Clinical Practice Guidelines

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EASL Clinical Practice Guidelines: Liver transplantation☆

European Association for the Study of the Liver*

Introduction

The first human orthotopic liver transplantation (LT) in Europe was performed by Sir Roy Calne in Cambridge in 1968 [1], only one year after the first successful human liver transplantation reported by Thomas Starzl in the United States [2]. Since then LT has evolved rapidly, becoming the standard therapy for acute and chronic liver failure of all aetiologies, with more than 80,000 procedures performed to date. Survival rates have improved significantly in the last 25 years, achieving rates of 96% and 71% at 1 and 10 years after LT respectively [3].

This great success is mostly attributable to several advances such as the introduction of new immunosuppressive agents and preservation solutions, to the improvements in surgical techniques and to the early diagnosis and management of complications after LT [4]. As a consequence of these achievements, indications for LT have been expanded resulting in a growing demand for transplantable grafts and in a dramatic organ shortage. Therefore, one of the main ongoing challenges the transplant community is facing is to expand the donor pool in order to minimize the rate of patient death on the waiting list [5]. On the other hand, liver transplanted patients are surviving longer after the operation and long-term outcomes are becoming the main concern for clinicians, who have to deal with direct and indirect side effects of immunosuppressive therapy.

This Clinical Practice Guideline (CPG) has been developed to assist physicians and other healthcare providers during the evaluation process of candidates for LT and to help them in the correct management of patients after LT.

The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [6]. The strength of recommendations reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

The candidate to liver transplantation

Indications to liver transplantation

LT should be considered in any patient with end-stage liver disease, in whom the LT would extend life expectancy beyond what the natural history of underlying liver disease would predict or in whom LT is likely to improve the quality of life (QoL). Patients should be selected if expected survival in the absence of transplantation is one year or less, or if the patient had an unacceptable QoL because of liver disease. A detailed medical evaluation is performed to ensure the feasibility of LT.

LT is indicated in patients with end-stage liver disease, in patients with the development of hepatocellular carcinoma (HCC) and in patients with acute liver failure. The most common indication to LT for end-stage liver disease in adults is cirrhosis. Patients should be referred to transplant centres when major complications of cirrhosis, such as variceal haemorrhage, ascites, hepatorenal syndrome and encephalopathy occur.

Conversely, acute liver failure represents an urgent indication to LT [7]. Viruses (especially hepatitis viruses A and B), drugs (acetaminophen), and toxic agents are the most common causes of acute liver failure, with the proportions varying between countries. Seronegative hepatitis is also an important cause of LT for acute liver failure, being the most common indication for LT in acute liver failure in the UK [8]. Prognosis is essentially determined by neurological status, but is also rapidly affected by damage to other organs. LT has revolutionized the prognosis of acute liver failure, causing survival to increase from 10–20% (all causes combined) to 75–80% at 1 year and 70% at 5 years. Indications for LT in Europe are summarized in Fig. 1.

In recent years, an extension of indications has been observed, but in contrast, the transplant community is currently facing organ shortages. Actually, limited organ availability and an increasing demand for organ transplantation has extended transplant waiting times and thus increased morbidity and mortality for potential recipients on these waiting lists. This has led to increased pressure on organ allocation programs. Since a successful outcome requires optimal patient selection and timing, the issue of which patients to list for LT and when to transplant cirrhotic patients has generated great interest as well as considerable controversy.

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Clinical Practice Guidelines

Table 1. GRADE system used in EASL Clinical Practice Guidelines [6].

Grade evidence	
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

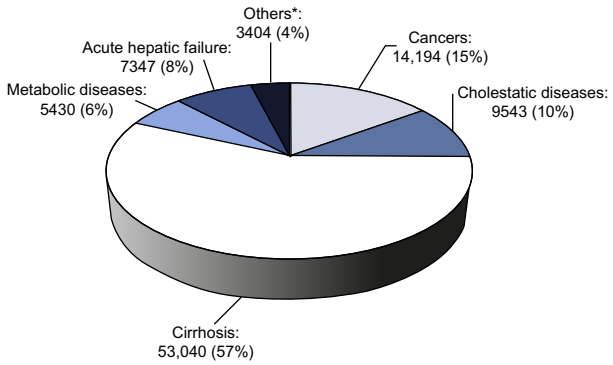

Fig. 1. Primary diseases leading to liver transplantation in Europe (01/1988–12/2011) [40]. *Others: Budd-Chiari: 792, Bening liver tumours or polycystic diseases: 1228, Parasitic diseases: 80, Other liver diseases: 1304.

Score and prognostic factors for end-stage liver disease

The timing of LT is crucial since patients who should be transplanted for end-stage liver disease need to undergo surgery before life-threatening systemic complications occur. They should not be transplanted too early since the advantage of transplant might be unbalanced by the risk of surgery and immunosuppression for all life.

Priority on the waiting list was based in the past by the waiting time, and severity of liver disease. The Child-Pugh-Turcotte classification and since 2002 also the model of end-stage liver disease (MELD) score (based on objective measures such as creatinine, bilirubin and international normalized ratio) are used for patient priority [9]. The MELD was developed to determine the short-term prognosis for patients undergoing TIPS after gastrointestinal bleeding [10], and then proposed for predicting 3-month mortality in patients with end-stage liver disease.

In patients with MELD $\leqslant$14, 1-year survival was lower with rather than without transplantation [11]. Consequently, a MELD score $\geqslant$15 is recommended to list patients with end-stage liver disease. However, it does not provide a prediction of mortality following LT except for those patients with very high MELD scores over 35 [12].

In very sick patients with MELD >30 the risk of mortality and morbidity after transplantation should be addressed.

MELD does not reflect the impact of complications such as refractory ascites and recurrent encephalopathy in the risk of mortality without transplantation.

In fact, there are several exceptions to MELD, including pulmonary complications of cirrhosis, hepatic encephalopathy, amiloidosis, primary hyperoxaluria, etc. (Table 2). In these cases, extra points could be attributed to patients in order to give them priority to transplantation [13].

Serum sodium (MELD-Na), serum sodium and age (integrated MELD) scores have been proposed to improve the predictive value of MELD [14]. Delta MELD (ΔMELD), meaning the change of MELD over time, might also be a better predictor of mortality [15,16].

Another exception to MELD is HCC. Waiting list time-dependent points can be added to laboratory MELD to give priority to patients with HCC. Additional points can be added depending on the type of tumour (size, number of nodules, alpha fetoprotein [AFP] level, waiting time, response to downstaging procedures).

MELD score is driving the allocation of grafts in many countries in Europe. However, the final decision for allocation is frequently based on multiple parameters besides MELD including the match with the donor, but also local/regional priorities.

Recommendations:

- Evaluation for LT should be considered when a major complication of cirrhosis occurs (**Grade II-2**)
- MELD score is good to predict short-term pre-transplant mortality risk (**Grade II-1**)
- MELD is based on objective laboratory tests and can be used in organ allocation (**Grade II-1**)
- As the MELD has several limitations, patients with liver diseases requiring LT, whose severity is not described by the MELD, should be recognised. A different priority needs to be given to these patients by experts (**Grade II-3/III**)
- HCC is a particular MELD exception that requires extra points to get access to the transplant. These points have to be standardized in each country and have to take into account size, number of nodules, AFP levels, recurrence after downstaging therapy (**Grade II-1**)

Management of patients with liver cirrhosis (without HCC)

The management of a patient in the waiting list aims at eliminating not only contraindications of surgery, but also contraindications to taking long-term immunosuppressive treatment. This assessment is not uniform and should be discussed in each transplant centre. Contraindications to LT are dynamic, changing over time and may vary among liver transplant centres, depending on their local expertise.

Evaluating and selecting a good recipient for LT thus requires the collaboration of several specialists, who account for all comorbidities. The final decision should be made, within each expert centre, among a multidisciplinary group of staff including transplant hepatologist, transplant surgeon,

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Table 2. Exceptions to MELD score.

Manifestations of cirrhosis
Refractory ascites
Recurrent gastrointestinal bleeding
Recurrent encephalopathy or chronic encephalopathy
Hepatopulmonary syndrome
Portopulmonary hypertension
Intractable pruritus resistant to medical therapies
Miscellaneous liver diseases
Budd-Chiari syndrome
Familial amyloidotic polyneuropathy
Cystic fibrosis
Hereditary haemorrhagic telangiectasia
Polycystic liver disease
Primary oxaluria
Recurrent cholangitis
Uncommon metabolic disease
Malignancy
Cholangiocarcinoma
Hepatocellular carcinoma
Uncommon liver tumours
Other

anaesthetist, intensivist, cardiologist, etc., that considers the benefit and risk for each recipient.

Hepatitis B virus (HBV)-related liver disease

The indication of decompensated HBV cirrhosis is declining probably due to the outcome of HBV vaccination and advent of oral antiviral agents. The indication for transplantation is similar to other causes of cirrhosis. In addition, it is essential to know the precise HBV status of the patient and in particular the existence of HBV replication. Whatever the level of HBV DNA, if detectable, antiviral treatment with entecavir or tenofovir should be started as soon as possible [17]. The need for an antiviral treatment with nucleot(s)ide analogues (NUCs) has two objectives: 1) the improvement of liver function; and 2) to decrease the risk of HBV recurrence after transplantation since viral replication level at the time of LT is correlated with the risk of HBV recurrence. Positive HBV DNA at the time of LT seems to influence the rate of death due to HBV recurrence in HBV/HCC patients [18].

Since interferon (IFN) is contraindicated in patients with decompensated cirrhosis, the only choice for these patients is treatment with NUCs. Lamivudine first and adefovir [19] have been widely used to treat hepatitis B in patients awaiting LT. However, tenofovir and entecavir are currently the first-line drugs in patients with chronic hepatitis B, which have a greater potency and higher barriers to resistance [17]. In case of previous resistance to lamivudine, tenofovir is the drug of choice; in case of resistance to adefovir the switch to entecavir is preferred (or tenofovir). The efficacy and safety of these drugs in patients with advanced liver disease have been assessed in different series, showing good efficacy in reducing levels of HBV DNA and a good safety profile [20–22]. Lactic acidosis has been reported in some patients with MELD score >20, particularly when treated with entecavir [23]. Clinical and laboratory follow-up of patients with these characteristics is warranted. It is important to note that the dose of all NUCs needs to be adjusted in patients with low creatinine clearance (<50 ml/min). Importantly, about one third of patients who initiate therapy have improvements in liver function, which in some cases might result in patient delisting [19,24].

Cases of severe HBV reactivation should be considered specifically: the treatment with NUCs is an emergency. In 25% of cases, despite effective antiviral treatment, there is a deterioration of liver function and death may occur during the first 6 months of treatment. There is no specific prognosis factor identified to predict those patients who will recover without LT or who will die without LT.

Patients with fulminant or severe hepatitis may benefit from NUCs treatment. Available data are based on study using mainly lamivudine [25], but as for chronic hepatitis, entecavir or tenofovir should be used.

In patients with HBV/hepatitis D virus (HDV) coinfection, HBV replication can be suppressed, but HDV replication cannot be treated at the decompensated stage. In case of deterioration of liver disease despite effective anti-HBV therapy, HDV might be the cause of the deterioration and HDV RNA in serum should be evaluated. The presence of HDV replication is not a contraindication to transplantation, since HBV prophylaxis after transplantation will prevent symptomatic HDV reinfection of the graft [26].

Recommendations:

- NUCs with high genetic barrier (entecavir and tenofovir) are the first choice treatment for HBV decompensated cirrhosis as they can achieve undetectable HBV DNA and improve hepatic function, maybe avoiding LT (**Grade II-2**)
- Severe HBV reactivation requires a prompt treatment with NUCs (**Grade I**)
- As there is no predictive factors for the evolution towards liver failure, patients should be rapidly evaluated for LT despite antiviral treatment (**Grade III**)
- Viral replication, HCC, hepatitis B immunoglobulin monoprophylaxis (*vs.* combined prophylaxis) are risk factors for HBV recurrence post-transplantation (**Grade II-2/3**)
- Patients with fulminant or severe hepatitis may benefit from NUC treatment. Entecavir or tenofovir should be used in these patients (**Grade II-3**)
- In patients with liver function deterioration in spite of anti-HBV therapy, active HDV infection should be ruled out. HDV replication is not a contraindication for LT (**Grade II-1/2**)

Hepatitis C virus (HCV)-related liver disease

HCV decompensated cirrhosis is frequently associated with a persistent HCV replication and an increased level of alanine aminotransferase. Until recently there was almost no possibility to treat

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Clinical Practice Guidelines

patients with decompensated liver disease with antiviral therapy. To date this strategy has been proven to be suboptimal when using IFN-based therapies, especially regarding safety and tolerability [27,28]. The advent of IFN-free antiviral therapy has modified this approach [29]. Importantly, recent data has shown that the clearance of HCV RNA from serum and sustained virological response (SVR) is associated with an improvement in liver function in some patients with decompensated liver cirrhosis [30] (and some individuals can be delisted). We do not know which variables are associated with liver function improvement after viral clearance and if there is a limit ("too advanced liver disease") after which improvement is not possible. This will be an important issue to address in the coming years also in patients with hepatocellular carcinoma in whom the priority to LT is not only liver disease but the risk of tumour progression and in these cases antiviral therapy would improve liver function, but would not change the priority based on tumour staging.

The presence of HCV replication at time of transplantation is not a contraindication for the procedure, but antiviral treatment will be necessary after transplantation.

The primary goal of antiviral treatment while on the waiting list is to prevent HCV infection of the new liver, which is universal in patients with detectable HCV RNA at the time of transplantation. A potential second aim would be to improve liver function in those patients clearing HCV (which might, in some cases, avoid the need for LT).

IFN-based regimens. Current IFN-based treatments are far from optimal in patients with advanced cirrhosis and should be only considered in those settings where IFN-free regimens are not available and in patients with compensated cirrhosis (and HCC). Peginterferon (PegIFN) plus ribavirin (RBV) administered on the waiting list can prevent graft infection in patients who achieve viral clearance (undetectable HCV RNA) at the time of LT. Rates of SVR are low in genotype 1-infected patients (~20%) and acceptable (~50%) in those infected with genotypes 2 and 3 [31,32]. Apart from genotype, variables associated with higher response rates are *IL28B* CC genotype and treatment duration (>16 weeks). IFN-based therapies are contraindicated in patients with advanced liver disease (Child-Pugh B and C, MELD >18) since they are associated with a high incidence of serious adverse events (particularly bacterial infections) [31,32].

The combination of PegIFN, RBV and first generation protease inhibitors boceprevir and telaprevir improved the efficacy of IFN-based therapies in genotype 1 patients. Unfortunately, response rates are low in cirrhotic patients, particularly in those who are previous null responders (a common situation in patients awaiting LT) [33]. Importantly, this regimen was associated with a relatively high incidence of severe adverse events (SAEs) in "real-life" cirrhotic patients (45.2% and 32.7% for telaprevir and boceprevir, respectively) [34]. Variables independently associated with the occurrence of SAEs (infections, clinical decompensation) were a low platelet count (<100,000/ml, as a marker of portal hypertension) and low albumin levels (<35 g/L, as a marker of impaired liver function). Thus, these drugs should not be used any more in patients awaiting LT.

Alternative drugs that can be used in combination with PegIFN and RBV are the protease inhibitor simeprevir (genotypes 1 and 4), the NS5B polymerase inhibitor sofosbuvir or the NS5A inhibitor daclatasvir. Data regarding the use of these drugs are available in compensated cirrhotic patients (mostly naïve patients); the higher SVR rates were obtained with the combination of PegIFN, RBV and sofosbuvir [35].

IFN-free regimens. In November 2013, the first data on the safety and efficacy of an all-oral IFN-free regimen (sofosbuvir plus RBV) in patients with compensated cirrhosis and HCC awaiting LT were reported. In this phase II open-label study, 61 patients infected with genotypes 1 or 4 received up to 48 weeks of treatment while on the waiting list (median duration 17 weeks) [36]; 46 of them were transplanted. The per-protocol efficacy was assessed in 43 patients with a HCV RNA level <25 IU/ml at the time of transplantation. Among them, 30 (70%) had post-transplantation SVR12, meaning no recurrence of infection. The duration of undetectable HCV RNA pre-transplant was the best predictor of response (undetectable HCV RNA for more than 30 continuous days). This proof of concept study demonstrated that an IFN-free regimen administered for a few weeks before transplantation prevented HCV graft infection in a majority of treated patients. Safety and tolerance of this regimen was good: the most frequently reported adverse events were mild and only one patient discontinued treatment due to anaemia attributed to RBV.

Data using other IFN-free combinations are available from clinical trials and real-life cohorts in patients with compensated and decompensated cirrhosis (not specifically awaiting LT). The combination of sofosbuvir and ledipasvir with RBV for 12 or 24 weeks was assessed in genotype 1 and 4 patients with compensated (Child-Pugh A) or decompensated (Child-Pugh B and C, up to 12 points) cirrhosis [30]. In Child-Pugh A patients, data from this study show SVR12 rates above 95%, both in treatment-naïve and treatment-experienced individuals, independent of treatment duration. In patients with decompensated cirrhosis, preliminary analysis showed SVR12 rates above 85% both in Child-Pugh B and C patients, independent of treatment duration. At week 4 post-treatment, the MELD scores had improved by 1 to 8 points in two thirds of decompensated cirrhotic patients. The safety profile of this combination was good and most serious adverse events, including death, were unrelated to the study drugs. Data on the efficacy and safety of the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with RBV in compensated cirrhotic patients infected with genotype 1 have shown SVR12 rates around 95% [37], with slightly lower efficacy (around 85–90%) in those individuals with lower platelet counts (<100,000 cells/ml) and low albumin levels (<35 g/dl). Thus, this combination can be considered in individuals with compensated cirrhosis and HCC who are on the waiting list. The combination of sofosbuvir and simeprevir, with or without RBV, has been assessed in large real-life cohorts including a significant number of patients with cirrhosis [38]. In patients with HCV genotype 1 infection and compensated cirrhosis, the SVR4 rates were in the order of 90%. Preliminary data in 81 genotype 1-infected patients with decompensated cirrhosis showed an SVR4 rate of 75%, with a good safety profile. The combination of sofosbuvir, daclatasvir and RBV has also shown a high efficacy in phase II studies including a small number of patients with compensated cirrhosis, and can be used in all genotypes [39].

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Recommendations:

- To reduce the risk of HCV recurrence LT candidates should be treated before transplant (**Grade I**)
- The achievement of negative HCV viral load can improve liver function either before (**Grade II**) or after transplant (**Grade III**)
- New IFN-free antiviral therapies are better tolerated and are a promising option for decompensated cirrhosis (**Grade I**). Sofosbuvir, ledipasvir and daclatasvir can be used in patients with decompensated liver disease (simeprevir in patients with Child-Pugh B) (**Grade II**)
- Patients that could not be treated before LT need to be treated afterwards (**Grade III**)

Alcoholic liver disease

Alcoholic liver disease is one of the most common indications of LT in Western countries [40]. LT for alcoholic cirrhosis has a favourable outcome, similar to other aetiology of end-stage liver disease [41]. Several centres developed an evaluation process based on medical and psychiatric criteria to better determine patients that would mostly benefit from the procedure. Alcohol abstinence of at least 6 months, in order to evaluate the need and timing of LT and obtain a better control of alcoholism, is usually required. This interval is neither a consensus nor an absolute requirement. The risk of recidivism is estimated between 15 to 40% depending on the series and how recurrence of alcoholism is defined. The risk of recurrence of alcohol consumption seems related to the duration of follow-up after LT, to the duration of abstinence before transplantation; however, this remains controversial [42]. The interest of the 6-month abstinence rule is double: a) abstinence can lead to significant improvement of liver function avoiding the need for transplantation; and b) this period of abstinence is an opportunity to assess the patient compliance. However, there are strong limitations to this rule: a) the duration of abstinence prior transplantation was not found to be related to the risk of recidivism in many studies; b) the improvement in liver function occurred mainly during the first three months of abstinence; c) during this period some patients with no risk of recidivism will die; d) several authors consider that the risk of recidivism is more related to psychosocial factors than to the duration of abstinence and these factors can be evaluated prior to transplantation. Therefore several groups have advocated breaking this 6-month abstinence rule [43]. Acute alcoholic hepatitis (AAH) has been considered an absolute contraindication to LT on the grounds that patients with this disorder have been drinking recently and that a period of abstinence will allow many to recover. Unfortunately, many patients die during this time interval. Patients who do not recover within the first three month abstinence are unlikely to survive [44]. If the AAH is severe, defined by a Maddrey's score over 32, treatment with steroids can improve the outcome [45]. The Lille score allows an evaluation at day 7 after therapy introduction, if it is over 0.45, the expected survival is below 30% at 6 months [46].

Consequently, LT centres face a dilemma when caring for a patient with alcohol abuse who has developed severe alcoholic hepatitis and whose condition deteriorates despite adherence to abstinence, nutritional support, steroids, and standard medical support [47]. In a recent multicentre French study, patients with a first episode of severe AAH resistant to steroids, a favourable psychosocial environment and a favourable addiction disease consultation, have been transplanted resulting with a dramatic improvement in survival in comparison to their spontaneous expected survival; a low rate of recidivism at 2 years was also reported [48]. This study needs confirmation before achieving a consensus on the indication of LT in relation with abstinence duration. In all cases it emphasises the importance of psychosocial management of these patients to ensure long-term success of LT.

Recommendations:

- A period of 6 months abstinence before the transplant could improve liver function avoiding unnecessary LT and could also improve compliance (**Grade II-3**)
- A psychiatric and psycho-sociological evaluation and support pre- and post-LT is required for patients with alcoholic liver disease in the need of LT (**Grade III**)
- LT can be offered to patients with acute alcoholic hepatitis non-responsive to steroids therapy. Nevertheless the procedure should be done in highly selected patients (**Grade II-2**)

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

In the setting of the metabolic or insulin resistance syndrome, NAFLD and NASH are becoming increasingly common medical problems in the developed world. Patients with histological necrotic-inflammatory changes and/or fibrosis may progress to end-stage liver disease and require LT. NAFLD and NASH are increasingly recognised as an indication to LT at the stage of cirrhosis and liver failure [49]. Some patients may have both NAFLD linked to metabolic syndrome and chronic alcohol consumption acting as a cofactor for cirrhosis development. One specific point that should be carefully evaluated is the presence of comorbid factors linked to metabolic syndrome, which might increase the risk of complications during a surgical procedure [50]. In particular obesity, hypertension, diabetes and dyslipidemia required a specific work-up in the pre-transplant phase or screening and should be addressed in the post-transplant setting as they might exacerbate [51]. It is likely that many potential LT candidates with NASH are excluded from LT due to comorbid conditions related to metabolic syndrome. In particular, morbid obesity might be a limiting factor to transplantation as it increases infection complications, as well as the length of stay in the intensive care unit (ICU) and hospital [52]. Indication to LT in obese patients with a body mass index (BMI) over 35 should be discussed within a multidisciplinary team including dietician, psychologist, hepatologist, anestethist and surgeon.

Recommendation:

- Comorbidities such as obesity, hypertension, diabetes and dyslipidaemia need to be assessed and controlled both in the pre- and post-transplant setting as they increase morbidity (**Grade III**)

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Clinical Practice Guidelines

Primary biliary cholangitis (PBC)

The advent of ursodeoxycholic acid as a recognised treatment of PBC has deeply modified the natural history of the disease, improved survival and the number of candidates to LT has dramatically decreased over the last decades. Nevertheless its efficacy in the long-term has yet to be determined [53].

The indication to LT should be given when the expected survival is less than one year, in the case of patients with decompensated cirrhosis at any stage and in the case of complicated portal hypertension. Uncontrolled and intolerable pruritus refractory to all medical therapies including MARS, even if isolated, represents an indication to LT, which provides a significant improvement in the QoL [54].

Recommendation:

- In PBC patients, indication to LT should be given for decompensated liver disease, complicated portal hypertension and for uncontrolled and intolerable pruritus refractory to all medical therapies (**Grade II-3**)

Primary sclerosing cholangitis (PSC)

Specific indications to LT for patients with PSC are long-standing severe jaundice, repeated episodes of cholangitis not controlled by antibiotics, secondary biliary cirrhosis with complications of portal hypertension or decompensation and liver failure. The risk of cholangiocarcinoma is increased in these patients with a prevalence over 10–15% after a 10-year disease course [55]. In some cases, discovery of cholangiocarcinoma is detected only during the surgical procedure, in other cases, cholangiocarcinoma is highly suspected on the progression of cholestasis, and increased level of carbohydrate antigen 19–9 (a tumour marker) but not found during surgery. On single centre studies when patients were transplanted for PSC, explant pathology showed an incidence of 10–20% unsuspected cholangiocarcinoma. Thus the diagnosis of cholangiocarcinoma on PSC might be difficult or impossible before the pathological analyses of the biliary and liver explant. A suspicion of cholangiocarcinoma on PSC might be an indication to LT; however, it can be a contraindication if it is at an advanced stage. Patients transplanted with an unsuspected cholangiocarcinoma have usually a high risk of recurrent cholangiocarcinoma and poor long-term prognosis [56]. Chronic inflammatory bowel disease (IBD) is frequently associated with PSC. IBD can be quiescent at time of LT and is not a contraindication to LT. Active IBD should be controlled before LT. Colon cancer should be searched for in patients with ulcerative colitis. Medical treatment of IBD and IBD surveillance is necessary after LT [57].

Recommendations:

- In PSC patients, indication to LT should be given for decompensated liver disease, complicated portal hypertension and repeated episodes of cholangitis (**Grade II-3**)
- PSC is a risk factor for cholangiocarcinoma, thus cholangiocarcinoma should be excluded by radiological and biological markers before LT (**Grade III**)
- Patients with PSC and ulcerative colitis should undergo colonoscopy annually before and after LT due to the higher risk of developing colon cancer (**Grade II-3**)

Autoimmune hepatitis (AIH)

AIH is more common in young woman, but may also affect older women, and in some few cases also men. The clinical presentation of the disease is variable; classically it presents as active chronic hepatitis, but may also present as established cirrhosis and in some rare cases as a fulminant course without chronic hepatic disease. A main characteristic of this disease is a good response to immunosuppressive treatment including steroids [58]. LT is indicated in AIH in case of end-stage liver disease, or in case of acute liver failure, when immunosuppressive treatment is usually ineffective and potentially deleterious because the risk of sepsis [59].

