed[34]. The results have been disappointing. Transient decreases in liver HCV RNA levels and lower serum aminotransferase levels were demonstrated in patients receiving the high dose of HCIG. However, these changes were not sustained and infection was not prevented[34]. Currently there is no role for HCV antibody therapy in the management of HCV patients post transplantation.

Alcoholic liver disease

In 1988, Starzl et al[35], demonstrated that alcoholic cirrhosis is a good indication for liver transplantation (LT). Since this first publication, alcoholic liver disease (ALD) became a leading cause of LT and now represents the second common indication for LT in the USA and in Europe[36]. One major issue is the likelihood of relapse, because there is the possibility of recurring alcohol abuse after LT that separates patients with ALD from those with other forms of chronic liver disease. The mean incidence of relapse is among one-third of the patients[37], but the published studies have reported very variable results that ranged from < 10% to more than 90%[38,39]. One of the main reasons explaining these variations are probably the lack of consensus about the definition of relapse that may range from the incidental alcoholic beverage to florid post-transplant alcoholism.

In many countries, there is a shortage of donor livers, which means the allocation decision must be made. Patients with alcoholic liver disease who undergo liver transplantation have been selected through a rigorous evaluation process, meticulous counseling, and targeted treatment of their underlying disease of alcoholism. Most programs accept these patients if they have undergone a minimum of six months of supervised well-documented abstinence from alcohol before evaluation and listing for transplantation. Some centers insist patients sign a formal contract to maintain abstinence. Overall, these selected patients have similar graft and patient survival outcomes as patients who undergo transplantation for non-ALD[37,40].

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) ranks fifth among the causes of cancer mortality worldwide and it is responsible for approximately 1 million deaths yearly[41]. This neoplasm almost invariably arises in the setting of hepatitis B virus (HBV) or hepatitis C virus (HCV)-induced cirrhosis at a 2.5% yr rate[42]. Patients with HCC may be transplanted, however, recurrence rates are high unless the patients are carefully selected. Most of transplant centers now select patients using the Milan criteria: those with a single tumor < 5 cm in diameter or three tumors < 3 cm in diameter. Using this criteria, Mazzaferro et al reported survival rate at 4 years was 74% and no different from the expected survival of non-HCC cases[43]. These criteria have come to be referred to as the "Milan criteria". Yao et al introduced the extended University of California, San Francisco criteria in 2001[44]. On the basis of retrospective data, they found that patients who had undergone transplantation with a single tumor up to 6.5 cm or no more than three tumors with maximum sum of diameters up to 8 cm and no tumor larger than 4.5 cm had acceptable disease free survival, similar to that of patients who met the Milan criteria. It must be noted, however, that the number of patients studied who were beyond Milan criteria were relatively few and extension beyond the Milan criteria is not universally accepted by all programs except on an individualized case-by-case basis.

HCC patients have some priority on the waiting list because of the risk of disease progression. Significant patients who fulfill the Milan criteria die owing to tumor progression while waiting for a cadaveric organ. The new allocation system gives additional points to MELD score for HCC patients to overcome this problem. Table 1 Patients with stage 1 lesions (solitary < 2 cm) will get no special priority. While the patients with stage 2 lesions (solitary HCC 2-5 cm or up to three nodules of 3 cm) will be assigned an automatic MELD score of 22. Because of often-rapid growth rate of HCC, tumor management while awaiting transplantation includes modalities such as radiofrequency ablation (RFA), percutaneous ethanol injection, transarterial chemoembolization (TACE) and hepatic resection might be considered as a bridge to transplantation. Surgical resection prior to transplantation has been shown to not increase the surgical risk or impair survival[45].

Autoimmune Liver Diseases

Primary biliary cirrhosis, chronic autoimmune hepatitis, and primary sclerosing cholangitis are the classical diseases treated with liver transplantation. In general, the prognosis of steroid responsive chronic autoimmune hepatitis is very good. They may attend liver or gastroenterology clinics for years or decades prior to an episode of decompensation. Ultimately, some patients may become transplant candidates.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a cholestatic liver disease that causes bile duct destruction and progresses in most cases to cirrhosis and death through liver failure.

