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TOPIC HIGHLIGHT

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# Liver transplantation in adults: Choosing the appropriate timing

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## Abstract

Liver transplantation is indicated in patients with acute liver failure, decompensated cirrhosis, hepatocellular carcinoma and rare liver-based genetic defects that trigger damage of other organs. Early referral to a transplant center is crucial in acute liver failure due to the high mortality with medical therapy and its unpredictable evolution. Referral to a transplant center should be considered when at least one complication of cirrhosis occurs during its natural history. However, because of the shortage of organ donors and the short-term mortality after liver transplantation on one hand and the possibility of managing the complications of cirrhosis with other treatments on the other, patients are carefully selected by the transplant center to ensure that transplantation is indicated and that there are no medical, surgical and psychological contraindications. Patients approved for transplantation are placed on the transplant waiting list and prioritized according to disease severity. Thus, the appropriate timing of transplantation depends on recipient disease severity and, although this is still a matter of debate, also on donor quality. These two variables are known to determine the "transplant benefit" (i.e., when the expected patient survival is better with, than without, transplantation) and should guide donor allocation.



**Key words:** Liver transplantation; Referral; Waiting list; Prioritization; Allocation; Timing; Cirrhosis; Hepatocellular carcinoma; Indications; Contraindications

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## INTRODUCTION

Liver transplantation (LT) represents the best treatment option for end-stage liver disease and liver-based metabolic conditions causing systemic disease. In fact, in Europe, ten years patient survival after LT performed in adults from 1988 to 2010 is 55%[1].

Access to LT at the appropriate timing depends on a three step process: (1) referral to a transplant center; (2) listing after careful evaluation by the transplant team; and (3) medical management, prioritization and allocation policy on the waiting list.

Every physician should know the appropriate timing to refer a patient with liver disease to a transplant center to give the same chances to every patient and access the best treatment available. Missing or late referral leading to limited access to surgery should be avoided[2,3]. Table 1 shows the general indications for primary LT in adults. Because of the unpredictable and often fast evolution of acute liver failure (ALF), patients with any severe acute hepatitis should be hospitalized where a transplant center is available. With regard to patients with cirrhosis, referral should generally occur at the moment of any complication, such as synthetic dysfunction, hepatic encephalopathy, ascites, hepatocellular carcinoma (HCC), hepatorenal syndrome, variceal or other portal hypertensive bleeding, hepatopulmonary syndrome, portopulmonary hypertension and conditions that impair quality of life (i.e., recurrent cholangitis, intractable pruritus, malnutrition, hepatic myelopathy). Finally, referral for patients with less common metabolic disorders and other miscellaneous diseases should be decided case by case, based on the severity of extrahepatic morbidity and/or liver-related complications.

Because of the gap between the number of patients that need a transplant and the number of deceased donors available, and considering that more than 2000 candidates in United States die each year while awaiting transplantation, once a patient has been referred, strict selection criteria are applied[4]. The aims of this selection are: (1) to ascertain that the severity of liver disease is sufficient to predict a short-term mortality risk that is lower with, than without, transplantation; and (2) to exclude patients with contraindications.

Table 2 shows the contraindications to LT. These can change between centers and over the years. The presence of one or more absolute contraindication imposes patient exclusion from listing. Relative contraindication can cause patient exclusion when more than one is present in the same patient. The decision of whether a patient is an appropriate candidate for LT is based on the evaluation of many factors other than the presence of liver disease and liver failure and is established by a "multidisciplinary transplant team". The decision not to list a patient can either be permanent or, if the disease is not advanced enough, temporary and the patient should enter a follow-up program. With regard to waiting list priority, patients with ALF have the highest priority and are on a separate urgent waiting list. Once a non-urgent patient is listed, the prioritization and allocation policies, together with clinical management which is critical to avoid temporary or permanent delisting, influence LT timing. Prioritization on the non-urgent waiting list is usually obtained according to the severity of liver dysfunction which is reflected by the model for end-stage liver disease (MELD) score[5,6]. When patient prognosis and/or quality of life are not reflected by the MELD score but by some untreatable complication, this should be judged to be an exception to the MELD score prioritization system and allow artificial increased priority. These additional MELD score points with different modalities around the world are currently granted as a general automatic rule or after case by case discussion by a "review board". Donor allocation policy can follow one of three possible principles: medical urgency, utility and transplant benefit.

Since the right timing of transplant referral and evaluation, the management of the patient while on the waiting list, and the prioritization/allocation policy are influenced by the etiology of liver failure and by the type of complications, we have organized the subsequent discussion according to the different commonest causes of liver disease and complications. In addition, in the present review we consider only primary transplants performed in adults.