Recommendation:

- LT is indicated in patients with decompensated cirrhosis due to autoimmune hepatitis not responding to medical therapy and in cases of fulminant autoimmune hepatitis (**Grade II-3**)

Genetic diseases

Genetic diseases represent a heterogeneous group of disorders, which affects 10 out of 1000 births. They could manifest as predominant liver parenchymal damage (genetic cholestatic disorders, Wilson's disease, hereditary haemochromatosis, tyrosinemia, alpha-1-antitrypsine deficiency) or they could be liver-based genetic disorders characterized by architecturally near-normal liver (urea cycle disorders, Crigler-Najjar syndrome, familial amyloid neuropathy, primary hyperoxaluria type 1, atypical haemolytic uremic syndrome-1). For the first group, hepatic complications are the main indications to LT while in the second extrahepatic manifestations are the main cause of morbidity and mortality while liver function is preserved [60].

Wilson's disease. Liver disease can manifest as acute liver failure, accompanied by haemolysis and kidney failure, or subacute or chronic liver failure, which can progress to end-stage liver disease. Treatments are copper-chelating agents (penicillamine, trientine, tetrathiomolybdate) or zinc salts (through the block of intestinal copper absorption) [61]. LT is indicated in the acute setting or in case of progression of the disease to end-stage liver disease. In case of disease progression under therapy, non-compliance and incorrect drug dosage should be ruled out. In patients with neurological symptoms LT can improve brain damage with a complete recovery in 57–77% of cases [62,63]. Nevertheless long-standing neurological disease is unlikely to improve, a severe worsening has been also reported in these patients with lower survival compared to patients with liver disease only. Therefore a neuropsychiatric evaluation is mandatory in LT candidates with neuropsychiatric symptoms.

Hereditary haemochromatosis (HH). Overall only 1% of patients with HH undergo LT for hepatic decompensation. The risk of developing HCC is increased compared with patients affected by other causes of cirrhosis [64]. Therefore another potential indication of LT is the development of HCC on cirrhosis due to HH.

Therapeutic phlebotomy is the general treatment for HH, which is safe and effective [65]. Phlebotomies are recommended if serum ferritin is >1000 ng/ml, usually started at 500 ml/week, and continued until reaching normalized iron store levels (serum

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ferritin <50 ng/ml) with concomitant follow-up of haematocrit (<20% change between phlebotomies).

Iron overload affects primarily the liver, but it can also lead to multiple organ damage; heart, pancreas, gonads, skin, and joints. Clinical manifestations are cirrhosis, cardiomyopathy, diabetes, arthritis, hypogonadism, and skin pigmentation. LT candidates should undergo extensive cardiac work-up taking into account the risk of cardiomyopathy. The outcome after LT for HH is good with 1- and 5-year survival rates of 80.7% and 74% respectively, the main causes of death after LT are infections (45%) and cardiac complications (22%) [66].

Primary hyperoxaluria type 1 (PH1). PH1 is an autosomal recessive disease that has been associated with an enzymatic defect of alanine-glyoxylate aminotransferase, resulting in less conversion of glyoxylate into glycine. The increased glyoxylate on its turn is converted into oxalate, which forms insoluble calcium salts that accumulate in the kidney and other organs [67]. The prevalence of PH1 ranges from one to three in 1,000,000. The natural history of PH1 is characterized by the decline of renal function as a result of progressive nephrolithiasis/nephrocalcinosis, with progression to end-stage renal disease (ESRD) and/or complications of systemic oxalosis [68]. Early diagnosis of PH1 and initiation of therapy may prevent renal failure. Pyridoxine (vitamin B6) stimulates the conversion pathway of glyoxylate to glycine, reducing the conversion to oxalate.

Approximately 10–30% of individuals with PH1 respond to treatment with pyridoxine. Isolated kidney transplantation restores oxalate excretion to normal, but is associated with a high rate of recurrence and in many cases early graft loss. Pre-emptive LT before ESRD and systemic oxalosis is a possible approach as replacing the liver corrects the metabolic defect and prevents kidney failure. Another possibility is the combined liver-kidney transplantation. The optimal approach and the timing of the transplant is still controversial [69,70].

Familial amyloid polyneuropathy (FAP). FAP is a progressive degenerative disorder of autosomal dominant inheritance. It is caused by the mutation of the transthyretin (*TTR*), one of the prealbumins, which is most commonly due to a single amino acid substitution of valine to methionine at position 30 (Val30Met). Plasma TTR is predominantly synthesized by the liver and mutated forms of TTR are the precursor protein of amyloid fibre and amorphous aggregates in patients' tissues. It is characterized by extracellular amyloid tissue accumulation. The clinical manifestations are mainly represented by progressive peripheral and autonomic polyneuropathy associated with sensory loss, motor weakness, and autonomic dysfunction. Liver tissue of TTR-FAP patients has normal structure and function, except for the production of amyloidogenic variant TTR. LT must be proposed to the symptomatic patients as early as possible as transplanted patients have significantly prolonged survival compared with the non-transplanted ones [71]. The outcome is generally favourable for those with an early onset of the disease [72]. Outcome after LT in patients with FAP not related to Val30Met mutation are inferior compared with patients transplanted for FAP related to Val30Met mutations [72]. In these patients, overall survival at 5 years is reported to be above 80% [71,73,74].

If the disease is in an advanced stage, LT does not improve the symptoms [75]. The pre-transplant work-up should take into account the cardiomyopathy due to TTR fibril deposit, which could impair the post-LT outcome [76]. Owing to the fact that the mutation is in the liver, but without liver injury, LT is often done as domino transplantation. The explanted liver of the FAP patient will then be transplanted into another patient with end-stage liver disease. The patient receives a FAP liver with the production of the mutant TTR protein, but the process of amyloid deposition is slow.

Domino LT has mainly been used in patients with a shorter life expectancy or higher chance of recurrence of liver disease. So far some cases of *de novo* polyneuropathy have been reported 7 to 9 years after domino LT with proven amyloid deposits [77]. Nevertheless amyloid polyneuropathy acquired after a domino LT can be reversible after liver retransplantation [78].

Recommendations:

- LT is indicated in both genetic diseases with parenchymal liver damage and liver-based genetic disorders with prevalent extrahepatic manifestations (**Grade II-3**)
- If the genetic defect affects other organs, the indication to LT is less evident and should be discussed in an expert centre (**Grade III**)
- The indication of LT in patients with Wilson's disease should be made in cases of acute liver failure or end-stage liver disease. LT can improve neurological symptoms but they can also worsen after the procedure. The neurological assessment before the transplant is mandatory (**Grade III**)
- Hereditary haemochromatosis can be an indication of LT, especially if complicated by HCC. Cardiac evaluation before LT needs to be accurate considering the cardiomyopathy associated with iron overload (**Grade III**)
- Timing and approach to transplant for primary hyperoxaluria type 1 are still controversial. In kidney transplant the disease can recur, one possibility is combined liver-kidney or liver transplant before kidney failure (**Grade III**)
- Liver transplant for patient with familial amyloid polyneuropathy should be proposed as soon as symptoms appear. LT outcome is good if the patients are transplanted with no advanced disease manifestations. LT is often done with a domino technique. FAP liver recipients can develop polyneuropathy symptoms in a shorter time compared to FAP patients. Nevertheless symptoms can be reversed by liver retransplantation (**Grade III**)

Management of patients with liver cirrhosis and hepatic malignancies

Hepatocellular carcinoma

HCC is the most common primary malignancy of the liver. LT is a suitable therapeutic option for early, unresectable HCC particularly in the setting of chronic liver disease. When Milan criteria (solitary HCC with diameter <5 cm or up to 3 nodules with diameter <3 cm) are applied for patient selection excellent results after LT can be achieved, with a 5-year survival exceeding 70%

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Clinical Practice Guidelines

[79]. More recently, Yao *et al.* [80] have shown that patients with one nodule <6.5 cm in diameter or with several nodules with the largest <4.5 cm in diameter and the total sum of all diameters <8 cm, named as UCSF criteria, have a recurrence-free survival not significantly different from patients within the Milan criteria. Other criteria have been described including poor prognosis criteria such as AFP over 500 ng/ml or an increase of 15 ng/ml/month [81]. Recently Duvoux *et al.* [82] have described a new model called "AFP model" which takes into account the number, the size of nodules, and the AFP level. A patient with an AFP score $\leqslant 2$ has a little risk of recurrence after the transplant with a 5-year survival of 70%. This can allow patients who are outside the Milan criteria to undergo transplantation resulting in a very good outcome. However, the Milan criteria remain the benchmark for the selection of HCC patients for LT and the basis for comparison with other proposed criteria. Considering the role of downstaging, LT after successful downstaging should achieve a 5-year survival comparable to that of HCC patients who meet the criteria for LT without requiring downstaging [83]. Moreover, since the drop-out rate from transplant waiting list is about 15–30% because of HCC progression, downstaging and bridging treatment should be offered to all patients with an estimating waiting time for transplant over 6 months [84,85].

HCC arising in a non-cirrhotic patient is rare and Milan criteria are not applicable to evaluate the suitability for LT. In general, non-cirrhotic patients with non-resectable HCC and patients who were treated by resection and have intrahepatic recurrence of HCC may be considered as appropriate candidates for LT if the absence of macrovascular invasion and extrahepatic spread has been shown. A recent analysis of the European Liver Transplant Registry (ELTR) showed 5-year survival rates at 50–70% in well-selected patients. Important determinants of poor outcome are macrovascular invasion, lymph node involvement, and time interval of <12 months when LT is used as rescue therapy for intrahepatic recurrence after a previous partial liver resection [86].

Cholangiocarcinoma

Cholangiocarcinoma is the second most common cancer among the primary hepatic neoplasm, accounting for 5 to 20% of liver malignancies. LT for cholangiocarcinoma remains a controversial issue due to a high risk of recurrence [87]. A protocol combining neoadjuvant chemoradiation and LT was first used in patients with unresectable hilar cholangiocarcinoma [88]. Results have confirmed that this approach leads to significantly lower recurrence rates and higher long-term survival rates than other existing treatment modalities [89]. For the extrahepatic cholangiocarcinoma the treatment of choice is surgical resection, LT can be effective for perihilar cholangiocarcinoma with 65% rate of disease-free 5-year survival in highly selected patients [90]. Despite this, protocols to treat patients with cholangiocarcinoma are not widespread and are available at only a handful of transplant programs.

Other hepatic malignancies

Others hepatic malignancies, without metastatic spread outside the liver, are succesfully treated by LT, as fibrolamellar carcinoma and epithelioid haemangioendothelioma. The results of the largest reported transplant series in the treatment of haemangioendothelioma showed excellent results with disease-free survival rates at 1, 5, and 10 years post-LT of 90%, 82%, and 64% [91].

Hepatic metastases

Classically, metastatic tumours of the liver have been considered a poor indication for LT, although some centres performed this procedure in parallel with other therapies, such as chemotherapy and radiotherapy. In metastases from neuroendocrine tumours, LT could be indicated for patients with symptoms related to massive hepatomegaly, hormone production, unavailability of effective therapeutic alternatives, diffuse metastases of the liver, slow growing tumour and patients with no extrahepatic disease [92]. Main advantages of LT in this setting would be a significant improvement of the QoL in many patients with a palliative therapeutic alternative and a possible cure in some cases. Other causes of liver metastasis are currently considered as contraindication to LT.

LT for colorectal cancer unresectable metastases is still controversial. A single centre study from Norway reports a 5-year survival of 60% with no long-term disease-free survival [93]. These results should be viewed with caution; moreover, organ use in this respect during a period of donor shortage is highly questionable.

There is an ongoing European randomized controlled trial (RCT) to explore whether LT in selected patients with liver metastases from colorectal cancer can obtain significant life extension and better health related QoL compared to patients receiving surgical resection (NCT01479608).

Recommendations:

- LT for HCC patients meeting Milan criteria has an excellent outcome. An expansion of these criteria is acceptable if the recurrence-free survival is comparable. All new models should be compared to the Milan model (**Grade I**)
- LT is usually not recommended for cholangiocarcinoma or mixed hepatocellular/cholangiocarcinoma since results are quite poor from the published data. LT for perihilar cholangiocarcinoma could be offered in centres with clinical research protocols employing adjuvant or neoadjuvant therapy (**Grade II-3**)
- LT can be offered to patients with fibrolamellar carcinoma and epithelioid hemangioendothelioma (**Grade II-3**)
- Liver metastasis from non-liver tumours, such as neuroendocrine might be considered for LT in very selected patients and only in trained liver transplant centres with experience in such indication for LT (**Grade II-3**)
- Liver metastasis from colorectal cancer is usually a contraindication to LT and might be proposed in very selected patients within research trials and only in trained liver transplant centres with experience in such indication to LT (**Grade II-3**)

Management of comorbidities

All potential candidates of LT should undergo an extensive work-up before their registration on the waiting list. Usually there is no formal age limit of potential LT recipient, but patients over 65 years of age need a multidisciplinary evaluation to exclude comorbidities. LT has been successfully performed in patients older than 70 years, although they have an increased risk of

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cardiovascular complications [94]. The trend in LT is an increase rate of recipients older than 65 years as the results are comparable to those for younger patients. The trend of increasing age of transplant candidates is related both to the changing demographics, with an aging society, but also to changing epidemiology of liver disease. Some teams consider that the physiologic age is more important than the chronologic age [95,96]. The final decision for listing a patient aged 65–70 or older than 70 years should be taken after a thorough multidisciplinary discussion.

Cardiovascular function

In patients with cirrhosis, increased cardiac output has been described. Moreover, the presence of a latent cardiac dysfunction, which includes a combination of reduced cardiac contractility with systolic and diastolic dysfunction and electrophysiological abnormalities are noticed. This syndrome is termed cirrhotic cardiomyopathy [97].

Although cardiac evaluation is very prominent in the assessment process, there is no ideal way to assess it and a lot of resources are being wasted in attempting to do so. Traditional cardiovascular risk factors are related to coronary artery disease (CAD) in patients with liver disease, and they might be used as indicators for careful preoperative evaluation of coronary risk [98]. Electrocardiogram and transthoracic echocardiography should be performed in all liver transplant candidates to rule out underlying heart disease. If the patient has multiple cardiovascular risk factors, and is older than 50 years, a cardiopulmonary exercise test should be done in order to uncover asymptomatic ischaemic heart disease. Aerobic capacity is markedly impaired in many patients with chronic liver disease. In patients undergoing LT, the anaerobic threshold measured during cardiopulmonary exercise testing is related to post-operative hospitalization and survival [99]. If coronary disease is suspected during the evaluation in high risk patients, coronary angiography should be performed.

When CAD is treated effectively before LT, survival after LT is not significantly different between patients with and without obstructive CAD [100]. To date there are no multicentre studies examining the impact of CAD on LT outcome.

Recommendations:

- Patients with an indication to LT should undergo an extensive work-up before their inscription onto the waiting list (**Grade III**)
- No age limit of potential LT recipients are established, considering the good outcome of elderly patients. A multidisciplinary evaluation should always be performed in elderly patients to exclude comorbidities (**Grade III**)
- Electrocardiogram and transthoracic echocardiography should be performed in all liver transplant candidates (**Grade II-3**)
- In patients with multiple cardiovascular risk factors, and in patients older than 50 years, a cardiopulmonary exercise test should be done. If the target heart rate is not achieved during a standard exercise test a pharmacological stress test is the test of choice (**Grade II-3**)

Respiratory function

To evaluate the respiratory function, lung function tests and a chest X-ray are recommended in all candidate patients to LT. When hepatopulmonary syndrome (HPS) or portopulmonary hypertension (PPHTN) are suspected, further investigations should be performed [101].

HPS is found in 10–17% of patients with cirrhosis and is characterized by intrapulmonary vascular dilatations especially in the basal parts of the lung. It results in hypoxemia and oxygenotherapy could be required. Because it could reverse HPS through closure of the shunts, LT is the only curative treatment. HPS can be diagnosed by calculating the alveolar-arterial oxygen gradient and by performing a contrast echocardiography [102]. The severity of HPS is not related to the severity of liver disease and can be an isolated indication for LT. It is important to properly assess the severity of HPS, since patients with PaO_2 <50 mmHg and no reversibility to 100% oxygen may have a risk of irreversible respiratory failure in the post-transplant period and a high risk of perioperative mortality [103]. It should also be remembered that in most patients with HPS, there is a deterioration of the respiratory function in the first days after LT due to the surgical procedure itself, and that improvement and reversibility of HPS may take months [104].

PPHTN occurs in 2–8% of the patients with cirrhosis. An imbalance between vasodilating and vasoconstrictive agents may be responsible for misguided angiogenesis and pulmonary hypertension [105]. The diagnosis of PPHTN is suspected when systolic pulmonary artery pressure is higher than 30 mmHg on echocardiography and should be confirmed by right heart catheterization. Moderate (mean pulmonary artery pressure [MPAP] $\geqslant$35 mmHg) and severe PPHTN (MPAP $\geqslant$45 mmHg) are associated with increased mortality after LT. In a series of 12 patients with MPAP between 34 and 60 mmHg who underwent LT, five died, all within one month post-LT [106]. The pre-LT management of patients with PPHTN requires early diagnosis and therapy with pulmonary vasodilators. Recently, pharmacological treatments such as epoprostenol (prostacycline), or prostacyclin analogues (iloprost, treprostinil), or endothelin receptor antagonist, or phosphodiesterase inhibitor type 5 (sildenafil) have been shown to improve pulmonary haemodynamics. Some cases of transplantation in patients treated with these agents have been reported to be efficacious; however, long-term results are pending [107]. Therefore LT could be considered in patients with PPHTN responding to medical therapy with pulmonary vasodilators and with MPAP $\leqslant$35 mmHg.

Careful perioperative attention to avoid right ventricular failure from acutely elevated pulmonary artery pressure or sudden increase in right ventricular preload is key to the management of PPHTN. With increased surgical and anaesthetic expertise, patients with PPHTN can be considered for LT [108].

Recommendations:

- Respiratory function needs to be assessed; in particular the presence and stage of hepatopulmonary syndrome and portopulmonary hypertension should be evaluated (**Grade II-3**)
- Hepatopulmonary syndrome is an indication to LT (**Grade II-2/3**)
- LT should be considered in patients with PPHTN responding to medical therapy with pulmonary vasodilators and with MPAP ≤35 mmHg (**Grade II-2/3**)

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Clinical Practice Guidelines

Renal function

Cirrhotic patients with renal failure have a 7-fold increased risk of death, with 50% of patients dying within one month [109], therefore the assessment of renal function is essential when evaluating a patient for LT. The hepatorenal syndrome, usually a reversible cause of renal failure, has to be differentiated from other causes of acute kidney injury, such as sepsis, hypovolemia and parenchymal renal disease.

Acute kidney injury is defined as a reduction in kidney function manifested by an absolute rise of serum creatinine of at least 0.3 mg/dl or the equivalent to a percentage increase of 50% (1.5-fold) from baseline, occurring within 48 h. Chronic kidney disease is defined as an estimated glomerular filtration rate (GFR) of <60 ml/min, calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula, [110] for more than three months.

The evaluation of renal clearance can be difficult in patients with cirrhosis [111], therefore performing inulin or other exogenous marker's clearance and renal biopsies might help in decision-making.

Patients with end-stage liver disease and with GFR less than 30 ml/min, or hepatorenal syndrome requiring renal replacement therapy more than 8–12 weeks, and patients with renal biopsy revealing more than 30% fibrosis and glomerulosclerosis would benefit from receiving both liver and kidney grafts [112]. There is a debate regarding the need for combined liver-kidney transplantation in patients with creatinine clearance between 30 ml/min and 60 ml/min. It should be balanced between the risk of deterioration of renal function after LT alone as a consequence of surgery and of drug toxicity, and the shortage of kidney grafts.

Recommendations:

- Hepatorenal syndrome is not a contraindication to LT (**Grade II-2**)
- Chronic kidney disease might be severe and irreversible requiring combined liver-kidney transplant (**Grade II-2**)

Nutritional assessment

Liver cirrhosis is associated with malnutrition, and cachexia is present in nearly 70% of patients with end-stage liver disease [113]. Malnutrition is associated with lower survival rate after LT, patients with BMI <18.5 are the group at highest risk of poor outcome [114]. The general condition and nutritional status are sometimes difficult to assess in patients with end-stage liver disease. The clinical and biological parameters classically used (BMI, prealbumin, etc.) may not apply in cases of severe hepatic insufficiency. Several authors have recently pointed out the role of sarcopenia assessed by a CT scan evaluation of the transversal psoas muscle thickness on the post-transplant morbidity and mortality [115]. More studies are needed to develop specific nutritional scores in cirrhosis. Nutrition intervention prior to transplantation may play an important role, nevertheless it is extremely difficult to achieve. To date, studies have been unable to identify a nutritional intervention that offers convincing benefits [116], and no nutritional protocol in cirrhotic patients waiting for LT has been established [117]. Considering patients with high BMI, outcomes after LT seem to be worse in patients with a BMI >40 compared with normal weight patients [114]. Moreover, diabetes mellitus is often present in obese patients and in patients with features of metabolic syndrome. Therefore, they are at higher risk of developing post-transplant diabetes mellitus and of cardiovascular events. Pre-transplant diabetes and dyslipidaemia should be managed as in the general population.

Evaluation of bone abnormalities

Osteoporosis is a common complication among patients with cirrhosis and most particularly in those with chronic cholestasis disease [118]. Bone densitometry could predict the risk of pathological fracture and prevention could be initiated. Female gender, lower BMI, and tobacco consumption are major risk factors for bone disease in cirrhotic patients. Bone densitometry must be included in the LT evaluation of all patients [119].

Recommendations:

- The nutritional status is hard to assess in a cirrhotic patient. The thickness and the area of psoas muscle have been correlated with worse outcome (**Grade II-2**)
- Improvement of nutritional status is indicated but no protocols have been approved so far (**Grade III**)
- As osteoporosis is associated with cirrhosis, densitometry should be part of liver transplant work-up (**Grade III**)

Immunological evaluation

The role of the donor-specific human leukocyte antigen alloantibodies (DSA) on acute and chronic antibodies-mediated rejection and also on different histological damage such as fibrosis, disease recurrence, biliary complications etc. has been recently raised. The correlation between the cut-off of DSA and liver damage, and moreover, the LT outcome, is still not clear [120]. DSA is an important tool but more research needs to be done in order to understand their usefulness.

Recommendation:

- The presence of donor-specific alloantibodies has been associated with acute and chronic antibodies-mediated rejection and with several histological damages. The best test and use of anti-DSA is still under study (**Grade III**)

Infection screening

Patients with cirrhosis are prone to develop infections that could result in the development of multiple organ failure and death [121]. A screening of latent infections is required in order to treat a potentially lethal infection before LT and to prevent an exacerbation after LT under immunosuppressive regimens. A correct evaluation of the presence of acute or chronic infections in the recipient is crucial. The infectious screening in liver transplant recipients should be graduated in different levels as follows: a) first level to be performed in all LT candidates; b) second level to be performed only in patients eligible to LT at the time of listing;

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and c) third level to be performed in patients with risk factors or who are from a geographic area with specific endemic infections [122].

The first level of screening consists of screening for human immunodeficiency virus (HIV) 1 and 2 antibodies, HBV serology, HCV antibodies, HAV antibodies, cytomegalovirus (CMV) and completing a chest X-ray [122].

The second level of screening consist of screening for: *Mycobacterium tuberculosis* (history + PPD-Mantoux + IFN-Gamma Release Assays), Epstein-Barr virus (EBV), human herpes virus 8 (HHV-8), varicella zoster virus (VZV), herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), urine culture, parasitological exam and stool culture (*Strongyloides stercoralis* serology, *Toxoplasma gondii* IgG, *Treponema pallidum* serology), immunoenzymatic assay with venereal disease research laboratory (VDRL), *Staphylococcus aureus* nasal/axillary swab, and dentist review [122].

The third level screening should be performed to a subset of patients according to the clinical history, comorbidities and to endemic diseases and local epidemiology [122].

Regarding vaccination, it is important to make sure that transplant candidates are immunised against HAV and HBV, varicella, *Pneumococcus*, influenza and tetanus.

Infections exposure that require monitoring. Dust exposure requires monitoring for aspergillosis. Recipients living in West Nile virus (WNV) endemic areas require specific monitoring with WNV serology and PCR.

Exposure to infections that require routine intervention. A chest radiograph should be performed to essentially search for indirect signs of bacterial or fungal lung infection, including tuberculosis. Some teams recommend conducting a skin test. The search for the tubercle bacillus is not systematic in the absence of other risk factors and with a normal chest radiograph.

Patients with positive PPD test results should be considered for prophylactic therapy with isoniazid, according to standard guidelines, after a careful evaluation to exclude active disease that would require combination therapy [122].

Serological screening and secondary prophylaxis for coccidioidomycosis in transplant recipients have been recommended for transplant candidates and recipients in areas where these diseases are endemic.

Infections that delay LT. Chronic oedema and increased bacterial translocation predispose cirrhotic patients to develop soft tissue infections, which represent nearly 11% of infections [123] and which can be caused by both Gram-positive (*S. aureus*, *Streptococci*) and Gram-negative bacteria (*Klebsiella* spp.). Cellulitis is the most frequent skin infection in cirrhotic patients and it has a recurrence rate of 20% [124].

Infections that contraindicate LT. In cirrhotic patients, bacteremia can occur spontaneously or as consequences of skin, lung or urinary infections. Although transient bacteremia, associated with therapeutic invasive procedures such as transarterial chemoembolization (TACE) and percutaneous sclerotherapy is relatively common, the risk of a relevant clinical impact does not warrant antibiotic prophylaxis [125].

Pneumonia is the third leading cause of infections in patients with cirrhosis [126,127], with an increased risk of bacteremia compared with the general population [128]. Community-acquired pneumonia is often caused by *S. pneumonia* and *H. influenza* [129]. Pneumococcal vaccination is recommended in patients with cirrhosis.

