Evaluation Process of the Liver Transplant Recipient

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Pierluigi Toniutto, Ezio Fornasiere, Elisa Fumolo, and Davide Bitetto

Overview

Liver transplantation (LT) is currently considered a standard surgical procedure offered to a large proportion of patients with end-stage liver diseases. LT is available in most regions of the world and is associated with excellent patient and graft survival. In USA and in Europe, the graft survival at 1 year is >90% and >60% at 10 years [1, 2]. Although the improvement in outcomes and better awareness have resulted in an increasing demand for LT around the world, its ubiquitous application is limited by the scarcity of available donor liver grafts [3].

The success of LT depends on many factors. The main one is related to the correct indication for LT and to the assessment of the urgency of performing the procedure. At the same time, in the selection process of the potential candidate for LT, the other crucial aspect is to identify the presence and assess the severity of extrahepatic comorbidities which could negatively impact post-transplant survival. Although no formal age limit for candidate patients for LT exists, the presence of comorbidities is expected to be particularly relevant in patients over 65 years of age. For this reason, the final decision regarding patients aged 65–70 or older, who are candidates for LT, should be taken after a thorough multidisciplinary discussion [4].

This chapter illustrates the selection process of the candidate for LT focusing on the preoperative evaluation of extrahepatic organs and systems. Furthermore, the impact of psychosocial or of more rare clinical problems in conditioning the eligibility of LT will be considered.

P. Toniutto (✉) · E. Fornasiere · E. Fumolo · D. Bitetto
Hepatology and Liver Transplantation Unit, University Hospital, Udine, Italy
e-mail: pierluigi.toniutto@uniud.it

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7.1 Introduction

The LT assessment process starts with a detailed history and physical examination of the candidate. Strong emphasis should be placed on eliciting any history of cardiopulmonary risk factors, extrahepatic malignancies, or other chronic ailments [5]. It is of particular importance to highlight a history of coronary artery disease (CAD), especially in patients with concomitant diabetes mellitus, hyperlipidemia, and obesity. Patients with a previous history of extrahepatic cancer, except cases of non-melanoma skin cancer, can proceed with the evaluation process for LT if they have received a curative treatment and have a sufficient recurrence-free interval in line with the cancer involved [6].

After having established with this initial clinical screening that there are no obvious extrahepatic contraindications to LT, the next step of the recipient evaluation process consists in performing laboratory (Table 7.1) and instrumental (Table 7.2) testing as well as visits with the physicians and nurses of the transplant team to more accurately assess the function of the extrahepatic organs and to verify the absence of extrahepatic contraindications to LT.

Table 7.1 Standard blood tests performed in the selection process of candidate for liver transplantation

Complete blood count
Reticulocyte count
Liver chemistry
AST, ALT, γGT, AF, total and direct bilirubin, LDH, albumin, and ammonia
Kidney profile
Creatinine, creatinine clearance (estimated by MDRD-6 formula), sodium, potassium, calcium, phosphorus, magnesium, PTH, arterial blood gas analysis, complete urine examination, and 24-h urine examination in cases of abnormal complete urine examination
Coagulation profile
INR and PTT
Glucose, lipid, protein, and vitamin profile
Glucose, HbA_{1c}, total and HDL cholesterol, triglycerides, protein electrophoresis, 25(OH) vitamin D, vitamin B12, and folate
Iron study
Iron, transferrin, transferrin saturation, and ferritin
Tumor markers
AFP, CEA, CA 19.9, and PSA (in men)
Autoimmunity
ANA, SMA, AMA, and ANCA
Additional tests
Ceruloplasmin, copper, α-1 antitrypsin, copper concentration in the 24-h urine collection, TSH, and Papanicolau test in women

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *γGT* gamma-glutamyl transpeptidase, *AF* alkaline phosphatase, *LDH* lactic dehydrogenase, *MDRD-6* Modification of Diet in Renal Disease-6, *PTH* parathormone, *INR* international normalized ratio, *PTT* partial thromboplastin time, *HbA_{1c}* glycated hemoglobin, *AFP* alfa-feto protein, *CEA* carcinoembryonic antigen, *CA 19.9* carbohydrate antigen 19.9, *PSA* prostate-specific antigen, *ANA* antinuclear antibody, *SMA* smooth muscle antibody, *AMA* antimitochondrial antibody, *ANCA* antinuclear cytoplasm antibody, *TSH* thyroid-stimulating hormone

Table 7.2 Standard imaging and endoscopy tests performed in the selection process of candidate for liver transplantation