## TIMING OF LT ACCORDING TO THE TYPE OF LIVER DISEASE

### *Acute liver failure*

ALF is a potentially reversible disorder that is the result of severe liver injury, associated with coagulopathy due to compromised hepatic protein synthesis and hepatic encephalopathy occurring within 8 wk of symptoms in patients without preexisting liver disease[7]. In 2009 in United States, 4.3% of deceased donor LTs were performed in patients with ALF[4]. Between 2007 and 2009, as reported by the "Liver Match" study group, the same figure was 2.9% in Italy[8]. Table 3 shows the causes of ALF. In the developing world, ALF is caused predominantly by hepatitis A, B and E, while in the United States and western Europe, drug-induced liver injury predominates. In many cases, ALF etiology remains unknown[8]. When a physician visits a patient who already fulfills criteria for ALF diagnosis, immediate referral to a transplant center is mandatory. However, even in the absence of encephalopathy, every patient with a severe hepatitis [i.e., international normalized ratio (INR) $\geqslant$ 1.5], should be referred to a hospital with a transplant center to enable the best clinical management. In fact, if encephalopathy occurs, ALF diagnosis is made and the clinical picture rapidly worsens, timed listing and urgent LT can be necessary. Death caused by sepsis, cerebral edema, cardiovascular collapse and multiorgan failure[9,10] may occur within days of the onset of stage 3 or 4 hepatic encephalopathy[11,12]. On the other hand, in some patients with ALF, critical care support alone can be sufficient to save the patient's life[8,13,14]. When the etiology is known, specific treatments, especially if started early, might prevent progression of liver injury. However, the rare and severe nature of the disease means that few randomized trials have been done to establish best practice and the evidence base is therefore small. Transplantation

**Table 1 General indications for liver transplantation**

| |
|---|
| Acute liver failure |
| Complications of cirrhosis |
| Ascites |
| Encephalopathy |
| Synthetic dysfunction |
| Liver cancer |
| Refractory variceal hemorrhage |
| Chronic gastrointestinal blood loss due to portal hypertensive gastropathy |
| Hepatopulmonary syndrome |
| Portopulmonary hypertension |
| Hepatorenal syndrome |
| Recurrent cholangitis |
| Intractable pruritus |
| Malnutrition |
| Hepatic myelopathy |
| Quality of life impairment |
| Metabolic disorders causing cirrhosis |
| Alpha-1-antitrypsin deficiency |
| Wilson disease |
| Nonalcoholic steatohepatitis and cryptogenic cirrhosis |
| Hereditary hemochromatosis |
| Tyrosinemia |
| Glycogen storage disease type Ⅳ |
| Metabolic disorders causing severe extrahepatic morbidity |
| Amyloidosis |
| Hyperoxaluria |
| Urea cycle defects |
| Disorders of branch chain amino acids |
| Miscellaneous conditions |
| Budd-Chiari syndrome |
| Metastatic neuroendocrine tumors |
| Polycystic disease |
| Biliary atresia |
| Alagille syndrome |
| Nonsyndromic paucity of the intrahepatic bile ducts |
| Cystic fibrosis |
| Progressive familial intrahepatic cholestasis |

**Table 2 Contraindications to liver transplantation**

| |
|---|
| Absolute |
| Extrahepatic malignancy |
| Hepatic malignancy with macrovascular or diffuse tumor invasion |
| Active and uncontrolled infection outside of the hepatobiliary system |
| Active substance or alcohol abuse |
| Severe pulmonary hypertension uncontrolled with medical therapy |
| Obesity (BMI > 40 kg/m$^2$) |
| Advanced cardiopulmonary disease |
| Psychosocial factors that would likely preclude recovery after transplantation |
| Technical and/or anatomical barriers |
| Brain death |
| Acquired immune deficiency syndrome |
| Relative |
| Age |
| Cholangiocarcinoma |
| Portal vein thrombosis |
| Chronic or refractory infections |
| Human immunodeficiency virus infection |
| Previous malignancy |
| Active psychiatric illness |
| Poor social support |

Age restriction varies by centers and its limit is not universally agreed. However, it is generally approved that transplantation should not be performed in patients older than 70 years, unless in highly selected cases. BMI: Body mass index.

indications for ALF usually are based on the original or modified King's college and Clichy-Villejuif criteria[7]. However, there may be no more weighty a management decision than whether a patient with ALF should be listed for LT, since they have the highest priority over all with cirrhosis, often resulting in a rapid offer of an organ and precluding the option of watchful waiting.

### *Hepatitis C*

Liver disease caused by hepatitis C virus (HCV) is the main indication for deceased donor LT, being 26% (2009) in United States and 46% (2007-2009) in Italy[4,15]. Timing of referral, listing and prioritization should follow the general rules for cirrhosis (see introduction) and liver cancer (see below)[16].