PBC is histologically characterized by a chronic inflammatory process that affects the small interlobular bile ducts. Without therapy, the average life expectancy of symptomatic and asymptomatic PBC patients once diagnosed is 7.5 and 16 years, respectively. Medical therapy only slows the disease progression and liver transplantation remains the only hope of cure[46-48]. Primary biliary cirrhosis often follows a predictable clinical path. In many patients, gradually increasing jaundice is followed by decompensation. The most reliable determinants of prognosis in PBC are the height of the serum bilirubin[49] and the Mayo risk score model[50]. As a rule of thumb, PBC patients should be referred for transplant when the serum bilirubin approaches 100 umol/l and certainly before it reaches 150 umol/l[51]. Occasionally patients with PBC may be considered for liver transplantation if they suffer from intractable pruritus or severe fatigue. There are quality of life indications. The results after liver transplantation are excellent with a 5 year survival of 80% to 90%[47,48,52,53]. The Mayo model uses five independent prognostic variables: the patient's age, total serum bilirubin, serum albumin, prothrombin time, and the severity of fluid retention. Of these variables, serum bilirubin concentration is the most heavily weighted. An advantage of the Mayo model is that it does not require liver biopsy. However, it is more useful when applied to a group of patients rather than to individuals. The Mayo model is now widely used to evaluate the efficacy of medical treatment in clinical trials. Survival when the patient receives medication is compared with that predicted by the Mayo model in untreated patients.

Primary sclerosing cholangitis

In view of the variable clinical course of the disease and the unpredictable risk of cholangio carcinoma development, which remains an absolute contraindication because of recurrence, determining the optimal timing of transplantation remains controversial. Transplantation earlier in the course of the disease reduces the operative risk and reduces the risk of the development of hepatobiliary malignancy[54]. However, PSC recurs in at least 30% of grafts, and colon cancer is a major cause of death in PSC patients after OLT[55, 56]. Although prognostic models using age, bilirubin, albumin and histological stage have proved useful in studying large populations; they are not applicable to individuals so these judgments remain extremely difficult[57-60]. Table 2 lists the generally accepted indications for liver transplantation in PSC. Generally, the current opinion in the United states as well as in Europe is that in patients with chronic cholestatic liver disease transplantation should be carried out before they reach the terminal, high risk stage of their disease, as the larger number of life years gained by transplantation in the high risk category is offset by lower survival after transplantation.

Cholangiocarcinoma

Cholangiocarcinoma (CCC) has been considered to be a contraindication to liver transplantation due to early disease recurrence and poor long-term survival. The 3-year survival rate was about 20% and the 5-year survival rate was only 5%-15%[61]. This observation was confirmed by the Cincinnati Transplant Tumor Registry. From 1968-1997, 207 patients

Table 2. Clinical Indications for transplantation in primary sclerosing cholangitis

Indications for liver transplantation
(1) Cirrhosis complicated by
• intractable ascites
• variceal haemorrhage uncontrolled by endoscopic methods
• muscle wasting
• recurrent bacterial peritonitis
• encephalopathy
(2) Intractable itch or fatigue
(3) Recurrent cholangitis
(4) Jaundice which cannot be treated endoscopically or medically (e.g. steroids in overlap syndromes)
(5) Hepatocellular carcinoma (if no extrahepatic growth and Tumor is within accepted size)
(6) Biliary dysplasia

were registered after undergoing a liver transplantation for CCC. Seventy-one patients (34%) were still alive after a median follow-up of 23 months. Only 11 patients (5%) had survived for more than 5 years. Of those who died, the median survival time was only 8.4 months[62].