Imaging tests
Chest X ray, chest CT scan (in cases of HCC or in patients with risk factors for lung cancer), abdominal ultrasonography with Doppler imaging, abdominal contrast CT scan or MRI, brain CT or MRI, and mammogram and transvaginal ultrasound for women. Echocardiography (with bubble/contrast if HPS is suspected) and ultrasonography with Doppler imaging of the carotid arteries and DEXA scan
Endoscopic tests
EGD and colonoscopy and ERCP in patients with PSC or biliary strictures
Additional tests
Complete lung function tests, electrocardiography, Dobutamine echocardiography, coronary artery CT scan or coronarography (in patients with risks for coronary artery diseases such as type 2 diabetes mellitus, obesity, smoking, hypertension, peripheral artery diseases, and obesity), and right heart catheterization in suspected PPH

HCC hepatocellular carcinoma, *HPS* hepatopulmonary syndrome, *DEXA* dual-emission X-ray absorptiometry, *EGD* esophagogastroduodenoscopy, *ERCP* endoscopic retrograde cholangiopancreatography, *PSC* primary sclerosing cholangitis, *PPH* portopulmonary hypertension

7.2 Assessing the Cardiovascular System

Cirrhotic cardiomyopathy defines several cardiac disorders consisting of abnormal systolic response to stress, diastolic dysfunction at rest, and several electrophysiological anomalies that have been identified in patients with advanced cirrhosis [6, 7]. Moreover, although patients with advanced cirrhosis typically present low levels of plasma lipids and arterial hypotension, the prevalence of silent CAD is of 13.3% in LT candidates older than 50 years [8]. It is expected that LT candidates in the near future will be older, and more frequently affected by metabolic syndrome associated with nonalcoholic steatohepatitis (NASH)-related end-stage liver disease. Thus, the prevalence of CAD and peripheral vascular diseases is presumed to be growing [9].

Perioperative cardiovascular complications are a leading cause of morbidity and mortality after LT [10]; thus, a careful assessment of cardiovascular disease in LT recipients is mandatory and it is advisable that an expert cardiologist should be involved [6]. Basic electrocardiography (ECG) and transthoracic echocardiography, as well as Doppler ultrasound analysis of carotid arteries, are required for all LT candidates [6]. These basic analyses can document several cardiac abnormalities. The demonstration of prolonged QT interval on ECG, as well as electromechanical dyssynchronies and chronotropic incontinence do not contraindicate LT, as these abnormalities generally disappear in the posttransplantation period. In cases of more complex and severe electrophysiological abnormalities, not amenable to medical or surgical treatment, the risk/benefit ratio to perform LT should be carefully discussed with an expert cardiologist [6]. Echocardiography is able to determine the presence of valvular heart diseases, to assess the left ventricular ejection fraction, and to estimate right ventricular and pulmonary systolic pressure. There is a general agreement in considering LT with caution in patients with left ventricular ejection fraction < 55%, taking into account any other features of cirrhotic cardiomyopathy [7].

More complex is the management of patients with suspected pulmonary artery hypertension (mean pulmonary arterial pressure > 25 mmHg) assessed by baseline echocardiogram. It is important to note that using receiver operating characteristic analysis, systolic right ventricular pressure cut-off > 47 mmHg, determined by echocardiography, was 59% sensitive and 78% specific to diagnose pulmonary artery hypertension in LT candidates [11]. Thus, in any patient evaluated for LT with a suspicion of pulmonary artery hypertension on echocardiography screening test, the confirmation by direct right-side heart catheterization and pressure measurement is required [6]. Besides the presence of interstitial lung diseases (see section regarding "assessment of the respiratory system") or heart diseases that can induce secondary pulmonary hypertension, in patients with cirrhosis and portal hypertension, a specific syndrome named portopulmonary hypertension (PPH) should be suspected.

PPH is reported in about 6% of LT candidates [12]. It is defined by mean pulmonary arterial pressure > 25 mmHg, elevated vascular resistances (>240 dyne/cm^2), and either a low pulmonary artery occlusion pressure (12 mmHg) [13]. The identification and the correct management of PPH are of paramount importance because it influences post-LT clinical outcome. LT is contraindicated in the presence of severe and uncontrolled PPH (> 50 mmHg) since the mortality rate after transplant approaches 100%. More debatable is the indication to perform LT in the presence of moderate PPH (between 35 and 50 mmHg) because the mortality rate after transplant remains higher than 50% [14]. Several pharmacological strategies have been proposed to treat PPH. These account for the use of prostacyclin or its analogues, endothelin receptor antagonists (bosentan), or phosphodiesterase inhibitor type 5 (sildenafil). There is a general agreement that in patients who respond to the aforementioned treatments and achieve mean pulmonary arterial pressure values ≤35 mmHg, LT can be proposed [4, 15].