With regard to clinical management and allocation policy, there are some issues specific for HCV positive recipients. Re-infection after OLT is almost universal in patients who are serum HCV-RNA positive at the time of transplantation. Progression of hepatitis C is accelerated in immunocompromised liver transplant recipients compared with immunocompetent patients and it significantly impairs patient and graft survival compared to non-HCV recipients, leading to histologically documented cirrhosis within 5 years in up to 30% of cases[17-19]. Several variables, including donor age, graft steatosis, degree of immunosuppression, viral load either pre-transplantation or early post-transplantation, timing of recurrence and early histological findings, are implicated in the severity of HCV recurrence[20,21]. Recently, recipient interleukin 28B (IL28B) polymorphism has been shown to be associated with more severe histological HCV recurrence, while the same polymorphism of both the recipient and the donor is strongly and independently associated with antiviral treatment response after LT[22,23]. Eradication of the virus before transplantation eliminates the possibility of recurrence and improves the long-term outcome post-transplantation[24]. Pre-transplant antiviral therapy is an option for patients with mildly decompensated liver disease and low MELD score[19]. Achievement of an on-treatment virological response is the goal of pre-transplant therapy, leading to high chances to be HCV infection-free post-transplantation. Post-transplant antiviral therapy in those with evidence of recurrent disease is the mainstay of management. A sustained virological response (SVR) is achieved with 48 wk of treatment in approximately 30% of treated patients. Survival is prolonged among those achieving a SVR. However, post-transplant antiviral therapy results are poor because of the high rate of virological relapse, dose reduction or discontinuations due to side effects. Since donor age, graft steatosis and donor and recipient IL28B polymorphism influence the severity of HCV recurrence and survival, in some transplant centers a specific allocation policy for HCV recipients is applied[25]. In this light, older donors (≥ 70 years) were

**Table 3 Main causes of acute liver failure**

| |
|---|
| Infective |
| Virus |
| *Hepatotropic*: HAV, HBV, HBV + HDV, HEV |
| *Non-hepatotropic*: Adenovirus, Epstein-Barr, Cytomegalovirus, Echovirus, Varicella Zoster virus, Yellow fever, Herpes simplex , Parvovirus B19, Coxsackie |
| *Rarely virus*: Lassa, Ebola, Marburg e Toga Virus |
| Bacteria: Salmonellosis, Tuberculosis, Septicemia |
| Others: Malaria, Bartonella, Leptospirosis |
| Drugs |
| Dose dependent: Paracetamol, Halothane |
| Idiosyncratic reactions: Isoniazid, Nonsteroidal anti-inflammatory drugs, Phenytoin, Sodium valproate, Carbamazepine, Ecstasy, Tioglitazone, Antibiotics, Allopurinol, Propylthiouracil, Amiodarone, ketoconazole, Antiretroviral drugs |
| Synergistic drug interactions: |
| Isoniazid + Rifampicin |
| Trimethoprim + Sulfamethoxazole |
| Barbiturates + Paracetamol |
| Amoxycillin + Clavulanic Acid |
| Toxins |
| Amanita phalloides (mushroom poisoning), Herbal medicines, Carbon tetrachloride, Yellow phosphorus, Industrial solvents, Chlorbenzenes |
| Metabolic disease |
| Galactosemia, Tyrosinemia, Hereditary fructose intolerance, Neonatal hemochromatosis, Niemann-Pick disease type C, Wilson's disease, Mitochondrial cytopathies, Congenital disorder of glycosylation, Acute fatty liver of pregnancy |
| Autoimmune hepatitis |
| Type 1 autoimmune hepatitis, Type 2 autoimmune hepatitis, Giant cell hepatitis with Coomb's positive hemolytic anemia |
| Vascular disease |
| Budd-Chiari syndrome, Acute circulatory failure, Heat stroke, Acute cardiac failure, Cardiomyopathies |
| Oncology disease |
| Hemophagocytic lymphohistiocytosis, Leukemia, Lymphoma |

HAV: Hepatitis A virus; HBV: Hepatitis B virus; HDV: Hepatitis delta virus; HEV: Hepatitis E virus.

preferentially allocated to HCV negative than to HCV positive recipients in the United States from 2002 to 2005. However, as recently shown in Italy, because of the high percentage of HCV positive recipients and of old donors, this strategy is not always feasible[15].

### Hepatitis B

Liver disease caused by hepatitis B virus (HBV) has decreased in recent years due to a better control of disease progression with drugs available. Deceased donor LT performed for HBV related cirrhosis represented 4% (1992-2007) in United States and 18% (2007-2009) in Italy[4,15].

Patients with HBV related chronic liver disease should undergo antiviral treatment independently of the liver transplant option[26]. Timing of referral and listing should follow the general rules for cirrhosis (see introduction) and liver cancer (see below)[16]. With regard to clinical management prioritization and allocation policy, there are some issues specific for recipients with HBV-related disease.

Since, in the past, transplanting patients with high HBV viremia was associated with severe HBV-related liver disease recurrence post-transplantation, nowadays the goal of nucleos(t)ide antiviral therapy in patients awaiting transplantation is to achieve a low level of serum HBV-DNA ($10^{2-3}$ copies)[27]. Prioritization can be reduced by clinical improvement secondary to antiviral treatment[28]. Although with most recent nucleos(t)ide the risk of viral resistance is very low, during the waiting list, serum HBV copies should be monitored at least every 3 mo to survey for antiviral efficacy and the development of viral resistance. While the optimal treatment regimen to prevent recurrence of HBV continues to evolve, most centers use hepatitis B immunoglobulin indefinitely with a nucleos(t)ide analogue and this reduces the risk of re-infection to less than 10% during the first 2 years following transplantation[20,29-33]. Patients with concomitant hepatitis delta virus (HDV) and HBV infection have the same indications for LT and benefit from the same pre- and post-transplant antiviral treatment as HBV mono-infected patients[34]. This results in the complete clearance of both HBV and HDV in most patients after LT, with very good survival rate at 5 years of almost 90%[35].

