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EASL Clinical Practice Guidelines on liver transplantation☆

European Association for the Study of the Liver*

Summary:

Liver transplantation (LT) is an established life-saving procedure. The field of LT has changed in the past 10 years from several perspectives, with the expansion of indications, transplantation of patients with acute-on-chronic liver failure, evolution of transplant oncology, the use of donations after cardiac death, new surgical techniques, and prioritisation of recipients on the waiting list. In addition, the advent of organ perfusion machines, the recognition of new forms of rejection, and the attention paid to the transition from paediatric to adult patients, have all improved the management of LT recipients. The purpose of the EASL guidelines presented here is not to cover all aspects of LT but to focus on developments since the previous EASL guidelines published in 2016.

Introduction

Liver transplant(ation) (LT) represents a life-saving procedure indicated for patients with end-stage liver disease, fulminant hepatitis or liver cancer. However, it remains an evolving field as basic science, clinical and translational research lead to new discoveries with consequences for the management of different aspects of LT.

In recent years indications for LT have expanded thanks to improvements in the management of patients with liver tumours[1] and severely ill patients with acute-on-chronic liver failure.[2] Furthermore, patients with acute severe alcohol-related hepatitis[3] or with neuropsychiatric manifestations of Wilson's disease[4] are now evaluated in LT programmes. The upper median age limit of LT recipients has generally been relaxed and knowledge of the impact of frailty on post-LT outcomes has improved. Together, this has pushed evaluation and counselling of LT candidates for rehabilitation and nutritional support to a higher level.[5] Also, particular attention is now paid to the cardiovascular risk and the importance of a comprehensive cardiac risk assessment prior to LT.[6] On the other hand, there remains a need to expand the donor pool, *e.g.* by increasing the use of donation after cardiac death donors[7] and living-related donors.[8] Thanks to successful treatment of hepatitis C, HCV-infected donor grafts can now be safely transplanted even into HCV-negative recipients.[9] Donor organ quality can be tested and preservation times lengthened by the utilisation of machine perfusion techniques, which are now widely used on a larger scale.[10–12] New prediction models to improve equal access to LT, in particular for female candidates, have been proposed.[13,14] Concerning post-transplant care, the recognition of antibody-mediated rejection and the impact of immunosuppression on long-term outcomes led to a re-think of immunosuppressive strategies.[15,16] Changes have also been proposed for handling autoimmune liver diseases which can recur post-transplant.[17–19] Increasingly more attention is focused on the successful transition of paediatric patients to adult services; something which requires close collaboration between both teams.[20] Other aspects such as quality of life, controlling metabolic complications, sexual function and safe pregnancy of LT recipients have become relevant outcome measures. Despite the great improvements made in the LT field, several questions remain.

The European Association for the Study of the Liver (EASL) Governing Board commissioned and charged international experts with drafting dedicated guidelines. The aim of the present effort was to complement the previous EASL clinical practical guidelines (CPGs) on LT, published in 2016, by considering developments that have had a meaningful impact on the management of LT recipients in recent years.

Methods

EASL nominated a chair and seven members of the guideline expert panel respecting gender balance, geographic representation and competence.

The Delphi panel was then constituted, consisting of 40 physicians with gender balance, broad geographical representation and competence and including patient representatives. The development of the CPG followed the EASL standard

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Clinical Practice Guideline Panel: Chair: Didier Samuel; Secretary to the Chair: Eleonora De Martin; EASL Governing Board Representative: Thomas Berg; Panel members, Marina Berenguer, Patrizia Burra, Constantino Fondevila, Julie K. Heimbach, Georges-Philippe Pageaux, Alberto Sanchez-Fueyo, Christian Toso.

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operating procedure. Objectives were defined, target users and key issues were identified. The expert panellists were involved in identifying critical clinical Key Questions (KQs), according to the PICO format (Population/problem, Intervention, Comparison, and Outcome). For the evaluation of evidence, a systematic literature review was carried out using PubMed, Scopus, Embase and/or Cochrane libraries. The level of evidence (LoE) and recommendations were developed and graded (according to Oxford Centre for Evidence-based Medicine - OCEBM) by a single member of the expert panel and then revised and voted on by all panellists (Tables 1 and 2). When an agreement >75% was reached among the expert panel, LoE and recommendations were submitted for voting to the Delphi group where the classification of consensus strength was as follows: strong consensus if >95% agreement, consensus if >75-95% agreement, majority agreement if >50-75% agreement, no consensus if <50% agreement. (see Appendix #1 for Delphi round agreement on the statements and recommendations). The technical solution has been supported by the Clinical Guideline Service group (https://www.guidelineservices.com), which has provided an online platform, where all CPG documents have been uploaded and reviewed.

Objectives: these guidelines are formulated with the objective to guide physicians towards an evidence-based approach to the management of LT candidates and recipients. Clinical recommendations, concerning donors, recipients both pre- and post-transplant, and surgical techniques are formulated in a pragmatic manner that considers the clinical outcomes with the greatest impact as well as patient needs.

Target users: the target users of these guidelines are specialised physicians and other healthcare providers involved in the care of LT recipients.

Liver transplant candidates and transplant indications

Should there be an upper age limit for LT recipients regardless of comorbidities?

Recommendations

- A potential candidate for LT should not be disqualified based on age alone **(LoE 2, strong recommendation, consensus).**
- The assessment of candidacy for LT in the elderly population should include cardiopulmonary, frailty-sarcopenia and nutritional status, anatomical and surgical factors, as well as age- and risk factor-based screening for asymptomatic malignancies **(LoE 3, strong recommendation, strong consensus).**

In both prior EASL and the American Association for the Study of Liver Diseases (AASLD) guidelines, chronological age was not considered a limitation for LT.[21,22] Instead, both societies emphasised the importance of considering biological age and the need to screen for comorbidities.

Since these two guidelines were published in 2013 and 2016, an increasing number of elderly people are being considered for LT in parallel with the aging population worldwide and the increase in certain transplant indications that particularly pertain to elderly individuals, such as liver cancer and metabolic dysfunction-associated steatohepatitis (MASH). For example in the US, the proportion of waitlisted patients over the age of 65 or 70 years rose from 8% and 1.4% in 2002 to 17% and 3.1%, respectively, in 2014.[23] The same trend is present in the European Liver Transplant Registry (ELTR); between 2000 and 2015, the proportion of recipients aged >65 or >70 years increased from 5% to 13% and from 0.3% to 1.3%, respectively (http://www.eltr.org) (Fig. 1).

Importantly the definition of elderly has also shifted with time. As the evidence suggesting favourable graft and patient survival in elderly LT recipients accumulated[24–30] so did the age "limit" assessed in studies such that more recent studies have focused on septuagenarians. In a recent systematic review and meta-analysis the authors compared those aged greater than 65 to those younger. Twenty-two studies were included involving a total of 242,487 patients (elderly: 23,660 and young: 218,827). The elderly group had comparable patient mortality (hazard ratio [HR] 1.26; 95% CI 0.97–1.63; $p = 0.09$; $I^2 = 48\%$) and graft loss (HR: 1.09; 95% CI: 0.81–1.47; $p = 0.59$; $I^2 = 12\%$) rates in comparison to those in the young group.[31] There are fewer studies focusing on septuagenarian registrants but both single-centre studies[24,32] as well as registry analyses[23,33–35] have been performed. Overall, these studies have reported an absence of impact of age on early outcomes, possibly related to stringent selection of elderly candidates, yet lower long-term survival rates. Importantly, elderly candidates have been shown to derive the same transplant-related survival benefit for equivalent model for end-stage liver disease (MELD) scores and regardless of the presence of hepatocellular carcinoma (HCC) as younger candidates. The post-LT outcome is logically inferior in the long-term in the elderly population, however, their risk of deteriorating and dying on the waiting list is higher.[23] Both elderly and younger recipients have a 20%-30% loss of potential life span beyond the first year after LT.[36,37]

One relevant consideration is the proper and careful selection of the elderly population. In all published studies, elderly candidates met a high threshold for listing. Indeed, in addition to cardiopulmonary reserve, the evaluation of candidacy for LT in these patients should take into account sarcopenia, high-risk anatomical and surgical factors, as well as frailty and nutritional aspects. In patients over 75 years old, cognitive impairment might occur early after LT, thus limiting the overall transplant benefit. Unfortunately, there is no consensus regarding the optimal patient selection process in this population and the cost-effectiveness of transplanting older as opposed to younger patients has not been addressed. Additional metrics, such as quality of life, have also not been sufficiently analysed.

Does sex have an impact on access to LT among waitlisted patients? Should we have a sex-adjusted MELD allocation system?