Candidemia represent a frequent infection in patients with chronic liver disease and in particular in patients with PSC, identified in up to 44% of bile samples in PSC patients, especially those with dominant strictures [130,131].

The presence of invasive fungal infection, such as aspergillosis, represents a contraindication to LT and the recipient should be treated at least until there is radiographic, clinical and microbiologic resolution [132].

HIV infection has been considered as a contraindication for LT before the era of antiretroviral therapies. This was due to the poor spontaneous prognosis of HIV infection. The advent of highly active antiretroviral drugs has been a therapeutic breakthrough, and the prognosis has been dramatically improved. The progression of chronic HBV and HCV seems more rapid in coinfected patients, and a high number of patients will develop life-threatening liver cirrhosis. Patients with a controlled HIV disease, absence of AIDS related event, and CD4 over 100–150/mm^3 can be considered for transplantation. While HBV/HIV coinfection is considered as a good indication for transplantation, the indication for transplantation in patients with HCV/HIV coinfection is more controversial due to the severity of HCV recurrence in these coinfected patients [133]. In a recent prospective, multicentre study patient and graft survival after LT were evaluated in 89 HCV/HIV-coinfected patients and were compared with 235 HCV-monoinfected liver transplanted patients, along with all US transplant recipients who were 65 years old or older. Among the HCV/HIV patients, older donor age, renal dysfunction requiring combined kidney-liver transplantation, and a BMI <21 kg/m^2 were independent predictors of graft loss [134]. The use of highly efficacious IFN-free regimens to treat HCV infection (both before and after LT) will most likely change the outcomes of these patients and HCV/HIV coinfection will become a standard indication for LT.

Recommendations:

- A screening for bacterial, fungal and viral infections is mandatory before LT. The presence of an active infection contraindicates the procedure (**Grade III**)
- CMV donor/recipient status determines time of prophylaxis (**Grade II-3**)

Anatomical evaluation

The surgeon must be warned about the type of vascularization of the recipient regarding the hepatic artery and the main portal system. The presence of portacaval shunts, which should be suture-ligated during surgery or arcuate ligament are routinely searched. It has replaced hepatic arteriography, which is indicated in cases of variant anatomy or previous hepatic surgery.

In the past, portal vein thrombosis (PVT) was considered an absolute contraindication for LT. As a result of improvements in medical care, surgical techniques and radiological interventions, PVT by itself can represent an indication for LT. Several studies showed that surgical thrombectomy, thromboendovenectomy

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Clinical Practice Guidelines

with venous reconstruction, interposition of vein graft, porto-caval hemitransposition, and radiological endovascular interventions can resolve venous obstruction in liver transplant recipients. Interestingly, PVT patients' survival rates at 1- and 5-years after LT are equal [135]. An isolated thrombosis of the portal vein is not a surgical contraindication, an anticoagulant is used to prevent thrombus extension; however, in some case a thrombosis of the whole portal system (including portal vein, superior mesenteric vein, splenic vein) can be a contraindication to LT.

Evaluation of the biliary tree anatomy is particularly important in patients who will receive living donor LT, and it can be achieved non-invasively with magnetic resonance tomography or magnetic resonance cholangiopancreatography or invasively with endoscopic retrograde cholangiopancreatography.

An overall surgical and anaesthesia consultations are mandatory at the end of the evaluation process to assess operational and post-operational risks.

Recommendations:

- Recipient anatomical evaluation is mandatory with a three-phase intravenous contrast CT scan (**Grade II-3**)
- The presence of portal vein thrombosis is not a contraindication to LT; nevertheless if the thrombosis extends to the whole porto-mesenteric system (Yerdel Stage IV), LT might not be feasible (**Grade II-3**)

Screening for neoplastic lesions

A past history of cancer already treated should not disqualify candidates for LT. In accordance, the survival and the risk of recurrence at 1-, 5-, and 10-years under a long-term immunosuppressive treatment should be estimated, case by case, with an oncologist. Common practice is to consider the patient suitable for LT if the risk of recurrence is estimated to be less than 10%. Moreover, usually an interval time of 5 years free-of-recurrence is often required to exclude potential recurrence, but this may vary considerably with the type of malignancy. However, to date no consistent data have been published on the optimal management of patients candidated to LT and with a previous extrahepatic malignancy.

Screening for neoplastic lesions should always be performed, when evaluating a patient for LT, taking into account age, gender, alcohol consumption and smoking status of the recipient.

Colorectal cancer screening is mandatory for candidates older than 50 years. If a colonoscopy under general anaesthesia is too risky, CT colonography may be an alternative, although its usefulness in cirrhotic patients with ascites has never been demonstrated. The search for pulmonary neoplasia, ear-nose-throat, stomatology, oesophageal and bladder is mandatory in cases of alcohol and smoking addiction. An ear-nose-throat examination associated with a nasofibroscopy, an examination of the oral cavity, and upper gastrointestinal endoscopy are recommended. Upper gastrointestinal endoscopy is commonly performed in all candidates, for both cancer screening and evaluation of the presence of oesophageal or gastric varices.

Women should have regular gynaecological care including Pap smear and mammogram if needed. Screening for prostate disease should be done according to the urologist indication.

An examination of the skin is important, taking into account that non-melanotic skin cancers rarely contraindicates LT. A special screening for hepatic malignancy is based on preoperative baseline metastatic work-up which includes bone scan and chest CT. Recently, positron emission tomography (PET) scan also tends to be included because of the usefulness to find otherwise undetected neoplastic lesions [136].

Recommendations:

- A screening for neoplastic lesions should be part of LT work-up (**Grade III**)
- The search for pulmonary neoplasia, ear-nose-throat, stomatology, oesophageal and bladder is indicated in cases of alcohol and smoking addiction (**Grade II-3**)
- History of a treated cancer is not an absolute contraindication to LT. A 5-year interval seems to be a reasonable time between curative cancer treatment and LT, depending on type and stage of previously treated cancer (**Grade III**)

Social assessment, psychiatric and addiction

It is important to assess social network, psychiatric illness and addiction in order to evaluate adherence of the recipient. In case of hepatic encephalopathy, neuropsychological testing, CT brain scan or NMR and electroencephalography could help to determine reversibility of neuropsychiatric conditions. Active drug or alcohol abuse is considered to be a contraindication to LT for many reasons: the risk of recidivism, the risk of non-compliance and the risk of injury to the graft.

Stably abstinent, methadone-maintained, opiate-dependent patients are generally good candidates for LT and show low relapse rates [137]. However, there are no conclusive evidence showing that patients with end-stage liver failure using methadone have poorer outcomes after transplantation compared with patients not using methadone. Moreover, nearly one third of liver transplant centres in the US require patients to be weaned off of methadone before they can become eligible for LT [138].

Current methods in toxicology screening can provide a positive result when screening for cannabinoids up to two months after the patient's last use. Patients who tested positive for marijuana had similar survival rates compared to those with negative test results. Whether patients who regularly use marijuana should be excluded from the waiting list remains a controversial issue [139,140]. In a recent survey among 102 adult liver transplant centres in the US, 46.7% of centres considered the daily consumption of marijuana as an absolute contraindication, whereas 43% a relative contraindication and 10.3% as no contraindication [141].

When patients with polysubstance abuse disorders undergo LT the rate of recidivism is nearly 27%, but this does not seem to influence post-transplant survival [142].

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Pre- and post-transplant smoking rates are high and cause significant morbidity and mortality due to cardiovascular events [143], increased incidence of hepatic artery thrombosis [144] and increased incidence of malignancies such as oropharyngeal [145]. Therefore smoking cessation should be mandatory in all transplant candidates.

Recommendations:

- Social, psychological and, when indicated, psychiatric evaluation should be performed to evaluate adherence of the recipient, and potential risk factors for non-adherence after LT (**Grade III**)
- Stably abstinent, methadone-maintained opiate-dependent patients should not be excluded from evaluation for LT (**Grade II-2**)
- Smoking cessation should be mandatory in all transplant candidates (**Grade III**)

Organ donation

Organ donation

Consent systems

In the EU, organs cannot be procured without the consent of donors and/or their relatives. However, the establishment of consent differs between Member States. National provisions usually foresee that citizens (donors or relatives) can "opt-in" (explicit consent) or "opt-out" for donation (presumed consent). Mixed solutions also exist, with or without central databases that register the wishes expressed by citizens. The ACTOR study found that most European countries have "opt-out", i.e. presumed consent systems, according to which no explicit consent is required for a person to become a potential donor. In practice, and in the absence of such explicit consent, most laws require the deceased's next of kin to consent to post-mortem organ removal. Though to date the majority of European countries have transplant laws based on the presumed consent principle, the practical application of national legislation particularly, with regard to the role of next of kin in objecting or consenting to organ donation, varies substantially between countries, regions, hospitals, and even individual requestors and thus may impact on ultimate efficiency of national laws. Regardless of the consent system, the opinion of relatives or "next of kin" is almost always asked and respected in almost all European countries.

A combination of legislation, potential of medically suitable donors, investments in health care and infrastructure, education, public attitudes, culture and religion may all play a role in determining the number of deceased organ donors in a country or region. Donation figures within the Eurotransplant area, however, seem to show a rather direct effect of legislative measures: donation rates per million population are nearly twice as high in Austria and Belgium (presumed consent) compared to those in Germany and the Netherlands [146].

Deceased and living donation

It is also the Member States' decision on whether they organise their transplant systems based purely on deceased donation or whether they also encourage living donation. While deceased donation is highly developed in several Southern European countries, some Northern European countries are more advanced in the area of living donation.

Brain death and circulatory death. A further distinction can also be made between different types of deceased donation that are allowed and organised within a country. Donation after brain death (DBD) is the most common type of deceased donation, while donation after circulatory death (DCD) is increasingly used as an additional source of organs for transplantation. These two kinds of deceased donation raise different ethical concerns and require different organisational set-ups.

Bilateral and multilateral agreements. Some countries have chosen to take part in multilateral "European organ exchange organisations", such as Eurotransplant (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia) or Scandiatransplant (Sweden, Finland, Denmark, Norway and Iceland), and manage waiting lists and allocation criteria (at least partially) together. The recently created Southern Alliance for Transplantation foresees a similar collaboration. Bilateral organ exchange agreements have been set up by some countries, e.g. just focusing on the exchange of a specific type of organ with a neighbouring country. Examples include:

- Italy and Malta 2008–2010: 20 organs (kidney, heart, liver, split liver) from Malta were transplanted in Italy.
- Spain and Portugal 2009: 41 organs offered to Spain from Portugal.

Such organ exchanges need, for being fully operational, to be supported by a wide set of organisational and practical agreements, aimed also at ensuring compliance with Article 3(2) c) of the EU Charter of Fundamental rights and excluding any risk of organ trafficking.

Waiting lists. The management of waiting lists is a national competence (which can partially be delegated to and co-managed with a "European Organ Exchange Organisation"). It includes the definition of criteria to place patients on the list or exclude patients from a waiting list. The lists are usually specific to the types of organ and transplant needed (kidney, liver, lung, heart, pancreas, small bowel, combined transplants) and are also specific for paediatric transplants.

Indirect effect of legislation on transplantation. Some legislation has had an indirect but significant effect on LT, for example the law restricting over-the-counter paracetamol pack sizes, introduced in the UK in September 1998. This was because of the large number of people taking paracetamol overdoses, and increasing numbers of deaths and liver transplants due to paracetamol induced hepatotoxicity. Such legislation was introduced following recommendations by the UK government agency currently known as Medicines and Healthcare Products Regulatory Agency, and restricted pack sizes of paracetamol to a maximum of 32 tablets in pharmacies and to 16 tablets for non-pharmacy sales.

These measures were followed by persistent significant reductions in deaths due to paracetamol overdose, with some

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Clinical Practice Guidelines

indication of fewer registrations for transplantation at liver units during the 11 years after the legislation [147].

A similar but much amplified effect may be expected in the future as a consequence of legislation on the funding of new direct-acting antiviral agents (DAA) against hepatitis C. Newer DAA with simplified dosing regimens and/or minimal toxicity which, when used in combination, have the potential to lead to viral eradication in most if not all HCV patients who undergo treatment. This is an area of vertiginously rapid basic sciences and clinical development, but the costs of DAA are currently prohibitive for funding of treatment on a large-scale. The implication of near-eradication of HCV in Europe in the next decades is that of a significant reduction of patients needing a liver transplant for HCV and HCC in the future.

Organ allocation

Liver allocation in Europe

Data from LT activity in Europe is collected by the ELTR [40], which is a service of the European Liver and Intestine Transplant Association (ELITA), with the following objectives:

- Registry of all LT procedures in Europe.
- Link between European liver transplant centres.
- Scientific use and publications.

Between 1968 and December 2012, the ELTR has collected data regarding 112,554 liver transplant procedures performed in 153 centres from 27 European countries.

Within Europe the LT activity and organ donation rates vary in the different countries and regions reflecting different organ allocation systems and organisations. Further differences in legislation, organ donation rates, indications for LT, and traditions in the practice of medicine exist in different countries and regions of Europe.

There are no uniform rules or systems for organ allocation in Europe or within the European Union. There are several organ exchange organisations for different countries and geographical areas, including:

- Organización Nacional de Trasplantes (ONT) in Spain.
- NHS Blood & Transplant (NHSBT) for the United Kingdom and Ireland.
- Scandiatransplant (Sweden, Norway, Finland, Denmark, and Iceland).
- Eurotransplant (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia) for a total population of over 112 million.
- Centro Nazionale Trapianti (CNT) in Italy.
- Agence de la biomedécine in France.

Most organisations have similar rules with an urgent priority group that includes acute hepatic failure and early retransplantation following primary-non-function (PNF) as well as hepatic artery or PVT. There are also similarities in allocation for children and rules to favour splitting of the best liver grafts. There are, however, important differences as well. Organ allocation can be patient-directed, as is the case in the US and some European countries, or centre-directed, which is the case of other European countries including the UK, Spain and Scandiatransplant. There is an increasing collaboration between the organ procurement organisations.

ONT – Spain. Liver transplant activity started in Spain in 1984 and has a mean activity of more than a 1000 liver transplants performed yearly [148]. There are 25 liver transplant teams, four of which are paediatric. The ONT provides essential support for organ procurement, allocation support, and management of waiting list at a national level [149]. Spain has one of the highest organ donation rates in the world thanks to the outstanding donor detection and organ procurement organisation, which is often referred to as the Spanish model. In 2013, deceased donor organ donation rate reached 35.12 donors per million population [148]. The ONT has set a large-scale, comprehensive strategy to achieve and sustain an important improvement in donation and transplantation in Spain [150].

Liver allocation in Spain is centre-oriented as all available organs are referred to the national coordinating office.

National priority is given to liver emergencies. Livers are allocated sequentially to the hospital, city or region in the effort to reduce cold ischaemia time. The decision about the donor-recipient matching is made by the transplant team of the accepting unit with the aid of consensus guidelines developed with the support of the Spanish Liver Transplant Society [151–153].

Emergency LT in Spain is considered in two situations: 1) acute liver failure in the absence of any previous liver disease; or 2) retransplantation within seven days after transplantation (up to 30 days in paediatric recipients).

Clearance of candidates from the liver transplant waiting list in Spain has not changed in the last five years with a waiting list ranging from 103 to 124 days.

NHSBT – United Kingdom. An organ donation taskforce was recently set up in the UK to improve the poor donation rates. The taskforce recommendations were implemented, which were followed by an increase in the number of DBD of 7% over the last 4 years. Since 2007, the numbers of DCD have rapidly increased by 118%. The total number of deceased organ donors reached a record total of 1320 in 2013. Of these, 780 were DBD and 540 were DCD [154].

In 2013, 871 liver transplants were performed. There are seven transplant units in the UK. Three of which also have a paediatric liver transplant program. In April 2014 there were 512 patients registered on the liver transplant waiting list. Currently, on average, adult patients wait 142 days for a liver transplant while paediatric patients wait on average 78 days.

The key players in regulating organ donation, allocation and transplantation in the UK include NHSBT, a special health authority of the National Health Service (NHS) and the Human Tissue Authority (HTA). The latter is an independent watchdog that protects public confidence by licensing and inspecting organisations that store and use tissue for transplantation and other purposes. Liver allocation in the UK is centre-oriented, though there is a plan to change the system to a patient-oriented, national allocation scheme. Donor zones are allocated to each centre based on the number of new registrations of prospective candidates to match the scale of the centre's waiting list. If the organ is declined, it will be offered, according to a rotation system, to the second in line centre through the liver allocation sequence.

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The allocation priority at each centre is decided by a multidisciplinary meeting, which includes liver transplant professionals, following a UKELD-based prioritisation system.

There are nine categories of patients suitable for listing on the super urgent national list and these are divided into paracetamol overdose and non-paracetamol overdose [155].

In summary for adult (age >16 years or weight >35 kg) and paediatric (age <16 years or weight <35 kg) liver donors the sequence for allocating liver grafts is similar and as follows:

- Super urgent list.
- Combined liver and small bowel adult recipients.
- Patients with hepatoblastoma.
- Designated zonal retrieval centre.
- Other designated UK and Ireland liver transplant centres.
- Designated zonal retrieval centres for adults.

Scandiatransplant. Scandiatransplant is a collaboration of all organ transplant centres in the Nordic countries—Sweden, Norway, Finland, Denmark and Iceland. There are currently five liver transplant centres within Scandiatransplant (two in Sweden and one in each other Nordic country except for Iceland). In 2013, out of a total of 421 actual deceased donors, 362 liver transplants were performed in the Scandiatransplant network [156,157].

There is no common waiting list in Scandinavia. Centre-oriented allocation is used and each transplant centre has its own waiting list and the right to transplant livers procured from a defined geographical area. The MELD score and/or the Child-Pugh scores are used in conjunction with clinical and non-clinical parameters (e.g. waiting time) to select patients to be transplanted.

Patients with acute hepatic failure (urgent call status) have priority to receive a liver from the next available deceased donor in the Scandiatransplant region for 72 h. The high urgent status is based solely on the diagnosis and clinical status. All livers that were received on urgent call status or as a kind request have to be paid back to the sending centre within a 6-month period.

High urgent status also applies for patients in need of an acute retransplantation within 14 days of the transplant due to PNF, hepatic artery or PVT.

Paediatric LTs represent 5% of all LTs performed in Scandinavia. In 2011, a common waiting list for paediatric patients in need of a left lateral segment liver graft was established in order to improve organ availability for children.

DCD donation is not practiced among the Scandiatransplant countries with the exception of Norway.

Eurotransplant. Eurotransplant is responsible for the allocation of donor organs in eight European countries: Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. This international collaborative framework includes all donor and transplant hospitals and tissue-typing laboratories. In Eurotransplant, allocation is governed by the different national laws on transplantation, resulting in a standard allocation algorithm; the Eurotransplant Liver Allocation System (ELAS) based on medical and logistical criteria with modifications according to the different national laws [158].

The allocation system for LT in Eurotransplant was changed in 2006 for elective recipients from a waiting time based allocation to an urgency-based system using the MELD scoring. Patient-oriented allocation according to MELD is effective in four Eurotransplant countries (Germany, Belgium, the Netherlands, and Luxembourg), whereas a centre-oriented allocation system is effective in Austria, Slovenia and Croatia. On the Eurotransplant matching list all patients have to be registered with a lab MELD which must be updated by the transplant centres at scheduled intervals. Patients whose disease severity is not adequately reflected by lab MELD can be requested for an exceptional MELD. Some diseases have been identified as standard exceptions and are comprised in a country-specific list.

Besides allocation in elective recipients, some urgency categories within Eurotransplant are given priority based on their respective medical urgency:

1. High urgency, which is the highest priority internationally.
2. Approved combined organ, which is a multiorgan liver transplant with exception of liver-kidney.

Urgency status is granted only after approval by Eurotransplant, and patients in these categories are ranked by the time they have spent in their current urgency [159]. A pay-back system ensures that the donor centre is re-offered the next available liver of the same blood group.

In contrast to adult recipients ranked by their calculated MELD, paediatric recipients are automatically assigned an initial paediatric MELD equivalent depending on age that is upgraded each 90 days until transplantation.

In conclusion different systems are used, ranging from centre-oriented to patient-oriented. Some systems are constructed using rigorous rules based on points and scores, whereas others are based on the clinical judgment of the responsible transplant surgeon. The current diversity makes it unlikely that we will manage to produce a uniform organ allocation system in Europe in the near future.

Extended criteria donors

The success of LT has resulted in a growing demand for transplantable grafts. The discrepancy between supply and demand and the increased morbidity and mortality of patients on the waiting list has led to a search for alternatives to the standard pool of organs from DBD. In the past 20 years the paediatric waiting lists have been successfully reduced due to the introduction of segmental LT including reduced/split LT and living donor LT (LDLT). These techniques have only marginally increased the organ pool for adults in the Western world. The most immediate source of organs capable of expanding the donor pool is that of extended criteria donors (ECD) also called marginal donors. These, although not universally defined, include a wide range of donors with unfavourable characteristics, historically associated with poorer graft and patient survival. These include advanced age, steatosis, hypernatremia, DCD and others. DCD is associated with severe ischaemia-reperfusion injury, which is responsible for PNF or delayed graft function and biliary ischaemia. However, if carefully selected and matched with appropriate recipients, livers from DCD donors can be used safely and effectively [160].

Scores have been developed to quantify the risk of graft failure of ECD donors, including the donor risk index (DRI), and more recently the Balance of Risk score (BAR score) (see chapters Donor risk index and Balance of risk score).

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Clinical Practice Guidelines

Protocols have been developed for the selection of ECD and DCD livers to allow a safer utilisation and an effective expansion of the donor pool.

Definition of ECD donors

The ECD graft represents an organ with unfavourable characteristics associated with suboptimal post-transplant outcomes that fall into two main risk categories: poor graft function and potential for disease transmission. Within the poor graft function category it is possible to differentiate two groups, the DCDs and the non-DCDs.

The Eurotransplant definition refers to the category of graft dysfunction [161]. According to this definition the following criteria defines a liver donor marginal:

- Donor age >65 years.
- ICU stay with ventilation >7 days.
- BMI >30.
- Steatosis of the liver >40%.
- Serum sodium >165 mmol/L.
- Transaminases: ALT >105 U/L, AST >90 U/L.
- Serum bilirubin >3 mg/dl.

DCD

In recent years, renewed interest in DCD has emerged as a strategy to increase the number of viable grafts, and to decrease the mortality on the waiting list. According to the setting in which circulatory death occurs, DCD can be classified using the Maastricht criteria [162,163] (Table 3). In Europe, the United Kingdom, the Netherlands, Spain, Belgium, and France have the highest DCD activity. DCD is based on the type III category in most countries; type II DCD is predominant in Spain and in France. DCD may be also divided into two main categories: controlled (CDCD) and uncontrolled (UDCD). The ethics, assessment, logistics, techniques of retrieval, and outcomes of transplant are very different with controlled and uncontrolled liver DCD.

Controlled donors (Maastricht type III) are generally victims of a catastrophic brain injury of diverse aetiology, deemed incompatible with meaningful recovery, but whose condition does not meet formal criteria for brain death and whose cardiopulmonary function ceases before organs are retrieved. The procedure of withdrawal of life support therapy (WLST) is planned by the medical team in agreement with the family of the injured patient. It is important to emphasise that this decision precedes, and is independent from the one to donate. In category III, circulatory arrest is induced by WLST and occurs either in the ICU or in the operating room. In type IV, a brain dead donor suffers an unpredicted cardiac arrest prior to the donation procedure or the latter is delayed after cardiac arrest if the family wishes so for religious or cultural reasons.

CDCD occurs in the presence of organ retrieval teams and limits the ischaemic injury associated with death. The process of dying in type III DCD; however, may be associated with a prolonged agonal period of hypotension and/or hypoxia, which are ultimately responsible for ischaemic injury that may prevent organ donation, or be accountable for graft dysfunction or non-function of the transplanted organ. In this respect it is crucial that we recognise that there is a total lack of arterial and portal blood flow through the liver long before the time of cardio-circulatory arrest [164].

Table 3. Categories of donation after circulatory death (modified from [162,163]).

Category	Description
Category I	Dead on arrival. Tissue (corneas, heart valves, skin, bone, etc.) can be recovered from category I donors or any individuals who die in a hospital in a manner not suitable for solid organ recovery. Since there are no immediate time constraints to minimize tissue injury, there is no requirement for a precisely timed approach to tissue recovery.
Category II	Unsuccessful resuscitation (CPR). These are patients who suffer a witnessed cardiac arrest outside the hospital and undergo unsuccessful cardiopulmonary resuscitation (CPR). When CPR fails in a medically suitable organ donor, uncontrolled organ donation is an option.
Category III	Awaiting cardiac arrest following withdrawal of care. With the permission of the donor or donor family, organs may be recovered after death is declared from patients with irreversible brain injury or respiratory failure in whom treatment is withdrawn. Death is declared after a predetermined period, usually 5 min, of circulatory arrest.
Category IV	Cardiac arrest after brain death. Rarely, a consented brain dead donor has a cardiac arrest before scheduled organ recovery. Such category IV donors should either proceed as for a normal multiorgan retrieval - if this has already started - or should be managed as a category III donor as appropriate to the circumstances of cardiac arrest.
Category V	Cardiac arrest in a hospital patient. Newly added in 2000, this category is made up of category II donors that originate in-hospital. The distinction allows for improved tracking of the outcomes.

UDCD occurs following the unanticipated cardiac arrest of a patient; due to logistical reasons and the associated degree of ischaemic injury only deaths occurring at a centre with established organ retrieval teams and pathways are suitable for donation of liver grafts (category II). It is possible to overcome some of these logistical challenges by directing intensive medical care resources outside of the hospital. In Madrid and Barcelona a network of mobile ICU teams are tasked to patients in out-of-hospital cardiac arrest. The subsequent effect is that this also maximises rates of UDCD.