### Alcohol

Alcoholic liver disease is the second commonest indication for deceased donor LT after viral hepatitis, being 17.4% (2009) in United States and 16% (2007-2009) in Italy[4,15]. Moreover, alcoholic abuse contributes to more rapid progression of other causes of liver disease, particularly hepatitis C, to cirrhosis and hepatic failure[36].

Timing of referral, prioritization and allocation should follow the general rules for cirrhosis (see introduction) and liver cancer (see below)[16]. With regard to listing, however, when the indication for LT is established, the transplant center starts a close alcoholic follow-up to help the patient to stop drinking alcohol and verify his long-term abstinence. Most centers require a minimum of 6 mo before patients can be listed for a LT for two reasons. Firstly, this period enables clinicians to ascertain that there is insufficient improvement after alcohol discontinuation and that transplantation is still needed. Secondly, a period of abstinence of at least 6 mo is generally accepted to prevent the recidivism of alcohol abuse after transplantation[37]. Despite these precautions, patients who undergo transplantation for alcohol-induced cirrhosis have a wide variation in the rate of recidivism after LT that ranges from 19% to 50%[38-40]. In patients who have a relapse, the pattern of drinking post-transplantation is variable, but only a minority of patients, who return to heavy abusive drinking, can result in graft loss and decreased survival [41-43].

### Nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is the leading cause of cryptogenic cirrhosis[44,45]. Hepatic steatosis may in fact disappear after the development of cirrhosis, which may mask the diagnosis of NASH in some patients with NASH-related end stage liver disease[46]. This

is supported by the high prevalence of obesity, insulin resistance or diabetes, hyperlipidemia and other manifestations of the metabolic syndrome among patients with cryptogenic cirrhosis[44,47]. Deceased donor LT performed for cryptogenic/NASH cirrhosis represented 12% (2009) in United States and 5% (2007-2009) in Italy[48,15]. The prevalence of non alcoholic fatty liver disease (NAFLD) and NASH has increased in recent years and is about 46% and 12%, respectively[49]. It has been projected that NAFLD will be the most common indication for LT in the next 10-20 years[50,51]. At any rate, patients with cryptogenic/NASH cirrhosis should be referred for transplantation early because many require weight loss or other lifestyle changes before becoming appropriate candidates. Once in the presence of decompensation, the indication for listing has been established, strict selection criteria to exclude patients with contraindications need to be applied to reduce the risk of both perioperative complications and post-transplantation metabolic syndrome[16,52,53]. In fact, the latter increases the risk of post-transplant mortality related to cardiovascular events and of recurrent NASH. NASH recurrence after LT is common, with an incidence that ranges from 24% to 29%, but only few patients develop cirrhosis or graft failure (0-3.4%)[54,55] and this does not lead to an increased mortality, at least up to the first 5 years after operation[54].

### Cholestatic liver diseases

Chronic cholestatic liver disease in adults can be caused by primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and secondary biliary cirrhosis. In cholestatic cirrhosis, MELD score may not be a good indicator for the assessment of disease severity. This has important implications for a patient's referral, listing and prioritization. Timing of referral should follow the general rules for cirrhosis but disease specific conditions are also very important. An appealed MELD score may be granted *via* this process to help prioritize patients with cholestatic cirrhosis with these disease-specific conditions for LT. No particular liver graft allocation policy is currently applied to patients with cholestatic liver disease.

Deceased donor LT performed for cholestatic liver diseases represents 7.9% (2009) in United States and 4% (2007-2009) in Italy[4,8]. With regard to PBC, early diagnosis and ursodeoxycholic acid (UDCA) treatment delay histological progression and improve survival without transplantation[56-58]. The most widely used prognostic score for PBC is the "Mayo risk score" which depends on age, bilirubin, albumin, prothrombin time and presence or absence of fluid retention. Patients should be referred to a liver transplant center for assessment when the Mayo risk score is $\geqslant$ 7.8, their bilirubin approaches > 6 mg/dL (103 mol/L) and the MELD score is > 12[59]. Disease specific reasons to refer a PBC patient to a transplant center are intractable pruritus and profound fatigue[60]. Also for PSC, a prognostic "Revised Mayo model", based on patient age, serum bilirubin, history of variceal bleeding and serum albumin, helps to predict patient survival[61]. However, the 2010 American Association for the Study of Liver Diseases guidelines advised against the use of prognostic models in an individual patient and it is known that disease progression and the quality of life of PSC patients can be impaired by recurrent episodes of angiocholitis, jaundice and intractable pruritus. Thus, early referral should be based on clinical signs and symptoms, biochemical parameters and, in some patients, the status of the concomitant inflammatory bowel disease[62]. A direct management of angiocholitis, jaundice, pruritus and possible dominant biliary strictures by the transplant team allows optimization of timing to list the patient. In addition, although the risk of future development of cholangiocarcinoma should not be considered a reason for listing on a prophylactic basis, careful surveillance is mandatory before transplantation. Secondary biliary cirrhosis can be caused by a previous surgical procedure, stones, cysts, parasite or malignancy. LT for secondary biliary cirrhosis is extremely rare.

