

Liver Transplantation

Indications, Contraindications and Timing of Referral

Eberhard L. Renner, M.D.
Section of Hepatology
Dept. of Internal Medicine
Health Sciences Center
John Buhler Research Center
809-715 McDermot Avenue
Winnipeg, MB, R3E 3P4

KEY MESSAGES

- ❖ Orthotopic liver transplantation (OLT) is the treatment of choice for end-stages of acute and chronic liver diseases of various etiologies. If electively performed for cirrhosis, OLT is characterized by 5-year survival rates of $\geq 80\%$ and results in excellent health related quality of life and professional re-integration.
- ❖ Indications include end-stage chronic liver disease (cirrhosis) by and large irrespective of its etiology, fulminant hepatic failure (far less frequent), and certain metabolic disorders (rare).
- ❖ End-stage chronic liver disease (cirrhosis) due to viral hepatitis (B, B/D, C), autoimmune hepatitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's, primary biliary cirrhosis and primary sclerosing cholangitis are well established indications. Alcoholic cirrhosis is an accepted indication if liver function does not recover despite 6 months of abstinence. Non-resectable hepatocellular carcinoma is an accepted indication provided there is only 1 nodule of less than 5cm or max. 3 nodules each less than 3 cm in diameter and no vascular invasion on imaging.
- ❖ Contraindications to OLT include uncontrolled extrahepatic infection (sepsis), presence of extrahepatic neoplasia (usually within the last 5 years), irreversible damage to other vital organs seriously limiting life expectancy and lack of compliance. There is no absolute chronologic age limit, rather biologic age, i.e. co-morbidity, is limiting. However, OLT at or above age 70 years is an exception.
- ❖ With waiting times ever increasing, reaching today more than two years in some patients, early referral is the key to success. Thus, cirrhotics should be referred for evaluation when either a) their liver function deteriorates into Child-Pugh B stage (≥ 7 points) or b) at the time they experience a first complication of portal hypertension (ascites, portal hypertensive GI-bleeding, jaundice or encephalopathy). Less frequently, seriously impaired quality of life attributable to chronic liver disease such as intractable pruritus or invalidating fatigue in patients with PBC may by itself represent an indication for OLT, irrespective of liver function.

Orthotopic liver transplantation (OLT) has long become the treatment of choice for end-stages of acute and chronic liver diseases of various etiologies. Today, elective OLT for end-stage chronic liver disease (cirrhosis) carries 1- and 5-year survival rates of around 90% and 80%, respectively. Survival beyond 1 year post-transplant does not much differ from that of an age and sex matched general population. This is accompanied by excellent health-related quality of life, a majority of liver transplant recipients rating their quality of life to be completely within normal limits. Quality of life impacts directly on professional occupation. Thus, a large proportion of liver transplant recipients become able to work again fully or at least part-time in their original profession/occupation within 3-6 months of surgery.

With the current shortage of cadaveric organs and the increasing demand for liver transplants waiting time ever increases: today, waiting time may exceed two years depending on blood group. Patients will only survive to OLT and benefit from an excellent post-transplant outcome if referral for evaluation is timely. The primary treating physician, be it family physician, internist, gastroenterologist or else, holds this key to success in his hands.

The following is a brief summary of indications and contraindications for liver transplantation, as well as of some issues concerning timing of referral for evaluation. It pertains to adults with liver diseases. Liver transplantation for metabolic diseases and in the pediatric age group would need separate discussion. The summary also does not discuss still debated differential indications for living donor or split liver transplantation, but focuses on liver transplantation in general. It is based on recommendations by the British Society of Gastroenterology¹ and the American Association for the Study of Liver Diseases (AASLD)², as well as the author's personal experience. The interested reader is further referred to the homepages of the European Liver Transplant Registry ELTR (www.ELTR.com) and the United Network for Organ Sharing UNOS (www.UNOS.com).

¹ Devlin J, O'Grady J for the British Society of Gastroenterology. Gut 45 (suppl VI): VI1- VI122, 1999.

² Clarithers RL. Liver Transplantation. Liver Transplantation 6: 122-135, 2000

1. INDICATIONS FOR LIVER TRANSPLANTATION

1.1 Risk/Benefit Balance and Prognostication

For listing on a waiting list, mid-term (>1-2 years) survival/quality of life without a transplant need to be weighed against those with a transplant. The former involves prognostication of the course of acute or chronic liver disease, the latter knowledge of current outcome data of liver transplantation (cf. above).