In patients with negative results of basic cardiac investigations, the decision to proceed with second-line cardiologic tests should be taken considering the presence of additional risk factors for CAD. These include age older than 50 years, presence of DM, hyperlipidemia, hypertension, obesity, preexisting or familial history of CAD, and cigarette smoking [16, 17]. Initial second-line noninvasive testing should consider exercise stress testing. However, in many patients, the presence of tense ascites, sarcopenia, and/or severe motility impairment prevent the achievement of a target heart rate during the exercise test [6]. For these reasons, initial noninvasive testing is usually achieved with direct inotropic stimulation with dobutamine stress echocardiography or with nuclear imaging techniques [4, 18]. Dobutamine stress echocardiography has negative and positive predictive values for significant intraoperative cardiac events of 78% and 30%, respectively [16], and is inconclusive in 37% of LT candidates [19]. Patients with inconclusive dobutamine stress test can be considered for other noninvasive tests such as computed tomography (CT) scan or cardiac magnetic resonance imaging (MRI) [16], if the probability pretest for having CAD remains elevated. This concept is important because dobutamine stress echocardiography identifies only patients with CAD so severe as to impair cardiac muscle oxygenation.

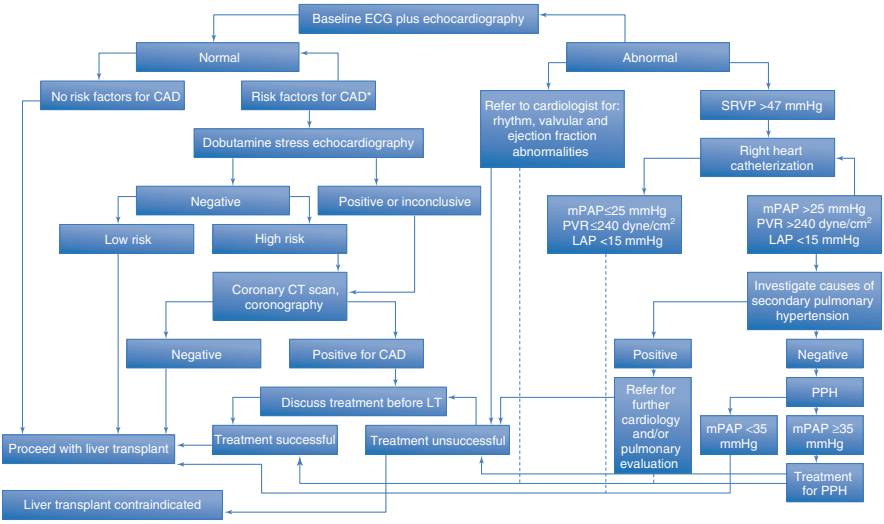

Fig. 7.1 Cardiologic diagnostic algorithm in liver transplant candidate. *ECG* electrocardiography, *CAD* coronary artery disease. Risk factors for CAD*: age > 50 years, obesity, type 2 diabetes mellitus, smoking, dyslipidemia, hypertension, familial history of CAD; *SRVP* systolic right ventricular pressure, *mPAP* mean pulmonary arterial pressure, *PVR* pulmonary vascular resistances, *LAP* left atrial pressure, *PPH* portopulmonary hypertension

Patients with multiple risk factors for CAD should proceed directly to coronary angiogram [20]. CAD involving multiple vessels negatively impacts post-LT mortality, length of hospitalization, and contributes to complicating posttransplant management. In the presence of critical CAD, percutaneous coronary revascularization can be performed before LT. By contrast, surgical revascularization before LT is generally contraindicated by the high perioperative risks of cardiothoracic surgery performed in patients with advanced cirrhosis [21].

An algorithm illustrating the cardiologic diagnostic workup in liver transplant candidate is proposed in Fig. 7.1.

7.3 Assessing the Respiratory System

Baseline respiratory function in patient candidates for LT should be assessed by means of: spirometry, measurement of the diffusion capacity of the lung for carbon monoxide, arterial blood gas analysis, and chest X-ray [6]. Since a CT scan of the abdomen is performed in all patients who are candidates for transplantation, the practice of always performing a chest CT scan, especially in patients with HCC, is increasingly widespread. Several reports indicate that preoperative clinical factors that are independently associated with respiratory complications following nonthoracic surgery include age >65 years, smoking of 40 pack-years, history of chronic obstructive airways disease, and exercise capacity of two blocks or less or one flight

of stairs [22]. Seldom do pulmonary abnormalities alone contraindicate LT (unless the abnormalities are extreme). However, increased pulmonary surgical risk added to other risk factors may help the liver transplant team decide for or against listing a patient for LT, and identify those who will require intense pulmonary management following surgery.