### Autoimmune cirrhosis

Deceased donor LT performed for autoimmune cirrhosis represented 4%-6% (1992-2007) in United States and 0.5% (2007-2009) in Italy[4,8].

Indications for LT in autoimmune end-stage liver disease do not differ from those of other cirrhotic patients[63], except for the cases in which it occurs as ALF (see above). Generally, early treatment with immunosuppressive therapy prevents irreversible liver damage and is associated with clinical remission in about 80%, obtaining ten year survival rates of > 90%[64,65] against a ten year survival < 30% in untreated patients[66,67].

A late diagnosis and treatment of autoimmune hepatitis, inadequate response or intolerance to immunosuppressive therapy or noncompliance with treatment cause a progression of liver disease requiring LT[68,69]. Most patients affected by autoimmune hepatitis who underwent LT had a history of long-standing immunosuppression with steroids, azathioprine or cyclosporin; thus, often they had comorbidities such as systemic hypertension, diabetes and osteoporosis. Moreover, in the early postoperative course, these patients have a high risk of developing severe sepsis. Recurrent autoimmune hepatitis in transplant allograft occurs in approximately 30% of patients at 5 years[70,71]. Moreover, the risk of acute and chronic rejection seems to be greater in these patients[70,72,73].

## TIMING OF LT ACCORDING TO THE TYPE OF CIRRHOSIS COMPLICATION

### Liver dysfunction

Referral to a LT center for cirrhotic patients should occur at the moment of any complication, including hepatic synthetic dysfunction. The severity of synthetic dysfunction is the most frequent determinant of patient listing, prioritization on the waiting list and timing of

transplantation. The degree of synthetic dysfunction is included in the Child-Turcotte-Pugh (CTP) classification, which was designed to stratify the risk of portacaval shunt surgery in patients with cirrhosis and variceal bleeding[74] and is widely used as a means for assessing the severity of a patient's chronic liver disease. However, the CTP classification is limited by subjectivity of the disease's assessment, with regard to the severity of ascites and encephalopathy, and by its poor performance to prioritize patients on the waiting list because there are only a few classes in which all patients are categorized. Moreover, another limitation of the CTP score is that it does not consider renal function, which is an independent predictor of survival in patients with end-stage liver disease[75].

The search for a prognostic scoring system based on objective variables has prompted the proposal of using a mathematical score, named the MELD score, determined from the patient's serum bilirubin, serum creatinine and INR, that was originally developed to assess short term postoperative prognosis in patients undergoing transjugular intrahepatic portosystemic shunts[6]. Using the MELD model, patients are assigned a score in a continuous scale from 6 to 40, which equates to estimated 3 mo survival rates from 90% to 7%, respectively[6]. Subsequent studies of this model demonstrated its usefulness as an effective tool for determining the prognosis of groups of patients with chronic liver disease[76].

Since 2002 in the United States, recipient prioritization on the liver transplant waiting list is based on the MELD score[77]. Donor allocation policies, once recipients are prioritized on the waiting list according to the MELD system, can follow three different policies: the first is "urgency" that is the sickest patients (i.e., with the highest MELD score) should be treated first and donors allocation corresponds to recipient prioritization. This policy is based on the fact that mortality on the waiting list increases proportionally to the MELD score at the time of listing and leads to a decrease of mortality on the waiting list[77-80]. However, the "urgency" policy has limitations due to the MELD calculation system (inter-laboratory variations for measurement of serum creatinine and INR of prothrombin time, and a systematic adverse female gender bias due to kidney function overestimation) and does not take into account donor factors associated with transplant outcome[81]. The latter limitation has been addressed by the "utility" policy of donor allocation that is based on avoiding combined poor recipient and donor characteristics leading to very poor outcomes. Finally, "transplant benefit" models rank patients according to the net survival benefit that they would derive from transplantation (i.e. better survival with, than without, transplantation), again taking into account both recipient and donor characteristics[82,83]. A careful analysis of patients with MELD scores < 15 showed that they face a greater mortality risk from the transplant procedure than from their liver disease without surgery[84]. As a result, although referral to a transplant center in the absence of other intractable complications can be done even for patients with a MELD score < 15, since 2005 different policies have been implemented to avoid transplants performed in patients with a MELD score < 15. The application modalities of the "transplant benefit" principle are still debated because of several reasons[85-87]. Firstly, while the principle implies that the higher the MELD score, the greater is the life gained after operation in relative terms, the absolute survival rates after LT performed in very sick patients are low. This poses the question of judging when a transplant is futile in terms of liver graft and resource utilization. Secondly, the "transplant benefit" principle is based on complex statistical models and unmeasured characteristics may unduly affect the models. In addition, the model is based on the assumption that the MELD score is a good prognostic tool both before and after LT. However, MELD score is a good predictor of pre-transplant wait list mortality, while it is not a widely accepted post-transplant prognostic tool[88-92]. Thirdly, in patients with relatively low MELD scores but severe and intractable complications considered as standard exceptions (e.g., HCC, refractory ascites, *etc*.), the MELD fails to display the urgency for LT.