There are several approaches to prognostication in acute liver failure. The Kings' College Criteria³ are best validated and most widely used.

There are many approaches to prognostication in chronic liver disease. The Child-Pugh scoring system⁴ has stood the test of time and is probably the most widely employed disease-independent tool. Generally, Child Pugh A patients do not benefit from a liver transplant, whereas OLT increases survival for Child Pugh B and C patients. In Child-Pugh C patients, however, outcome may be compromised and health care resource utilization heavily increased due to more seriously impaired general and nutritional states. This may render OLT less cost-effective and bears the potential of wasting a scarce resource (i.e. donor liver) that may have benefited a patient with less advanced disease with a higher likelihood. Thus, the level of weighing benefits/risks for an individual patient needs to be balanced with the meta-level of acting in the best interest of all patients in need for a transplant. Both are not always congruent. This may require difficult decisions by the transplant team and all involved, health care workers, the patient and his family.

Some other hallmarks of prognosis in cirrhotics are worth to be kept in mind and are summarized in Appendix III.

Finally, it should be remembered that during the entire process from becoming aware a transplant may be indicated, over referral, evaluation and deciding on proceeding to transplant, to waiting until an appropriate organ becomes available time runs, i.e. the underlying liver disease progresses with all its associated morbidity and mortality. Thus, early referral by the primary care physician is mandatory in order to assure the patient is able to benefit optimally from this highly effective, life saving and quality of life restoring therapy.

1.2 General Indications for Listing

Conceptually, indications for initial referral to a transplant hepatologist/transplant center are not necessarily identical with those for listing. Patients should ideally be referred before all criteria for listing are fulfilled (cf. below Timing of Referral)

1.2.1 Acute Liver Failure (irrespective of etiology)

- For paracetamol-induced and non-paracetamol induced acute liver failure the Kings' College Criteria⁵ apply for listing.

³ cf. Appendix I

⁴ cf. Appendix II

⁵ cf. Appendix I

1.2.2 **Chronic Liver Disease** (irrespective of etiology)

- Child-Pugh score B or C (≥ 7 points)

OR

- Selected patients with Child-Pugh score < 7 points, but decompensation with ascites, encephalopathy, portal hypertensive bleeding or jaundice, or with otherwise not curatively treatable hepatocellular carcinoma

OR

- Selected patients with serious impairment of quality of life due to liver disease such as intractable pruritus, invalidating fatigue and/or performance status

1.3 **Special Issues according to Underlying Liver Disease**

The following summarizes key issues for some of the more common indications for liver transplantation.

1.3.1 **Chronic Liver Disease**

1.3.1.1 **Viral Hepatitis**

1.3.1.1.1 **Hepatitis B** (and B/D)

- Patients with end-stage chronic hepatitis B virus related liver disease should be considered for liver transplantation. They should ideally exhibit low levels of HBV replication (HBV DNA $< 10^6$ Mio copies/ml by PCR) at time of transplant. The benefits of a prophylaxis with nucleoside analogues while on the waiting list needs to be individually balanced with the risk of selecting resistant HBV strains. This depends on the presumed waiting time and should be discussed with the transplant center.

All patients need to be started on long-term prophylaxis with a nucleoside analogue and passive immunoprophylaxis (anti-HBs immunoglobulin) at time of transplant.

- Patients with acute liver failure due to Hepatitis B virus infection should be considered for liver transplantation. They may have immune-cleared the virus at time of transplant (HBe-/Anti-HBe seroconversion) and then do not need prophylaxis. In all other cases, prophylaxis is performed, as in chronic hepatitis B.
- Infection with HBe negative HBV mutants does not preclude transplantation.
- Patients with B/D infection are treated as Hepatitis B infected patients, although the likelihood of recurrent hepatitis B/D and - if occurring - its severity is less.

1.3.1.1.2 **Hepatitis C**

- Patients with end-stage chronic hepatitis C virus related liver disease should be considered for liver transplantation.
- In the presence of a history of concomitant heavy alcohol use, there should be a ≥ 6 months period of supervised community abstinence (cf. alcoholic cirrhosis).

- In the presence of a history of concomitant i.v. drug use, there should be a ≥ 6 months period of supervised community abstinence. Compliant participation in an opiate substitution program is per se not a contraindication for transplantation, but these patients require multidisciplinary psychosocial assessment.
- Hemophilia is not a contraindication for transplantation.
- HIV co-infection is per se not a contraindication for transplantation.