Several groups have reported excellent results with the use of CDCD grafts for LT. In this sense, 1- and 3-year graft survivals are 80% and 70%. Regarding the development of intrahepatic biliary strictures also defined as ischaemic-type biliary lesions (ITBL) or ischaemic cholangiopathy (IC), groups with specific expertise including King's College Hospital in London have reported less than a 3% rate of ITBL. It is important to remark that this is not only a reliable graft source for the adult population; in the paediatric population, where graft scarcity is even greater than among adults, CDCD grafts achieve excellent results. Results from the UDCD programs are excellent as well. With a median follow-up between 20 and 34 months, Spanish groups have reported graft and patient survivals between 70% and 87.5% with rates of PNF and ITBL around 10%. Grafts obtained from DCD are not optimal; graft and patient survival comparisons with standard DBD generally show a lower performance. On an intention-to-treat basis though DCD may compare better with DBD grafts as there may

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be an advantage with an earlier transplant accepting a DCD liver rather than deteriorating and possibly dying, waiting for a DBD organ.

Moreover, recipients of DCD grafts show mortality rates comparable to other well-established, accepted risk predictors such as advanced age, hepatitis C or HCC, in recipients and older donor age. As recently suggested, combining DCD grafts with these risk factors must be carefully considered as it may create an unacceptable risk. For this reason, physicians should not shy away from using DCD grafts. Perhaps the optimal environment for a DCD graft is a low risk recipient. Malignancy seems to be a good indication as the risk of dropping out of the HCC criteria on the waiting list may outweigh that of receiving a graft from a DCD. In conclusion, both controlled and uncontrolled programs have a huge potential to clearly expand the pool of donors for the adult and paediatric populations. Future advances in the fields of *in situ* donor recirculation and *ex situ* perfusion will surely not only add but also rescue grafts. The process to obtain a valid consent is probably the most important legal requirement associated with DCD programs. In this sense, legislation can be based on either the opting out (presumed consent) or the opting in (explicit consent) principle. From an ethical point of view, two problems may arise in UDCD and CDCD programs. In the first group, there is an urgent need to start preservation to ensure organ viability. This commonly happens when the family is not present. In an opt-out system, the next of kin have the right to object to organ donation, even when the deceased themselves have not declined the option. In an opt-in system, the family can decide whether to donate when the deceased has not made a choice. From a legal point of view, this means that when the next of kin are not available to consent or to object, there is no legal basis to start manoeuvres, and the organs would be lost. An optimal example of a legal pathway to gain sufficient time for proper consent and to avoid unnecessary conflicts may be the one proposed by Dutch legislation: "The necessary measures to maintain the organ in a suitable condition for transplantation may be taken after death, so long as the procedure for obtaining the necessary consent in accordance with this law has not been completed".

In the CDCD group, the ethical conflict will emerge in the context of decisions regarding WLST or ending of resuscitation efforts. Teams should ensure that there are no conflicts of interest; thus, transplant team members cannot be involved in decisions related to patient prognosis, withdrawal of ventilatory or organ perfusion support or determination of death.

Non-DCD

Older donors, usually deceased from cerebrovascular disease, are generally affected by a number of medical comorbidities including, diabetes, hypertension, previous history of malignancy and obesity. The latter, now pandemic in the Western world, is responsible for steatotic transformation of a large proportion of potential donor livers.

Older donor age. Utilisation of livers from older donors represents a logical means to expand the donor pool. In the non-transplant setting, the liver's physiologic function remains well preserved throughout life, likely a result of its unique regenerative capacity. However, patients transplanted with livers from older donors are at increased risk of developing graft failure and mortality due to an increased vulnerability to ischaemia/reperfusion and a diminished regenerative ability of older livers [165]. A further mechanism could be the increased burden of comorbidities in older donors such as, hypertension, diabetes, dyslipidaemia and obesity, which may lead to atherosclerotic vessels and steatotic grafts. Several studies have shown that older donor livers are associated with PNF [166], hepatic artery thrombosis [167] and ischaemia-reperfusion injury.

Although increasing donor age adversely affects survival after LT [168], liver grafts have been used from selected deceased donors older than 70 years. While there are reports of excellent short-term results, long-term follow-up with septuagenarian and octogenarian deceased donors showed no differences in long-term patient or graft survival between hepatitis C negative recipients of livers from older compared with younger donors. In contrast, the 7-year survival for HCV positive recipients of older donor livers was less than half that of HCV negative recipients. Transplantation of livers from septuagenarian and octogenarian donors can achieve excellent long-term patient and graft survival for selected HCV negative patients [169].

There is consistent evidence of an interaction between older donor age and positive recipient HCV status that predisposes patients to fibrosing cholestatic hepatitis, post-transplant infections, graft failure and mortality [170].

Liver grafts from donors with diabetes. A retrospective analysis of the Scientific Registry of Transplant Recipients database (2004–2008) (25,413 patients) showed that recipients from diabetes mellitus donors experienced worse 1- and 5-year graft survival than recipients from non-diabetes mellitus donors and this was particularly lower for recipients from donors with diabetes mellitus duration >5 years. However, in patients without HCV infection, using diabetes mellitus donors was not independently associated with worse post-transplantation graft survival. Matching these diabetes mellitus donors to recipients without HCV may be safe [171].

Steatotic liver grafts. Hepatic steatosis is defined as the accumulation of droplets of fat in the hepatocytes and is associated with a range of post-transplant complications and poor graft function in particular. The key to this dysfunction is the ischaemia-reperfusion injury. The reported incidence of steatosis in the liver graft is between 9–26% among the liver donor population [172].

Steatosis is classified as mild (10–30%), moderate (30–60%), or severe (>60%) [173], but it is believed that steatosis will disappear after LT. There are two patterns of hepatic steatosis, microvescicular and macrovescicular. Microvescicular steatosis refers to the accumulation of tiny lipid droplets measuring <1 mm giving a foamy appearance of the cytoplasm and it is associated with rare conditions including drug toxicity, acute fatty liver in pregnancy and Reye disease. Macrovescicular steatosis is defined by the presence of small to large droplets that may end up occupying the whole cytoplasm; it is typically associated with alcohol, obesity and diabetes. Small fat droplets seem not to be involved with poor graft function. The volume of large droplet macrosteatosis in the liver graft is closely linked to its suitability for transplantation.

Mild macrosteatosis (<30% volume) is considered suitable for transplantation. Livers with moderate macrovescicular steatosis (30–60%) may result in acceptable outcomes in select donor-

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Clinical Practice Guidelines

recipient combinations. Severe macrosteatosis (>60%) is linked with unacceptable risks of graft failure, acute kidney injury, biliary complications and mortality [174,175].

Low-grade macrosteatotic liver grafts (⩽30% macrosteatosis) resulted in a 5-year graft survival rate of 60% or more up to BAR 18, comparable to non-steatotic grafts [176]. Microsteatotic or ⩽30% macrosteatotic liver grafts can be used safely up to BAR score of 18 or less, but liver grafts with more than 30% macrosteatotis should be used with risk adjustment, that is, up to BAR score of 9 or less. Microvescicular steatosis does not preclude the use of grafts.

Current developments of extracorporeal normothermic machine perfusion devices may allow in the near future to assess moderately and severely steatotic grafts prior to implantation, furthermore it is foreseeable that normothermic machine perfusion-based defatting protocols may be developed to allow further expansion of the donor pool.

HBcAb positive donor grafts. One of the current efforts to overcome the organ shortage is based on the use of grafts from anti-HBV core antigen (anti-HBc) positive donors. These grafts are common in countries with high prevalence of HBV infection, such as Asia and the Mediterranean countries. This is despite the risk of HBV transmission to the recipient after LT [177].

HBcAb positive donor grafts have better outcomes when transplanted into HBsAg positive than HBsAg negative recipients. These findings suggest that donor HBcAb positivity requires more stringent allocation strategies.

Anti-HBc positive liver donors frequently have occult HBV infection, i.e. persistent liver and/or serum HBV DNA without serologic evidence of active HBV infection so that viral replication may increase with the use of post-transplant immunosuppression and in particular with corticosteroids. The liver grafts from anti-HBc positive donors are currently the main sources of *de novo* HBV infection after LT [178]. Many centres now use grafts from anti-HBc positive donors for HBsAg negative recipients. Since the probability of such *de novo* HBV infection is substantially lower in anti-HBc and/or anti-HBs positive compared to HBV naïve recipients (15% *vs.* 48%), it is reasonable to recommend that liver grafts from anti-HBc positive donors should be preferentially directed to HBV-exposed liver transplant candidates. The presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs positive recipients can safely receive anti-HBc positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection <2%). Pre-transplant vaccination alone does not appear to be an effective strategy, as *de novo* HBV infection after LT developed in 10% of successfully vaccinated recipients without any post-transplant prophylaxis. However, HBV vaccination should be offered to all naïve HBV patients early in the course of non-HBV chronic liver disease (i.e. in the pre-cirrhotic stage), even though additional anti-HBV prophylaxis will be needed in cases of LT with grafts from anti-HBc positive donors.

If *de novo* post-LT HBV infection develops, antiviral treatment is needed and it is reasonable to think that the efficacy of treatment is similar to that of post-transplant HBV recurrence. Given the poor resistance profile of long-term lamivudine monotherapy and the low potency of adefovir, both entecavir and tenofovir may be the agents of choice at present, despite the current lack of data.

In summary, liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg positive or anti-HBc/anti-HBs positive recipients. HBsAg negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all [179,180].

Lastly, a series of eight cases of LT using grafts from deceased HBsAg positive in HBsAg positive recipients showed that it is feasible, and may provide further expansion of the pool of organ donors with appropriate antiviral management and monitoring [181].

HCV positive donors. Chronic donor shortages, made it necessary to consider HCV positive donors as an alternative organ source. While the use of HCV antibody–positive grafts in recipients with HCV infection is a common practice and is generally considered safe [182,183], LT of HCV positive grafts in HCV negative recipients is avoided. The transplantation of HCV positive donor livers into HCV positive recipients has not been associated with greater disease progression or graft loss [184] and has shown similar graft and patient survival to HCV positive recipients who received HCV negative livers. Superinfection with a different donor genotype from that of the recipient may occur with all genotypes. HCV positive donors (whose genotype may not be known at the time of procurement) are often avoided for candidates with non-type 1 infection, since there is a reduced ability to treat type 1 genotype superinfection. However, the newer generation DAAs may change the recommendation in the future [185,186].

The use of HCV antibody–positive grafts in recipients with HIV and HCV co-infections has been associated with poorer graft and patient survival [134,187]. Optimal strategies for donor and recipient selection have not been fully defined in this population to date.

It is important to note that stored fresh arterial and venous grafts from HCV- and HBV-infected donors used for different types of vascular reconstruction during LT, were recently found to be the route of transmission of infection from donor to uninfected recipients [188]. In order to avoid these problems the HTA in England has set rules and a registry to avoid wastage of these vessels, the American Organ Procurement and Transplantation Network (OPTN) policy was amended to preclude their storage for use in recipients other than the recipients of the corresponding organ [189].

Donors with previous or current malignancy. Livers from a donor with previous history of malignancy can be used in selected situations, as donor tumour transmission through LT has been rare. Between 1965 and 2003, thirty-eight such cases have been reported by the Israel Penn International Transplant Tumour Registry.

Transmission of donor-related malignancy by organ transplantation may occur and is often a fatal complication in immunosuppressed transplant recipients. Acceptance of livers from donors with a current or past history of cancer is a challenging decision for both surgeons and patients.

Primary intracranial malignancy have generally a low risk of spread outside the central nervous system, hence the relatively low risk of transmission to transplant recipients [190].

However, case reports describe transmission of malignancy has occurred from donors with primary malignancy of the central

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nervous system. These cases are typical of donors with high-grade malignant tumours and who have undergone debulking surgery, radiotherapy and ventricular-systemic shunt interventions that compromise the blood brain barrier. Advice from the Council of Europe in 1997 stated that while the use of organs from donors with low-grade primary malignancy was safe, organs from potential donors with high-grade malignant tumours of the central nervous system, especially where the integrity of the blood brain barrier is compromised, should no longer be considered safe for transplantation. In 2003 a monothematic ASTS meeting issued recommendations about the use of organs from donors with a history of malignancy. Glioblastoma multiforme, along with melanoma, choriocarcinoma and lung cancer were considered absolute contraindications to liver donation [191].

A retrospective analysis of UK registry data has shown that none of the 448 recipients of organs from 177 donors with primary intracranial malignancy developed a transmitted tumour. Among donors with high-grade tumours, there were 23 grade IV gliomas (glioblastoma multiforme) and nine medulloblastomas. Despite the reassuring study there remains a small but definite risk of transmitting cancer from donors with primary intracranial malignancy. The surgeon should be aware of all the relevant donor information, including tumour histology and treatment, including radiotherapy and surgery. At the time of organ retrieval a thorough examination of the thoracic and abdominal cavities for metastatic tumour should be undertaken.

In terms of non-central nervous system tumours, as previously mentioned, melanoma, choriocarcinoma and lung cancer constitute absolute contraindications to donation. More common tumours such as colorectal and breast cancers are absolute contraindications to donation if in advanced stage (CRC >T3 or breast cancer >T1c). Organ donation needs careful consideration depending on the exact tumour stage and the disease-free interval.

Finally, it is paramount to counsel potential recipients regarding the small but definite risk of transmission of malignancy, as well as their chance of survival if they choose to remain on the waiting list.

Use of liver grafts from infected donors. Organ transplantation is not without risk of microbial infections, since in contrast to the US CDC principle of 'zero' risk, the European philosophy is that risk cannot be eliminated, but must be put in a clinical context (Table 4). In general, a risk classification has been used to evaluate the safety and the acceptability of donors according to the type of infection.

Unacceptable risk. This classification includes absolute contraindication. An example of a donor with unacceptable infections is the positivity for HIV-1 or HIV-2. Despite the important progress in the treatment of this infection, which have led to a significant increase in the survival and to an important improvement in the QoL of patients with HIV, the absence of definitive therapies makes this infection an absolute contraindication for accepting a donor.

The same principle has to be applied to all the systemic infections due to micro-organisms, such as multidrug-resistant bacterial infections or WNV, for whom a practical therapeutic option does not exist. Donors with proven WNV infections of the central nervous system should not be considered eligible because of the risk of recipient transmission [192]. The detection of IgM occurs approximately 4 days after viremia, and seroconversion to IgG occurs at approximately 8 days. Nonetheless, WNV serum IgM may persist for up to 500 days after acute infection. Thus, neither the presence of WNV serum IgM nor its absence is sufficient to exclude active infection; donor screening requires the use of nucleic acid test to identify acutely infected donors [193]. Transmission from infected donors to transplant recipients has not occurred in every instance, and pre-existing immunity in recipients may limit transmission. Once an infection occurs, symptomatic disease is more common among

Table 4. Organ-donor-derived infectious transmissions (Adapted from [513]).

Expected
Cytomegalovirus
Epstein-Barr virus
HBV
HCV
Toxoplasma gondii
BK polyomavirus
Unexpected
Viruses
Adenovirus
Herpes simplex virus
HIV
HBV
HCV
Hepatitis E virus
Human T-cell lymphotropic virus 1 and 2
Influenza A/B
Lymphocytic choriomeningitis virus
Parvovirus B19
Rabies
West Nile virus
Fungi
Aspergillus spp.
Candida spp.
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Scopulariopsis brevicaulis
Zygomycetes (Mucor)
Bacteria*
Gram-negative: *Pseudomonas*, *Acinetobacter*, *Legionella*, *Klebsiella*, *Ehrlichia*, *Serratia*, *Escherichia coli*, *Veillonella*
Gram-positive: *Brucella*, *Enterococcus* (for example, vancomycin-resistant *Enterococcus*), *Staphylococcus spp.* (for example, methicillin-resistant *Staphylococcus aureus*), *Listeria*
Mycobacterium tuberculosis
Nocardia spp.
Rickettsia rickettsii (Rocky Mountain Spotted Fever)
Treponema pallidum (Syphillis)
Borrelia (Lyme disease)
Parasites
Babesia microti
Balamuthia mandrillaris
Malaria spp.
Naegleria fowleri
Toxoplasma gondii
Trypanosoma cruzi
Schistosoma spp.
Strongyloides stercoralis

*Including multi-drug resistant gram-negative infections.

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Clinical Practice Guidelines

immunocompromised patients, and significant persistent neurological morbidity or mortality may ensue. There are no proven treatments for WNV at this time.

In general, encephalitis, particularly with fever, without a documented source is typically associated with viral infectious disease transmission. In many instances of transmission, encephalitis is not initially suspected in the donor. Therefore, most experts believe that donors with clinical encephalitis without a proven cause should likely be avoided [194].

Donors with evidence of active tuberculosis should not be considered as organ donors; if donors with untreated latent *Mycobacterium tuberculosis* infections are used, the recipients should be treated following the recently published guidelines [195]. Isoniazid seems to be effective and its hepatotoxicity occurs in 6% of treated recipients. Donor-derived tuberculosis infections usually become symptomatic less than 3 months after transplantation. It is important to note that symptoms, particularly in liver recipients, may be atypical and include fever, sepsis, and elevated liver enzymes. If recognised early, recipient with active tuberculosis have a better chance of survival [196].

Increased, but acceptable risk. This classification includes cases where transmissible organisms or diseases are identified during the evaluation process of the donor, but organ utilisation is justified by the specific health situation of the recipient or the severity of their clinical condition. Specifically, this category includes those cases in which the risk of death of the recipient without transplantation is higher compared with the risk of transplantation [197]. An example is the use of HCV or HBsAg positive donors in HCV or HBV negative recipients.

Although the transmission of syphilis from an infected donor has been rarely reported, the prophylactic treatment of recipients who receive organs from donors with positive syphilis serology generally prevents transmission. Typically, recipients are treated for late latent syphilis (i.e., 3 doses of intramuscular penicillin G benzathine (2.4 million units) [198]. Donors with a positive non-treponemal serology (i.e., rapid plasma reagin or VDRL test) should have confirmatory testing performed even if these results become available after transplantation because the rate of false positivity among organ donors is high [199]. Confirmed positive syphilis serology is considered a marker for risk behaviours that place the donor at an increased risk for HIV, HBV, and HCV, as stated by the US Public Health Service guidelines.

Calculated risk. This classification includes all cases where, even in the presence of transmissible diseases, transplantation is allowed for recipients with the same disease or with a protective serological status; this risk applies also to donors with documented bacteremia and/or bacterial meningitis provided that the donor was on targeted antimicrobial treatment for a minimum duration of 24–48 h [197]. Donors with HCV or HBV infection belong to this category (see previous sections).

The transmission of bacterial infections is frequently mitigated by the common use of perioperative antibiotics. Much has been learned about the risk of bacterial infections in donors: donors with select bacterial infections can be safely used as long as appropriate therapy is provided to both the donor before procurement and the recipient after transplantation. Available information suggests that organs from a donor with a bacteremia who has received active antibacterial treatment for at least 48 h can be safely used as long as the same effective antibiotic therapy is continued in the recipients [200]. Although the ideal duration of antimicrobial therapy in the recipient has not been prospectively studied, most experts recommend treating the recipient with active therapy directed against the cultured bacteria for at least 14 days [200,201]. The donor should be assessed for disseminated foci of infection because this may represent a higher risk of transmission, which is especially high if the organ to be retrieved has evidence of involvement. The strongest data come from donors with documented bacterial meningitis who received effective antimicrobial therapy for at least 24 to 48 h: the risk of transmission was exceptionally low with the active treatment of the donor and the recipient. Infection at sites other than the liver or the biliary tree (e.g., sputum and urine), without demonstration of disseminated infections, do not typically require treatment of recipients. Bacteremia with virulent organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* in particular, may result in early post-transplant sepsis or mycotic aneurysm formation at the site of allograft vascular anastomoses. The standard of care is to administer longer courses of therapy in the recipient (e.g., two weeks) if the donor is known to have been bacteremic with a virulent organism [202].

EBV is of particular concern because of its association with post-transplant lymphoproliferative disorder, especially in the paediatric population. Donor and recipient screening should be performed, and there should be consideration of pre-emptive monitoring in high risk situations (i.e. D+/R−). A concomitant reduction in immunosuppression is a mainstay of treatment. Early graft dysfunction should prompt an evaluation for hepatic involvement of post-transplant lymphoproliferative disorder; later presentations of post-transplant lymphoproliferative disorder are more likely to present with disseminated disease.

Livers from donors who are seropositive for the parasite *T. cruzi*, responsible for Chagas disease, can be considered for transplantation [203]. *T. cruzi* can remain asymptomatic for a prolonged period of time after infection. Symptoms include fever, often associated to a painful, erythematous rash. Recipients whose donors have proven *T. cruzi* seropositivity should be screened regularly after transplantation for parasitemia and, if found positive, should undergo treatment [204]. Donors with proven Naegleria meningoencephalitis, can be used with a low risk of transmission [205].

Non-assessable risk. This classification includes cases where the evaluation process does not allow an appropriate risk assessment for transmissible diseases [197]. Organs from donors infected with highly resistant bacteria (i.e., vancomycin-resistant *Enterococcus, Acinetobacter baumannii*, carbapenemase-producing *Klebsiella pneumonia*) have rarely been used safely and such offers should be discussed with an experienced infectious diseases physician, given the high risk of graft loss and mortality in case of transmission of infection to the recipient [198].

Turning to fungal infections, the most commonly transmitted from donors to recipients include Candida species, endemic mycoses (particularly *Coccidioides immitis*), and *Cryptococcus*. When transmitted, these mycoses are associated with significant morbidity in addition to frequent graft and/or recipient loss. Contamination of the organ during procurement and preservation appears to occur more commonly than transmissions of infection. Positive cultures for Candida species of the preservation fluid

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should prompt for treatment. Most centres include azole antifungals in their post-transplant prophylaxis regimen. Appropriate dosing and close monitoring of drug levels is necessary as azoles interact with calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors [206].

Standard risk. This classification includes cases where the evaluation process did not identify a transmissible disease [197].

Recommendations:

- Utilisation of livers from older donors is associated with increased risk of mortality and graft loss, especially in HCV-related patients. However, in selected patients excellent results can be achieved (**Grade II-2**)
- Utilisation of livers from donors with diabetes mellitus might represent a good option only in HCV negative recipients (**Grade II-3**)
- Grafts with microsteatosis or mild macrosteatosis are considered suitable for transplantation. Livers with moderate macrovescicular steatosis may result in acceptable outcomes in select donor-recipient combinations. Grafts with severe macrosteatosis should not be used as they are associated with increased risks of graft loss and mortality (**Grade II-2**)
- Liver grafts from anti-HBc positive donors should be preferentially directed to HBV-exposed liver transplant candidates. Prophyaxis of HBV recurrence in patients who received a liver from an anti-HBc positive donor should be initiated immediately after LT if recipients do not have anti-HBs. Lamivudine monotherapy is the best cost-effective treatment (**Grade II-2**)
- The use of anti-HCV positive grafts in recipients with HCV infection is generally considered safe, whereas it should be avoided in HCV negative recipients (**Grade II-2**)
- Livers from a donor with previous history of malignancy can be used in selected situations according to tumour site and its stage (**Grade II-3**)
- Donors with select bacterial infections can be safely used as long as appropriate therapy is provided to both the donor before procurement and the recipient after transplantation. Livers from donors with isolated fungal infections should be routinely used. Grafts from donors with viral or parasitic disease should be used according to the type of infection and to the severity of recipient liver disease (**Grade II-3**)

Donor risk index

Feng *et al.* [207] developed, in 2006, a DRI with the aim to quantify the effect of specific donor characteristics on the risk of post-transplant graft failure. The value of such information is heightened by the life-saving and life-threatening potential of every decision to either accept or reject a particular opportunity for transplantation. The characteristics of the donor that independently predict and significantly increase risk of graft failure are 5: age (>40 years), race (African American *vs.* White), cause of death (cardiovascular accidents, others, DCD), partial/split liver graft and height (per 10 cm decrease). Two independent transplant factors, cold ischaemia time and donor location respect to recipient location, are also significantly associated with increased risk of graft loss. To note, a limitation of the DRI is that it does not include liver steatosis.

Balance of risk score

The BAR score was calculated on 37,255 patients in the UNOS (United Network for Organ Sharing) database and identifies the six strongest predictors of post-transplantation patient survival [208]. Partial transplants (split and living donor LT), DCD and combined liver transplants were excluded to reduce confounding variables. Six strongest predictors of post-transplant survival included: recipient MELD score, cold ischaemia time, recipient and donor age, previous transplantation, and dependence from life support prior to transplantation. With increasing BAR points, patient survival decreases. However, while mortality is linearly increasing with higher MELD or SOFT scores, mortality remains stable in the BAR up to 16, and then increases exponentially at BAR 18.

The BAR seems appropriate to define the threshold when the risk of LT is too high. This threshold was determined at 18 BAR score points, being the sum of several independent risk factors. Interestingly, high MELD situations can be balanced in BAR system by accepting only a low donor and recipient age and short cold ischaemia. In regards to steatosis, liver grafts with microsteatosis or 30% or less macrosteatosis could be used safely up to a BAR score of 18 or less, but liver grafts more than 30% macrosteatotic should be used with risk adjustment, that is, up to BAR score of nine or less [176].

Liver transplantation

Different types of liver transplantation

The shortage of available grafts and the large number of indications for LT have led to the research for alternative strategies in order to obtain organs for as many patients as possible [209]. In Europe and the US, the most common type of LT is the so-called "conventional" or "standard", that uses whole liver grafts [40,209]. However, in Asian countries, where deceased donation is scarce, the most common type of transplantation is partial grafts from living donors [210].

Conventional or "Standard" liver transplantation – Whole liver grafts

The liver graft is implanted in the right upper quadrant, in the place formerly occupied by the diseased liver. The surgical technique differs according to whether or not the recipient's inferior vena cava (IVC) is preserved. In most European countries, the piggy-back technique is used, which involves the preservation of the native IVC [211,212]. Anastomosis of the donor's suprahepatic IVC to the recipient's three hepatic veins is performed (Fig. 2), as well as reconstruction of the portal vein, hepatic artery and biliary tree, using duct-to-duct anastomosis between the donor's main biliary tract and the recipient's one [213]. When the recipients IVC cannot be preserved, this surgical procedure involves vascular reconstruction with end-to-end anastomoses between the donors IVC and the recipient infra- and suprahepatic IVC.

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Clinical Practice Guidelines

Classification depending on donor type
Brain dead donor. This is a graft donation from a donor who is brain dead.