It is a matter of discussion whether and how to artificially modify the calculated MELD score in these patients (see below).

### HCC

Deceased donor LT performed for HCC represent 18% (2009) in United States and 44% (2007-2009) in Italy[4-15].

Cirrhosis, particularly when HCV or HBV related, represents a risk factor for the development of HCC; thus, systematic screening using ultrasound examination at 6 mo intervals is strongly recommended[93] and widely applied, allowing detection of HCC at an earlier stage. Ideal candidates for LT, allowing for the best survival rates, are HCC patients within the so called "Milan criteria" (single nodule 2 cm or larger and less than 5 cm, or no more than three lesions, the largest of which is less than 3 cm, with no evidence of macrovascular invasion or metastasis). Many centers have proposed expanding the limits of tumor size and number of nodules; however, the expansion of Milan criteria have not been widely accepted[94-98]. Although LT offers the best results in the long term because it allows curing both HCC and the underlying liver disease, donor shortage impose that, according to the transplant center policy, HCC patients within the "Milan criteria", if indicated according to tumor location, number and size and severity of the underlying cirrhosis, can initially be submitted to potentially curable non-transplant therapies (i.e., hepatic resection or radiofrequency thermo ablation)[99]. The same approach should also be applied to patients with a single HCC nodule between 1 and 2 cm (very early HCC), leaving the transplant option in a timely fashion only to those that are not cured and progress. Thus, early referral to a transplant center is advisable, even for very early HCC, so that

the best treatment strategy, including its eventual failure and listing, are managed by the same multidisciplinary team. In addition, according to the single center policy, patients exceeding the Milan criteria but with no evidence of macrovascular invasion or metastasis can be referred and submitted to hepatic resection or locoregional treatments to downstage the tumor, allowing subsequent patient listing. This strategy, however, remains controversial and the need and duration of a period of observation proving disease response or stabilisation before the patient can be listed is critical[93,100].

A further field of debate is the opportunity to submit patients with HCC already listed for bridging procedures. The term bridging is reserved for locoregional strategies that are implemented in patients who already qualify for transplantation according to standard selection criteria so that they can wait until they receive a graft without a significant progression. It is suggested that the option to treat patients within a bridging strategy is considered when expected waiting time is longer than 6 mo[101].

With regard to prioritization, in HCC patients with compensated cirrhosis and low calculated MELD score, MELD exception points are granted to perform transplantation before the tumors have the time to progress to dropout criteria. Ideally this strategy should aim to balance the chances of HCC patients and non-HCC patients to get LT.

Since the risk of graft failure after LT is increased by allocating poor quality donor organs to recipients with a very high calculated MELD score, it has been shown that, in countries with a high percentage of poor quality donors like Italy, these donors are preferentially allocated to HCC patients with a relatively low calculated MELD score[15].

### *Refractory ascites, hyponatremia, spontaneous bacterial peritonitis and hepato-renal syndrome*

When cirrhosis decompensation is characterized by the first episode of ascites, referral to a transplant center allows prospective follow-up of the patient and establishes the right timing for listing. The latter is indicated by the presence of refractory ascites with or without hyponatremia and by the occurrence of spontaneous bacterial peritonitis (SBP) or hepato-renal syndrome (HRS).

The International Ascites Club defined refractory ascites as "ascites that cannot be mobilized or the early recurrence of which (i.e., after large volume paracentesis) cannot be satisfactorily prevented by medical therapy" [102,103]. The diagnostic criteria for refractory ascites allow to distinguish "diuretic-resistant ascites" when this cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment; and "diuretic-intractable ascites" when this cannot be successfully treated because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage[104]. The lack of response is defined as mean weight loss < 0.8 kg over 4 d and urinary sodium output less than the sodium intake with a maximal diuretic therapy (spironolactone 400 mg/d and furosemide 160 mg/d) and a salt-restricted diet (less than 90 mmol/d)[104]. Once ascites becomes refractory to medical treatment, patients have a median survival of approximately 6 mo[103,105,106]; thus, they should be considered for LT.

Once on the waiting list, refractory ascites can be managed by large volume paracentesis with albumin administration, continuing diuretic therapy (if effective in inducing natriuresis) or transjugular intrahepatic portosystemic shunt (TIPS) insertion. TIPS cannot be recommended in patients with severe liver failure (serum bilirubin > 5 mg/dL, INR > 2 or Child-Pugh score > 11, current hepatic encephalopathy grade 2 or chronic hepatic encephalopathy), concomitant active infection, progressive renal failure, or severe cardiopulmonary diseases[104]. MELD exception points are not usually granted to prioritize patients with refractory ascites on the waiting list.