Recommendation

- New allocation systems should be implemented to address the compromised access of women to LT **(LoE 3, strong recommendation, consensus).**

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

Despite efforts to allocate deceased donor livers using objective metrics, female LT candidates experience higher rates of waiting list mortality and are less likely to receive LT than male candidates.[38–43] Data accrued for the most part in US databases show that women have 17-30% less likelihood of undergoing LT compared to men and, in contrast, a 30% greater likelihood of dying while on the waiting list.[38,41,44] Reasons are likely multifactorial, including underestimation of renal dysfunction in women when serum creatinine levels are used in allocation models, such as the MELD and MELD-Na scores.[39,45–48] In addition, decreased access to size-appropriate livers[49–52] and worse frailty scores than men, despite similar MELD-Na scores, may play a role.[53] Furthermore, women are less likely to receive exception points due to the lower prevalence of liver cancer as an indication for LT.[54,55] Yet, neither of these hypotheses is fully explanatory. In a study assessing monthly transplant rates, women had a 25% lower probability of receiving an organ than men. After controlling for MELD score, liver volume and weight, women still had a 13% lower chance of transplant. At least half of the sex disparity remained unexplained.[50]

Alternative models have been proposed to reduce these disparities, including replacement of serum creatinine with estimated glomerular filtration rate (eGFR)[46] or granting additional MELD points to women.[39]

Models suggest that an adapted MELD score can help mitigate sex disparity in LT rates and mortality rates. By using a simulated liver allocation model to estimate the impact of implementing a corrected MELD-Na score that the authors refer to as the MELD-Na-Shift, the researchers found that use of MELD-Na-Shift eliminated sex disparity in transplant and mortality rates.[56] In this study, the authors compare four scores to determine waiting list priority – MELD-Na, the previously proposed MELD-Na-MDRD and MELD-Na-GRAIL, and a new MELD-Na-Shift – and consider their effect on waiting list outcomes and transplant rates. While corrections to replace serum creatinine with eGFR (by MDRD or GRAIL) did not optimally improve sex disparity, the new score, MELD-Na-Shift, which the investigative team had developed by adding points for women to approximate the MELD where they would be at similar mortality risk compared with men, equalized both the 90-day without-transplant survival and the simulated transplant rates between men and women. The main problem with this solution is the model itself. MELD-Na-Shift is "reverse-engineered", adding 1 point for women with certain MELD-Na scores (16, 18–26, 28–31, 33, 35, 37, 38), and 0 points for the remainder – a relatively simple modification similar to the "exception granted point system" for diseases such as liver cancer in which mortality risk is not adequately grasped by the MELD system. This type of extra-point system requires continuous assessment and recalibration based on changes in

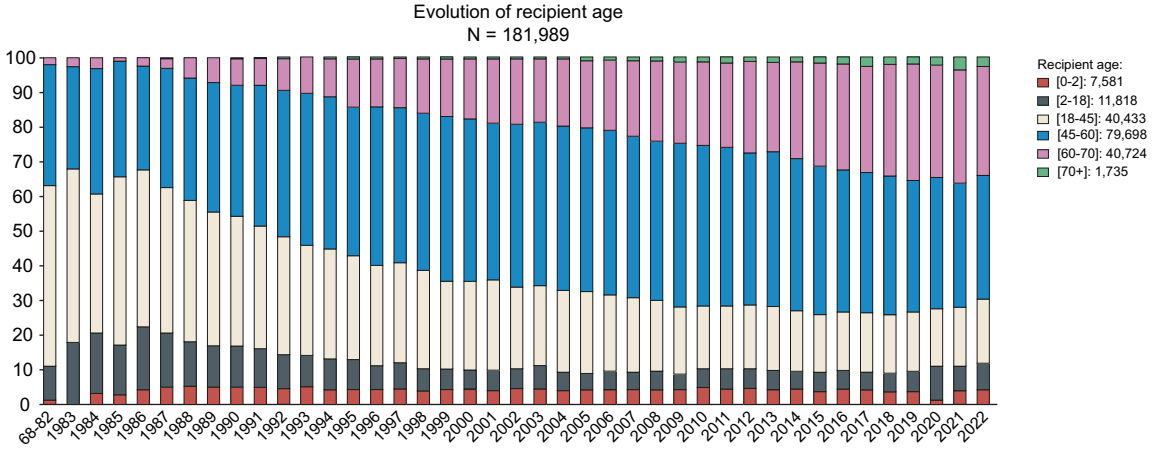

Fig. 1. Evolution of liver transplant recipient age in the past three decades. *Data from the ELTR Registry*. www.eltr.org. ELTR, European Liver Transplant Registry.

waitlisted patient phenotypes. In turn, frequent adjustments of MELD score calculations for women on the waiting list could lead to a sense of uncertainty, lack of transparency, and distrust in the system.

Another alternative is the new MELD 3.0 score, based on refit MELD coefficients to more accurately weigh creatinine in its prediction of 90-day mortality and incorporation of sex (and albumin) in the model. In a recent re-analysis of the US national registry (Jan 2016 to Dec 2018), the final multivariable model was characterised by (1) additional variables of female sex and serum albumin, (2) interactions between bilirubin and sodium and between albumin and creatinine, and (3) an upper bound for creatinine at 3.0 mg/dl. The final model (MELD 3.0), had better discrimination than MELD-Na (concordance statistic 0.869 *vs.* 0.862, p <0.01), and correctly reclassified a net of 8.8% of patients to a higher MELD tier, affording them a meaningfully higher chance of transplant, particularly in women. Overall, MELD 3.0 credits an extra 1.3 points to women. Furthermore, the liver simulated allocation model, which was used to estimate the impact of replacing MELD-Na with the new model, showed that MELD 3.0 resulted in fewer waiting list deaths compared to MELD-Na (7,788 *vs.* 7,850, p = 0.02).[13]

The GEMA (gender-equity model for liver allocation) was recently developed in the UK and externally validated in Australia showing improved discrimination compared to MELD-Na and MELD 3.0 and eliminating gender disparities for accessing LT. The GEMA models were derived by replacing creatinine with the RFH-GFR (Royal Free Hospital GFR) within the MELD and MELD-Na formulas, with re-fitting and re-weighing of each component.[14] Data from countries where both deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) are widely available suggest that women can overcome the complex problem of allocation inequity with access to liver grafts from living donors.[57]

Other models have shown a better mortality prediction compared to the MELD, however these models did not address the gender disparity issue.[58,59]

Should patients with ACLF grade 3 be considered for LT?

Recommendations

- Patients with ACLF grade 3 (and CLIF-C ACLF score ≤64) should be evaluated for LT **(LoE 3, strong recommendation, strong consensus).**
- Patients with ACLF and more than three organ failures according to the CLIF-C organ failure score or CLIF-C ACLF score >64 should be re-evaluated daily and only listed for LT when organ failures and/or ACLF grade improves to ≤3 (or CLIF-C ACLF score ≤64). In cases of acute respiratory distress syndrome and/or high lactate levels, the indication for transplantation should be a cautious decision as this is associated with increased postoperative mortality **(LoE 3, strong recommendation, consensus).**

In the absence of LT, patients with ACLF-3 have 28-day mortality between 68% and 89% compared to 18%-25% for those with ACLF-1[60,61]. One-year survival after LT is significantly higher compared to non-transplanted patients (83.9% *vs.* 7.9%, p <0.0001). Moreover, in selected patients with ACLF-3, the survival rate after LT is comparable to that of patients with ACLF-1 (82.3%), ACLF-2 (86.2%) or no ACLF (90%).[2,62] Five-year survival rate is lower in ACLF-3 compared to ACLF-0-2, but still excellent (67.7%) and above the 50% threshold used to define the utility of liver grafts.[63]

Data from the United Network for Organ Sharing (UNOS) database identified mechanical ventilation and donor risk index above 1.7 as factors independently associated with 1-year mortality whilst LT within 30 days after listing was associated with good survival.[64] In the ELITA/EF-CLIF collaborative study factors independently associated with post-LT mortality included lactate levels >4 mmol/L, need for renal replacement therapy (RRT) at LT, and infections with multidrug-resistant organisms while on the waiting list.[65] An ACLF-3 model was proposed to identify the optimal transplantation window for patients with ACLF-3, it is based on four pre-transplant risk factors associated with 1-year mortality after LT: age ≥53 years; arterial lactate level ≥4 mmol/L, mechanical ventilation with PsO_2/FiO_2 ≤200 mmHg and pre-LT leukocyte count ≤10 G/L.[66] The cut-off of lactate level beyond which LT should not be performed is controversial and is identified as high as 9 mmol/L according to an expert opinion panel.[67] Established (or refractory) respiratory and/or circulatory failure are considered contraindications to LT. The transplantability of these critically ill patients should be reassessed on a daily basis as the situation can change very quickly. Improvement from ACLF-3 at listing to ACLF 0-2 at transplant enhances post-LT survival.[68]

Frail LT recipients had a higher risk of post-LT death but with acceptable post-LT survival.[69] Furthermore, the presence of sarcopenia in ACLF-3 LT recipients was associated with the lowest survival rate at 1-year post-LT, however this rate was >75%.[70] Therefore, sarcopenia and frailty should be assessed during the evaluation process but cannot be considered as an absolute contraindication to LT. Considering hospitalisation in the intensive care unit, not all the available tests can be applied to these patients. Sarcopenia can be evaluated through radiological parameters (using transversal right psoas muscle thickness at the umbilical level/height in mm/m and psoas muscle index in cm^2/m^2 at the L3-L4 level).