1.3.1.2 Alcoholic Liver Disease

- Selected patients with end-stage alcohol related liver disease should be considered for liver transplantation.
- Alcohol dependence should be differentiated from alcohol misuse.
- A ≥ 6 months supervised community abstinence is required prior to listing in most transplant programs and offers the patient a chance to recover his/her liver function beyond the need for transplantation.
- In selected young patients with first medical presentation and a high probability of not surviving this 6 months period, liver transplantation may be considered without stringently adhering to this criterion.
- All patients require multidisciplinary psychosocial assessment.
- Exclusion of relevant alcohol (and smoking) related co-morbidity is particularly important in these patients.
- Especially if (ex-)smokers, these patients are at higher risk for malignancies (airways, esophagus) and may require respective surveillance post-transplant.

1.3.1.3 Cholestatic Liver Disease

1.3.1.3.1 Primary Biliary Cirrhosis

- Patients with end-stage liver disease related to primary biliary cirrhosis should be considered for liver transplantation.
- The Mayo Risk Score for PBC allows disease specific prognostication (www.mayoclinic.org/gi-rst/mayomodel2.html) during the disease course.
- Patients should be considered for listing once serum-bilirubin increases to 75-100 $\mu\text{mol/l}$, or liver function (INR, serum albumin) starts to decrease, or complications of portal hypertension occur (ascites, portal hypertensive bleeding, encephalopathy).
- In selected patients, liver transplantation may be indicated for palliation of otherwise intractable and invalidating symptoms including pruritus or fatigue even in the presence of an intact liver function and without complications of cirrhosis/portal hypertension.

1.3.1.3.2 Primary Sclerosing Cholangitis

- Patients with end-stage liver disease related to primary sclerosing cholangitis should be considered for liver transplantation.

- The optimal timing of liver transplantation has not been stringently defined. The Mayo risk score for PSC allows disease specific prognostication (<http://www.mayoclinic.org/gi-rst/mayomodel3.html>) during the disease course.
- Patients should be considered for listing once the Mayo Risk score reaches values ≥ 5 (Child Pugh score C) and/or serum-bilirubin increases to 75-100 $\mu\text{mol/l}$ (provided this is not caused by an endoscopically treatable dominant biliary tree stenosis), and/or liver function (INR, serum albumin) starts to decrease, and/or complications of portal hypertension occur (ascites, portal hypertensive bleeding, encephalopathy).
- In selected patients, liver transplantation may be indicated for palliation of otherwise intractable and invalidating symptoms including frequently recurring cholangitis, pruritus or fatigue even in the presence of intact liver function and without complications of cirrhosis/portal hypertension.
- Superimposed cholangiocarcinoma needs to be ruled out, knowing that all available means are limited.
- There is no established precursor lesion for cholangiocarcinoma detectable with current diagnostic means that would allow therapeutic intervention. Pre-transplant surveillance is therefore not established.

1.3.1.4 Autoimmune Hepatitis

- Patients with end-stage liver disease related to autoimmune hepatitis should be considered for liver transplantation.
- In fulminant disease failing to or presenting beyond a stage potentially reaching remission with immunosuppressive therapy patients should be listed for liver transplantation.
- In chronic disease, listing for liver transplantation should be considered once there is progressive decline of liver function and/or decompensation, despite adequate medical therapy.

1.3.1.5 Hereditary Liver Diseases

1.3.1.5.1 Hemochromatosis

- Patients with end-stage liver disease related to hemochromatosis should be considered for liver transplantation.
- Cardiac (myopathy, arrhythmias) and endocrine (diabetes, latent adrenal insufficiency) involvement is associated with increased perioperative risk and needs to be checked for during evaluation.
- Generally, liver transplantation for hemochromatosis carries a higher mortality than transplantation for end-stage liver disease of other etiologies of comparable severity.
- Liver transplantation does not cure the underlying defect, i.e. increased intestinal iron absorption. Thus, post transplant, iron

stores need to be monitored and re-accumulation/recurrent disease prevented by phlebotomy, as necessary.

1.3.1.5.2 Wilson's Disease

- Patients with end-stage liver disease related to Wilson's should be considered for liver transplantation once decompensation (ascites, portal-hypertensive bleeding, encephalopathy., jaundice) occurs, despite adequate medical therapy.
- In fulminant Wilson's, a disease-specific score⁶ for prognostication has been published.
- In Wilson's disease, the defect resides in the liver (defective Cu-ATPase in ER) and is cured by liver transplantation.