This view is also supported by the publication by Peter Ghali et al[63] who reported the Canadian experience in liver transplant for incidental CCC in patients originally diagnosed with primary sclerosing cholangitis (n = 12). The 3-year survival for these patients was 30%. The median time to recurrence was 26 months, and the median time to death was 30 months. These data have led to a general consensus that, in light of limited donor organ availability, liver transplantation is not a suitable therapeutic approach for patients with CCC.

However, trials in highly selected patients with new adjuvant and neoadjuvant protocols have shown encouraging results. A study from the Mayo Clinic treated 28 patients with unresectable, stage I/II perihilar cholangiocarcinoma and negative staging laparotomy with external-beam irradiation, systemic 5-FU, and brachytherapy with 192Ir plus oral capecitabine before liver transplantation[64]. Overall 5-year survival was 82%, which is comparable to overall results for liver transplantation across the USA and is better than surgical resection survival rates[64].

These results are promising and would support further clinical trials to optimize patient selection and chemoradiotherapy regimens.

HIV patients

Previously the presence of AIDS was an absolute contraindication to liver transplantation and asymptomatic HIV infection was a relative contraindication. Since in the pre-HAART era, the results of liver transplantation were poor. The prognosis of HIV infection has improved dramatically in recent years with the initiation of protease inhibitors and highly active antiretroviral therapy (HAART). Because of shared routes of transmission, hepatitis C and HIV coinfection is common in the United States, affecting 16% to 29% of HIV-infected individuals in different population[65,66]. While HIV-infected patients have experienced dramatically prolonged survival and decreased morbidity, hepatitis C virus related liver disease has emerged as a significant cause of morbidity and mortality in this patient group with well controlled HIV infection. Moreover, the data showed the outcome of viral hepatitis is more severe in coinfected patients. As a result, a high percentage of them die as a consequence of viral hepatitis rather than the HIV infection itself and an increasing number of patients with HIV infection are being referred for liver transplantation. Accordingly, the American Association for the Study of Liver Disease guideline for the management of HCV recommends that patients with HIV/HCV undergo medical evaluation for HCV-related liver disease and consideration for HCV treatment and, if indicated, orthotopic liver transplantation.

The following is a typical listing for inclusion and exclusion criteria for transplant listing for coinfected patients, although it must be stressed that only a small minority of transplant centers in North America will consider HIV infected patients as viable candidates and many consider this area to remain experimental until more long-term outcome studies are published.

Inclusion:

1. Historical documented HIV infection
2. HIV viral load negative
3. Limited opportunistic complications

4. Current CD4+ T-cell count > 200/mL although some centers will accept > 100/mL

5. Meet standard listing criteria for placement on transplant waiting list

6. Coinfected with chronic HCV and/or HBV

7. History of compliance with medical protocol

Exclusion:

1. Ongoing opportunistic infection or cancer

2. History of documented resistant fungal or bacterial infection

3. Does not meet or comply with standard transplant listing criteria

4. Ongoing substance abuse

5. Fulminant hepatic failure

6. History of any neoplasm except cutaneous Kaposi's sarcoma or hepatocellular carcinoma

Ragni et al [67] evaluated 24 patients who had HIV and end-stage liver disease. The patients underwent orthotopic liver transplant at five centers. The cumulative survival among patients who had HIV was similar to that among age and race comparable patients who did not have HIV (p = 0.365). At 12, 24, and 36 months after transplant, survival was 87.1%, 72.8%, and 72.8%, respectively among patients who had HIV, versus 86.6%, 81.6%, and 77.9% among patients who did not have HIV. Survival was poorer among patients with post-transplant antiretroviral intolerance, a CD4+ count of less than 200 cells/ml, HIV viral load of greater than 400 copies/ml, and hepatitis C infection.

The optimal management team in the post-operative course is an interdisciplinary one. The variability in the rate of liver allograft recovery, dosing of immunosuppressive agents and complex drug interactions, as well as the possibility of HCV recurrence can confuse the clinical picture. Serious drug interactions have been reported between antiretroviral drugs and the immunosuppressive agents used after liver transplantation[68,69].