Median time from listing to transplant ranges from 4 to 8 days, indicating that the decision process and candidate's evaluation must be rapid.[64,71]

MELD-Na underestimates the risk of 90-day mortality of patients with ACLF.[72] In the US, 14-day mortality has been reported to be higher in patients with ACLF-3 than in those listed as status 1a, suggesting that these patients may need specific scoring systems, and consideration for transplant priority.[73] Moreover, there is inequity of access to LT, for example in Europe, with significant disparities in results as the 1-year survival for all patients with ACLF-3 admitted to the intensive care unit (including patients not listed, listed and transplanted) was significantly higher in centres that listed and transplanted more patients with ACLF-3 (>10 patients) than in centres that listed and transplanted fewer: 36% *vs.* 20%, respectively (p = 0.012).[74] A specific model to prioritise these patients on the waiting list is needed, which would balance access to LT, survival benefit and available resources.[75,76]

LDLT can be offered to these patients with similar results to deceased donor recipients. However, in an Indian multicentre

study only 35% of patients with ACLF-3 finally underwent LT.[77] The 3-year and 5-year survival rates after LDLT were 95.5% and 92.9% and 94.2% and 91.1% in ACLF and non-ACLF groups, respectively. Moreover, patients with ACLF-3 who underwent LDLT achieve similar long-term survival as ACLF-1 and ACLF-2 recipients. Again only 17.9% of patients with ACLF had ACLF-3.[78] Offering LT to patients with >3 organ failures remains controversial, even if good results have been reported, with a 1-year post-LT survival rate of 81% for recipients with 5-6 organ failures.[71] It seems that the type of organ failure and the dynamics of the clinical course (uncontrolled infection, increase in vasopressors, respiratory failure) rather than the number of organ failures has a greater impact on survival[67,76] (Fig. 2).

ACLF 3 should not be a contraindication to LT as transplant-free survival is poor and early and long-term post-LT survival is good.[79]

Optimal management, optimal timing for transplantation, and the rapid decision to transplant and thereby reduce waiting time are key for good outcomes.

Which patients with acute severe alcohol-related hepatitis without a 6-month sobriety period can be considered for LT?

Recommendation

- Selected patients with severe acute alcohol-related hepatitis not responding to medical treatment should be considered for early LT if they present with favourable predictors for post-LT sobriety **(LoE 3, strong recommendation, consensus).**

Acute alcohol-related hepatitis was traditionally a contraindication to LT. The 6-month rule of abstinence is not applicable to this special population due to the high rate of short-term mortality which could reach about 70%-80%.[80] Several papers have demonstrated that early LT improves both short and long-term survival of patients with severe alcohol-related hepatitis.[81,82] In the first French paper, survival rate was 89% *vs.* 11% in matched cohorts of transplanted and non-transplanted patients.[81] US experience showed 1- and 3-year post-transplant survival rates of 94% and 84%, respectively.[82] It should be noted that there are substantial differences between American and European experiences. In the former, a histological confirmation of the disease was not required, leading to the absence of alcohol-related hepatitis in 59% of the explants. The prognosis after LT depends on the severity of the alcohol consumption relapse, with any alcohol consumption reported in between 25% and 35% of patients at 2 years[3] and sustained relapse in 10% at 1 year and 20% at 3 years.[82] The amount of alcohol relapse is highly variable among series. Although alcohol relapse does not seem to impact post-LT survival, heavy alcohol consumption is associated with increased mortality.[83]

More recently, it has been demonstrated that sustained alcohol resumption significantly reduces the benefit of early transplantation with a predicted survival of 3.6 years compared to 10.8 years for patients without alcohol use.[84]

Therefore, selection criteria seem to be key in the decision-making process.[85] Patients with severe AH not responding to medical therapy (corticosteroids) can be identified through the application of several scores such as the Lille model[86] and the combination of the Lille model and the MELD score.[87] Not being aware of the severity of liver disease, first hospitalisation/decompensation of alcohol-related liver disease, the absence of psychiatric comorbidities, and a family support network are some of the required criteria in order to put patients on the waiting list. Psycho-social assessment is a key part of the evaluation process. Several scoring systems have been proposed to help in the prediction of alcohol relapse, though none have shown sufficient performance to be used alone for patient selection[88] (Table 3).

A multidisciplinary approach including a senior hepatologist, a specialist in addiction, a specialist nurse, an anaesthetist, a surgeon and a social worker improves outcomes.

However, in a prospective controlled study, the 2-year rate of high alcohol intake was greater in the early transplantation group than the standard transplantation group, despite similar survival rates in patients offered an early transplant without 6 months of abstinence compared to patients transplanted after 6 months of abstinence.[3] These findings confirm the benefit of early transplant in patients with severe alcohol-related hepatitis and suggest the need to improve post-transplant addiction management in these patients.

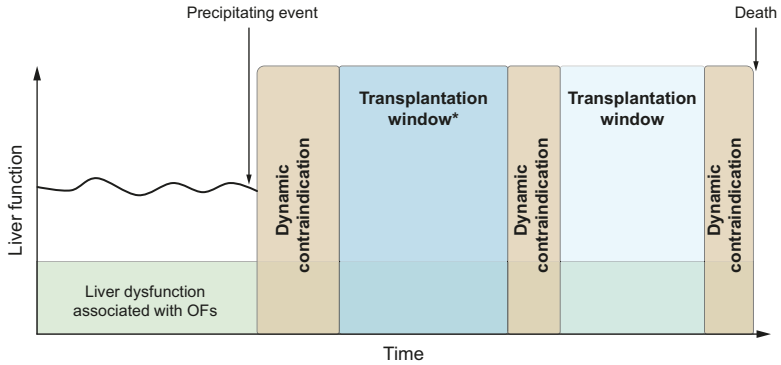

Fig. 2. Illustration of the concept of "transplantation window" and its relation to "dynamic" contraindication in ACLF. *The first transplantation window is bluer than the second suggesting a more favorable timeframe for liver transplantation. *Adapted from Artru & Samuel, JHEP Reports 2019.*[76] ACLF, acute-on-chronic liver failure; OF, organ failure.

Table 3. Scoring systems for the prediction of alcohol relapse after liver transplantation (see Shenoy *et al.*[88])

Scoring system name	Conceptualisation and intended utility	Risk factors assessed	Proposed interpretation of score
Michigan alcoholism prognosis score (MAPS)	Developed at the University of Michigan to prognosticate relapse in addicted patients undergoing LT. Risk factors were derived from the addiction literature. No threshold for selection was intended	Insight (acceptance of alcoholism) • Patient and family • Patient only • Family only • Neither Prognostic indices • Substitute activities, yes/no • Behavioural consequences, yes/no • Hope/self-esteem, yes/no • Rehabilitation relationship, yes/no Social stability • Steady job • Stable residence • Does not live alone • Stable marriage	Total score range: 5–20 Higher score indicates reduced risk for relapse
High-risk alcoholism relapse scale (HRAR)	Three variables derived from a large data set of Veterans Affairs patients in the Midwest. Intended to predict relapse and time to relapse for patients suffering from alcoholism	Duration of heavy drinking (years) <11, 11–25, >25 No. of drinks per day <9, 9–17, >17 No. of prior inpatient visits for alcohol use disorder 0, 1, >1	Total score range: 0–6 <4: low risk ≥4: high risk
Alcohol use disorders identification test-consumption (AUDIT-C)	Three item screening tool which was validated against the longer 12 item scale to identify patients who are at risk for hazardous drinking or have active alcohol use disorders	How often did you have a drink containing alcohol in the past year? Never, less than monthly, 2–4 times/month, 2–3 times/week, > 4 times/week How many drinks did you have on a typical day when you were drinking in the past year? None, 1 or 2, 3 or 4, 5 or 6, 7 to 9, 10 or more How often did you have six or more drinks on one occasion in the past year? Never, less than monthly, monthly, weekly, daily or almost daily	Total score range: 0–12 0–3: low risk 4–5: moderate risk: 6–7: high risk 8–12: severe risk
Alcohol relapse risk assessment (ARRA)	Derived from 25 known risk factors for alcohol relapse in a cohort of patients with alcohol dependence who underwent LT at Beth Israel Deaconess	1. Absence of hepatocellular carcinoma 2. Tobacco dependence 3. Alcohol use after liver disease diagnosis 4. Low motivation for treatment 5. Poor stress management skills 6. No rehabilitation relationship 7. Limited social support 8. Lack of nonmedical consequences 9. Social activities with alcohol present	Total score range: 0–9 0: minimal risk 1–3: mild risk 4–6: moderate risk 7–9: severe risk
Sustained alcohol use post-liver transplant (SALT)	Derived from multicentre data of alcohol relapse in patients with AH	1. >10 drinks/day at presentation 2. ≥2 prior failed rehabilitation attempts 3. History of prior alcohol-related legal issues 4. History of non-cannabis illicit substance abuse	Total score range: 0–11 <5: low risk ≥5: high risk

AH, alcohol-associated hepatitis; LT, liver transplant(ation).