Hyponatremia (< 130 mEq/L) is associated with a poor prognosis in cirrhosis. In patients with cirrhosis and ascites, the risk of developing hyponatremia is 15% at 1 year with a 25% probability of survival at 1 year. Serum sodium concentration improves the prognostic ability of the MELD score in patients awaiting LT[88,107,108]. While during an episode of SBP LT is contraindicated, patients who recover from an episode of SBP have a reduced survival and should be listed for LT. Due to the high prevalence of SBP in patients with ascites, diagnostic paracentesis should be performed routinely in all cirrhotic patients admitted to the hospital with ascites, especially in those on the waiting list for LT and when systemic or local signs suggestive of SBP (i.e., fever, leucocytosis, shock, abdominal pain, rebound tenderness, ileus) are present. LT is the treatment of choice for both type 1 and type 2 HRS, with survival rates of approximately 65% in type 1 HRS. The lower survival rate compared to patients with cirrhosis without HRS is due to the fact that renal failure is a major predictor of poor outcome after transplantation. Moreover, patients with type 1 HRS have a high mortality whilst on the waiting list and ideally should be given priority for transplantation. Patients with HRS who respond to vasopressor therapy should be treated by LT alone. Patients with HRS who do not respond to vasopressor therapy and who require renal support should generally be treated by LT alone, since the majority will achieve a recovery of renal function post LT. There is a subgroup of patients who require prolonged renal support (> 12 wk) and it is this group that should be considered for combined liver and kidney transplantation.

The reduction in serum creatinine levels after treatment and the related decrease in the MELD score should not change the decision to perform LT since the prognosis after recovering from type 1 HRS is still poor. LT is the best treatment for both type 1 and type 2 HRS. Although the impact of pre-transplant medical treatment of HRS on post-transplant survival is still debated, this may allow a longer survival on the waiting list and better

access to LT[109].

### Hepatic encephalopathy

Hepatic encephalopathy (HE) is a complex and potentially reversible neuropsychiatric syndrome that frequently occurs (28% to 41%) in patients with cirrhosis, associated with poor prognosis[110]. HE in cirrhotic patients involves the coexistence of two predisposing factors: liver dysfunction and portocaval anastomosis. The diagnosis is clinical and confirmed after excluding other causes of changes in mental status. When cirrhosis decompensation is characterized by the first episode of encephalopathy, referral to a transplant center allows prospective follow-up of the patient and establishes the right timing for listing[11,111]. In this light, is important to avoid and prevent HE precipitating factors, including the institution of prophylactic measures[112]. Protein restriction is not recommended. Oral synthetic disaccharides (lactulose and lactitol) and rifaximin are currently used to prevent new HE episodes. In patients without any other indication to be listed, this can be proposed if HE is persistent or episodic and all the other therapies fail. There is currently no justification for automatically and systematically increasing priority for candidates with symptoms of HE. At this time, because of the lack of a quantifiable, verifiable and reproducible method of documenting HE, intractable or complicated HE should be addressed by the "Review Boards" and additional priority be assigned case-by-case[113]. Reasons for prioritization other than reduced quality of life due to HE are both a negative effect on patient nutritional status in the pre-transplant period through decreased oral intake and the increased risk for post-transplant neurological complications associated with the severity of HE before transplantation[114,115].

### Uncontrolled variceal bleeding

Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients and despite the availability of effective therapy to prevent re-bleeding, it is associated with a mortality of at least 20% at 6 wk[116-118].

In patients with medium/large varices that have not bled but have a high risk of hemorrhage, nonselective β-blockers (propranolol or nadolol) or endoscopic variceal ligation (EVL) may be recommended for the prevention of first variceal hemorrhage. Patients with cirrhosis who survive an episode of active variceal hemorrhage should receive therapy to prevent recurrence of variceal hemorrhage (secondary prophylaxis) with combination of nonselective β-blockers plus EVL[119,120]. TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy[121,122]. TIPS may be used as a bridge to transplantation[120]. Surgical shunt in Child-Pugh A and B patients is an alternative if TIPS is unavailable[119,120].

Patients who experience a first episode of variceal bleeding should be referred to a transplant center for evaluation. In patients without any other indication to be listed, this can be proposed if all the other therapies fail to reduce the bleeding risk. MELD exception points are not usually granted to prioritize patients with uncontrolled variceal bleeding.

### Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder characterized by the triad of a widened age-corrected alveolar-arterial oxygen gradient (more than 15 mmHg) while breathing room air, the presence of liver disease and/or portal hypertension, and evidence for intrapulmonary vascular dilatation[121]. The mechanism by which portal hypertension results in pulmonary vascular dilatation is unknown but appears to involve local effects of increased nitric oxide leading to ventilation–perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion. Another feature of HPS is impairment in hypoxic pulmonary vasoconstriction leading to a relatively fixed pulmonary vascular tone unable to respond to gravitational changes[122-125].