Massive ascites and pleural effusions are common in patients with cirrhosis and can negatively affect oxygenation and ventilation. Hepatic hydrothorax is defined as the presence of pleural effusion in patients with liver cirrhosis in the absence of primary cardiopulmonary disease [23]. This condition is present in about 5–10% of cirrhotic patients with ascites, although up to 20% of the cases may not have detectable ascites [24]. Thus, candidates for LT who present pleural effusion require, in addition to chest and heart imaging, a detailed laboratory evaluation of the pleural fluid. The typical fluid from hepatic hydrothorax is a sterile transudate with low cell counts, low protein levels (< 2.5 g/dl) with a fluid protein-to-serum protein ratio < 0.5, a lactate dehydrogenase fluid-to-serum ratio < 0.6, and pleural fluid amylase lower than serum amylase [25]. It is important for the fluid to be processed using Gram stain, acid-fast bacilli stains, and fungal stains. Furthermore, cultures of the fluid must be obtained to rule out the presence of infections and cytologic examination must be performed to rule out malignancies. If a suspicion of infection or malignancies remains, thoracoscopic inspection and pleural biopsy should be considered [23]. Candidates for LT with a large hepatic hydrothorax should have their pulmonary function tests and gas exchange evaluated following therapeutic thoracentesis. The management of hepatic hydrothorax is challenging because repeated thoracenteses are often ineffective in reducing the pleural effusion's reappearance. Furthermore, the insertion of a chest tube should be avoided since the associated protein and fluid loss carries a high morbidity and mortality [26]. A more recent approach to treating hepatic hydrothorax is the insertion of transjugular intrahepatic portosystemic shunt (TIPS); however, in a significant proportion of patients, pleural effusion reappears with this technique too [27]. Since hepatic hydrothorax frequently relapses, at many transplant centers, this condition allows for the requesting of priority in the waiting list (see Chap. 9).

In patients who, in the baseline arterial blood gas analysis, presented an alveolar-arterial oxygen gradient (AaO_2) > 20 mmHg and/or pO_2 <70 mmHg breathing room air, hepatopulmonary syndrome (HPS) should be suspected [28]. HPS is characterized by the presence of chronic liver disease, abnormal gas exchange resulting in an increased alveolar-arterial oxygen gradient, and the evidence of intravascular pulmonary vasodilation and shunting [29]. Intrapulmonary shunts are identified on transthoracic contrast-enhanced echocardiography [30] or a macroaggregate albumin lung perfusion scan ([99 m]Tc-MAA) [31]. Contrast transthoracic echocardiography should be considered the preferred diagnostic tool. Agitated saline solution is used as a contrast by creating a stream of microbubbles after intravenous injection. These microbubbles are larger than the diameter of the pulmonary capillaries. They appear on the right side of the heart in the normal subject and then are filtered into the pulmonary vascular bed but they should not appear on the left side of the heart. If microbubbles appear in the left side of the heart within three heart beats, an intracardiac

right to left shunt is suspected. Appearance of microbubbles on the left side of the heart four to six beats after the appearance in the right side of the heart suggests the presence of pulmonary vascular dilation or pulmonary vascular arteriovenous malformations that allow right to left intrapulmonary shunting [32].

The severity of HPS can be graded in relation to the level of hypoxia as: mild ($PaO_2 \geq 80$ mmHg), moderate ($PaO_2 < 80$ mmHg and ≥ 60 mmHg), severe ($PaO_2 < 60$ mmHg and ≥ 50 mmHg), and very severe ($PaO_2 < 50$ mmHg) [6]. The very severe form of HPS is frequently associated with a $PaO_2 < 300$ mmHg when the patient is given 100% oxygen [30]. Although LT has been shown to reverse HPS and improve survival, it is crucial to precisely identify the severity of HPS because patients with a $PaO_2 < 50$ mmHg and no reversibility on 100% oxygen are at increased risk of post-LT respiratory failure and death [33].

7.4 Assessing Renal Function

Renal disease is a common consequence of hepatic failure. Proper assessment of renal function is important in candidates for LT since preoperative renal failure increases post-LT mortality [34]. The differential diagnosis of renal function impairment in candidates for LT is difficult and includes the presence of sepsis, hypovolemia, parenchymal kidney diseases, drug nephrotoxicity, and more commonly the presence of acute kidney injury (AKI) leading to the development of hepatorenal syndrome (HRS). The definition of AKI in patients with cirrhosis has recently been revised and is now defined as an increase in serum creatinine of at least 0.3 mg/dl within 48 hours, or a 1.5-fold increase from the baseline within 7 days [35]. The change made to the definition of AKI in patients with cirrhosis highlights the need to revise the old definition criteria of type 1 HRS. The new definition criteria for AKI-HRS, previously named type 1 HRS, are as follows: the presence of cirrhosis with ascites, diagnosis of AKI, no improvement in renal function (return of serum creatinine to a value within 0.3 mg/dL of the baseline value) after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin at a dose of 1 g/kg of body weight/day (maximum 100 g/day), absence of shock, no current or recent use of nephrotoxic drugs, and no signs of structural kidney injury. Structural kidney injury is indicated by the presence of proteinuria (>500 mg/day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography [36].