Ethical considerations and stigmatisation towards patients with alcohol-related liver disease may still cause considerable heterogeneity in allocation policies among LT centres.[89]

Definitive selection criteria are still under debate and prone to change over time, however, evidence-based medicine should direct the decision-making process to improve outcomes after transplantation, and avoid stigmatisation, stereotypes or prejudice against self-inflicted illness.

How should patients with acute severe autoimmune hepatitis with liver dysfunction be managed?

Recommendations

- Patients with acute severe autoimmune hepatitis should be considered for early corticosteroid therapy before hepatic encephalopathy onset **(LoE 3, strong recommendation, strong consensus).**
- Patients with acute severe autoimmune hepatitis with severe coagulopathy and hepatic encephalopathy III-IV should not be treated with corticosteroids but considered for early LT **(LoE 3, strong recommendation, consensus).**
- Patients with severe autoimmune hepatitis not responding to corticosteroids (no improvement or worsening in liver biochemistry and liver synthetic function parameters or development or worsening of hepatic encephalopathy) should be considered for early LT **(LoE 3, strong recommendation, strong consensus).**

Acute severe autoimmune hepatitis (AS-AIH) is a rare presentation of AIH. Patients with AS-AIH have a heterogeneous presentation as they can present with true acute liver failure without an underlying liver disease or ACLF.[90] Currently, the management of AS-AIH, regardless of liver fibrosis severity, consists of early introduction of high-dose corticosteroids (1 mg/kg/day). Treated patients have a better survival rate compared to non-treated patients in both acute liver failure[91] and ACLF groups.[92]

Although treatment may not be effective in all patients or all stages of AS-AIH, it is important to note that introduction of corticosteroids does not generally jeopardise patient survival.[91,93,94] It should, therefore, be considered as early as possible,[95] ideally before the onset of hepatic encephalopathy. However, low-grade hepatic encephalopathy should not be considered a contraindication.[96] A multicentre Spanish study found that a nomogram combining older age, MELD score, encephalopathy, and ascites at initiation of corticosteroids accurately predicts response to therapy.[97] In the most severe subgroup of patients with fulminant hepatitis, a trial with corticosteroids showed no associated benefit.[98]

According to previous EASL guidelines, patients not responding to corticosteroids at day 7 following treatment introduction should be evaluated for LT, while the recent AASLD guidelines[99] recommended to stop therapy at 2 weeks of therapy if there is no biochemical improvement or even deterioration. The definition of non-response to medical therapy is still challenging and the timepoint for treatment withdrawal arbitrary. A recent study found that a MELD score of 20 on day 7 of corticosteroid therapy was associated with non-response to corticosteroids. However, in this study, the definition of AS-AIH was based on an international normalised ratio (INR) >1.3 and not 1.5 as proposed for the definition of acute severe hepatitis.[100] A model based on the INR at onset of therapy and INR and bilirubin improvement at 3 days since its introduction has recently been proposed[101] and validated, although with a different cut-off, in two independent cohorts[102,103]. Consistent with this report, two studies found that the increase of bilirubin and/or INR and not MELD score was predictive of the need for LT after 2 weeks of therapy.[104,105]

Prolonged use of corticosteroids in these patients seems deleterious due to the high risk of infection and may unduly delay the benefit of early transplantation.

Despite steroid therapy, patients with severe AIH have a large heterogeneity in reported outcomes (Table 4). In most studies, steroid therapy was started relatively late, about 1 week after hospital admission. Early initiation, before significant impairment of liver synthesis (increase in INR) occurs, appears to be the most important factor that can improve prognosis in this condition.

In patients with decompensated liver disease due to Wilson's disease, are severe neuropsychiatric manifestations a contraindication to proceed with LT? Are isolated severe neuropsychiatric manifestations an indication for LT?

Recommendations

- In patients with Wilson's disease and end-stage liver failure, neuropsychiatric manifestations should not preclude referral, evaluation and waitlisting for LT **(LoE 4, strong recommendation, strong consensus).**
- Patients with Wilson's disease and isolated neuropsychiatric manifestations should ideally be referred for evaluation by a multi-disciplinary team at a LT centre. The decision to proceed with LT screening needs to be taken on a case-by-case basis after careful discussion **(LoE 4, strong recommendation, strong consensus).**

In a single-centre retrospective study, patients transplanted for a hepatic indication of Wilson's disease but suffering neurological manifestations, not including hepatic encephalopathy, showed a significant improvement of neuropsychiatric symptoms, but a shorter survival rate compared to patients with hepatic involvement alone.[106] Complete or partial neurological recovery after LT was also reported by a multicentre study including patients transplanted for a hepatic indication of Wilson's disease, with no difference in survival between patients with or without neurological symptoms.[107] Based on the excellent post-LT patient and graft survival reported for patients with Wilson's disease, careful multidisciplinary evaluation for transplantation is warranted for this patient group. Of note, this patient group may face disadvantaged access to transplantation due to unconscious bias and general healthcare inequalities for patients with disabilities and intellectual impairment.

This observation raises the question of considering isolated neurological symptoms as an indication for LT *per se*.

A pilot study suggested that LT can be a rescue therapy for patients with neurological symptoms of WD, such as dystonia

Table 4. Studies on AS-AIH in adult patients.

Authors	Country	Year	No. of treated patients/overall	Median INR	LT or death
Ichai *et al.*[98]	France	2007	12/16 (75%)	6.85	11/12 (92%)
Yeoman *et al.*[91]	UK	2014	23/32 (75%)	2.3	10/23 (43%)
Moenne-Locoz *et al.*[93]	Belgium	2016	15/17 (88%)	2.3	9/15 (60%)
Fujiwara *et al.*[104]	Japan	2016	20/20 (100%)	PT 29%	12/20 (60%)
Anastasiou *et al.*[94]	Germany	2018	32/32 (100%)	1.7	3/32 (9.4%)
Zachou *et al.*[95]	Greece	2019	34/34 (100%)	1.52	1/34 (2.9%)
De Martin *et al.*[101]	France	2021	101/128 (79%)	2.0	39/101 (39%)
Noguchi *et al.*[100]	Japan	2021	27/27 (100%)	-	9/27 (33%)
Lin *et al.*[102]	UK	2021	19/19 (100%)	1.9	7/19 (37%)
Tellez *et al.*[97]	Spain	2022	203/242 (84%)	2.0	62/203 (30%)
Joao *et al.*[103]	Portugal	2022	26/26 (100%)	1.5	7/26 (27%)

AS-AIH was considered when INR ≥1.5.
AS-AIH, acute severe autoimmune hepatitis; INR, international normalised ratio; LT, liver transplant(ation); PT, prothrombin time.

and parkinsonism, resistant to anti-copper therapy.[108] This was confirmed by a multicentre French study, which showed, despite the small sample size (n = 18 patients), a neurological improvement after LT (major in 8, moderate in 4 and stable status in 2 patients).[4] Substantial improvement after LT, however, could not be proven for all patients transplanted for isolated neurological symptoms in all known series.[109] The outcome of LT in patients with Wilson's disease and neurological symptoms is highly variable even in case of identical genetic background.[110]

As patients with neurological disorders may present with normal liver tests, and compensated cirrhosis detected by abdominal ultrasound,[111] referral of patients with Wilson's disease complicated by isolated neurological symptoms to a LT centre is recommended.

These patients should be evaluated by transplant specialists in conjunction with neurologists. The decision to proceed with the transplant should take into account the possible irreversibility of neurological damage and must therefore be carefully discussed within a multidisciplinary team.