1.3.1.5.3 Alpha-1-Antitrypsin Deficiency

- Patients with end-stage liver disease related to Alpha-1-Antitrypsin deficiency should be considered for liver transplantation.
- Relevant lung disease needs to be ruled out during evaluation.

1.3.2 Liver Tumors

1.3.2.1 Hepatocellular Carcinoma

- Patients with non-resectable hepatocellular carcinoma should be considered for liver transplantation, provided the Milan criteria⁷ are fulfilled: 1 nodule \leq 5 cm in diameter OR \leq 3 nodules each \leq 3 cm in diameter AND no vascular invasion on imaging (CT or MRI) AND no extrahepatic spread.
- This includes selected patients with Child A cirrhosis, in whom the tumor, not end-stage liver disease, represents the indication for a transplant. Liver transplantation is the only therapy not only allowing to remove the tumor, but also to cure the underlying risk factor, i.e. the pre-cancerous diseased liver.
- More recently it has been proposed by several groups that the Milan criteria may be safely expanded⁸. This is however not yet universally accepted.
- Waiting time is crucial in these patients. Chemoembolization or radiofrequency ablation may be used to locally control tumor growth in order the tumor does not outgrow the size limits mentioned above while awaiting transplantation.
- Adjuvant or neo-adjuvant chemotherapy has not been proven to benefit these patients, is associated with significant morbidity and

⁶ Nazer H, Ede RJ, Mowat AP, Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut 27:1377-1381,1986.

⁷ Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334: 693-699, 1996.

⁸ cf. e.g. Yao FY, Ferrell L, Bass NM, Bachetti P, Asher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the pittsburgh modified TNM criteria. Liver Transplantation 8: 767-774, 2002.

mortality and should not be performed outside controlled clinical trials.

1.3.2.2 Cholangiocarcinoma

- Centrally located cholangiocarcinoma is not an established indication for liver transplantation.
- Highly selected patients may benefit from a transplant in conjunction with novel pre- and/or postoperative strategies, i.e. within clinical trials.
- Selected rare patients with a peripherally located and incidentally detected small cholangiocarcinoma may benefit from a transplant.

1.3.2.3 Others primary liver tumors

- Epitheloid hemangioendothelioma confined to the liver may be considered for liver transplantation, but needs to be thoroughly differentiated from hemangiosarcoma by appropriate expert imaging/histopathology studies.

1.3.2.4 Liver Metastases

- Selected patients with symptomatic liver metastases of a gastrointestinal neuroendocrine tumor may be considered for (palliative) liver transplantation, provided the extrahepatic primary tumor is curatively (R0) resected and there is no extrahepatic spread (imaging, octreotide szintigraphy).
- All other metastases to the liver of any other extrahepatic primary tumor are not an indication for liver transplantation.

1.3.3 Others

1.3.3.1 Budd Chiari Syndrom

- Selected patients with Budd Chiari syndrome may benefit from liver transplantation once other decompressive therapeutic options have failed or are not applicable, i.e. end-stage chronic liver diseases is established or complications of portal hypertension can otherwise not be controlled.

1.3.3.2 Familial Amyloid Polyneuropathy

- In patients with familial amyloid polyneuropathy liver transplantation may halt progression of the disease. Once polyneuropathic symptoms appear, liver transplantation should be considered.

2. CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Conceptually, contraindications to liver transplantation can be divided in absolute and relative ones. The former preclude liver transplantation, the latter need to be thoroughly weighed against the risks/benefits of a) the individual patient and b) all other patients in need for a transplant.

2.1 Absolute Contraindications

- Extrahepatic malignancy
- Uncontrolled extrahepatic infection (uncontrolled sepsis)
- Severe irreversible damage to other vital organs
- Lack of compliance