Donation after cardiac death. This is a graft donation from a donor who has suffered an irreversible cardiac arrest.

Domino liver transplantation. The most common indication for this type of procedure is FAP or Corino de Andrade's Disease. Since the disease involves extrahepatic organs and the liver function is otherwise absolutely normal, the FAP patient liver is given to another patient while he receives a deceased organ (domino effect) [214]. One of the necessary conditions for recipients of FAP domino liver grafts is that they are older than 55 years, to minimize the risk of developing the disease. There are a number of important technical aspects regarding this procedure. One of them is that preservation of the IVC in the FAP patient involves a graft that has three separate suprahepatic veins that require bench surgery for their reconstruction. In the FAP donor, the entire hepatectomy is performed while preserving the blood supply, although the absence of portal hypertension makes it less complex [215].

Partial graft transplantation
Partial liver grafts are used at times. It may be necessary to provide partial support for metabolic needs due to a specific or complete metabolic deficiency. In the latter case, one of the major preconditions is that the volume of the graft must be sufficient in order to have the capacity to sustain life in the patient immediately after transplantation. It is well-established the importance of the correlation between the weight of the patient and of the graft, as defined by the graft to recipient weight ratio. This ratio should be of at least 0.8% that is for a patient who weighs 80 kg a minimum graft weight of 640 g is needed. This is a problem associated with adult living donor liver patients and is usually solved by using the right lobe for transplantation [216].

Auxiliary liver transplantation. Auxiliary transplantation essentially provides an alternative in two situations. The first is in the cases of patients with acute liver failure in whom a partial graft is used to provide support to the patient's diseased liver while it recovers [217]. Once the native liver returns to normal function, the graft is removed and immunosuppression is withdrawn. The second case is for patients with functional congenital or metabolic disorders affecting a normal liver. Implanting a partial graft while preserving the native liver allows correction of the metabolic disorder while avoiding a full liver transplant [218]. The best results are obtained in young patients with acute liver failure, mainly viral or autoimmune [219]. Poorer outcomes are obtained in Budd-Chiari syndrome and Wilson's disease [220], while acute hepatitis B is a controversial indication, for the risk of graft reinfection [221]. Auxiliary LT may be performed orthotopically or heterotopically.

Split LT. This alternative involves dividing a liver in two parts and depends on who the intended recipients are. If those sharing the graft are an adult and a child, the liver will be divided into a right lobe that includes also the segment IV and a partial left graft that includes segments II and III (Fig. 3) [222–224]. Whereas, if the liver is to be divided between two adults, it will be split in two,

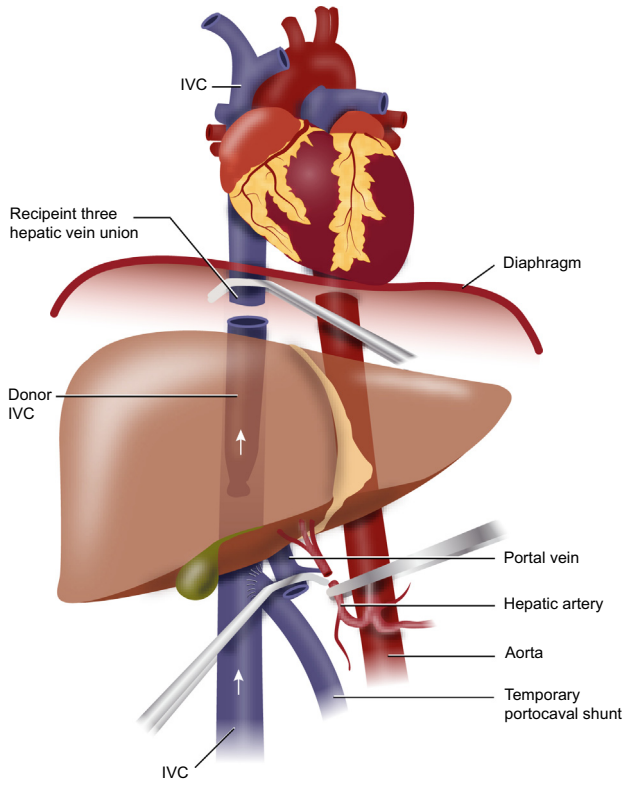

Fig. 2. Liver transplantation with piggy-back technique. Anastomosis of the recipient three hepatic vein union with the donor inferior vena cava (IVC).

the right lobe (segments V to VIII) and the left lobe (segments I to IV). The major determinant for this type of transplant is, above all, the size of the recipient left lobe, since normally this lobe has a weight of about 450 g, which only allows it to be implanted in patients with low weight (50–55 kg) [225,226].

Living donor LT. The impossibility of transplanting a child with a donor organ of the appropriate size led to the development of a number of alternatives, one of which is the use of segments II and III of an adult donor for transplantation into a child [227]. In Asian countries, where the LT with deceased grafts is negligible [210], the use of LDLT gradually expanded, culminating with the procedure of adult patients receiving right lobe grafts from living donors [228]. Tanaka showed that the procedure was feasible for the recipient from a clinical point of view and safe for the donor [228]. Although LDLT was highly boosted in Asian countries, in the US and Western Europe the practice is still limited, barely exceeding 5% of the number of transplants [40].

In children, living donation has led to a reduction in waiting list mortality. With the improvement of the surgical technique, many paediatric patients are now transplanted adult split liver grafts. The establishment of a single transplantation list, together with the prioritisation under the MELD system, makes it very difficult to perform this procedure, which is limited to highly committed groups [229].

In adults, living donation generally uses the donor's right liver lobe, which comprises of segments V to VIII. Right hepatectomy requires meticulous dissection on which the right hepatic artery, right portal vein, right bile duct and right suprahepatic vein are

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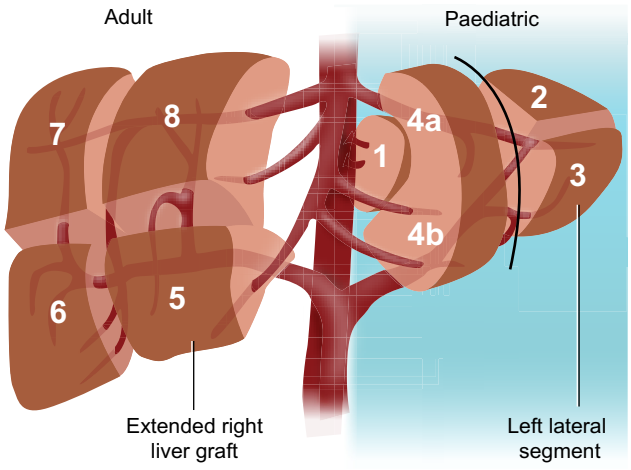

Fig. 3. Split liver transplantation – adult and child as recipients.

isolated. The minimum size of the graft (Fig. 4) must be of at least 0.8% in order to ensure the viability of the patient and the graft [216]. Aside from the technical difficulties in the donor hepatectomy, there is a significant morbidity that affects 38% of donors and a mortality rate estimated to be around 0.18% [3]. Furthermore, the recipient procedure is also challenging, due to the size of the anastomoses, especially of the artery and bile duct that are of 3 to 4 mm in diameter. Nevertheless, outcomes are good and at present they are similar to those obtained with whole grafts from deceased donors [3].

Donor hepatectomy entails morbidity and mortality risks [230]. Approximately one third of the patients experience some kind of complication, the majority of which are type I or II according to the Clavien-Dindo classification system [231]. Biliary fistulas are the most common complication and are usually managed conservatively. Some donors need to be rehospitalized and even to undergo further surgery [230,232].

The overall complication rate, as well as Clavien II and IIIa complication rate of right lobe donors is significantly higher when compared with that of left lobe donors. Furthermore, left lobe donors seem to present a more rapid normalization of levels of serum bilirubin and prothrombin time [233].

Finally, although the donor mortality is very low, the idea that a healthy individual may die because of an organ donation is something that has had a definite impact on the Western world mindset. The ELTR data has been audited and includes all of the most serious complications. At present, this registry believes the risk of death to be around of 0.18% (Table 5) [3], although the incidence of donor death is generally considered to be underreported [234].

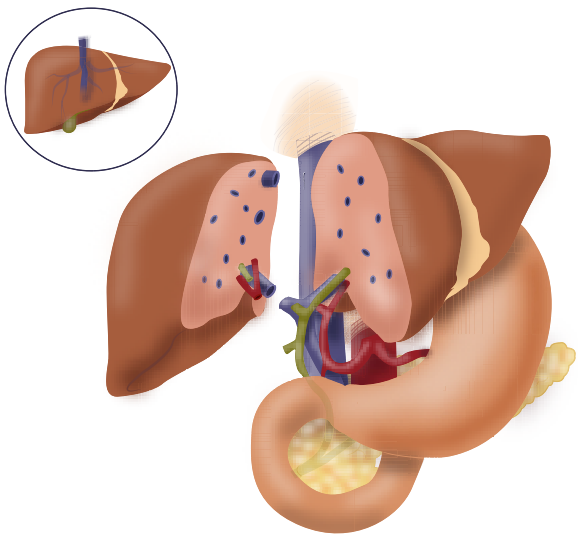

Fig. 4. Adult living donor liver transplantation.

Graft and patient survival in Europe

Since 1988 outcomes of LT have been very good, and have gradually improved over the last several years. Europe keeps a registry that allows continuous monitoring of transplantation activity and outcomes [40]. The large number of indications is a consequence of these good results, and for that reason, although the transplantation activity has increased exponentially, we face a shortage of organs that forces us to develop new alternatives.

At present, after nearly 100,000 transplants, the chances of surviving one year are close to 90% and the 5-year survival rate is around 70% [3]. HCV is the most important determinant with regard to long-term survival. Table 6 shows the probability of survival in relation to different indications. Life expectancy of transplanted patients is excellent, limited mostly by recurrent disease such as HCV or HCC [235], and the occurrence of side effects associated with immunosuppression such as the onset of diabetes, chronic renal failure, hyperlipidaemia, atherosclerosis, or *de novo* malignancy [236]. At present, the most important objective is to reduce these long-term issues though a modification of immunosuppression, especially considering that there are no new treatments with lower toxicity on the horizon. The possibility at present of an effective treatment for HCV means that 10 years from now there will probably be a decrease in the number of indications due to HCV-related complications (cirrhosis, HCC, etc.) [237].

Surgical complications

Although complications from surgery following LT have been significantly reduced, they continue to have a major impact during the post-operative course, and determining the prognosis, not only in the short, but also in the long-term.

Vascular complications

Arterial complications. There is a relatively low incidence of hepatic artery thrombosis, between 1 and 7%. The most common presentation is graft dysfunction, which can change dramatically the graft survival, reported to be as low as 27.4% at 5 years [238]. About 50% of cases are treated with re-intervention and revascularization, while the remainder require retransplantation [239]. The most serious long-term consequence is the occurrence of ischaemic biliary lesions or IC, which in the majority of cases could raise the issue of retransplantation.

Venous complications. Outflow obstruction by IVC anastomosis stenosis following LT is a rare but serious complication, with a reported incidence of 1–6% and generally related to intimal hyperplasia or fibrosis at the anastomotic site [240]. Preservation

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Clinical Practice Guidelines

Table 5. Living donor liver transplantation *vs.* deceased liver transplantation: complications and mortality (1991–2009) – European Liver Transplant Registry [40].

	Living donor liver transplantation
Total number	3622
Adult LDLT (%)	65%
Donor mortality rate	0.18%
5-year graft survival	69%
Children	78%
Adult	63%
Causes of graft loss	
Technical complications	26%
Infection	18%
Rejection	8%
Tumour recurrence	12%
General complications	20%
Non-tumour disease recurrence	4%

Table 6. Overall result in liver transplantation by indication (European Registry 1998–2012) [40].

Primary indication of liver transplantation	Number of patients	Percentage within the group	5-year survival (%)	10-year survival (%)
Chronic liver diseases	66,808		74	64
Alcoholic related cirrhosis		27.6	74	60
Virus C related cirrhosis		18.9	65	53
Virus B related cirrhosis		7.2	75	69
Virus D related cirrhosis		2.3	89	85
Primary biliary cirrhosis		7.5	80	72
Malignant tumours	15,197		60	47
Hepatocellular carcinoma		86.5	63	49
Cholangiocarcinoma		2.8	31	23
Metastases		3.9	49	31
Acute liver diseases	7585		64	59
Metabolic diseases	5699		79	71
Benign tumours	1317		83	76

of the IVC (piggy-back technique) has drastically reduced the occurrence of complications secondary to anastomotic stenosis [240]. Endovascular techniques are the preferred method of treatment [241].

The utilisation of the piggy-back technique and the consequent need for anastomosis of the three hepatic veins initially resulted in outflow problems in the post-operative course, occurring in up to 30% of the patients. This complication has become very rare by performing anastomosis between the union of the three hepatic veins of the recipient and the IVC of the graft [242].

PVT is not uncommon in patients undergoing LT with an incidence between 2.1% and 26% [243]. It may cause problems in paediatric transplantation as a result of hypoplasia due to biliary atresia. On the other hand, in patients with previous partial or complete PVT, LT is associated with a higher surgical complexity. Surgical alternatives including portocaval transposition, renoportal anastomosis, mesentericoportal anastomosis, multivisceral transplantation. However, they are associated with higher morbidity and mortality [243]. In this type of recipient patient, the rate of re-thrombosis is usually higher and may reach 13%. Therefore, short-term anticoagulation is generally recommended [243].

Biliary tract complications

Leakage. Biliary leakage is a rare problem, which depending on what the cause is, often has a relatively easy solution, ranging from performance of an ERCP and sphincterotomy, to the temporary placement of a prosthesis. Incidence is around 5% [244]. In cases of partial grafts, the leak is sometimes on the raw surface of the split liver and is caused by tubules whose flow progressively decreases. Very rarely the embolization of these tubules or the reoperation are required [245].

Ischaemic bile duct injuries. Ischaemic bile duct injuries may have different causes: ABO incompatibility, artery thrombosis, ischaemia/reperfusion injury etc. It is also one of the most common complication in LT with livers from DCD donors, being described in 15–37% of the patients who are receiving a DCD graft [246]. One other cause is the recurrence of PSC, which has been described in 20–30% of transplanted patients [247,157]. They are characterized by intrahepatic strictures and primarily affect their confluence, producing a beaded appearance along with stenosis and dilatation along the entire biliary tract. Usual symptoms are cholestasis with intractable pruritus, repeated episodes of cholangitis of hepatic abscesses. Retransplantation is the treatment [248].

Anastomotic type. Anastomotic stenosis has a reported incidence of 4–9% [249]. In contrast to non-anastomotic stenosis, the underlying causes for anastomotic strictures are linked with a suboptimal surgical technique (with resulting fibrosis or ischaemia) or with bile leak [250]. The majority of which are presented in the first year after LT, although incidence continues to increase even after this period [250]. The first diagnostic tool that can be used is magnetic resonance cholangiography, which has a sensitivity and specificity close to 90% [251], but lacks therapeutic ability. The conventional treatment is endoscopic treatment (ERCP) with balloon dilatation and use of protesis with an overall success rate of 70–100% [249]. The role of percutaneous transhepatic cholangiography is reserved for cases of endoscopic treatment failure or with complicated hepatico-jejunostomies, with a success rate of 50–75% [252]. In cases without response to such therapies, a hepatico-jejunostomy must be performed.

Associated to partial grafts. Anastomotic stenosis is one of the major problems of partial liver grafts. One of the most important related factors seems to be the presence of bile leak [253]. The underlying process is not known, although it has been suggested that it may be related with the local inflammatory effect of the bile or with the poor local vascularity. There are studies, which associate the size of the duct-to-duct anastomosis with the presence of stenosis [254]. The incidence can reach 50% of the recipients (some groups have reported a rate of less than 5%), and although it does not seem to affect long-term survival, it does

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affect QoL [249]. The success rate of endoscopic treatments is statistically lower than in anastomotic stenosis after whole graft LT, reaching 60–75% [255]. Therefore, interventional radiology plays an important role in its treatment, through dilatation or stent insertion. About 50% of patients require reoperation and the duct-to-duct anastomosis ends up becoming a hepatico-jejunostomy [245].

Recommendations:

- The preservation of the inferior vena cava by piggy-back technique is recommended during LT whenever it is possible. The use of this technique is associated with greater hemodynamic stability during surgery (**Grade II-3**)
- The domino transplant can be used for patients with familial amyloid polyneuropathy, as long as recipients are older than 55 years in order to reduce the risk of developing the disease (**Grade II-3**)
- Auxiliary transplantation may be indicated in patients with acute liver failure or functional, congenital or metabolic disorders affecting a normal liver. The advantage of this type of transplantation would be the possibility of removing the graft and withdrawing the immunosuppression once the native liver returns to its normal function (**Grade II-3**)
- Because of the low number of available organs in paediatric LT, the use of split LT is an acceptable option, as long as the liver graft volume is sufficient. In this case the child receives a graft that includes segments II and III (**Grade II-2**)
- In adult LT, the use of the split LT may be an alternative giving the organ shortage, but the left liver graft recipients must have a low weight. The use of the left lobe of the graft is associated with worse outcomes (**Grade II-2**)
- Giving the organ shortage, adult LDLT is recommended in the case in which there is an available donor, as long as the estimated volume of the graft is at least 0.8% of the weight of the recipient (**Grade III**)
- It is necessary to prevent hepatic artery thrombosis during LT and post-operative period. The occurrence of this complication requires retransplantation in 50% of cases (**Grade III**)
- Portal vein thrombosis prior to LT usually does not represent an absolute contraindication. In cases of extensive thrombosis a non-anatomical portal revascularization technique such as a renoportal anastomosis can be performed (**Grade II-3**)
- If a biliary anastomosis leakage in the post-transplatation period is diagnosed, initial ERCP with sphincterotomy is recommended. If the leakage persists, a temporary biliary stent can be used (**Grade II-3**)
- In patients with impaired coagulation, a temporary packing of 48 hours may be necessary (**Grade III**)
- In advanced cases of ischaemic cholangiopathy, the final treatment is retransplantation (**Grade II-3**)
- In cases of stenosis of the biliary anastomosis without improvement after conservative treatment, it is recommended to perform a hepatico-jejunostomy (**Grade II-3**)
- In partial grafts recipients with bile duct anastomosis stenosis or leakage, interventional radiology plays an important role (dilatation, stent insertion), but 50% of patients eventually require a hepatico-jejunostomy (**Grade III**)

Retransplantation

After LT, graft loss still occurs in 7–10% of adults [256] and liver retransplantation is the only suitable therapy for this type of patient [257]. The main causes have to be divided in early (hepatic artery thrombosis or primary graft non-function) and late (IC, chronic rejection or recurrence of the primary liver disease). The timing of retransplantation represents a key point in both patient and graft survival. Patients with a retransplantation interval less than 30 days display lower survival rates when compared to those with later retransplantation [258]. Retransplantation carries a high morbidity and mortality compared with LT, with statistically lower survival rates [256]. One-, five- and 10-year patient survival rates after retransplantation were 61%, 53.7%, and 50.1%, respectively. These percentages were significantly less than those after LT during the same period: 82.3%, 72.1%, and 66.9%. In some centres patients could receive three, four, or more transplants.

At present, multiple elective retransplants are becomingly rare and whether the indications for elective retransplantation should be the same as for chronic liver disease is still an open issue.

Timing for retransplantation

There is no consensus among transplant physicians to define specific retransplantation survival outcomes below which retransplantation is to be avoided. Only the MELD scoring system for organ allocation provides an objective stratification of retransplantation candidates based on severity of illness.

A reduction in short-term survival to less than 60% was observed in all retransplantation patients with a MELD score over 25 [259]. While mortality was increased in all groups with a concomitant rise in MELD score, patients with a score over 30 had a survival rate from 20% to 40%. While retransplantation may exhibit survival rates similar to primary transplant in select patients, it is more likely to be successful in healthier recipients with a lower MELD score.

The effect of allograft quality is exceedingly recognised as one of the important parameters that determine success of transplantation in general and retransplantation in particular. More studies are needed to clearly define parameters but older donors and long cold ischaemia time (>8 h) seem to be critical factors.

HCV used to be considered as an independent risk factor for higher mortality rate. Nevertheless, several studies tend to show that reasonable survival can be achieved following retransplantation and no significant survival differences are observed between HCV positive, cryptogenic, cholestatic, or alcoholic liver disease patients when adjusted for age and MELD scores [260–262].

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Clinical Practice Guidelines

These data suggests that the selection of the recipient should integrate the severity of the illness, the interval time since the primary LT and the graft quality more than the cause of retransplantation.

Recommendations:

- Retransplantation has inferior outcome compared with the first transplant, nevertheless it should be considered in cases of acute or chronic graft failure (**Grade II-2**)
- A patient candidate for retransplantation should undergo a liver work-up as for the first transplant (**Grade III**)
- HCV recurrence is not a contraindication for retransplantation (**Grade II-3**)

Immunosuppression

Standard regimens

The liver is considered a privileged organ in terms of immunological interactions. Spontaneous resolution of severe acute rejection episodes has been described in patients after LT, and these findings have switched the clinician's aim in using immunosuppression from a complete suppression of acute rejection to a reduction of immunosuppression-related side effects particularly renal toxicity. Therefore long-term outcome for patients is becoming the main concern for clinicians, as long-term direct and indirect side effects of immunosuppressive therapy are a major cause of morbidity and mortality. New immunosuppressive protocols have been adopted using combination of drugs with different modes of action, but this has not necessarily resulted in lower immunopotency despite lower doses of each drug. Moreover, new agents with promising results are entering clinical practice.

CNIs are the principal choice for immunosuppression after LT both in Europe and in the US, with nearly 97% of liver transplanted patients discharged from the hospital on CNIs [263]. Both cyclosporine (CsA) and tacrolimus (Tac) bind to cytoplasmic receptors (cyclophilin and FK-binding protein 12, respectively), and the resulting complexes inactivate calcineurin, a pivotal enzyme in T cell receptor signalling. Calcineurin inhibition prevents *IL2* gene transcription, thereby inhibiting T cell IL production.

Among CNIs, Tac is the drug of choice in almost 90% of liver transplanted patients, resulting in a significant increase in its use since 1998 to date.

The best evidence for comparison of the two CNIs is derived from a meta-analysis [264,265] including 3813 patients, which shows immunosuppression with Tac reduces mortality at 1- and 3-years post-transplant, reduced graft loss, reduced rejection and steroid-resistant rejection.

A prolonged-release formulation of Tac has been developed to provide once-daily dosing, with similar efficacy and safety to the twice-daily formulation [266,267]. This formulation seems to have also a positive impact on adherence to immunosuppressive therapy [268].

Azathioprine (AZA) and mycophenolate mofetil (MMF) are the two antimetabolites used in LT. AZA is a prodrug of 6-mercaptopurine that inhibits inosine monophosphate dehydrogenase (IMPDH) and reduces purine synthesis, affecting T and B lymphocyte proliferation [269]. Mycophenolic acid is the active metabolite of MMF and is a selective, non-competitive inhibitor of IMPDH. It is used for both treatment and prevention of rejection in combination with CNI [270].

Their use has constantly increased in the last two decades, due to the clinical need to reduce CNI doses in order to minimize side effects such as nephrotoxicity. Since its introduction MMF has progressively become the most used antimetabolite agent, replacing AZA. However, the evidence for a significant benefit in terms of preventing acute cellular rejection using MMF rather than AZA is very poor.

Only two randomized controlled trials (RCTs) directly compared MMF with AZA [270,271], with one update [272], and no difference was found between MMF and AZA in terms of patient and graft survival [270].

An enteric-coated formulation of mycophenolate sodium (EC-MPS) has been developed to reduce the gastrointestinal side effects by delaying mycophenolic acid (MPA, the active metabolite of MMF) release until the small intestine. Bioequivalence has been shown in renal transplantation for both pharmacokinetics [273–275] and a RCT [276]. In LT EC-MPS use is limited [277,278].

Sirolimus (SRL) and everolimus (EVR) are inhibitors of the mammalian target of rapamycin (mTOR). Their immunosuppressive activity is related to the blockade of IL-2 and IL-15 induction of proliferation of T and B lymphocytes.

SRL was first approved for renal transplantation; however, a black box warning was placed on its use in LT after two multicentre trials (Wyeth 211 and 220) found that SRL was associated with increased incidence of early hepatic artery thrombosis, and with excess mortality and graft loss after LT. However, since 2000, several studies have been performed on *de novo* mTOR inhibitor use after LT showing either a reduced or a similar incidence of hepatic artery thrombosis in patients receiving SRL compared to controls [279–281]. SRL is a promising alternative that may be equivalent to CNI in preventing graft rejection. The adverse effects of SRL include dose-dependent hyperlipidaemia, thrombocytopenia, anaemia, leukopenia, with the absence of neurotoxicity, nephrotoxicity and diabetogenesis, but it has adverse effects on wound healing [282]. Further studies are needed to assess the value of SRL as the primary immunosuppressor after LT, either as a single agent or in combination with other agents.

There has been a gradual, but constant, increase in the use of induction agents, particularly in the last ten years. This has been done to reduce immunosuppression toxicity by minimizing CNIs and steroid use. This has paralleled the introduction of the MELD allocation system, which has resulted in more patients with renal impairment undergoing LT and a greater risk of renal toxicity.

Among induction agents, IL-2 receptor (CD25) monoclonal antibodies (daclizumab and basiliximab) have been the ones mostly used. They are chimeric and humanized antibodies that act on a receptorial subunit, expressed only on activated T lymphocytes, and selectively inhibit their proliferation. Daclizumab has been recently removed from the market, because of diminishing demand.

In a sub-analysis of the basiliximab registration trial no difference was found in death/acute rejection/graft loss between

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patients receiving basiliximab (52.8%) compared to placebo (44.1%) (both in association with CsA and steroids). When HCV negative patients were evaluated separately, patients treated with basiliximab had a significantly lower incidence of acute rejection at 6 months compared to placebo [283].

These data were confirmed in a recent literature review including 18 studies showing that liver transplanted patients, receiving IL-2R antagonists, experienced lower albumin creatinine ratio at 12 months or later, less steroid-resistant acute rejection, less renal dysfunction, when associated with reduced or delayed, and less incidence of post-transplant diabetes mellitus. No difference was found in patient and graft survival [284]. However, these agents should always be used in combination with CNIs to avoid high incidence of acute rejection, as shown in some studies [285,286].