An important component of many HAART regimens is the protease inhibitors, which have a high propensity to cause drug interactions by prolonging the half-life of calcineurin inhibitors and sirolimus via cytochrome P450 inhibition. This drug interaction can easily result in toxic levels of calcineurin inhibitors and sirolimus and must be carefully monitored whenever given concomitantly with immune suppression[70]. Moreover, recurrence HCV infection is also often rapid and severe in coinfected patients following liver transplantation. Antiviral treatment for this patient group is certainly challenging as well as drug interaction with antiretroviral agents. Ribavirin used in combination for HCV therapy has been shown to inhibit phosphorylation of zidovudine, stavudine and zalcitabine. Ribavirin may also increase the potency of didanosine and improve antiviral activity. This interaction may be associated with severe mitochondrial toxicity characterized by development of lactic acidosis, pancreatitis, or fulminant hepatic failure. Because of these various issues, the care of transplantation recipients with HIV infection requires a well-coordinated, multidisciplinary team with expertise both in transplantation and HIV management.

Co-existent medical diseases

Many patients with end stage liver disease will have other medical conditions. These need to be evaluated as part of the liver transplant assessment process. For non-malignant diseases, there are two essential questions. Does the co-existent disease affect life expectancy and if so how much? If the expected survival from the co-morbid disease is less than 5 years then the patient should probably not be transplanted. Secondly, does the co-morbid disease increase the surgical and anesthetic risks of liver transplantation and if so, could these risks be minimized or eliminated? An example would be coronary artery or valvular heart disease that may require investigations and/or interventions. From a surgical perspective, clearly, if the abdominal surgical anatomy from previous operations or portal vein thrombosis is such that transplant surgery is not technically feasible, then transplantation is contraindicated.

Age

Increasingly, older patients are being referred for liver transplantation. With increasing age, the burden of co-morbidity raises particularly cardiovascular and respiratory disease. Many series have reported satisfactory results in patients over 60 years of age. In general, most centers will consider patients up to the age of 65 years. Patients between 65-70 years may be considered if they appear biologically young with minimal co-morbidity. In some cases, the likelihood of survival beyond the standard three to five years may need to be considered**.**

Conclusion

Liver transplantation can clearly be a life-saving therapeutic modality for many patients. The challenge for many transplant centers, however, is the

great disparity between the need for organ transplantation and its availability. Even with increasing live donor liver transplantation, in addition to increasing utilization of cadaveric organs that would have been rejected as "unsuitable" in by-gone years, this tragic discrepancy can be expected to worsen in the years to come. Appropriate utilization of available grafts and careful selection of patients can at least ameliorate some of the effects of the current organ shortage.

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การปลูกถ่ายตับในผู้ใหญ่: ข้อบ่งชี้และการคัดเลือกผู้ป่วยที่เป็นโรคตับวายชนิดเรื้อรัง

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การปลูกถ่ายตับเป็นการรักษาผู้ป่วยโรคตับวายทั้งชนิดเรื้อรังระยะท้ายและชนิดเฉียบพลันที่ไม่สามารถรักษาได้โดยวิธีรักษาอื่น ปัจจุบันนี้ผลสำเร็จของการผ่าตัดดีขึ้นอย่างมาก โดยมีอัตราการรอดชีวิตของผู้ป่วยและผลสำเร็จของการปลูกถ่ายตับที่ 1 ปี หลังการผ่าตัดสูงถึงร้อยละ 90 ข้อมูลปัจจุบันในด้านข้อบ่งชี้ในการพิจารณาการปลูกถ่ายตับและการคัดเลือกผู้ป่วยเข้ารับการผ่าตัดได้มีการเปลี่ยนแปลงไป รายงานทบทวนบทความฉบับนี้จะกล่าวถึงหลักการทั่วไปในการพิจารณาคัดเลือกผู้ป่วยที่มีโรคตับวายเรื้อรังเข้ารับการปลูกถ่ายตับรวมถึงระยะเวลาที่เหมาะสมในการพิจารณาการปลูกถ่ายตับ