2.2 Relative Contraindications

- Age
There is no universally accepted absolute age limit for liver transplantation. The biologic age, i.e. co-morbidity, is more important than chronologic age. In real life, however, it is rare that the risk/benefit ratio is favoring a transplant in a patient aged 70 years or older.
- HIV positivity
Medically well controlled HIV infection (HIV viral load <50 copies/ml) with a relatively well preserved immune status (>200 CD4 cells) and in the absence of AIDS defining events is per se not a contraindication to liver transplantation.
- Severe neuropsychiatric disorder
This should not per se disqualify from a liver transplant. However, the risks (compliance) and benefits need to be especially balanced at the individual's and the waiting list population's level.
- Portal venous system thrombosis
This does not preclude liver transplantation as long as there is a vessel available (superior mesenteric vein, collateral) suitable for portal anastomosis of the graft. Extrahepatic portal system thrombosis may however require technically more demanding vascular reconstruction with all its associated increased morbidity/mortality.
- Pulmonary hypertension
Severe pulmonary hypertension (PAP >40mm Hg) is a contraindication for liver transplantation. A trial with prostacycline to decrease PAP is warranted. If PAP drops and can be kept below 40mm Hg, liver transplantation may become again feasible.
- Severe hyponatremia
Severe hyponatremia (serum Na \leq 125-127 mmol/l) is a contraindication to liver transplantation in some, but not all centers. The inevitably rapid correction of serum Na intraoperatively attributable to transfusion requirements (FFP, volume) increases the risk of postop acute pontine demyelination.

- History of malignancy
A history of malignancy within the last 5 years is usually regarded as absolute contraindication for liver transplantation. Liver transplantation may be considered if the tumor is in full remission/cured for ≥ 5 years. This depends however on the type/location of the tumor and its biology and needs to be individually assessed in a multidisciplinary approach.

3. TIMING OF REFERRAL FOR LIVER TRANSPLANTATION

The following criteria for referral to a transplant hepatologist are suggested:

3.1 Acute Liver Failure (irrespective of etiology)

- Contact transplant hepatologist when INR is >2.

3.2 End-stage Chronic Liver Disease (irrespective of etiology)

Refer to transplant hepatologist when

- Child-Pugh score reaches 7 points, i.e. patient switches from Child-Pugh A to B

OR

- At first decompensation with ascites, encephalopathy, variceal bleeding or jaundice

OR

- At diagnosis of otherwise not curatively treatable hepatocellular carcinoma, provided the Milano⁷ criteria are not overtly exceeded

OR

- Impairment of quality of life due to liver disease becomes intolerable (intractable pruritus, invalidating fatigue and/or performance status)

The transplant hepatologist may decide liver transplantation is not yet indicated, but only this early referral leaves enough time for a thorough evaluation with the patient and his family and enables optimal timing of transplantation.

APPENDIX I

Kings College Criteria⁹ for Prognostication in Fulminant Hepatic Failure,
(spontaneous recovery/survival without a transplant <20%, if criteria fulfilled;
thus, list for super-urgent OLT, if criteria fulfilled)

Non-Paracetamol induced Fulminant Hepatic Failure

- **INR >6.7**

OR

≥3 OF THE FOLLOWING

- **Age <10 or > 40 yrs.**
- **Drug-induced or non-A-non-B-non-C Hepatitis**
- **Jaundice >7days prior to encephalopathy**
- **INR >4**
- **Serum bilirubin >300umol/l**

Paracetamol induced Fulminant Hepatic Failure

- **Art. pH <7.3 (on admission)**

OR

ALL OF THE FOLLOWING

- **INR >6.7**
- **Serum creatinine >300umol/l**
- **Encephalopathy stage 3 or 4**

⁹ O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 97: 439-445, 1989.

APPENDIX II

Child-Pugh Scoring System¹⁰ for Prognostication in Chronic Liver Disease

	<i>Points</i>	1	2	3
Bilirubin	(umol/l)	<35	35-50	>50
Albumin	(g/l)	>35	28-35	<28
Ascites	Y/N	None	med. controlled	poorly controlled
INR		<1.7	1.70-2.20	>2.20
Encephalopathy	Y/N	None	med. controlled	poorly controlled

Child-Pugh stage	Points
A	5 - 6
B	7 - 9
C	10 – 15

¹⁰ modified after Pugh RNH, Murray-Lyon IM, Dawson JL et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60:649-9, 1973.

APPENDIX III
Hallmarks of Prognosis in Chronic Liver Disease¹¹

EVENT	MEDIAN SURVIVAL FROM FIRST OCCURRENCE (years)
Any Decompensation (ascites, portal hypertensive bleeding, encephalopathy, jaundice)	1.6
Portal Hypertensive Bleeding	2 (heavily dependent on Child-Pugh stage)
Acites	2
Spontaneous Bacterial Peritonitis	<1
Hepatorenal Syndrome	Weeks-Months

¹¹ modified after Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keefe EB, Kneteman NM, Lake JR, Martin P, Rakela J, Shiffman ML, So S, Wiesner RH. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Transplantation 66: 956-962, 1998