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2, calculated by means of the Modification of Diet in Renal Disease 6 (MDRD-6) formula, persisting for more than 3 months [37]. CKD-HRS, previously named type 2 HRS, is a specific form of CKD that only occurs in cirrhosis and is characterized by chronic renal function impairment and lack of signs suggestive of parenchymal kidney disease (i.e., hematuria, proteinuria, and/or abnormal morphology of kidneys evaluated by ultrasonography) [36].

Treatment of AKI-HRS is initially linked to the identification of precipitating factors (mainly infections such as spontaneous bacterial peritonitis or

gastrointestinal bleeding) and their clinical management. The use of vasoconstrictor drugs such as terlipressin in combination with albumin has been shown to induce reversal of AKI-HRS (defined as a reduction in serum creatinine by > 50% to a final value of < 1.5 mg/dl) in 55.5% of patients [38, 39]. Treatment with terlipressin and albumin should be continued until serum creatinine reaches a final value < 1.5 mg/dl or more properly until it reaches the same baseline value taken before the occurrence of renal impairment. In patients who do not respond, treatment should be discontinued within 14 days [36]. After discontinuation of terlipressin plus albumin, AKI-HRS recurs in about 20% of cases and these cases can be retreated with the same scheme with an excellent rate of response [40]. Response to treatment with terlipressin and albumin is associated with a better short-term survival compared to nonresponders [41, 42]. This advantage in the short-term survival of patients with AKI-HRS who respond to treatment can be important in those who are on the waiting list for LT.

Patients with CKD-HRS have a high rate of treatment response to terlipressin and albumin, although the recurrence of renal impairment after treatment withdrawal is frequent [43]. Patients with CKD-HRS present similar clinical outcomes after LT, independently from the pre-LT treatment with terlipressin and albumin. Thus, in these patients, treatment with terlipressin and albumin cannot be considered even in patients on the waiting list for LT [36].

The correct identification of the etiology and prognosis of kidney dysfunction in patients on the waiting list for LT is crucial to guide the decision as to whether to perform a single LT or a combined liver and kidney transplant (LKT). Although LKT may improve the survival for the recipient, it also decreases the availability of kidney grafts that could improve the survival of patients waiting for a single kidney transplant [44]. Taking into account the aforementioned principles, AKI-HRS and CKD-HRS are not a systematic indication to perform LKT. In order to optimize the use of kidney grafts, the accepted criteria to consider a combined LKT are as follows: the presence of stage IV renal disease in patients with cirrhosis without AKI-HRS; CKD with glomerular filtration rate 2 mg/dl or higher of acute cause (including patients with AKI-HRS) in patients with cirrhosis who have been on dialysis for at least 8 weeks [4, 6, 45]. There is still some debate regarding the need for LKT in patients with creatinine clearance between 30 ml/min and 60 ml/min. The decision as to whether or not to perform LKT should be balanced between the risk of deterioration of renal function after LT alone as a consequence of surgery and drug toxicity, and the shortage of kidney grafts [4].

7.5 Screening for Extrahepatic Malignancies

Screening for the presence of occult extrahepatic malignancies must be performed in all candidates to receive a liver graft. It can be performed taking into account several demographic and lifestyle characteristics of the recipient such age, gender, and alcohol or smoking habits. In all candidates older than 50 years or with familial history of gastrointestinal cancer, colonoscopy is mandatory. If the exam

cannot be tolerated by the patient or cannot be performed without risk under general anesthesia, CT colonography could represent an option. To screen for malignancies of the respiratory system, particularly in patients who smoke, a CT scan of the chest is recommended. A further ENT assessment with nasofibroscopy, oral cavity, and upper gastrointestinal endoscopy must be routinely performed [4]. Women should be carefully evaluated using Papanicolau smear test and mammogram, while men should be screened for the presence of prostate cancer. More recently, the use of positron emission tomography (PET) scan as a tool for the diagnosis of occult neoplasms in liver transplant candidates is increasingly widespread.