The other group of induction agents is represented by antithymocyte (ATG) and anti-lymphocyte (ALG) polyclonal antibodies. These are heterologous preparations consisting of an infusion of rabbit- or equine-derived antibodies against human T cells. In two retrospective studies [287,288], a three-day induction with ATG in combination with standard CNI dosage was associated with better renal function, but no difference in terms of post-transplant survival. In one study [288] the rate of albumin creatinine ratio was lower in the ATG group.

Between 2000 and 2010, the Food and Drug Administration approved several generic formulations of CNIs (both CsA and Tac) and antimetabolites (both MMF and AZA). Despite the indisputable economic benefits provided by generic drugs, concerns still persist on their use in clinical practice [289–291].

The general consensus in the transplant community is that immunosuppressive drugs should be classified as critical-dose drugs, and such generic drugs should be subjected to different standards for approval [292].

Current opinion among the transplant community is that the use of generic immunosuppressive therapy is safe compared with branded drugs; however, precautions have to be taken [293]. It is mandatory to be aware of the lack of proven bioequivalence between different generic compounds, and that stringent therapeutic drug monitoring is in place during the initial switch phase [294]. Additional studies are needed to assess the true impact of generic immunosuppression.

Recommendations:

- CNI-based immunosuppression is still the cornerstone of immunosuppressive regimens in LT. Tac results in better long-term graft and patient survival than CyA including HCV patients (**Grade I**)
- To date there is no evidence that combination of MMF with CNI improves graft or patient survival compared to CNI and steroids or AZA (**Grade I**)
- Induction agents are safe when used together with CNIs, allowing a reduction of CNI dose especially in patients with pre-transplant renal impairment (**Grade I**)
- Some concern still remains for the high costs of IL-2R agents and their potential negative influence on tolerance (**Grade III**)

Regimens for specific categories of recipients (with renal failure, HCV positive, at risk of infections, at risk of metabolic syndrome, with de novo tumours, etc.)

Immunosuppression in patients with renal impairment

Chronic renal dysfunction, defined as a GFR of $\leqslant$29 ml/min/1.73 m^2 of body-surface area or the development of ESRD, occurs approximately in 18% of liver transplant recipients by five years post-transplant [295]. The most important risk factor for the development of nephrotoxicity is the use of CNIs. CNI-induced nephrotoxicity has a component of reversible renal vasoconstriction. Eventually, tubulointerstitial chronic fibrosis and irreversible change can develop [296].

In patients with renal dysfunction the administration of induction agents and in particular IL-2R antibody can be used together with delayed introduction of CNIs [297–299].

Three multicentre, RCTs [297–299] evaluated the use of IL-2R antibodies as part of a CNI-sparing strategy in patients with kidney dysfunction after LT. In these studies IL-2R antibodies were given in association with MMF followed by delayed introduction of Tac at standard dose [299] or at reduced dose [298]. Patients receiving IL-2R antibodies with delayed and low dose Tac plus MMF and steroids had significant GFR preservation in one study [298], and a significant improvement in the GFR at 1 and at 6 months after LT compared with the control group in another [299]. Conversely an open, randomized, multicentre trial did not find any benefit in terms of renal function using immunosuppressive protocols based on daclizumab induction with delayed Tac [297].

The association of MMF with CNI reduction (at least 50%) or CNI withdrawal is associated with a significant improvement in renal function and a low risk of biopsy-proven acute rejection [300–305]. The combination of MMF with CNI withdrawal [306–310], despite the improvement of renal function in nearly 60%-80% of patients, is associated with a significantly increased risk of acute rejection (between 3% and 30%) [311], too high for current standards.

Only three studies have explored the role of AZA in association with CNI reduction or withdrawal [312–314] showing an improvement in renal function, but again this increased the risk of rejection in some cases [314]. To date no RCTs have been performed directly comparing MMF and AZA with respect to renal function [315].

SRL has been used in liver recipients with renal dysfunction, in order to reduce or stop CNI use. However, the role of mTOR inhibitors in patients with CNI-induced renal impairment is controversial.

In a recent meta-analysis, based on 11 studies (including three RCTs), SRL was not associated with an improvement in renal function at 1 year with a statistically significant increase in infection, rash, mouth ulcers, and discontinuation of therapy [316].

A large prospective, open-label, randomized trial evaluated conversion from CNI to SRL-based immunosuppression for preservation of renal function in LT patients. Overall, 607 patients were randomized early after transplant (within 24 h) and converted from CNI to SRL (n = 393) or CNI continuation for up to 6 years (n = 214). Changes in baseline-adjusted mean Cockcroft–Gault GFR at 12 months were not significant between the two groups [317]. In a more recent prospective, open-label, multicentre study, patients were randomized 4 to 12 weeks after transplantation to receive SRL plus MMF (n = 148) or CNI plus MMF (n = 145). Immunosuppression based on SRL plus MMF

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Clinical Practice Guidelines

was associated with a significantly greater renal function improvement from baseline with a mean percentage change in GFR compared with CNI plus MMF [318].

Data on EVR in combination with CNI withdrawal or reduction are encouraging but not completely conclusive.

The application of an immunosuppressive protocol with EVR and the withdrawal of CNIs has been associated with an initial improvement of renal function tests without an increase in the risk of rejection [319]. However, in a prospective, randomized, multicentre study the mean change in creatinine clearance from baseline to 6 months was similar between patients treated with EVR in association with CNI reduction or discontinuation groups and patients using CNI at standard dose [320].

Further RCTs confirmed that early EVR-based CNI-free immunosuppression is feasible following LT, and patients benefit from sustained preservation of renal function *vs.* patients on CNI for at least 3 years [321,322]. In a 24-month prospective, randomized, multicentre, open-label study the adjusted change in estimated GFR from randomization to month 24 was superior with EVR plus reduced Tac *vs.* Tac control (p <0.001). However, the randomization to Tac elimination was stopped prematurely due to a significantly higher rate of treated biopsy-proven acute rejection [323,324].

Recommendations:

- IL-2R antibodies with delayed and low dose Tac plus MMF and steroids is safe and significantly improves renal function after LT (**Grade I**)
- MMF monotherapy should not be used due to the significantly high incidence of acute cellular rejection (**Grade I**)
- MMF in combination with CNI reduction of at least 50% is associated with significant improvement in renal function and it has a low risk of acute rejection (**Grade I**)
- To date no RCTs have been performed directly comparing MMF and AZA with respect to renal function (**Grade III**)
- Conversion to SRL can be done safely and provide adequate immunosuppression without increased incidence of rejection, graft loss or infection in liver transplant recipients (**Grade I**)
- Early EVR-based CNI-free immunosuppression seems to improve renal function after LT; however, this can be responsible for an increased incidence of acute rejection (**Grade I**)
- RCTs with longer follow-up are needed. Moreover, some concerns still persist on the safety of these immunosuppressive protocols (**Grade III**)

Immunosuppression in HCV liver transplanted patients

Immunosuppression for HCV patients represents a fine balance between suppressing immunity and maintaining optimal host viral responses. However, the use of highly efficacious IFN-free regimens to cure HCV infection will most likely be unnecessary to individualize immunosuppressive therapy in this setting.

CsA has been shown to have a suppressive effect on the HCV replicon RNA level and HCV protein expression in a HCV subgenomic replicon cell culture system [325]. However, there is still controversy about the effect of CsA on HCV replication *in vivo*, in the setting of clinical organ transplantation.

A meta-analysis including five RCTs did not find any significant differences in terms of mortality, graft survival, biopsy-proven acute rejection, corticoresistant acute rejection or fibrosis cholestatic hepatitis between Tac-based *vs.* CsA-based immunosuppression in HCV liver transplant recipients [326].

Considering the potential influence of CsA on the efficacy of antiviral therapy in transplant recipients, several studies explored this field with controversial results. In the only randomized controlled study available to date the antiviral effect of CsA during therapy with PegIFNα-2a and RBV in liver transplant recipients with HCV recurrence (Ishak Fibrosis Stage = 2) was assessed. In patients who switched from Tac to CsA, SVR was higher than in patients on Tac receiving PegIFN/RBV therapy, but the difference was not statistically significant [327].

Although the data on the increase of HCV viral loads due to steroid boluses are convincing [328,329], the effects of steroid maintenance are still controversial. The link between steroid therapy and viral replication after LT in HCV recipients prompted many centres to advocate steroid therapy withdrawal. However, robust data are limited as to the efficacy of this approach. A rapid reduction in the dose of steroid dosage may be harmful for HCV recurrence [330].

Short-term maintenance with steroids (<6 months) with slow tapering has been shown to be associated with less fibrosis progression [331–333].

Considering steroid-free immunosuppressive regimens, three prospective, randomized studies did not find a significant difference with regard to liver fibrosis and viral loads when steroid maintenance was compared with steroid-free regimens in HCV liver transplanted patients [334–336]. These data were confirmed in a meta-analysis. However, HCV recurrence was assessed heterogeneously and data on fibrosis progression and on steroids dose and withdrawal were not reported. Moreover, no individual trial reached statistical significance [337].

When MMF and AZA are compared with respect to their potential impact on HCV recurrence after LT, there is little evidence supporting the use of MMF over AZA, and indeed AZA appears better. In a recent review of the literature 70% of the studies found that severity of HCV recurrence was decreased using AZA, whereas only three studies showed similar severity in HCV recurrence whether AZA was used or not. No study showed that AZA was associated with increased severity of recurrent HCV. Conversely six out of 17 studies, which used MMF, showed an increased severity of HCV recurrence, whereas nine out of 17 showed no effect [315].

Wiesner *et al.* [270] directly compared MMF and AZA in HCV positive liver transplanted patients. A significant reduction in the incidence of acute hepatic allograft rejection or graft loss in the MMF group compared with the AZA group was seen at 6 months after LT. The incidence of HCV recurrence, defined histologically and in the presence of HCV RNA, was 18.5% in the MMF group and 29.1% in the AZA group at 6 months after LT, but no long-term data is available.

Recently Kornberg *et al.* [338] performed a prospective study revealing that in patients treated with MMF, recurrent disease was diagnosed earlier than in the AZA group, but they experienced less severe allograft fibrosis at diagnosis. However, the

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stage of fibrosis significantly increased in the MMF group during 6-months of antiviral treatment compared to the AZA group.

The anti-fibrogenic properties of mTOR inhibitors have been shown in animal models of liver disease where fibrosis progression was attenuated with a low dose of SRL, with SRL and EVR being associated with significantly less fibrosis progression and portal hypertension than treatment with CNIs [339]. Moreover, mTOR inhibitors may affect HCV progression by reducing HCV replication [340]. *In vivo* data are scarse and mainly based on retrospective studies showing that SRL reduces the incidence of advanced fibrosis (stage $\geqslant 2$) both at 1- and 2-years after LT in HCV transplanted patients receiving *de novo* SRL compared to a control group [341]. Very few data are available on EVR and HCV recurrence after LT [320,342].

Considering ATG, in a randomized study comparing thymoglobulin induction plus Tac monotherapy *vs.* Tac plus steroids without induction HCV recurrence was similar in the two groups, but the mean time to histologic recurrence was shorter in the thymoglobulin group [343]. ATG during the induction phase was associated with a lower frequency of recurrence of HCV in patients undergoing LT. This, however, did not affect the 1- and 2-year survival and the frequency of acute rejection, infections, or neoplasms [344].

No significant difference with regard to liver fibrosis and viral loads were found in HCV liver transplanted patients treated with induction therapy based on daclizumab/basiliximab [283,334,336].

A cross-sectional study evaluated the use of alemtuzumab (anti-CD52) in liver transplanted recipients. HCV positive patients did significantly worse than those who were HCV negative, both in the induction and the control group. Moreover, increased HCV viral replication was worse with alemtuzumab, but there was no data on histological recurrence [345].

Recommendations:

- It is not possible to conclude that there is a meaningful clinical difference between the CNIs with respect to the course of HCV recurrence after LT (**Grade I**)
- A rapid decrease in steroid immunosuppression could determine in some patients a worse graft evolution (**Grade I**)
- The 'protective role' of slow steroid withdrawal shown in several studies also requires further investigation (**Grade III**)
- There is still controversy regarding the best anti-proliferative agent for HCV recipients. Observational studies suggest that maintenance of AZA is associated with less fibrosis progression compared to MMF (**Grade II-1**)
- Only properly designed RCT will confirm if mTOR inhibitors are useful in HCV transplant recipients. There are very few HCV specific data on EVR (**Grade III**)
- OKT3 and alemtuzumab are associated with severe HCV recurrence (**Grade I**)
- Data for IL-2R antagonists are contradictory, most studies showing no harm, but some showing worse recurrence (**Grade I**)

Immunosuppression in patients with HCC

The immunosuppression plays a central role in the increased risk of cancer after LT, including the recurrence of HCC.

In vitro studies and animal models have shown that CNIs increase the production of TGF-β in a dose-dependent fashion, promoting tumour cell invasiveness and resistance to apoptosis. *In vitro* data also showed that CsA can induce an invasive phenotype in adenocarcinoma cells through a TGF-β-mediated mechanism [346]. Moreover, in rats with HCC, treatment with CsA was associated with reduced survival and increased metastasis [347].

In retrospective studies a dose-dependent relationship between CNIs and recurrence of HCC after LT was found [348,349].

When CsA is compared to Tac in terms of HCC, recurrence data are not conclusive, and is based on a retrospective study. There are some evidence that CsA is associated with increased 5-year disease-free survival [350] and reduced recurrence rate [351], but these data were not confirmed in subsequent studies [348].

The studies evaluating the role of immunosuppression on HCC recurrence showed no influence of MMF [348,351]. No data are available on the influence of AZA on HCC recurrence after LT.

mTOR inhibitors in LT have a potential anticancer effect. This is due to their inhibitory effect on cancer stem cell self-renewal, on cancer cell growth/proliferation and on tumour angiogenesis. These properties could make mTOR inhibitors the potential immunosuppression of choice in patients transplanted for HCC. To date several studies have been performed to test the impact of SRL on HCC recurrence and on patient survival after LT, however no RCTs have been published. Although most of these studies showed beneficial effect in using SRL, the available evidence is based on clinical reports and retrospective studies.

Two recent meta-analysis [352,353] demonstrated lower HCC recurrence and lower overall mortality in patients treated with SRL.

The results from the only prospective, multicentre, randomized, open-label trial (SILVER trial) showed that SRL improves recurrence-free survival and overall survival in the first 3 to 5 years in low risk patients with HCC within Milan criteria [354,355].

Considering there are no randomized controlled studies on EVR this suggests a protective effect against HCC recurrence. Data from phase I and phase I/II clinical studies suggest that EVR monotherapy may stabilize advanced HCC progression [356,357].

Recommendations:

- To date there is evidence that SRL does not improve long-term recurrence-free survival beyond 5 years (**Grade I**)
- The benefit of SRL is evident in 3–5 years in patients with HCC within Milan criteria (**Grade I**)

Immunosuppression in patients with de novo tumours

The risk of *de novo* malignancy should be considered similarly in clinical practice with Tac or CsA-based immunosuppressive regimens. In only one single centre study patients treated with CsA had an increased risk of malignancy compared with Tac treated patients [358]. However, the lower rejection rates detected in CsA group suggests higher immunosuppressive potency with CsA in this series. The risk of malignancy related to CNI in clinical

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Clinical Practice Guidelines

practice may come from the dosage rather than the type of CNI used, as shown in a RCT performed in kidney transplant recipients [359].

To date there is no evidence suggesting a link between the use of MMF and *de novo* malignancy after LT. Data on MMF and *de novo* malignancies are available only in renal transplanted [309] and heart transplanted patients [360]. In heart transplanted patients the use of MMF had a protective effect against *de novo* malignancy.

There are no published RCTs evaluating the effect of mTOR inhibitors in preventing *de novo* malignancy after LT. The available evidence is based on clinical reports and retrospective studies, thus making it difficult to extract solid conclusions. There are reports of improved outcome of lymphoproliferative disorders and Kaposi sarcoma after switching to an mTOR inhibitor [361]. Despite this, many transplant centres frequently add or convert to an mTOR inhibitor when there are risk factors for malignancy after LT, or even when a tumour has been diagnosed.

Recommendations:

- Risk of *de novo* malignancy should be considered similar in clinical practice with Tac or CsA-based immunosuppressive regimens (**Grade II-2**)
- The risk of malignancy related to CNI in clinical practice may come from the dosage rather than the type of CNI used (**Grade I**)
- No evidence suggesting a link between the use of MMF and *de novo* malignancy after LT (**Grade III**)
- There are no published RCTs evaluating the effect of mTOR inhibitors in preventing nor treating *de novo* malignancy after LT (**Grade III**)

Total withdrawal of immunosuppression

The main aspiration of transplant clinicians is the acceptance of the graft by the recipient without any long-term pharmacological help [362–364]. Long-term survivors following LT are often systematically and excessively immunosuppressed. Consequently, drug weaning is a strategy which should be considered providing it is done gradually under careful physician surveillance. Several studies have explored the possibility to completely withdraw immunosuppression in liver transplant recipients [365–375]. In these studies, the complete withdrawal of immunosuppression was achieved in nearly 20% of patients, on average. However, the incidence of acute rejection was significantly high with percentages ranging between 12% and 76.4%. Moreover, in two cases, chronic rejection led to graft loss among patients undergoing immunosuppression weaning protocols [369,373].

Patients achieving immunosuppression withdrawal experienced a reduced infection rate, less medication requirement to treat comorbidities [376] and an improvement in creatinine, glucose and uric acid serum levels [377] compared with patients who failed immunosuppressive drug withdrawal.

Despite these promising results, most of the studies exploring immunosuppression withdrawal are based on retrospective analysis, small sample size and on single centre experience. Moreover, the lacking of a specific and well-defined protocol of immunosuppression withdrawal and patient monitoring, make these data not applicable to general clinical practice [378].

More recently the first two prospective multicentre trials of immunosuppression withdrawal in paediatric and adult patients have been performed [368,379]. In the paediatric multicentre study, 20 stable paediatric recipients of parental living donor liver transplants underwent immunosuppression withdrawal at a median age of 8 years and 6 months. Immunosuppression withdrawal was achieved gradually over a minimum of 36 weeks, and patients were followed-up for a median of 32.9 months. Of 20 paediatric patients, 12 maintained normal allograft function for a median of 35.7 months after discontinuing immunosuppression therapy. Of interest, patients with operational tolerance initiated immunosuppression withdrawal later after transplantation compared with patients without operational tolerance [368]. In the adult trial, stable liver recipients at least 3 years after transplantation were included. Among the 98 recipients evaluated, 41 successfully discontinued all immunosuppressive drugs, whereas 57 experienced acute rejection. Tolerance was associated with time since transplantation, recipient age and male gender. No benefits in terms of renal function, diabetes and hypertension were seen in patients who underwent immunosuppression withdrawal [379].

Recommendation:

- Intended immunosuppression withdrawal is still experimental and can only be considered in the setting of rigorous clinical trials under strict conditions and with intensive follow-up (**Grade III**)

Medical complications

Early post-transplant and long-term follow-up

The majority of deaths occur within the early post-liver transplant period. The causes of death and graft loss vary according to the time period from LT. Infections, intra- and perioperative surgical complications account for almost 60% of deaths or graft losses in the first operative year, whereas *de novo* malignancies and cardiovascular diseases are the major reasons for deaths thereafter.

Recurrence of the underlying liver disease, in particular hepatitis C infection, is a significant growing cause of late allograft dysfunction. The prevalence of acute and chronic rejection has been constantly declining over the previous years, mainly due to new potent immunosuppressive regimens. Approximately 15–30% of LT recipients develop one or more episodes of acute cellular rejection, which can be successfully treated with increased immunosuppression in almost all patients. In contrast, chronic (ductopenic) rejection can be effectively treated only in early cases and may lead to graft loss. However, the rate of graft loss due to ductopenic rejection has significantly decreased to less than 2%. Therefore, acute or chronic rejections are uncommon complications leading to allograft dysfunction or death.

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Management of HCV recurrence

Hepatitis C recurrence is universal after LT in patients with detectable HCV RNA [380]. Progression of hepatitis C is accelerated after LT and HCV-infected recipients have a reduced graft and patient survival when compared to HCV negative recipients [381]. Around one third of HCV-infected LT recipients will suffer an aggressive HCV recurrence after LT and are at risk of clinical decompensation and graft loss [28,382]. Follow-up of patients with recurrent hepatitis C is usually performed with protocol liver biopsies, which are used to assess the degree of necroinflammation and the fibrosis stage, as well as to exclude other potential causes of graft damage (rejection, drug toxicity). Early identification of patients with progressive hepatitis C is crucial and liver biopsy, hepatic venous pressure gradient (HVPG) measurement or transient elastography (TE) performed one year after LT have shown an excellent ability to identify "rapid fibrosers" [383–385]. Indeed, the presence of significant fibrosis (F $\geqslant$2 METAVIR), portal hypertension (HVPG $\geqslant$6 mmHg) or high TE values (>8.6 kPa) one year after LT are excellent predictors of graft loss. These patients should be considered for early antiviral therapy. TE can be repeated over time to assess fibrosis progression without the need to use an invasive test.

Recommendation:

- Follow-up of recurrent hepatitis C after LT should include a regular assessment of graft damage. Liver biopsy, HVPG measurement or TE are useful tools to assess graft damage and should be part of the follow-up protocol of these patients (**Grade II-2**)

HCV treatment after LT

When eradication of HCV is not feasible before LT, the graft becomes infected universally and immediately after the procedure. HCV infection after LT is characterized by an accelerated fibrotic progression towards chronic hepatitis and cirrhosis. Fibrosis is the main consequence of an imbalanced repair process occurring in the liver in response to the viral injury.

Antiviral therapy after the graft becomes infected can be initiated at early stages (pre-emptive therapy) or once liver damage has already been established [386]. During the first months following LT, patients are still under strong immunosuppression, at risk of opportunistic infections or surgical complications and undergoing treatment with multiple drugs. Several trials assessing pre-emptive therapies with PegIFN and RBV in early phases after LT reported very poor efficacies and poor tolerability due to the presence of renal impairment, infections and cytopenia. To date, the most common and classical approach to treat hepatitis C after LT has been to start antiviral therapy once histological damage is confirmed [27,28]. Overall SVR rates with PegIFN plus RBV have been shown to be low (30–40%) after transplantation, mainly explained by the high rates of treatment discontinuation (20–38%), dose drug reductions (66–73%) and poor tolerance observed in these patients. Liver transplant recipients are prone to haematological toxicity (particularly anaemia). Although the risk of rejection is not high, it has been reported to occur in ~5% of IFN-treated patients. Different series have evaluated the safety and efficacy of triple therapy with first generation protease inhibitors (telaprevir or boceprevir) in over 300 HCV-infected liver transplant recipients [387–389]. Most of these patients had already significant fibrosis in the graft ($\geqslant$F2) or fibrosing cholestatic hepatitis at time of treatment initiation and around half of them were already treatment-experienced after LT. Overall, reported SVR12 rates ranged between 48% and 59%. Nevertheless, the rate of SAEs leading to treatment discontinuation (13–26%) was high; anaemia was the most frequent adverse event and the use of erythropoietin and the need for RBV dose reduction were almost universal. Only one prospective study has evaluated the safety and efficacy of triple therapy with telaprevir in genotype 1-infected patients with less severe recurrence: final results suggest a good safety profile and improved efficacy, with an SVR12 of 72% (53 of 74 patients) [390]. Since telaprevir and boceprevir are substrates and inhibitors of the CYP3A4 system (as well as P-glycoprotein transporter), patients need significant adjustments of CsA and Tac doses; drug levels need to be monitored closely when treatment is initiated as well as when the protein inhibitors are interrupted [391].

Currently, all HCV-infected liver transplant patients should undergo treatment with IFN-free regimens, if available.

The safety and efficacy of sofosbuvir plus RBV administered for 24 weeks was investigated in a phase II pilot single-arm study in 40 patients (naïve or treatment-experienced) with hepatitis C recurrence at least 6 months after LT [392]. Patients with decompensated cirrhosis were excluded. SVR24 was reached in 70%. Despite the small sample size the safety profile was good and most reported side effects were mild. Similarly, a compassionate use program of sofosbuvir plus RBV in patients with severe hepatitis C recurrence after LT was initiated in 2013. Results from the first 104 patients (including some with fibrosing cholestatic hepatitis) were reported recently [393] and indicated SVR12 rates higher than 50%. More importantly, patients' clinical condition was considered to improve significantly (reduction or disappearance of clinical decompensation, significant amelioration of liver function) in around 2/3 individuals. Both viral clearance and clinical improvement were significantly higher in individuals with early severe recurrence (diagnosed during the first year after LT) than in those with advanced cirrhosis years after LT. These results can be considered excellent taking into account the poor outcomes of the disease.

The safety and efficacy of ABT450/r, ombitasvir, dasabuvir and RBV was assessed in 34 genotype 1-infected liver transplant recipients. Patients were treatment naïve and had mild fibrosis. Safety was good and SVR12 rates were very high (97%). Due to the interactions of ABT450/r with Tac and CyA, changes in immunosuppression were necessary during antiviral therapy [394].

Preliminary data from an ongoing clinical trial assessing the efficacy and safety of the fixed-dose combination of sofosbuvir and ledipasvir with RBV for 12 or 24 weeks were recently presented. The study included treatment-naïve and treatment-experienced patients with genotype 1 or 4 infection, with all fibrosis stages (F0 to F4) including patients with Child-Pugh B and C decompensated cirrhosis [395]. The SVR rates were 97% (108/111) in F0-F3 patients, 96% (49/51) in Child-Pugh A patients, and 84% (37/44) in Child-Pugh B patients. There were no differences in efficacy between 12 and 24 weeks of therapy and the

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Clinical Practice Guidelines

combination had an excellent safety profile. MELD scores at week 4 post-treatment improved in the majority of Child-Pugh A and B patients who achieved viral clearance.