Selection of liver transplant candidates

What criteria should be used to select patients with a history of recent extrahepatic malignancy in remission for LT that cannot be delayed due to poor liver function?

Recommendations

- Patients with a history of a recently treated non-hepatic cancer, who have undergone a curative therapy and are tumour-free/in remission, should undergo a multidisciplinary assessment for suitability and timing of LT that includes detailed cancer- and treatment-specific information, including "recurrence-free survival" estimates, and therapeutic options for potential post-LT cancer recurrence **(LoE 3, strong recommendation, strong consensus).**
- Patients with active malignancy should be excluded from the LT waiting list except those with selected indolent or very low-grade cancers **(LoE 3, strong recommendation, strong consensus).**

The risk of recurrence from previously curatively treated non-hepatic cancers after LT depends on the nature of prior malignancy and duration of cancer remission. The added survival benefit of LT must be balanced against the risk of cancer recurrence (during the evaluation process). Data that need to be assessed in each candidate are the type of cancer, histological analysis of specimen, exact TNM stage, time of diagnosis, complete treatment history including all modalities administered, response to treatment, and date of completed treatment/remission. Based on the predicted recurrence risk from the non-transplanted population, a projected cancer-specific long-term survival probability in the setting of LT has to be established. Unfortunately, data on specific tumours treated at different stages and with different therapies prior to solid organ transplantation are limited, and the effect of chronic immunosuppression on the risk of cancer recurrence is still unclear.[112–118] Based on these cancer-free recurrence rates, a minimal waiting time from complete cancer response/remission to listing for transplantation is required and variable between tumour type, except for very low-grade cancers, such as superficial non-melanoma skin cancer, incidental renal tumours with diameter <1 cm, *in situ* breast cancer, superficial bladder cancer, or prostate cancer with Gleason score <6, for which there is no need to ask for a certain time on remission because the risk of recurrence is negligible.[114,116,119,120] In a recent modelling study based on data from 13 cancer registries, patients with curatively treated non-liver cancer who underwent solid organ transplantation exhibited high cure probabilities, reflecting selection on the basis of existing guidelines and clinical judgment. Nonetheless, there was a range of cure probabilities among transplanted patients, and organ transplant recipients with low predicted cure probabilities exhibited increased cancer-specific mortality after transplantation. Compared with the tertile of transplanted patients with the highest cure probability, those in the lowest tertile more frequently had lung or breast cancers and less frequently colorectal, testicular, or thyroid cancers.[120]

Of note, because of the immune-modulatory effect of immune checkpoint inhibitors, associated in several series to severe rejection episodes[121–124] and their variable half-life, a minimum washout period is recommended between discontinuation of these anti-cancer therapies and LT[121,125,126] and

while 4 to 6 weeks is suggested, the optimal duration is still unknown.

How should coronary artery disease be evaluated and what are the contraindications to LT?

Recommendations

- Coronary imaging, invasive or non-invasive, should be considered as the initial strategy in LT candidates who are at high risk of significant coronary artery disease **(LoE 3, strong recommendation, strong consensus).**
- In LT candidates, unrevascularisable significant coronary artery disease (defined by ≥50% stenosis in ≥1 segment of the three major coronary arteries, or ≥70% stenosis in moderate-size branch vessels) should be considered a contraindication to LT **(LoE 3, strong recommendation, strong consensus).**

Cardiovascular disease is the leading cause of early death (40% of deaths in the first month) and the third leading cause of death after 1 year in LT recipients. If we consider all cardiac events, *i.e.* myocardial infarction, need for coronary revascularisation, heart failure, clinically significant arrhythmia, cardiac arrest or death related to cardiovascular pathology, 8 to 25% and 15 to 30% of patients will have an event in the first month and in the first year, respectively.[127] Heart failure and cardiac dysrhythmia account for 70% of cardiac events within 90 days post-transplant, while coronary artery disease (CAD) predominates beyond the first year.

These data underscore the need for a comprehensive cardiac risk assessment prior to LT (Fig. 3). Any patient who is a candidate for LT must have a minimal cardiological evaluation consisting of electrocardiogram and transthoracic echocardiogram. These examinations will identify pathologies that may represent a contraindication to LT: recurrent and/or unstable ventricular arrhythmias, cardiomyopathy and heart failure which affects one-third of LT candidates with decompensated cirrhosis, left ventricular ejection fraction <40%, and uncontrolled severe valvular heart disease.[128]

The crucial point concerns patients at high risk of cardiovascular events related to CAD. It is estimated that 25% of LT candidates have moderate CAD, even if they are asymptomatic. The following risk factors identify patients with high risks for CAD: age ≥60 years, male gender, BMI ≥30, diabetes, dyslipidemia, smoking, hypertension, history of CAD, family history of CAD, left ventricular hypertrophy, renal disease, and transplant indication for MASH. The literature is very heterogeneous regarding the use of these predictive factors to predict significant CAD: 2 factors + MASH, ≥3 factors, construction of a risk score combining all or some of these factors (CAD-LT score).[129]

These risk factors will guide the diagnostic strategy for identifying CAD. There is a significant variation in practice between transplant centres, and no recommendation can be provided to define a threshold for further cardiac screening. Consensus was identified to perform additional tests in patients at high risk of CAD to identify patients at increased risk who would benefit from cardiac interventions to improve their risk, or patients with unacceptable risk who should not undergo transplantation.

Given the low sensitivity of non-invasive tests in this setting, *i.e.* stress echocardiography and functional cardiovascular testing, coronary angiography (invasive or non-invasive) can be offered as a first-line procedure. Invasive coronary imaging (ICA) has several advantages: precise mapping of lesions (major vessel or moderate-sized vessel, multivessel or unique), characterisation of significant CAD defined by ≥50% stenosis in ≥1 segment of the three major coronary arteries, or ≥70% stenosis in moderate-size branch vessels, categorisation of significant stenosis as moderate (50-69%) or severe (≥70%),

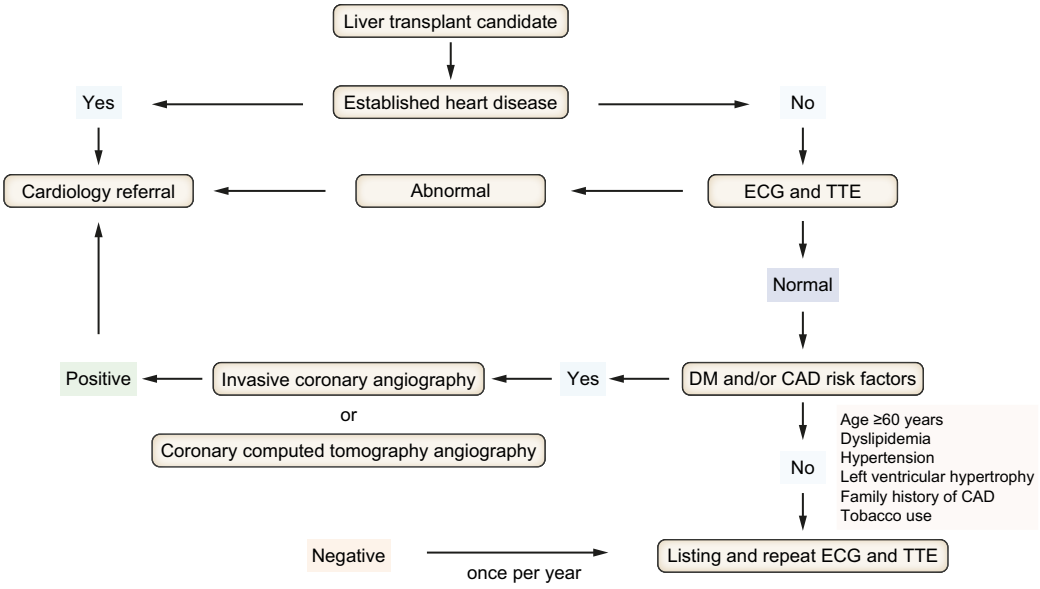

Fig. 3. Algorithm for the cardiovascular assessment pre-transplant. CAD, coronary artery disease; DM, diabetes mellitus; ECG, electrocardiogram; TTE, transthoracic echocardiography.

low rate of side effects especially if the radial approach is used, and the possibility of simultaneous revascularisation by stent placement. This last point is important because it has been shown that aggressive CAD screening with ICA is associated with a low rate of myocardial infarction and cardiac mortality after LT.[6] Coronary computed tomography angiography (CCTA) could be an alternative to ICA, and has been recommended as the initial testing strategy in LT candidates who are at risk of significant CAD.[130,131] In the general population, CCTA has an excellent negative predictive value (95%–100%) for excluding clinically significant CAD.[130] In addition, it must be noted that with the advent of fractional flow reserve assessment on CCTA images, CCTA is as capable of precise mapping of the lesions, as well as characterisation of anatomic stenosis and its exact impact on flow limitation. However, these two techniques have never been compared in this specific population. Both procedures are associated with nephrotoxicity, but the risk may be lower with CCTA.[131] In case of significant lesions, ICA will be necessary to allow for revascularisation of the stenotic arteries. The management of CAD in LT candidates must be individualised according to CAD severity and degree of liver failure. Revascularisation with drug-eluting stents may be performed with a short course (3–6 months) of dual antiplatelet therapy, with the recognition that this approach is associated with substantial mortality in candidates with advanced decompensated cirrhosis. It has been shown that the severity or extent of CAD does not impact post-LT survival, if appropriately revascularised.[132] On the contrary, failure of revascularisation in patients with significant CAD should be considered a contraindication to LT, given the high risk of perioperative mortality and poor midterm outcomes from progressive coronary heart disease.[133]

How should patients with obesity in need of LT be managed?