A careful evaluation of the skin is also suggested, although the presence of non-melanoma skin cancer does not represent an absolute contraindication to LT [4].

7.6 Assessing Nutritional Status

Malnutrition, sarcopenia, and obesity are common comorbidities with a significant impact on pre- and post-LT outcomes. In this chapter's section, undernutrition and sarcopenia will be evaluated since obesity has been discussed separately (see Chap. 6).

Undernutrition can be defined as a disorder induced by an inadequate intake or uptake of nutrients that leads to an altered body composition (a reduction in fat-free mass) and body cell mass, diminished physical and mental performance, and a worse clinical outcome in the event of disease [46]. Sarcopenia is a distinct syndrome characterized by a progressive, generalized loss of skeletal muscle mass, strength, and function, associated with an increased risk of adverse outcomes [46]. In patients with end-stage liver disease on the waiting list for LT, the prevalence of undernutrition and sarcopenia is quite variable because different diagnostic methods and criteria for the diagnosis have been adopted. Malnutrition is recorded in 20%–90% of patients with liver cirrhosis [47], and sarcopenia in 40–70% of cases [48]. Malnutrition negatively affects in-hospital mortality and increases clinical complications in patients with cirrhosis [49]. Moreover, in the context of LT, it has been associated with an increased risk of posttransplant morbidity and mortality mainly due to increased rates of bacterial and fungal infections [50]. A simple method to identify patients on the waiting list that should be considered at high risk of pre- and post-LT complications due to malnutrition is the body mass index (BMI) value. A BMI value <18.5 kg/m^2 has been associated with a significant increase in post-LT mortality in a large analysis of UNOS database [51].

Interestingly, sarcopenia negatively influences mortality after LT in patients with MELD scores < 15. Thus, a MELD score incorporating the presence of sarcopenia (MELD-sarcopenia) has been adopted to improve the prognostic capacity of the MELD score alone in selecting patients with higher risk of post-LT complications [52].

Because nutritional status impacts both pre- and post-LT outcomes, every effort should be made to properly evaluate all LT candidates regarding this issue. The first

step in a nutritional assessment may be to administer screening tool, so that patients can be stratified by their risk of malnutrition [6]. Examples of tools developed and applied, though not extensively validated, in patients with cirrhosis are the Royal Free Hospital-Global Assessment (RFH-GA) [53] or the Royal Free Hospital-Nutritional Prioritizing Tool [54]. The measurement of muscle mass on CT scan or MRI is currently the gold standard to assess the presence of sarcopenia. Among the several techniques available [55], calculating the cross-sectional area of psoas muscle area (PMA) normalized by height squared or body surface area [56] or the third lumbar skeletal muscle index normalized by height squared (L3SMI) [57] has been validated for use in patients with cirrhosis on the waiting list for LT. The cut-offs selected to discriminate patients with sarcopenia considering the aforementioned measuring methods are 1561 mm^2 in men and 1464 mm^2 in women [58] for PMA, while for L3SMI the cut-off values are < 50 cm^2/m^2 in men and < 39 cm^2/m^2 in women [57]. Furthermore, muscle function can be easily assessed with the handgrip strength test, and a few physical exercises such as the 6-minute walking test and chair standing test. The results of these tests correlate positively with the severity of sarcopenia. Considering the simplicity of performing these tests and their good reproducibility, they are suitable for use in longitudinal assessment to monitor the efficacy of nutritional interventions [59].

An area that is garnering increasing interest is the planning of nutritional care and the monitoring of nutritional outcomes in patients awaiting LT. These goals should preferably be managed by an expert dedicated dietitian/nutritionist in close collaboration with the transplant hepatologist [6]. The general recommendations regarding energy and dietary intake, based on the international guidelines, may be summarized as follows [6]:

- Provide a daily intake of 30–35 kcal/kg of dry body weight; 50% of them deriving from carbohydrates and 20–30% from fat.
- Provide a daily intake of 1–1.5 g of protein per kg of body weight, with the intention of patients with hepatic encephalopathy achieving the protein intake needed by including vegetable and dairy proteins, and/or branched chain amino acid supplementation.
- Distribute the dietary intake over four to six meals a day, including a late evening snack.
- Consider adding vitamins and trace elements on the basis of the patient's symptoms and/or serum levels.
- In patients who are severely malnourished and/or unable to take sufficient calories from oral diet, consider providing enteral supplemental nutrition.