Data from real-life cohorts with a combination of sofosbuvir and simeprevir with or without RBV for 12 weeks were recently reported. SVR12 was achieved in 91% (60/66) of patients infected with genotype 1, most of whom were treatment-experienced with one third having advanced fibrosis or cirrhosis [396]. In the TARGET real-life cohort study, in which most patients were treatment-experienced and more than half had cirrhosis, the combination of sofosbuvir and simeprevir yielded a 90% (61/68) SVR4 rate [397].

The impact of HCV clearance in the transplant setting is high due to the accelerated course of the disease. The latter is particularly relevant in individuals with advanced liver disease: liver fibrosis can regress, HVPG values improve and at the end patient survival is better compared to non-responders or non-treated individuals [398,399]. Although these data are derived from IFN-based treated cohorts, they are most likely applicable for all treatments, regardless of the type of antiviral regimen used. This is further supported by data from the sofosbuvir compassionate program discussed above.

The development of direct-acting antivirals is the beginning of a new era for treatment of HCV patients.

Recommendations:

- Antiviral therapy is recommended for all patients with hepatitis C recurrence; treatment should be initiated early in those with significant graft damage (F ≥2). SVR is associated with improved outcomes in these patients (**Grade II-1**)
- Treatment with PegIFN and RBV has a low efficacy (SVR ~35%) and is no longer recommended in this setting (**Grade II-2**). The addition of a first generation protein inhibitor (boceprevir, telaprevir) for genotype 1-infected patients increases efficacy but also side effects and is no longer recommended in LT recipients (**Grade II-2**)
- Sofosbuvir/ledipasvir plus RBV and sofosbuvir plus simeprevir (with or without RBV) are safe and achieve high SVR rates in genotype 1- and 4-infected LT recipients, including cirrhotic patients. Sofosbuvir alone or in combination with ledipasvir has also shown to be safe and efficacious in severe forms of recurrence (i.e., fibrosing cholestatic hepatitis) (**Grade II-1**). In naïve patients with mild recurrence, the combination of ABT450/r, ombitasvir, dasabuvir and RBV has shown high efficacy, but cyclosporine and Tac adjustments are necessary due to drug-drug interactions (**Grade II-1**)
- Other IFN-free regimens are being evaluated in clinical trials (**Grade III**)
- More data on drug pharmacokinetics and drug-drug interaction studies are required in LT recipients (**Grade III**)

Prevention and treatment of HBV recurrence

Before the use of the hepatitis B immunoglobulin (HBIG) in the early 1990s, more than 75%–80% of liver grafts became infected in HBV-infected patients. The risk for graft infection was high (~70%) among individuals with HBV-related cirrhosis, intermediate (~40%) among those with HDV-related cirrhosis, and low (<20%) among patients with acute liver failure. High levels of HBV DNA at the time of LT is the most important determinant of hepatitis B recurrence [400].

In the last two decades, the availability of HBIG and NUCs have changed the prognosis for patients with HBV infection who underwent LT, by reducing recurrence of infection. Patients undergoing LT for HBV-related cirrhosis have currently excellent long-term outcomes, with 5-year survival rates equal to or greater than 80% [18,401]. These figures are comparable or even superior to those of individuals who received LT for other chronic liver diseases.

Preventing HBV recurrence after LT

Samuel *et al.* [400] reported a large reduction in graft infection (from 75% to 33%) and an increase in 3-year survival (from 54% to 83%) among patients given long-term therapy with parenteral HBIG, starting at the time of LT. HBIG probably acts through several different mechanisms, such as binding to circulating virions, blocking the HBV receptor in hepatocytes, and promoting lysis of infected cells by antibody-dependent cell-mediated cytotoxicity. However, monotherapy with HBIG still resulted in unacceptable rates of hepatitis B recurrence in individuals with detectable levels of HBV DNA at the time of LT. Thus, the current strategy to prevent recurrence of HBV infection after LT includes a combination of HBIG and NUCs (usually lamivudine), with a success rate higher than 90% [402–404]. Among more than 2162 patients treated with variable HBIG regimens and lamivudine, HBV infection recurred in only 143 patients (6.6%) during a follow-up period of 6–83 months [402]. Moreover, a meta-analysis of six studies found that combining HBIG and lamivudine (compared to only HBIG) reduced HBV recurrence and HBV-related death more than 10-fold [405]. The optimal strategy for patients who have developed lamivudine resistance is not well-established, but tenofovir is used in this situation. In the setting of LT, nephrotoxicity should be always considered and renal function should be carefully monitored because of the concomitant use of CNIs.

Due to the high cost of HBIG, several studies have assessed the efficacy of lower doses of HBIG, intramuscular or subcutaneous injections, or even HBIG withdrawal in selected patients. All these minimized prophylactic strategies, in combination with NUCs, have effectively prevented recurrence. Gane *et al.* [406] reported a recurrence rate of only 4% 5-years after patients were given intramuscular injections of HBIG (400–800 IU/month) in combination with lamivudine. Importantly, this approach reduced costs by as much as 90%, compared with the high-dose intravenous HBIG regimens. A short course of HBIG plus lamivudine, followed by lamivudine monotherapy, was effective in patients with undetectable levels of HBV DNA at the time of transplantation [407]. Thus, withdrawal of HBIG, with NUCs appears to be a feasible approach for HBeAg-negative patients who undergo LT with undetectable levels of HBV DNA.

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As NUCs therapies have become more efficacious, the question whether HBIG is needed at all has been debated. The largest study published recently by Fung *et al.* [408] using prophylaxis with NUCs (no HBIG) would suggest that this is a feasible strategy: the rate virological relapse in 176 patients treated with entecavir at 3 years was 0%. Preliminary safety and efficacy data with tenofovir and emtricitabine with or without HBIG have also been reported [409]. Some of these patients treated only with NUCs may have reappearance of HBsAg in the absence of detectable HBV DNA or ALT elevation. This opens the problem of deciding if what we want is prevention of graft infection (which would necessitate the use of HBIG) or just to control recurrent infection (in this case HBIG is probably not necessary) [409]. Since specific prophylaxis for HDV reinfection is not available, the most effective strategy to prevent HDV reinfection is the the standard HBV prophylaxis with HBIG and antiviral therapy.

Recommendations:

- Combination of HBIG and NUCs is an effective strategy to prevent HBV recurrence in most HBV-infected patients undergoing LT (**Grade I**)
- Patients with undetectable HBV DNA at the time of LT and no history of resistance to NUCs are the best candidates to use low dose HBIG or a short course of HBIG (1-3 months) followed by NUC monotherapy (**Grade I**)
- Monotherapy with entecavir or tenofovir appears to be efficacious in controlling infection recurrence, but is probably not sufficient to prevent HBV graft infection (**Grade II-2**)

Treatment of HBV recurrence after LT

Recurrence is characterized by reappearance of HBsAg in serum and quantifiable levels of DNA; it is frequently associated with clinical evidence of recurrent disease. The aim of therapy is to control HBV replication over time, to prevent graft loss. Entecavir might be a better choice for individuals with renal failure. Tenofovir is the best alternative for patients with lamivudine resistance [17].

Recommendation:

- Treatment of HBV recurrence should be initiated promptly with entecavir or tenofovir (**Grade II-3**)

Prophylaxis in patients receiving livers from anti-HBc positive donors

Cholongitas *et al.* [179] reviewed 38 studies on the use of livers from anti-HBc positive donors in 788 HBsAg negative recipients. The probability of *de novo* HBV infection of recipients who did not receive immunoprophylaxis was as high as 47.8% in seronegative patients (anti-HBc negative and anti-HBs negative) and 15.2% in patients with serologic markers of past infection (anti-HBs and/or anti-HBc positive); HBV infection was particularly low (1.5%) in anti-HBc and anti-HBs positive recipients. Post-transplant immunoprophylaxis against HBV significantly reduced the probability of *de novo* infection, from 28% (no prophylaxis) to 8.2% (prophylaxis).

Different post-LT prophylaxis strategies (HBIG only, lamivudine only, a combination of HBIG and lamivudine, and/or HBV vaccination) have been tested in patients who received livers from anti-HBc positive donors. However, lamivudine monotherapy is the best cost-effective treatment due to the low rates of graft infection (<3%). HBIG should not be used in HBsAg negative patients, who received a liver from an anti-HBc positive donor.

Recommendations:

- Prophyaxis of HBV recurrence in patients who received a liver from an anti-HBc positive donor should be initiated immediately after LT if recipients do not have anti-HBs (**Grade II-2**)
- Lamivudine monotherapy is the best cost-effective treatment. HBIG should not be used in patients HBsAg negative, who received a liver from an anti-HBc positive donor (**Grade II-2**)

Management of patients transplanted for alcoholic liver disease

Post-transplant outcomes for patients undergoing LT for alcoholic liver disease are good, similar to individuals transplanted for other forms of liver disease [410]. The natural history of alcoholism is often a relapsing-remitting pattern of alcohol use, which means that a thorough assessment of the disease before indication of a LT and a follow-up after the procedure are crucial to achieve success. Due to the lack of a generally accepted definition of alcohol relapse the recurrent rates are highly variable ranging between 10–50% [411,412], which is, as expected, significantly lower compared to non-transplanted population. Most of these studies defined relapse as any alcohol use regardless of alcohol amount. It has shown that the majority of patients remain abstinent or consume only small amounts of alcohol following LT [413]. Long-term studies have demonstrated that occasional or moderately heavy drinking does not impact graft function or patient survival. Nearly 10–20% of relapsers will have a harmful drinking pattern [414]. Despite differences in the literature, most studies suggest that harmful drinking after LT is associated with a decreased survival [411,415,416]. Lower survival in recidivists is very clear in studies with 10 years of follow-up [42,415]; however, in studies with 5 years of follow-up this difference is less evident [417,418]. Therefore, all patients with a positive history of alcoholic liver disease should be encouraged to remain completely abstinent from alcohol post-LT and to enter psychiatric therapy or counselling if they relapse into regular alcohol consumption in the post-operative course.

Since patients with alcoholic liver disease are very frequently heavy smokers, it is important to remember that higher incidence of oropharyngeal neoplasms: a complete examination of the oral

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Clinical Practice Guidelines

tract should be performed before transplantation and also periodically after transplantation.

Recommendations:

- All patients with a prior diagnosis of alcoholic liver disease should be encouraged to remain abstinent from alcohol after LT (**Grade II-2**)
- In the case of relapse into regular alcohol consumption patients should enter psychiatric treatment or counselling (**Grade II-3**)
- Specialist follow-up is relevant to assess alcohol abuse after LT, since harmful drinking, though not very frequent, is associated with decreased patient survival (**Grade II-2**)

Recurrence of non-alcoholic fatty liver disease

NAFLD and NASH, either *de novo* or recurrent, are commonly seen after LT [419,420]. BMI prior and following LT, diabetes mellitus, arterial hypertension and hyperlipidaemia are the major risk factors for post-LT NAFLD/NASH. New onset or recurrent NAFLD/NASH may present with elevated serum transaminases and/or typical features on ultrasound; however, in order to distinguish NAFLD/NASH from other causes of elevated liver tests a liver biopsy may be required.

So far, there is no evidence that recurrent NASH may lead to significant fibrosis or even liver cirrhosis; however, most of these studies are limited by short follow-up periods [421]. No specific recommendations regarding prevention and treatment of recurrent NASH can be made, except to avoid excessive weight gain and to control diabetes and dyslipidaemia.

Although there are no strong data suggesting a specific immunosuppressive strategy for patients undergoing LT for NASH cirrhosis, minimizing corticosteroids seems to be prudent.

Recommendations:

- Liver biopsy may be required to confirm recurrent or *de novo* NAFLD/NASH and to exclude other causes of elevated biochemical liver tests (**Grade III**)
- No specific recommendation regarding prevention and treatment of NAFLD and NASH in LT recipients can be made, except to avoid excessive weight gain and to control diabetes, dyslipidaemia and arterial hypertension (**Grade III**)

Recurrence of cholestatic liver disease

Recurrent AIH, PBC and PSC vary between 10–50%; however, the impact on graft function and patient survival is minimal [422,423]. Nevertheless, a recent study has shown that recurrent PSC may lead to graft loss in up to 25% of patients with recurrent disease [157]. In addition, the rate of recurrent PSC seems to be increased in living donor LT [424].

Recommendations:

- Recurrent autoimmune and cholestatic liver disease should be confirmed by liver biopsy and/or cholangiography (PSC) (**Grade II-3**)
- There is no evidence for prophylactic use of ursodeoxycholic acid in patients transplanted for PBC and PSC (**Grade III**)

Management of HCC recurrence

Literature on the management of recurrent HCC after transplantation is very scarce. Most efforts have been placed in a good selection of candidates for transplantation in order to minimize HCC recurrence. The latter is associated with a ominous prognosis since therapeutic options at time of diagnosis are usually very low: HCC recurrence occurs in 8–20% of recipients and is usually seen during the first 2 years after LT, with a median survival lower than 1 year [83].

One of the main research topics in patients undergoing LT due to HCC is the effect of immunosuppression on HCC recurrence. There are no RCTs available to demonstrate that stronger immunosuppression is associated with a higher risk of recurrence. Regarding the potential impact of mTOR inhibitors on HCC recurrence, this is still a matter of debate. mTOR inhibitors have gained popularity in the transplantation context because of their low nephrotoxicity and potential anti-tumour effect. The mTOR pathway is a key regulator of cellular proliferation and angiogenesis implicated in carcinogenesis. SRL and EVR have been approved by the Food and Drug Administration for treatment of advanced renal cell carcinoma after failure of first-line treatment (sunitinib or sorafenib). Nevertheless, the only solid data showing an impact of mTOR inhibitors on HCC growth are based on preclinical models [425]. Clinical data suggesting a potential benefit rely on uncontrolled pilot and retrospective analyses [83,425,426]. Currently, mTOR inhibitors are been assessed in several clinical trials for the treatment of advanced HCC, and as adjuvant therapy in HCC patients after LT and TACE. Results of these trials will emerge in the coming years [425].

A large RCT in non-transplant patients demonstrated that systemic treatment with the multikinase inhibitor sorafenib prolonged survival in patients with advanced HCC [427]. Since most HCC recurrences after LT are associated with systemic tumour dissemination, a few retrospective cohort studies, isolated case reports and a small case-control study have assessed the safety and efficacy of sorafenib in this setting [428,429]. Although the data suggest that sorafenib might be associated with a benefit in survival with an acceptable safety profile, a recommendation on its use cannot be established with the current data.

A different situation arises in patients who have progressed to liver cirrhosis over the years, in most cases due to hepatitis C recurrence. In the latter situation, *de novo* HCC may occur

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and treatment should probably follow the same algorithms used for immunocompetent patients: liver resection, radiofrequency ablation or TACE (when technically possible) and even retransplantation may be indicated in selected cases.

Recommendations:

- To date there is evidence that SRL does not improve long-term recurrence-free survival beyond 5 years (**Grade I**)
- The benefit of SRL is evident in 3–5 years in patients with HCC within Milan criteria (**Grade I**)
- Treatment of HCC recurrence after LT should be individualized. There are no data supporting the use of sorafenib in cases of disseminated recurrence (**Grade III**)

Management of renal dysfunction

The majority of patients who survive the first six months after LT then present with impaired kidney function. Between 30–80% of patients develop chronic kidney disease stage 3–4 with a cumulative risk of ESRD requiring maintenance dialysis or even renal transplantation of 5–9% within the first 10 years post-LT [295,430]. The number of patients with renal failure after LT has recently further increased due to the implantation of MELD based allograft allocation and the need to use marginal grafts.

Chronic renal failure is a very important issue regarding the management of LT patients. Renal impairment may be present already before LT, may develop or be aggravated during LT and/or occur in the early and late post-operative course. The aetiology of impaired kidney function following LT is multifactorial, including (long-term) exposure to CNI-based immunosuppressive regimens, preoperative kidney dysfunction (hepatorenal syndrome, pre-existing kidney diseases), perioperative acute kidney injury and hypertension, diabetes mellitus, atherosclerosis pre- and/or post-LT. CNIs are considered to be responsible for >70% of cases of ESRD after LT [430]. Acute kidney injury as well as chronic renal disease are associated with a statistically significant increased risk of mortality in the early and late post-LT course [295,431].

Therefore, a continuous screening for and sufficient treatment of potential risk factors as well as a regular monitoring of renal function and adjustment of the immunosuppression is mandatory. There is currently no guideline regarding the place of renal biopsy in the setting of kidney injury after LT [311]. Studies have been conducted with the aim either to prevent or to reduce CNI associated renal failure by using CNI-free immunosuppressive regimens or by early CNI minimization [310,321,432]. However, until now CNI-free regimens have been associated with a high rate of acute cellular rejection.

Recommendations:

- Continuous monitoring of renal function in LT recipients for the detection and management of chronic kidney disease, including sufficient treatment of potential risk factors is mandatory and should be started immediately after LT (**Grade II-2**)
- Reduction or withdrawal of CNI associated immunosuppression or alternative CNI-free protocols should be considered as soon as possible in patients with impaired renal function (**Grade I**)
- Kidney transplantation should be considered the optimal treatment for LT patients with end-stage renal disease (**Grade II-3**)

Prevention and treatment of infections

Infectious complications are a major cause of morbidity and mortality following transplantation and indeed, around 2/3 transplanted individuals will develop an infection after transplantation. Prevention of infections and an aggressive diagnostic strategy are cornerstones in solid organ transplant programs.

Antimicrobial prophylaxis has decreased the incidence and severity of post-transplant infections and has contributed to increased patient survival [433]. From a simplistic point of view one can divide the type of infections occurring after LT in three different timelines [434]: 1) first month after the procedure, where nosocomial infections mostly related to surgery and post-operative care are common; 2) 2–6 months after transplantation, when immunosuppression is at its maximum and opportunistic infections and reactivation of latent infections are the major cause of morbidity; and 3) later than 6 months after the procedure, when community-acquired infections are the major source of problems.

Bacterial infections

Bacterial pathogens are the most common causes of infection after LT. Gram-negative bacteria, such as *Escherichia coli*, *Enterobacter*, *Pseudomonas* are the most common in a majority of series. Bacterial infections involve mainly the surgical site, the abdominal cavity, the urinary tract and the bloodstream. Although surgical site infections are associated with an increase in morbidity rate, intra-abdominal infections are associated with increased mortality and graft loss [435].

Viral infections

CMV. CMV infection remains the most significant opportunistic infection in liver transplant recipients. An adequate prophylactic strategy has been shown to significantly reduce its incidence but it still produces relevant morbidity. The most common clinical syndromes are viremia, bone marrow suppression and involvement of the gastrointestinal tract (i.e. colitis) and the liver (hepatitis) [436,437].

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Clinical Practice Guidelines

The use of CMV-seropositive donors in CMV-seronegative recipients increases the risk of developing CMV infection as well as past acute rejection episodes and the use of intense immunosuppression.

Treatment with ganciclovir or valganciclovir should be implemented in patients with persistent or increasing viremia (CMV infection), and in all individuals in whom CMV infection evolves into CMV disease. The detection of viremia by CMV-PCR during the first months after LT is essential for early diagnosis of this common infection [433,436,437]. Intravenous ganciclovir or oral valganciclovir is the treatment of choice in patients with mild disease, whereas intravenous ganciclovir should be used in patients with more severe infections [436,437].

EBV. Patients with EBV seropositivity before LT, and patients treated with aggressive immunosuppressive regimens (i.e. anti-lymphocyte globulin) are at higher risk of developing post-transplant lymphoproliferative disorders (PTLD) [438]. PTLD should always be suspected in liver transplanted patients, especially those at high risk, presenting with fever, weight loss, night sweats, even in the absence of lymphoadenopathy. Radiographic analysis should be performed as EBV viremia is not a diagnostic for EBV-associated PTLD [439].

The first step in treating patients with PTLD is reducing the immunosuppressive therapy. Additional therapies including rituximab, chemotherapy, radiation and surgery may be necessary if no response is achieved by immunosuppression reduction. The multidisciplinary assessment, including oncologist, should always be performed.

HEV. Despite the prevalence of HEV infection in Central European, liver transplant recipients is low, it can result in graft hepatitis and graft dysfunction after LT. Therefore screening for HEV RNA should be part of the diagnostic work-up of patients who are evaluated for LT.

Fungal infections

Over the last two decades, the overall incidence of invasive fungal infections remained unchanged; however, a significant decline in the incidence of invasive candidiasis and an insignificant increase in invasive aspergillosis has been shown [440]. Identified risk factors for invasive fungal infections are: a decrease in the length of transplant operation, intraoperative transfusion requirements, cold ischaemic time, use of roux-en-Y biliary anastomosis, PVT, biopsy-proven rejection episodes, retransplantation and renal replacement therapy [440–442].

Diagnosis of invasive fungal infections is difficult since blood cultures are relatively insensitive. Other tests have a variable accuracy: beta-d-glucan (for Candida) and galactomannan testing (for Aspergillus) have inconsistent accuracy, whereas serum and cerebrospinal cryptococcal antigen testing is highly reliable [437]. Antifungal therapy relies not only on an adequate election of the drug but also on a reduction in immunosuppression.

Candida species. Fungemia or peritonitis due to *Candida albicans* and non-albicans Candida species (e.g. *C. glabrata, C. krusei, C. tropicalis*) are leading causes of early invasive infection after LT. Oral prophylaxis against Candida species is recommended during the first months, as it reduces mortality due to fungal infection. At present, fluconazole is the most commonly used antifungal agent [443].

Aspergillus. Infection with Aspergillus species may be activated in individual colonized pre-transplantation or as a result of new environmental or nosocomial exposures. The lungs are the primary site of infection, and dissemination commonly involves the central nervous system. Clinical signs of central nervous system infection necessitate radiologic and cerebrospinal fluid evaluations.

Prophylaxis against Aspergillus is only recommended in certain high risk situations: prolonged use of corticosteroids before transplantation (such as AIH), acute renal failure requiring hemodialysis, acute liver failure, retransplantation, high transfusion rate during surgery, early re-exploration after LT and maintained renal failure after LT. If the risk of infection is moderate inhaled amphotericin B is the treatment of choice, but if the risk is high (3 or more risk factors) micafungin is indicated [437].

Pneumocystis jirovecii. Pneumocystis pneumonia is rare during trimethoprim-sulphamethoxazole (TMP-SMX) prophylaxis [444]. Prophylaxis against *Pneumocystis jiroveci* is mainly accomplished by 6–12 months of cotrimoxazol (dapsone or pentamidine can be used if sulfonamide allergy) [437,444]. The clinical presentation is insidious with shortness of breath occurring early but with relatively subtle findings by chest radiography. TMP-SMX is the agent of choice but may provoke renal toxicity. Corticosteroids are useful as adjunctive therapy to both reduce pulmonary inflammation and reduce post-infection fibrosis.

Mycobacteria

Active tuberculosis can be diagnosed in 0.47–2.3% of liver transplanted patients, and mostly in the first 12 months after LT [445,446]. Fever, night sweats and weight loss are common symptoms; however, since extrapulmonary tuberculosis are present more frequently in liver transplanted patients compared to the general population, atypical presentations can occur.

Treatment of latent tuberculosis is relevant since diagnosis of this infection in transplant patients is not always easy and has a high mortality rate. Treatment with isoniazid for 9 months (supplemented with vitamin B6) is the standard therapy and should be indicated in the following situations: PPD positive skin test, history of untreated tuberculosis, chest radiography findings compatible with tuberculosis.

Treatment of active tuberculosis in liver transplant recipients is not standardized and it is not based on RCTs [447]. Moreover, active tuberculosis therapy is complicated by the interactions between antituberculous and immunosuppressive drugs, and by the potential hepatotoxicity associated with first-line tuberculosis treatment [445]. Therefore, in cases of non-severe tuberculosis, treatment should include isoniazid and ethambutol avoiding rifamycins. Levofloxacin can replace isoniazid if its use is not possible. Patients with severe tuberculosis should be treated with rifamycin during the initial and maintenance phases.

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Recommendations:

- CMV prophylaxis for at least 3 months should be used in patients at a higher risk of developing CMV infection (**Grade II-2**)
- PTLD should always be suspected in liver transplanted patients, especially those at high risk, presenting with fever, weight loss, night sweats, and even in the absence of lymphoadenopathy (**Grade III**)
- Oral prophylaxis against *Candida* species is recommended during the first months, as it reduces mortality due to fungal infection (**Grade II-3**)
- Prophylaxis against *Aspergillus* is only recommended in high risk situations (**Grade II-3**)
- Prophylaxis against *P. jirovecii* with trimethoprim-sulphamethoxazole should be given to all liver transplanted patients for 6-12 months (**Grade II-2**)
- Treatment of *P. jirovecii* infection consists of trimethoprim-sulphamethoxazole. Corticosteroids are useful as adjunctive therapy to both reduce pulmonary inflammation and reduce post-infection fibrosis (**Grade II-3**)
- Patients undergoing treatment for tuberculosis should be monitored for potential hepatotoxicity and for acute rejection (**Grade II-3**)

Prevention and treatment of diabetes, hypertension, cardiovascular disease (metabolic syndrome), bone disease and de novo tumours

Metabolic syndrome

Metabolic syndrome is a mounting challenge in the management of LT recipients. The clinical features of metabolic syndrome, in particular insulin-resistant (type 2) diabetes mellitus, obesity, dyslipidaemia and arterial hypertension, either alone or in combination contribute to late post-operative morbidity and mortality. The prevalence of metabolic syndrome lies between 50–60% in the LT population [420]. Diabetes mellitus is diagnosed in 10–64% of LT patients, obesity (BMI >30 kg/m^2) in 24–64%, dyslipidaemia in 40–66% and arterial hypertension in 40–85% [437].

Due to the high prevalence of metabolic syndrome and its different clinical features, LT recipients have a significantly increased risk of cardiovascular events and mortality compared to an age and gender-matched general population [448]. Based on several publications this elevated risk of cardiovascular diseases ranges from around 10% at five years to up to 25% at 10 years [448,449]. Therefore, cardiovascular disease accounts for almost a quarter of deaths in the long-term follow-up after LT [449,450].

Numerous publications have shown that the currently issued immunosuppressive regimens cause both an exacerbation of pre-existing systemic and metabolic disorders and *de novo* post-LT arterial hypertension, hyperlipidaemia, diabetes and obesity [449].