Recommendations

- In patients with obesity with compensated cirrhosis and a BMI >35 without clinically significant portal hypertension, bariatric surgery may be considered in centres with experience in both LT and bariatric surgery **(LoE 4, weak recommendation, consensus).**
- In patients with obesity with decompensated cirrhosis and a BMI >35, bariatric surgery should be considered only at the time of LT or thereafter **(LoE 3, strong recommendation, consensus).**
- Sleeve gastrectomy should be proposed as the technique of choice in selected patients with obesity with well-compensated cirrhosis, or in the setting of LT **(LoE 3, strong recommendation, strong consensus).**

As obesity rates and the incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) increase worldwide, obesity is no longer seen as a contraindication to LT. More patients with obesity become candidates for LT. In 2025, the estimated global prevalence of adults living with obesity will be 16% (World Obesity Atlas 2022). In addition, MASLD has become the second leading indication for listing and the third leading indication for LT in the USA. Most transplant teams consider that a BMI >40 is a relative or absolute contraindication to LT. The results of LT depend on the presence of numerous co-morbidities encountered in patients with obesity: diabetes, metabolic syndrome, sleep apnea syndrome, cardiovascular complications. Some of these are amplified by the immunosuppressive treatment administered after the transplant. This results in a higher rate of surgical and cardiovascular complications. In terms of survival, the results in the literature are sometimes contradictory, but it seems that graft and patient survival are not significantly affected when patients with obesity are compared with non-obese patients. The management of obesity is therefore crucial, and the question arises as soon as LT is considered. Prehabilitation is becoming a standard asset of the LT screening procedure. Dietary and exercise interventions are offered as an initial approach to pre-habilitation in LT centres, with some encouraging results. In the Mayo Clinic study of LT candidates who were morbidly obese, among 74 patients with a pre-transplant BMI ≥35, 45 were able to lose weight significantly (BMI <35) and receive a transplant.[134] New anti-obesity medications are now recommended in several clinical guidelines. In a phase II trial involving patients with MASH, treatment with semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, resulted in a significant and sustained dose-dependent reduction in body weight.[135] In a phase III, double-blind, randomised-controlled trial (RCT) involving patients with BMI >30, tirzepatide, an agonist of both GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 receptors, provided a substantial and sustained reduction in body weight.[136] There are no data in the field of LT. It must be emphasised that GLP-1 receptor agonists are contraindicated in patients with Child-Pugh C cirrhosis, and should be used with caution in Child-Pugh B cirrhosis.

If non-invasive and pharmacological interventions fail, the other option is bariatric surgery. It must be part of an interdisciplinary approach, including behavourial intervention. The optimal times for surgery and best methods remain unclear.[84,137–139] Bariatric surgery can be performed before, during or after LT.

To date, there are 10 published studies (285 patients) describing results of bariatric surgery prior to LT. These studies include both patients with a history of bariatric surgery who become candidates for transplantation, and patients for whom bariatric surgery is scheduled during the pre-transplantation workup or waiting time with the intention to improve post-transplant outcomes. The early postoperative period was marked by zero mortality within 30 days after bariatric surgery, and the rare occurrence of major complications (gastric staple line leak and bleeding). The average excess body weight loss at 1 year after bariatric surgery was -30% and was maintained at 1-year post-transplant. Liver disease severity was infrequently reported in these studies. In a small case series, the median MELD score at the time of bariatric surgery was 9, which is below the threshold (MELD 15) of waitlisting for LT. In other studies on bariatric surgery, outside the field of LT, mortality risk after bariatric surgery was considered low in patients with cirrhosis with MELD scores below 8-9.

An alternative option is to combine bariatric surgery at the time of the LT procedure. Six studies have been published, including two by the same team.[134,140] The Mayo Clinic study with results at 3 years after LT combined with bariatric surgery shows maintenance of weight loss, decreases in

metabolic and cardiovascular risk factors and identical survival compared to patients with morbid obesity who had isolated LT.

The third option proposes surgery in the medium to long-term after LT. It has been reported in 16 publications (75 patients). Apart from two retrospective studies,[141,142] these are case reports only. No deaths, graft loss or episodes of rejection were observed. In patients with diabetes, insulin requirements were reduced by 60%.

There are no studies comparing the different bariatric surgery techniques. Sleeve gastrectomy was the most performed bariatric surgery (84%) followed by a Roux-en-Y bypass. The advantages of sleeve gastrectomy would be to maintain access to the biliary tree via endoscopy (endoscopic retrograde cholangiopancreatography), to accommodate future options for Roux-Y hepaticojejunostomy, and to avoid malabsorption induced by the bypass in patients with cirrhosis and during essential phases of pre- and post-habilitation for LT. With the sleeve procedure, great attention must be paid to the risk of gastric fistula which can become deleterious in a context of immunodepression.

Non-surgical endoscopic procedures for weight loss are still under study and refinement. Endoscopic sleeve gastroplasty seems beneficial to patients with BMI <40.[143] There are no data in the field of LT.

In summary, the level of evidence is very low, according to the paucity of available data, and the quality of studies, mostly small retrospective studies or small case series. Whatever the timing, it seems that the procedure is safe and effective in terms of weight loss. The optimal timing remains an open question and further well-designed prospective studies are needed.

Porto-pulmonary hypertension: Should the mean pulmonary arterial pressure threshold be revised based on response to treatment?

Recommendations

- In patients with compensated liver disease, portopulmonary hypertension alone is not an indication for LT **(LoE 2, strong recommendation, strong consensus).**
- Vasomodulator therapy should be offered to all LT candidates with porto-pulmonary hypertension and mean pulmonary arterial pressure ≥35 mmHg and pulmonary vascular resistance ≥3 Wood units **(LoE 2, strong recommendation, strong consensus).**
- A mean pulmonary arterial pressure >45 mmHg despite vasomodulator treatment should be considered as an absolute contraindication to LT **(LoE 2, strong recommendation, strong consensus).**
- In patients with porto-pulmonary hypertension in need of LT, an adequate haemodynamic response to vasomodulator therapy is required to proceed to transplant and should be defined as mean pulmonary arterial pressure <35 mmHg and portal vascular resistance <5 Wood units or mean pulmonary arterial pressure of 35 to 45 mmHg and portal vascular resistance <3 Wood units **(LoE 2, strong recommendation, consensus).**

During the pre-transplant assessment, the cardiopulmonary evaluation not only enables the assessment of perioperative risk but also the identification of possible contraindications to the transplant. Portopulmonary hypertension (PoPH) is identified in about 5% of LT candidates.[144] The probability of PoPH can be assessed by transthoracic echocardiography which is part of the screening of all candidates. In the presence of an increase in systolic pulmonary artery pressure (≥38 mmgHg on echocardiography,[145] and/or dilatation of the right heart cavities, the diagnosis could subsequently be confirmed by right heart catheterisation. Diagnosis includes mean pulmonary arterial pressure (mPAP) >25 mmHg and pulmonary vascular resistance (PVR) ≥3 Woods units and a pulmonary capillary wedge pressure ≤15 mmHg.[146] It is clearly recognised that PoPH is associated with a perioperative risk of cardiac decompensation and death. A mPAP >45 mmHg and/or right ventricular dysfunction is considered an absolute contraindication to LT. A mPAP between 35 and 45 mmHg increases the risk of mortality.[147]

Unlike hepatopulmonary syndrome, PoPH is not an indication in itself for LT. It is the severity of the underlying liver disease that guides the timing and indication for LT. The diagnosis of PoPH in a LT candidate raises several questions. How to improve PoPH in order to make a safe and successful transplantation possible? Will LT enable resolution of PoPH? What prognostic factors influence patient and graft survival and thus enable selection of patients for LT?