A further important and novel area is the planning of a personalized physical activity program in patients awaiting LT. In fact, patients with cirrhosis are scarcely physically active, with an impaired aerobic capacity, and these factors increase their risk of frailty [60]. Several trials enrolling a small number of patients have suggested that adapted physical activity programs are effective in increasing maximal oxygen intake, 6-min walking distance, and muscle strength, without negative side

effects [61–63]. In the absence of specific clinical guidelines regarding physical activity recommendations in patients with cirrhosis, the international recommendations for physical activity in adults aged 50–64 years with clinically significant chronic conditions or functional limitations affecting their mobility, fitness, or physical activity levels may be adopted [6, 64]. It is important to highlight that any physical activity program must be accompanied by a correct nutritional assessment and intake since physical exercise with an insufficient nutritional intake accelerates protein catabolism and muscle loss in patients with cirrhosis [60].

7.7 Assessing Bone Abnormalities

Osteoporosis is a frequent complication observed in patients with end-stage liver disease. It is reported that the estimation of bone density alteration in cirrhotic patients is 12% to 55% [65]. As a rule, low bone mass or density is a significant risk factor for fracture. The rate of fracture in CLF patients is reported to be 5–20% and highly related to age and stage of disease [66]. The prevalence of low bone density is higher in females with liver cirrhosis due to chronic cholestasis such as those with primary biliary cholangitis [67]. Other factors such as lower BMI and alcohol and tobacco consumption have been recognized as independent risks for the development of osteoporosis in patients with end-stage liver disease [4]. Considering the high prevalence of osteoporosis in these patients, bone densitometry must be performed in all candidates for LT to assess the presence and severity of the disease [68]. If the T-score is more than −1.5 or between −1.5 and −2.5, treatment aimed to correct vitamin D deficiency with an oral daily dose of 800 IU of vitamin D, and 1–2 g of elemental calcium supplementation, seems reasonable. In patients with T-score values less than −2.5, treatment with bisphosphonates or, in selected cases, with hormone replacement therapy is encouraged [68].

7.8 Infection Screening

Infections are a major cause of morbidity and mortality after LT, in part, because of the immunosuppresive drugs required to prevent rejection of the graft. Although not every infection can be anticipated, many types of infection can be predicted and some can even be prevented. Taking these conditions into consideration, it is important to screen potential candidates to LT for the presence of infections. It is widely suggested that infection screening in LT candidates should be graduated in three different levels. The first screening level must be performed in all LT candidates, the second level must be performed only in patients eligible for LT at the time of listing, and the third level must be adopted in patients with risk factors or who are from a geographic area with specific endemic infections [4, 69]. Examples of third screening levels are the serology and PCR for West Nile Virus and serological screening of coccidioidomycosis in candidates living in areas where these diseases are endemic [4]. The laboratory parameters required in the first and second level of

Table 7.3 First and second level of infection tests recommended in the screening of LT candidate

First level
HIV 1 and 2 Ab
HBV serology (HDV serology in patients with HBsAg positive)
HCV Ab
HAV Ab
CMV Ab
HCV-RNA and HCV genotype
HBV-DNA
Second level
PPD-Mantoux or IFN-gamma release assay for Mycobacterium tuberculosis
EBV Ab
HHV-8 Ab
Varicella-zoster virus Ab
Type 1 and 2 herpes simplex virus Ab
Toxoplasma gondii Ab
Treponema pallidum Ab
Immunoenzymatic assay with venereal disease research (VDRL)
Parasitological exam and stool culture (Strongyloides stercoralis)
Staphylococcus aureus nasal/axillary swab

HIV human immunodeficiency virus, *HBV* hepatitis B virus, *HDV* hepatitis delta virus, *Ab* antibodies, *HCV* hepatitis C virus, *HAV* hepatitis A virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HHV-8* human herpes virus 8

screening are reported in Table 7.3. Regarding vaccinations, there is a general agreement that LT candidates are immunized against hepatitis A (HAV) and B (HBV) viruses, varicella, pneumococcus, influenza, and tetanus [4].

There are infections that can delay or contraindicate LT. An example of the former are soft tissue infections that are frequently observed in cirrhotic patients and are caused by both Gram-negative and Gram-positive bacteria [70]. In addition to septic shock, active infections that contraindicate LT are those related to bacteremia such as pneumonia, urinary tract infections, and endocarditis. The presence of invasive fungal infections such as aspergillosis or candidemia is considered contraindication to LT until the candidate has been successfully treated and presents radiologic, clinical, and microbiologic resolution of the infection [71]. Following the availability of effective drugs in treating HIV infection, this condition is no longer considered an absolute contraindication to LT. Patients with controlled HIV, in the absence of AIDS-related events, and CD4 > 100–150/mm^3 can be currently considered as candidates for LT [4].