Therefore, a continuous cardiovascular risk stratification and an aggressive management of the metabolic syndrome, in particular, the rapid detection and treatment of metabolic disorders, as well as modification of risk factors including tailoring the immunosuppressive regimen are mandatory in order to avoid cardiovascular morbidity and mortality.

In patients treated with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, potential interactions with CNIs should always be considered, due to the fact that both statins and CNIs are metabolized by cytochrome P450–3A4. This can result in increased statin concentrations, with an increased risk of developing rhabdomyolysis. Therefore statins should always be started at a lower dose and gradually titrate upwards, and patients should be followed-up closely to detect any potential side effects.

Hydrophilic statins such as fluvastatin and pravastatin are preferred as they are not metabolized by cytochrome P450–3A4 and they may cause less metabolic interactions.

Recommendations:

- As LT recipients have an increased risk for cardiovascular diseases, efficacious and prompt treatment of modifiable risk factors in the form of lifestyle changes, pharmacological therapies and modifications of the immunosuppression is imperative to prevent serious cardiovascular complications (**Grade III**)
- Various pharmacological therapies must be initiated as soon as possible to control arterial hypertension, hyperlipidemia, diabetes and obesity (**Grade II-3**)
- A healthy diet and regular exercise programs represent additional effective management options (**Grade III**)

Bone disease

Patients with end-stage liver disease present with decreased bone density compared with age-matched control population. Bone loss accelerates in the first 6 months after LT, independently of the pre-transplant bone mineral density, and it is associated with increased risk of fractures causing pronounced morbidity and reduced QoL [451,452]. The first 6–12 months after LT, bone loss reverses and there is a gain in bone density.

Among risk factors for developing post-transplant bone disease the most important is a low bone mineral density before LT [453,454]. This can be caused, in general, by malnutrition and physical inactivity, by malabsorption of vitamin D in cholestatic liver disease, steroid use in patients with AIH and direct toxicity in alcoholic patients [455]. Post-LT immunosuppression regimen, in particular steroids, female sex, older age, lower BMI and renal dysfunction represent risk factors for low bone mineral density and an increased incidence of fractures.

Therefore, a regular measurement of bone mineral density is recommended pre- and post-LT. In the case of osteopenia and low bone mineral density, calcium and vitamin D supplementation and, if tolerable preoperative, a weight-bearing exercise should be started. Bisphosphonate therapy must be considered for patients with osteoporosis and/or recurrent fractures.

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Clinical Practice Guidelines

Recommendations:

- Bone mineral density screening should be performed yearly for patients with pre-existing osteoporosis and osteopenia and every 2-3 years in patients with normal bone mineral density. Thereafter, screening depends on the progression of changes in bone mineral density and on risk factors (**Grade II-3**)
- LT patients with osteopenia should perform regular weight-bearing exercise and receive calcium and vitamin D supplementation (**Grade II-3**)
- Bisphosphonate therapy should be considered in patients with osteoporosis or recurrent fractures (**Grade II-2**)

De novo malignancies

Besides cardiovascular diseases *de novo* malignancies are the leading cause of mortality following the first post-LT year. Observational studies have shown a 2–3-fold elevated risk of solid organ cancers and a 30-fold or higher increase in the rate of lymphoproliferative malignancies compared to the general population [450,456,457]. Several papers have reported an incidence of *de novo* cancers ranging from 3% to 26%, mainly dependent on follow-up duration, with a continuous rise in risk up to 19% and 34% at 10 and 15 years, respectively, following LT [450,456,457].

The major cause of *de novo* malignancies in the post-LT course is related to the loss of immunovigilance induced by immunosuppressive agents, as well as other risk factors associated with carcinogenesis, such as viral infections with oncogenic potential (e.g. EBV, human papilloma virus), PSC, smoking and alcohol abuse. In general, an increased frequency is not detected in many of the common cancers in the absence of identified risk factors.

Skin cancer is the most common *de novo* malignancy in patients who underwent LT [458]. Among these, non-melanoma skin cancers such as squamous and basal cell carcinomas are more frequent than melanomas. Their incidence is 20-fold higher in liver transplant recipients compared to age and sex-matched population, and generally tend to be more aggressive, recurring and metastatizing more frequently than in non-transplant population [459]. Major risk factors for developing non-melanoma skin cancers after LT include: older age, chronic sun exposure and sunburn, fair skin, and a history of skin cancer [460].

Patients with alcoholic cirrhosis are of particularly increased risk for the development of cancer in the upper gastrointestinal, oropharyngeal-laryngeal, as well as lung cancers [450,461]. A positive smoking history both pre- and post-LT further increases the risk of head/neck and pulmonary *de novo* malignancies in these patients underscoring the importance of discontinuing smoking in LT candidates and recipients [462].

Patients with EBV seropositivity before LT, and patients treated with more aggressive immunosuppressive regimens (i.e. anti-lymphocyte globulin) are at a higher risk of developing PTLD. Therefore PTLD should always be suspected in liver transplanted recipients, especially those at high risk, who present with fever, weight loss and night sweats, even in the absence of lymphoadenopathy.

Significantly higher rates of colorectal cancer have been demonstrated for patients with PSC and inflammatory bowel disease in the post-LT course [450]. Therefore, annual screening colonoscopies are recommended in these patients [463].

The development of *de novo* solid organ cancers has a major impact on the outcome of LT due to a poor prognosis in the majority of patients with *de novo* neoplasia. The probability of survival for LT recipients after the diagnosis of *de novo* cancers mainly depends on tumour location, type and stage. In general, the outcome is worse compared to the general population with the same malignant diseases. One recent study showed a median survival lower than 3 years after the diagnosis of *de novo* cancer [457].

Many known risk factors for *de novo* malignancies cannot be modified, such as age and underlying liver disease. Therefore, regular cancer surveillance programs have been proposed by several groups; however, none of these recommendations are based on scientific evidence [463]. A recent paper has shown improvements of both cancer detection rates and non-cutaneous cancer patient survival after applying a strict surveillance protocol to all LT recipients [457]. More data, however, are needed to define the optimal surveillance protocol after LT with individualized emphasis laid on patients' particular risk profiles.

Recommendations:

- Cancer screening protocols are warranted after LT, especially in populations at increased risk, in order to detect *de novo* tumours at an early and potentially curative stage (**Grade II-2**)
- Patients transplanted for alcoholic liver disease should undergo a more intensive surveillance protocol for the detection of upper gastrointestinal, oropharyngeal-laryngeal as well as lung cancers (**Grade II-3**)
- Patients transplanted for PSC with associated inflammatory bowel disease should undergo annual colonoscopy (**Grade II-3**)

Lifestyle in the long-term follow-up

Quality of life

The goal of transplantation is not only to ensure a patient's survival, but also to offer the patient the same state of health that he or she enjoyed before the disease and achieve a balance between the functional efficacy of the graft and the patient's psychological and physical integrity. This is the reason that a change has taken place in the evaluation of medical interventions in the field of organ transplantation, just as in other medical fields [464,465].

Previously used parameters, such as clinical judgment, biochemical and instrumental tests, and survival rates, have been integrated with new indicators that evaluate the relationship between the costs (both human and economic) and benefits of any intervention in terms of QoL [466,467].

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Unfortunately, the measurement of QoL in liver transplant recipients has not been rigorously studied and is not standardized as reported by a recent review of instruments used to assess QoL after LT. More than 50 different instruments are available for assessing QoL in liver transplant candidates or recipients, and among these, generic health assessment questionnaires are the most widely used [468].

Several studies have assessed QoL during the first few years after LT and have shown encouraging results; however, studies of the long-term evaluation of the QoL after LT are less optimistic.

Somatization, depression, and anxiety usually improve during the first year after transplantation, but they worsen again during the long-term follow-up, especially at 1 and 2 years. This is mainly due to the fact that in the early post-transplant, patients experience the perception of a new life, whereas in the long-term side effects of medication, especially of immunosuppression, can develop. Conversely, mental functioning, physical functioning and life satisfaction scores improve significantly during the first year after transplantation, and this improvement persist over time [469]. Another factor that can influence long-term QoL after LT is the aetiology of liver disease. Considering HCV liver transplanted patients, histological abnormalities, commonly seen at post-transplant protocol biopsies, have been considered a potential cause of anxiety in patients at 1 to 2 years after transplant. Although a specific correlation between HCV recurrence after LT and a decrease in the physical domain of QoL has never been shown, patients with HCV recurrence can show significantly greater levels of depression, anxiety, phobic anxiety, and paranoid ideation in comparison with HCV negative patients [470].

Considering patients transplanted for alcoholic liver disease, no differences in returning to society with active and productive lives have been compared with non-alcohol-related liver transplanted recipients [471].

Interestingly, a recent study found that patients who underwent transplantation for autoimmune disease had decreased QoL in the physical, social/role function, personal function, and general health perception domains [472].

QoL has been considered at 10 and 30 years after LT, and patients' perception of their QoL was generally good, being reduced only in older individuals who can develop a reduction in their ability to carry out physical activity in comparison with the general population [473].

As far as gender is concerned, data on the different QoL after LT in male and female recipients are still controversial [474]. Usually no difference in terms of post-transplant QoL between male and female patients is seen, but a study reported a higher degree of overall QoL in male compared with female recipients [475].

Recommendation:

- Quality of life after LT should always be considered as an outcome measure (**Grade II-2**)

Adherence

It is widely reported that the effectiveness of any treatment depends not only on the correct choice of therapy, but also, and considerably, on active cooperation by the patient [476]. Adherence can be defined as the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider [477–479]. In patients before and after transplantation, adherence to medical prescriptions and immunosuppressive therapy in particular is crucial to prevent medical complications that negatively influence graft function and patient survival and increase costs. Across all types of transplantation, average non-adherence rates ranged from 1 to 4 cases per 100 patients per year for substance use (tobacco, alcohol, illicit drugs), to 19 to 25 cases per 100 patients per year for non-adherence to immunosuppressants, diet, exercise, and other healthcare requirements. Demographics, social support, and perceived health showed little correlation with non-adherence, whereas pre-transplant substance use predicted post-transplant use [480]. Assessing patient adherence to medical regimens and lifestyle recommendations is the first step towards understanding the reasons for poor adherence or non-adherence [481,482].

Although poor adherence is a common phenomenon among liver transplant patients, the literature on the topic is still scarse. Most of these studies have been based on small numbers of patients and have assessed adherence with different methods; this has often prevented any comparisons of the results.

Non-adherence rates range between 20% and 50% in published studies. Among a sample of organ transplanted patients a non-adherence to immunosuppressive therapy, to correct lifestyle, and to general medical prescriptions of 38%, 39%, and 13% respectively has been reported. Non-adherent patients to immunosuppressive therapy and to general medical prescriptions displayed a longer interval from transplantation compared with adherent patients. In addition, non-adherent patients to the correct lifestyle, the rates of men and of patients with disability pension were significantly higher compared to adherent patients [483].

The alarming picture emerging from these studies is that poor adherence is an issue for nearly one of every two liver transplant patients, and this coincides with substantial increases in the rates of graft loss and death. This phenomenon seems to particularly affect young liver transplant recipients, who are more prone to this behaviour for several reasons. Healthcare providers dealing with liver transplant patients, therefore, need to be properly trained to address non-adherence and be able to use all available means to improve their patients' adherence. Patient education alone is apparently not enough to ensure adherence, so multidisciplinary measures developed by professional educators, supported by psychologists, and coordinated by physicians are warranted [484].

Adherence in adolescents

The outcome of LT is usually reported in terms of graft and patient survival, medical and surgical complications, and QoL, but when it comes to transplanted adolescents such conventional parameters are unable to give a full account of their life with a new liver, and their transition from adolescence to adulthood is a time when they are particularly vulnerable.

Adolescents with liver transplants have excellent survival rates, over 80% of them surviving more than 10 years. Graft loss is most often associated with complications such as chronic rejection, hepatic artery thrombosis, and biliary complications. CNIs may have various side effects, including hypertension and

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Clinical Practice Guidelines

nephrotoxicity. Liver transplanted adolescents are also exposed to viral infections, among which the EBV is very common and associated with the onset of PTLD. Growth retardation may also be an issue in some liver transplant recipients. Future studies will determine the best way to assess the functional immune status of adolescents with a transplanted liver with a view to ensuring the best treatment to induce tolerance without the complications of excessive immunosuppression. Schooling may be disrupted due to adolescent transplant recipients' poor adherence. Non-adherence is associated with a poor medical outcome. Both physical and psychosocial functioning is reportedly lower among young liver transplant recipients than in the general population [485].

Schooling. Liver transplant adolescents are at a higher risk for developing cognitive deficits compared to the age-matched normal population [486,487].

Schooling may be negatively affected by poor adherence to prescribed medication. In a recent study, when data on adherence were pooled together, it emerged that at least 3 in 4 adolescent liver transplant recipients were non-adherent on at least one measure of adherence. It was clear that the group of non-adherent recipients experienced more severe limitations on their school activities and their mental health suffered more; they also had a worse perception of their health and a lower self-esteem and family cohesion [488].

School performance is an important aspect of functional outcomes in the adolescent population. An interesting longitudinal survey on school attendance, performance, and educational outcomes (including the need for targeted educational programs) was recently published [489]. This retrospective study had been performed on 823 liver transplant recipients whose median age at the time of their transplant surgery ranged from 0.05 to 17.8 years. These 823 cases came from 39 liver transplant centres in the US. A third of the children and adolescents had missed more than 10 days of school a year, and absences were higher for older recipients and for shorter times elapsing since LT. More than a third of the sample needed extra teaching and one in five had repeated a school year. The type of immunosuppression taken 6 months after the transplant, the occurrence of CMV infection and the teaching services used before the transplant were the main factors associated with the need for special support. The most striking predictor was the pre-transplant need for extra teaching (OR 22.46), suggesting that most neurocognitive impairments seen after transplantation originated beforehand [488].

An editorial on this topic published in the same journal as the survey emphasised that the article looked at functional outcomes, as well as surgical and biological results, in survivors of paediatric LT, and congratulated the authors on their contribution to moving the field towards a broader approach to outcome assessment [490].

A multicentre study on cognitive and academic outcomes was recently performed in 5–7 year-old children two years after their transplantation: it confirmed that these young liver transplant recipients performed significantly below test norms in terms of their IQ and achievement measures, and 26% had mild-to-moderate IQ delay, whereas the normally expected rate is 14%. Four percent had severe mental delays and learning difficulties [487].

Recommendations:

- Physical and psychosocial functions after LT should be properly assessed in adolescent liver transplant recipients as they are typically lower compared to the general population (**Grade II-2**)
- Adherence to medical prescriptions and particularly to immunosuppressive therapy should always be evaluated after LT. Special attention should be posed on immunosuppression-related physical side effects as they represent the major reason for non-adherence among adolescent recipients (**Grade II-2**)
- A specific structured support should be a planned in transplanted children and adolescents concerning schooling (**Grade II-2**)
- Multidisciplinary measures developed by professional educators, supported by psychologists, and coordinated by physicians are warranted to improve adherence before and after LT (**Grade III**)

Employment

The percentage of liver transplant recipients who return to work after transplantation ranges from 26% to 57%, with the rates differing with the length of the follow-up period considered. Employed patients have a significantly better QoL than those who are unemployed [491].

Among working-aged patients, employment rates were highest in the PSC (56%) group and lowest in the acute liver failure (39%) and PBC (29%) groups. In age-adjusted logistic regression, patients with PSC or alcoholic cirrhosis were 2.4- and 2.5-fold more likely to resume work after LT than patients with PBC [492].

The opposite was reported from the UNOS database, where the authors found that patients with alcoholic liver disease had a significantly lower rate of employment than patients with other aetiologies of liver disease [493].

Recommendation:

- Even though no clear correlation has been found between aetiology of liver disease and returning to work after LT, special attention should be devoted to patients transplanted for alcoholic liver disease, as they seem to be at higher risk of unemployment (**Grade II-2**)

Sexual function and pregnancy

Successful LT leads to improvements in sex hormone disturbances in both men and women, but immunosuppressive drugs may interfere with hormone metabolism [494].

A significant improvement of sexual function after transplantation has been shown in a meta-analysis based on seven studies. When sexual activity was evaluated in female liver transplant

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subjects, 70% of sexually active patients reported satisfaction with their sexual health [495].

However, recent studies described less favourable data. In one of the studies, 23% of men and 26% of women reported decreased libido, and 33% of men and 26% of women reported difficulty in reaching orgasm with intercourse [496]. In the other study, 40% of the patients who underwent LT reported a decreased frequency of sexual intercourse, and among men, partial and complete erectile dysfunction was reported by 20.6% and 34.3%, respectively [497].

Male population

Usually the proportion of sexually inactive men decreases after transplantation, but erectile dysfunction may remain unchanged. Cardiovascular disease, diabetes, alcohol abuse, antidepressants, and angiotensin II receptor blockers were associated with erectile dysfunction after LT [498]. When the erectile dysfunction was compared between pre- and post-LT, the percentage for severe erectile dysfunction was significantly greater in patients with cirrhosis *vs.* liver transplant patients (43% *vs.* 22%, p <0.04). Moreover, a worse International Index Erectile Function score was seen in patients with cirrhosis *vs.* patients who underwent transplantation (14.3 *vs.* 19.5, p <0.04). Sexual dysfunction correlated with old age (p <0.03), whereas after transplantation, it was greater in patients with depression (p <0.02). Therefore sexual dysfunction, despite improvement, was still present after LT, with depression being the major risk factor [499]. The role of immunosuppression on erectile function has been studied; however, data concerning the impact of different drugs on erectile function and fertility are still lacking and mainly reported in kidney transplant recipients. Laboratory studies on rats and primates seem to demonstrate a direct link between SRL and decreased spermatogenesis [500], but in a recent cross-sectional study, despite lower total testosterone levels and higher follicle stimulating hormone and luteinizing hormone levels, no significant difference in sexual scores was found between patients treated with SRL and a control group [501].

Female population

The prevalence of sexual dysfunction was reported from a single centre analysis, to be broadly similar for patients who underwent transplantation and patients with cirrhosis (65% *vs.* 60%). After transplantation, sexual dysfunction was correlated with depression (p <0.01) and reduced QoL (p = 0.02) [499]. Women achieve normal menstrual function and fertility a few months after transplantation. In the year before transplantation, 42% of women reported regular menstrual cycles, 28% reported irregular and unpredictable bleeding, and 30% reported amenorrhea, whereas after transplantation, 48% experienced regular menses, 26% experienced irregular bleeding, and 26% experienced amenorrhea [502]. When liver transplant recipients are of reproductive age, they must be counselled about the possibility of pregnancy and the use of contraception, and pregnancy should be avoided for the first 6 to 12 months after transplantation, although some centres advocate waiting 24 months [499]. Barrier contraception seem to be the safest option for these patients [503]. Pregnancy is often successful after LT, despite the potentially toxic effects of immunosuppressive drug therapy. Acute cellular rejection may occur in pregnant liver transplant recipients, but no difference is generally reported in comparison with non-pregnant recipients. The treatment is usually based on an increase in immunosuppression or on the use of intravenous boluses of steroids [503]. Liver transplant recipients with recurrent hepatitis C nonetheless appear to be at risk of worse graft function in the event of pregnancy, and antiviral drugs are generally contraindicated in pregnancy because of their teratogenic effects. The use of immunosuppressive drugs should be maintained during pregnancy since CNIs, azathioprine and steroids have not been found to be teratogenic. MMF has been reported to cause malformations in animal models and is not recommended in pregnancy in humans. mTOR inhibitors have been reported to affect spermiogenesis in males. Immunosuppressive drug concentrations should be carefully monitored [503]. The US Food and Drug Administration categorizes the safety of drugs in pregnancy on the basis of available evidence as reported in Table 7 [504]. Fetal loss, prematurity, and low birth weight have been reported in women who have undergone transplantation, and maternal risks include hypertension, preeclampsia, gestational diabetes, and graft dysfunction. The rate of caesarean section is considerably higher in post-LT patients. It is crucial for post-transplant patients who conceive, to be managed by centres with multidisciplinary care teams including a liver transplant hepatologist and surgeon, an obstetrician, and a paediatrician [499]. After delivery, most transplant physicians advise against breastfeeding because of concerns over the safety of neonatal exposure to immunosuppressive drugs [499].

Recommendations:

- LT patients of reproductive age should always be counselled about the possibility of pregnancy and the use of contraception (**Grade III**)
- Pregnancy should be avoided for the first 12 months after transplantation, although some centres advocate waiting 24 months (**Grade II-3**)
- Immunosuppression should be maintained during pregnancy. Steroids, CNIs and azathioprine have not been reported to be teratogenic (**Grade II-3**)
- Mycophenolate mofetil and azathioprine are usually not recommended (**Grade II-3**)
- mTOR inhibitors may affect spermatogenesis in male recipients (**Grade II-2**)
- More studies should be designed to investigate the role of immunosuppression on sexual dysfunction, in both male and female recipients (**Grade III**)

Physical activity and weight control

After transplantation patients have an improved functional capacity and can perform tasks independently [505]. The use of a structured exercise program increased exercise capacity and fitness for the first six months after transplant followed by a plateau [506], and exercise performance remains lower than in age-matched controls [506,507]. Only a quarter of patients were found to be physically active after transplant [508].

There are little data regarding nutritional composition and caloric intake after transplantation and up to two-thirds of

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Clinical Practice Guidelines

Table 7. US Food and Drug Administration pregnancy categories for commonly used immunosuppressive drugs in liver transplantation [504].

Drug	Pregnancy category*
Corticosteroids	B
Basiliximab	B
Cyclospoprine	C
Tacrolimus	C
Sirolimus	C
Mycophenolate mofetil	D
Azathioprine	D

*FDA category definition: A = controlled studies show no risk: adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus; B = no evidence of risk in humans: either animal findings show risk (but human findings do not) or, if no adequate human studies have been performed, animal findings are negative; C = risk cannot be ruled out: human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk; D = positive evidence of risk: investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the risk; X = contraindicated in pregnancy: studies in animals or humans or investigational or postmarketing reports have shown fetal risk that outweighs any possible benefit to the patient.

subjects were found to have more than the recommended energy intake [509].

The influence of LT on physical fitness during the first post-operative year was studied in 23 men with a mean age of 45.1 years and 15 women with a mean age of 44.6 years. Preoperative maximal oxygen uptake during graded ergometer bicycling, isokinetic knee extension/flexion moments, and functional performance was measured. Preoperative fitness and strength was 40 to 50% less than expected in the age-matched general population. All post-LT patients underwent a supervised exercise program for 8 to 24 weeks. Follow-up data showed a significant increase in all tested physical performance parameters after LT. Six months post-transplant, patients' maximal oxygen uptake had increased by 43%; knee strength 60 to 100%; and functional performance 22 to 27%. One year post-surgery, general health was improved and perceived as excellent or good in all patients. All patients were independent in activities of daily living, and the level of physical activity increased after LT. No further improvement in either physical performance parameters or self-assessed parameters was seen beyond 6 months after transplantation. In conclusion, these findings indicate that LT combined with a supervised post-transplant exercise program improves physical fitness, muscle strength, and functional performance [506]. There are no data regarding the impact of an exercise program on the prevalence of the metabolic syndrome or singular components after transplant [510], but no specific recommendations regarding the prevention or treatment of NAFLD or NASH in liver transplant recipients can be made other than general recommendations to avoid excessive gain in body weight and control hypertension and diabetes [437]. A single randomized trial evaluated the effects of exercise and dietary counselling after LT, it reported an improvement in cardiorespiratory fitness in the intervention group, but no changes were noted in body composition or muscle strength [507]. Exercise training is effective in improving the cardiovascular risk profiles of non-transplanted patients, but the health benefits and potential harms of routine exercise training after solid organ transplantation are unclear. A systematic review of all RCTs comparing the outcomes of exercise training programs in solid organ recipients against standard care was published. In total, 15 eligible RCTs involving 643 patients were included. Among non-heart transplant recipients, no significant improvements in exercise capacity or cardiovascular risk factors such as incidence of new onset diabetes after transplantation were observed, but all effect estimates were very imprecise. Therefore the authors concluded that exercise training is a promising but unproven intervention for improving the cardiovascular outcomes of solid organ transplant recipients. Existing trials are small, of relatively short duration, and focus on surrogate outcomes therefore large-scale RCTs are required [511].

In another study, the authors reported that those that were physically active had less hypertension and decreased BMI [508]. Obesity is common after LT. A study performed on 597 patients reported that the median weight gain at 1 and 3 years was 5.1 and 9.5 kg above dry weight pre-transplant. By 1 and 3 years, 24% and 31% had become obese (defined as a BMI >30 kg/m^2). There was no significant difference in weight gain between the sexes, those who were obese before transplantation or those who received corticosteroids for >3 months. Weight gain was significantly greater in patients aged >50 years and those transplanted for chronic liver disease compared with fulminant liver failure. A pre-transplant BMI >30 was a strong indicator that the patient would still have a BMI >30 at 3 years. There was no effect of the type of immunosuppression on weight gain, therefore confirming that it seems to be unrelated to any specific immunosuppressive drug. The greatest weight gain occurs after the first 6 months and intervention with dietary advice at this point could be implemented to minimize the long-term morbidity and mortality risks associated with obesity [512].

Recommendation:

- Physical activity in liver transplant recipients should be proposed as part of their therapeutic regimens (**Grade III**)

Conflict of interest

Patrizia Burra: has received clinical study support, and sponsored lectures as well as being advisor Astellas, Novartis, Kedrion, Grifols, Biotest, Gilead, Alfe-Wassermann; Andrew Burroughs was a consultant for Norgine. Xavier Forns has received grants and research support from Roche, MSD and Jansen, he has also been a consultant for MSD, Gilead and Jansen as well as completing sponsorsed lectures for Jansen. Paolo Muiesan is a consultant for Novartis. Didier Samuel has received grants or research support from Astellas, Novartis, Roche and LFB, as well as being a consultant or advisor for Astellas, Novartis, Gilead, LFB, Biotest, Roche, BMS and MSD.

Jacques Pirenne, Ivo Graziadei and Juan Carlos Valdecasas have no conflict of interest to declare.

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Clinical Practice Guidelines

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