Vasomodulatory treatments are used to improve pulmonary haemodynamics. Three classes of drugs are used in monotherapy or double/triple combination therapy: endothelin-receptor antagonist (oral), phosphodiesterase type-5 inhibitor (oral), prostacycline analogue (parenteral). In a candidate for LT with PoPH treated with vasomodulatory treatments, an adequate haemodynamic response to treatment is defined as mPAP <35 mmHg and PVR <5 WU, or mPAP of 35 to 45 mmHg and PVR <3 WU.[148]

In a systematic review with meta-analysis of observational, case-control and randomised studies, the results of different strategies (no treatment, vasomodulatory treatment alone, LT alone, vasomodulatory treatment + LT) have been analysed[149] across 26 studies with 1,019 patients. Considering a significant improvement of pulmonary haemodynamics as measured by right heart catheterisation and functional status as measured by a 6-minute walking distance, 44% of patients treated with vasomodulatory agents became eligible for LT. Most of these patients had Child-Pugh B or C cirrhosis. Post-diagnosis survival was 82% at 1 year and 67% at 3 years. After this meta-analysis, data from 637 patients included in the French Pulmonary Hypertension Registry have been published.[150] 90% of them received vasomodulatory treatments. The survival of patients who underwent LT was better than that of patients who had an indication for transplantation but did not undergo LT and those with no indication for transplantation: 92%, 83%, 81% at 1, 3 and 5 years from PoPH diagnosis, *vs.* 65%, 39%, 20% and 85%, 70%, 50%, respectively. Prognostic factors were strongly related to the severity of liver disease. The most recent study has reported on the potential predictors of post-LT patient and graft survival.[151] The study design was to compare 269 patients with PoPH who underwent LT with MELD exception points with 62,873 LT patients without any MELD exception. Although the MELD score is good at predicting

mortality in most patients, it is recognised that this score is imperfect and some conditions, such as PoPH, require assigned MELD exception points to account for this. Overall survival was similar between the two groups, but graft failure risk was increased in the group of patients with PoPH. Pre-LT mPAP and PVR were significantly associated with post-LT outcome. The cut-offs associated with best survival were pre-LT mPAP ≤25 mmHg and PVR <1.6 WU.

When should patients with cirrhosis be evaluated for combined liver and kidney transplantation?

Recommendations

- In the situation of cirrhosis with chronic kidney disease, combined liver-kidney transplantation is recommended in patients who are on dialysis for end-stage renal disease or have a most recent eGFR/creatinine clearance value of ≤30 ml/min. **(LoE 2, strong recommendation, strong consensus).**
- In the situation of cirrhosis with chronic kidney disease for which reversibility is uncertain, both simultaneous or sequential liver-kidney transplantation is recommended **(LoE 2, strong recommendation, consensus).**
- In the situation of cirrhosis associated with sustained acute kidney injury, simultaneous liver-kidney transplantation is recommended in patients with GFR ≤25 ml/min and/or on haemodialysis for at least the last 6 weeks **(LoE 2, strong recommendation, strong consensus).**
- In patients with compensated cirrhosis who are candidates for kidney transplantation, KT alone can only be proposed in the absence of clinically significant portal hypertension. The diagnosis of clinically significant portal hypertension in this situation warrants specific studies **(LoE 5, open recommendation, consensus).**

Chronic kidney disease in patients with cirrhosis

According to the KDIGO guidelines, chronic kidney disease (CKD) is defined as kidney structure alterations (urinary and electrolyte abnormalities, histological and ultrasound signs of renal damage) or function (GFR <60 ml/min/1.73 m^2) for at least 3 months. CKD is classified based on GFR category, with severe CKD defined as GFR <30 ml/minute. In patients with chronic liver disease, the prevalence of any renal dysfunction in a broad sense varies from 30% to 90%,[152] while the reported prevalence of CKD is between 22% and 32%.[153] The burden of CKD is rising among patients with cirrhosis and candidates for LT: in a study from the UNOS/OPTN (Organ Procurement & Transplantation Network) registry including 78,640 patients, the prevalence increased from 12.1% in 2002-2005 to 17.2% in 2014-2017.[154] In the same study, among 39,719 LT recipients, CKD at the time of transplant was reported in 15.7% of patients. Acute kidney injury (AKI), which is a driver of the transition to CKD, occurred in 20-30% of hospitalised patients with cirrhosis.[152] CKD has an impact on pre- and post-LT survival. In a cohort of 78,640 patients listed for LT, CKD at transplant was associated with a 16% higher risk of mortality after LT (HR 1.16; 95% CI 1.10-1.22).[154] In patients with cirrhosis and severe CKD, combined LKT is associated with improved graft and patient survival compared to LT[155,156] alone. The eligibility criteria are based on the presence of CKD or sustained AKI. In the situation of CKD, LKT is indicated in patients with GFR ≤30 ml/min (estimated with the MDRD-6 equation) or those requiring haemodialysis or peritoneal dialysis. It must be noted that two studies showed that a significant proportion of patients with GFR ≤30 ml/min just before transplant can have significant partial or full recovery of kidney function after LT[157,158]. This point argues for a possible delayed KT after LT. In the situation of sustained AKI (6 consecutive weeks), LKT is indicated in patients on RRT or with GFR ≤25 ml/min for ≥6 weeks.[159,160]

In recent years, the precise timing of LKT has become an important topic for discussion with the choice of simultaneous LKT (SLKT) or delayed KT after LT (KALT) in those recipients not recovering renal function being considered. Small single-centre studies have suggested an increased risk of futility and graft loss in SLKT. Patients with severe cirrhosis according to MELD score that underwent SLKT had a 20% risk of early loss of the transplanted kidney graft.[161] Two recent studies from the UNOS database provide important results on early KALT (60 to 365 days between the two procedures) strategy. The first study[162] had patient and kidney graft survival as endpoints, comparing LT alone (11,501 patients), SLKT (6,774 patients), KALT 60-365 days (120 patients), KALT 1-2 years (145 patients), and KALT >2 years (852 patients). Mortality was decreased by 18% in patients who underwent SLKT compared to patients with renal failure undergoing LT alone. Early KALT was associated with similar survival rates as SLKT. There were no significant differences between overall kidney graft survival rates between SLKT and any of the KALT groups. The second study[163] had 90-day and 1-year kidney graft failure as endpoints, comparing SLKT in patients with MELD <25 (1,579 patients), SLKT in patients with MELD 25-34 (1,832 patients), SLKT in patients with MELD ≥35 (1,384 patients), and KALT any time after LT (1,481 patients). Compared to KALT recipients, SLKT recipients with MELD ≥25 had significantly higher risk of early kidney graft failure, suggesting that delaying the KT procedure should be preferred in patients with severe cirrhosis. Although most transplant physicians agree to the fact that irreversible renal failure in a LT candidate justifies performing SLK at the time of LT, it is important to note that recovery of AKI or CKD after LT is possible but difficult to predict.

In patients undergoing LT, two received any duration of pre-transplant RRT, one-third were liberated from RRT at 1 month and 50% were at 1 year. Longer duration of pre-transplant RRT, post-reperfusion syndrome (defined as a decrease in mean arterial pressure greater than 30% below the baseline value, lasting for at least 1 min, occurring during the first 5 min after reperfusion of the liver graft), and older age were risk factors for persistent dialysis. Patients who required pretransplant RRT had worse graft and patient survival compared to matched patients who did not require RRT, however, those who were liberated from RRT post-LT had similar outcomes to patients who never required pre-LT RRT.[164] On the other hand, in a more recent paper, patients on short-term dialysis pre-LT alone (≤12 weeks) were more likely to develop severe renal dysfunction (31.7% *vs.* 18.1%), especially in patients with MASLD, and were more likely to receive a further KT (15.3% *vs.* 3.7%) and

experience lower survival (48.6% *vs.* 50.4%) after LT alone (p <0.001 for all).[165]

Indication for KT in patients with underlying compensated advanced chronic liver disease

In contrast to the discussion above, information in this patient group is very limited and often restricted to the prevalence of viral hepatitis in patients undergoing haemodialysis: HCV infection has been reported in 1.4% to 28.3% of patients in developed countries.[152] There is limited evidence on the prevalence of MASLD or alcohol-associated liver disease in patients with CKD. Regardless of the aetiology, a prevalence of cirrhosis of 3-5% has been reported in patients on haemodialysis. In a French regional database of 7,658 patients treated with chronic haemodialysis, the prevalence of cirrhosis was 4%.[166] Cirrhosis was compensated in 57% of patients. Two-year survival was different in patients without cirrhosis, with compensated cirrhosis and with decompensated cirrhosis, 71.7%, 62.8%, 44.1%, respectively. These data emphasise the poor prognosis of those patients with CKD associated with compensated cirrhosis and raise the question of SLKT in this situation. The 2008-consensus conference, dedicated to patients with CKD and HCV infection, recommended that KT alone could not be proposed for patients with compensated cirrhosis and portal hypertension.[167] The recent report of the Baveno VII Consensus meeting could be very useful to refine our strategies.[168] Using non-invasive tools, liver stiffness measurement and platelet count, and taking into account the aetiology of liver disease, the report has proposed the term "compensated advanced chronic liver disease" with or without clinically significant portal hypertension. Thus, in patients with a liver stiffness measurement by thromboelastography ≤15 kPa and platelet count ≥150x10^9/L and without radiologic findings of clinically significant portal hypertension (*e.g.*, shunts or collaterals on cross sectional imaging), KT alone could be proposed.