7.9 Psychosocial Evaluation

In all LT candidates, a careful identification of significant psychiatric comorbidities or social difficulties, such as transportation from home to the transplant center, family and social support, and financial limitations must be performed. This is of great importance since these comorbidities may impair the patient's ability to adopt a healthy lifestyle and adhere to the complex medication

schedules needed after LT [18]. A large proportion of patients with psychiatric comorbidities are those who have active alcohol or illicit drug abuse. These conditions are analytically treated in the Chap. 31 referring to "psychosocial evaluation of liver transplant candidate with alcoholic liver disease and/or substance abuse."

Most psychiatric disorders make patients relatively unsuitable for LT, and warrant psychosocial and psychiatric assessment and monitoring before and after any transplant is undertaken [6]. Repeated suicide attempts and active psychosis not controlled with adequate pharmacological therapy in patients without social and family support, independently from alcohol or substance dependence, should be considered for psychiatric conditions that contraindicate LT [6]. In some cases, there may be difficulty in making a correct differential diagnosis between a psychiatric condition and the presence of a chronic hepatic encephalopathy (HE). Patients with chronic HE should undergo neuropsychological testing, brain CT scan or preferably MRI, and electroencephalography to ascertain the reversibility of their neuropsychiatric conditions [4].

7.10 Anatomical Assessment

The anatomical evaluation of the vascular and biliary system of the liver in candidates for LT is important to help the surgeon plan the operation. This can be done by adopting the more advanced imaging techniques, such as contrast CT or MRI scan with tridimensional imaging reconstruction. The assessment of the presence and the exact position of a transjugular portosystemic shunt (TIPS) in those patients who have been treated for severe complications of portal hypertension before LT is of great importance for the surgeon to plan the proper type of operation [27]. At the same time, the presence of surgical portocaval shunts, which should be closed during surgery, or arcuate ligament is routinely screened for. After the improvement in surgical techniques and radiological interventions, portal vein thrombosis is no longer considered an insurmontable obstacle to LT. A number of reports indicate that several interventions can resolve portal vein obstruction in LT candidates. Among these interventions, surgical or radiologic thrombectomy, thromboendovenectomy with venous reconstruction, interposition of vein graft, and porto-caval hemitransposition are those more frequently successfully adopted [4]. At present, only a few candidates with thrombosis of whole portal system (including portal vein, superior mesenteric, and splanchnic vein) are rejected for LT. The evaluation of biliary tree anatomy is particularly important for candidates to receive living donor liver transplantation or receiving split liver grafts [4].

It is mandatory that overall surgical and anesthetics consultations be performed at the end of the evaluation process of the candidate to receive LT to assess pre- and postoperational risks [4].

7.11 Conclusion

The selection of the candidate for LT is a particularly complex and delicate process. It is necessary for many specialists to intervene in the execution and correct interpretation of the numerous biochemical and instrumental examinations required. The final decision to enroll the patient on the waiting list for LT or not to consider it suitable must be taken within a multidisciplinary team after careful evaluation of each individual patient.

Key Points

- Preoperative evaluation of liver transplant candidates is a team effort.
- Cardiac function must be evaluated carefully since it has a great impact in conditioning post-liver transplantation morbidity and mortality.
- Coronary artery disease and portopulmonary hypertension must be carefully recognized and properly treated before liver transplantation.
- Lung function must be assessed by means of lung functional tests including arterial blood gas analysis and pulmonary imaging studies.
- In patients with alveolar-arterial oxygen gradient (AaO_2) > 20 mmHg and/or pO_2 < 70 mmHg breathing room air, hepatopulmonary syndrome should be suspected. Contrast-enhanced echocardiography or a macroaggregate albumin lung perfusion scan must be performed to confirm the diagnosis.
- Renal function must be carefully evaluated and, in the cases of renal impairment, the correct differential diagnosis between AKI-HRS and AKI of different origin must be performed.
- The correct identification of the etiology and prognosis of kidney dysfunction is crucial to guide the decision as to whether to perform a single LT or a combined liver and kidney transplant.
- Screening for the presence of occult extrahepatic malignancies must be performed in all candidates to receive a liver graft.
- Undernutrition and sarcopenia are common comorbidities associated with poor pre- and post-liver transplantation outcomes.
- Nutritional assessment and customized nutritional care must become an integral part of the evaluation process of the candidate for liver transplantation.
- Assessment of bone density is important in liver transplant candidates, especially in women with chronic cholestatic liver diseases.
- Treatment to increase bone density should be started before liver transplantation in the presence of osteoporosis.
- Infection screening is mandatory in all liver transplant candidates since the presence of active infections is generally considered a contraindication to the transplant procedure.
- Anatomical evaluation of the native liver vascularization as well as the biliary anatomy help the surgeon to plan the most appropriate type of transplant operation.

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