The suspicion of HPS stands on the findings of arterial hypoxemia (< 80 mmHg) measured when the patient is sitting and at rest, associated with unremarkable pulmonary function testing and chest radiographs. The use of the more sensitive alveolar-arterial oxygen gradient ⩾ 15 mmHg) is important because it can increase abnormally before the partial pressure of oxygen itself becomes abnormally low as the gradient measure compensates for the reduced levels of arterial carbon dioxide and hyperventilation, along with respiratory alkalosis, that are common in cirrhosis[126]. The clinical picture of HPS consists in an insidious onset of orthodeoxia (when the partial pressure of oxygen in arterial blood decreases by 5% or more or by 4 mmHg or more when the patient moves from a supine to an upright position). This can be associated with platypnea (he or she may describe worsening dyspnea by changing position). Since the median survival of patients with cirrhosis and severe HPS is less than 12 mo[127], the condition is reversible after LT and no other treatment is effective[128,129], referral to a transplant center should be done when the suspicion of HPS is present, even in the absence of any other complication of cirrhosis. In addition, every cirrhotic patient who is a candidate for LT should undergo screening for HPS regardless of symptoms. HPS diagnosis is confirmed by contrast two-dimensional transthoracic echocardiography (TTE). Owing to its sensitivity and noninvasive nature, TTE using agitated saline is able to visualize micro bubbles created by injection of agitated saline into a peripheral vein in the left atrium and left ventricle within 3-6 cardiac cycles. In individuals with normal pulmonary vasculature, injected micro bubbles do not pass through the pulmonary microcirculation and therefore do not appear on the left side of the heart. In addition, very rapid (faster than 3 heart beats) micro bubbles passage is due to intracardiac shunt. Degrees of severity of HPS according to $PaO_2$ are: mild (⩾ 80 mmHg), moderate (⩾ 60 to < 80 mmHg), severe (⩾ 50 to < 60 mmHg) and

very severe (< 50 mmHg)[126].

In the absence of other indications, the optimal LT timing is when HPS is severe, while mortality and morbidity after LT are unacceptable when it is very severe. Thus, patients are listed according to each transplant center policy and receive MELD exception points to enhance prioritization only when HPS is severe.

### Portopulmonary hypertension

Portopulmonary hypertension (POPH) is defined by the presence of a mean pulmonary artery pressure above 25 mmHg at rest (> 30 mmHg with exercise) and a pulmonary capillary wedge pressure less than 15 mmHg or an elevated transpulmonary gradient (the mean pulmonary artery pressure minus the pulmonary artery occlusion pressure; abnormal is > 12 mmHg) on right-heart catheterization, occurring in the context of confirmed portal hypertension[130]. In addition, increased pulmonary vascular resistance (> 240 dyn·s·cm$^{-5}$) is required for the diagnosis of POPH[131]. Inclusion of this pulmonary vascular resistance criterion is important to distinguish "true" POPH from pulmonary hypertension caused by a hyperdynamic circulatory state frequently present in cirrhosis[132].

The pathogenesis of POPH, still unclear at present, involves circulating vasoactive mediators and genetic factors in addition to the hyperdynamic circulation secondary to portal hypertension. Many patients are completely asymptomatic in the early stages of POPH, followed by nonspecific dyspnea on exertion. Diagnosis of POPH is based on doppler echocardiography. Doppler-derived systolic pulmonary artery pressure above 40 mmHg should lead to right-heart catheterization to confirm elevated mean pulmonary artery pressure (mPAP). On the basis of the level of mPAP at rest, severity of POPH may be classified into mild (mPAP 25-35 mmHg), moderate (mPAP 36-45 mmHg) and severe (mPAP > 45 mmHg)[131]. Since patients with moderate or severe POPH have low survival rates after LT, when these conditions are unresponsive to medical treatment, LT is considered contraindicated. Thus, the occurrence of POPH must be excluded in every patient evaluated before listing and periodically on the waiting list. LT, however, can be performed with excellent survival in patients with moderate or severe POPH who are able to respond to medical treatment (intravenous prostanoids, blockers of endothelin receptors, and inhibitors of phosphodiesterase-5) and reduce their mPAP to < 35 mm Hg[132].

Since medical treatment can reduce its efficacy over time, even in the absence of other indications for LT, patients with cirrhosis and moderate or severe POPH who respond to therapy should be promptly referred to a transplant center. In addition, mPAP values should be closely followed-up and, although this is still debated, prioritization on the waiting list by MELD exception points should be implemented[133].

## CONCLUSION

Patients should be referred to a liver transplant center if they have evidence of severe hepatitis, fulminant hepatic failure, a life-threatening systemic complication of liver disease or a liver-based metabolic defect, or, more commonly, cirrhosis with complications. While the complications of cirrhosis can often be effectively managed with other treatments, they indicate a change in the natural history of the disease that should lead to consideration of LT. The decision regarding the appropriateness of transplantation and listing the patient should usually be left to the transplant center by judging the severity of disease, complications and eventual contraindications. Prioritization policy on the waiting list, based on the MELD score, is a field of debate with regard to which complications, other than HCC and a few rare conditions, should be prioritized and how.

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