Frailty, sarcopenia, malnutrition: Are there contraindications to LT?

Foreword: We have used the definitions endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN guidelines on definitions and terminology of clinical nutrition).[169]

Malnutrition can be defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.

Sarcopenia is a syndrome of its own characterised by the progressive and generalised loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes.

Frailty is a state of vulnerability and non-resilience with limited reserve capacity in major organ systems. This leads to reduced capability to withstand stress such as trauma or disease and thus frailty is a risk factor for dependence and disability. These definitions must be adapted to the context of patients with cirrhosis who are candidates for LT.[170] Frailty is defined by the clinical manifestations of impaired muscle contractile function and sarcopenia by the loss of muscle mass. Malnutrition is one of the aetiologic factors contributing to frailty and sarcopenia.

Recommendations

- During pre-transplant evaluation, all patients with cirrhosis should be assessed for frailty **(LoE 3, strong recommendation, strong consensus).**
- Frailty *per se* should not be a contraindication to LT **(LoE 3, strong recommendation, strong consensus).**
- Any frail patient should be evaluated for rehabilitation and nutritional support **(LoE 4, strong recommendation, strong consensus).**

The diagnosis of frailty and sarcopenia is part of the initial workup of any patient being assessed for LT. A standardised assessment is needed, using objective, reproducible tools that can be repeated during the waiting period. The diagnosis of frailty and sarcopenia is part of the initial workup of any patient applying for LT. The aim is to stratify the risk of mortality on the waiting list, to determine whether severe forms constitute a contraindication to LT, and to predict, if possible, the evolution and the consequences of these syndromes on post-transplant outcomes.

The diagnosis of sarcopenia and therefore of muscle mass loss is best assessed by the skeletal muscle index which measures the total skeletal muscle area at L3 using CT imaging performed for clinical reasons during the transplantation evaluation work-up. It affects 30% to 70% of patients with end-stage liver disease, and 21% of females and 54% of males awaiting LT.[171] Sarcopenia is a predictor of outcomes, such as mortality, hepatic decompensation, and increased infection risk, in patients with cirrhosis. There are few studies assessing the consequences of pre-transplant sarcopenia and post-transplant outcomes. In the Mayo Clinic study, sarcopenia was present in 50% of patients. It progressed up to 1 year after LT, and was associated with an increase in post-transplant length of stay, but not mortality.[172] These results were complemented by a larger and longer study that showed sarcopenia progresses up to 3 years post-transplant and affects half of males, but does not influence post-transplant outcomes.[173] In the setting of LT, the limitation of sarcopenia-related studies is the acquisition of measures from non-protocol-driven imaging.

The diagnosis of frailty and therefore of impaired muscle contractile function is best assessed by the following metrics: Karnofsky performance scale (useful in patients with decompensated cirrhosis), liver frailty index (LFI), and 6-minute walk test. It affects 68% of hospitalised patients with decompensated cirrhosis when using Karnofsky performance scale <80%, 26% of outpatients listed for transplant when using LFI ≥4.5, 12% of listed outpatients when using 6-minute walk test <250 meters.[174] Karnofsky performance scale, before and after LT, has been identified as an independent predictor of graft and patient survival.[71] The most widely used tool has been the LFI, particularly in order to predict waiting list mortality. LFI cut-offs of 4.4 and 4.2 were predictive of waiting list mortality at 3 months and 6 months, respectively. The addition of LFI to MELD-Na improved the prediction of 3-month mortality.[175] The longitudinal measurement of this index during the waiting period identified a worsening ΔLFI group associated with death/delisting independent of baseline frailty.[5] This point

opens the way to the concept of prehabilitation used in major surgery.[176] Individual components of frailty are potentially modifiable with individualised exercise prescription and nutritional recommendations. In a recent systematic review of prehabilitation analysing 8 out of 563 potentially eligible studies, a significant improvement was observed in aerobic capacity, 6-minute walking distance, and LFI.[177] In one of them including 517 patients, the authors found a significant correlation with an improvement of the LFI and a survival advantage.[176] A few studies have been specifically focused on pre-LT nutritional management.[178] In one prospective randomised study including 82 patients on the waiting list, the supplemented group received a calorie-dense enteral feed taken daily.[179] One limitation of studies using the LFI is the intermediate severity of cirrhosis with a median MELD-Na of 18 (14-22). In the most severe patients, MELD-Na >25, who by definition will have a shorter waiting period, the issue remains how to integrate the diagnosis of frailty into the transplant decision-making process.

How should patients with complete portal vein thrombosis before LT be managed?

Recommendations

- Anticoagulation is recommended in LT candidates with cirrhosis and a newly diagnosed bland portal vein thrombosis **(LoE 3, strong recommendation, strong consensus).**
- A transjugular intrahepatic portosystemic shunt procedure should be considered in selected transplant candidates with portal vein thrombosis **(LoE 3, strong recommendation, weak consensus).**

The introduction of anticoagulation is recommended in patients with cirrhosis and a newly diagnosed fresh-appearing bland portal vein thrombosis, which can be identified as a non-enhancing defect in the portal vein without calcification, narrowing of the vein or cavernous transformation. Anticoagulation leads to portal vein recanalisation in two-thirds of patients.[180] However, in the absence of recanalisation after at least 3 months of anticoagulation or in the presence of a chronic thrombosis, which is more difficult to manage by anticoagulation only, a transjugular intrahepatic portosystemic shunt (TIPS) could be considered as a bridge to transplantation. It leads to a marked improvement or a complete resolution of thrombosis in about 80% of patients, with a 1-year rate of encephalopathy of 16%.[181–183] Such a strategy requires case-by-case multidisciplinary assessment, taking the anatomy of the thrombus (favouring Yerdel 1-3, Charco and Jamieson 1 & 2), liver function, the presence/absence of baseline encephalopathy and local expertise into account, as no prospective controlled studies have been performed to evaluate TIPS implantation in this setting. A correct strictly intrahepatic TIPS position is also mandatory to avoid making transplantation technically more difficult. Alternative strategies for more advanced and chronic thrombosis include the use of a transsplenic approach, alone or combined with TIPS, with patency maintained in 55/60 (92%) patients over a median follow-up of 19.2 months in an experienced centre.[184] Finally, LT may still be discussed in the presence of a persisting diffuse splanchnic vein thrombosis thanks to the anastomosis of the graft portal vein onto the left recipient renal vein (when spontaneous spleno-renal shunts are present), or on the superior mesenteric vein via a jump graft, if permeable[185,186] (Fig. 4). For most teams internationally, diffuse splanchnic thrombosis persisting after anticoagulation and endovascular strategies remains a contraindication to LT.[187]

Liver transplant oncology

How should patients with HCC beyond Milan criteria be managed?

Recommendations

- Selected patients with HCC beyond the Milan criteria (without macrovascular tumour invasion and extrahepatic spread) should be considered for LT if downstaged to within Milan criteria or other criteria (*i.e.* UCSF and AFP score) according to country allocation system criteria **(LoE 2, strong recommendation, strong consensus).**
- Patients with unresectable HCC who present with an AFP level >1,000 ng/ml should not be considered for transplantation (regardless of whether they are within or beyond Milan criteria) except when treated with liver-directed therapy resulting in a significant sustained and persistent decline in AFP levels **(LoE 2, strong recommendation, strong consensus).**

Because it treats HCC as well as underlying cirrhosis, LT is an optimal treatment for early-stage, unresectable HCC and it is associated with a significantly reduced incidence of recurrent cancer compared with alternative treatments. While the Milan criteria have been long established as the standard for patient selection, additional strategies to allow access for patients with larger or more numerous tumours have been proposed. The most well-known of these are the UCSF (University of California, San Francisco) criteria (81% survival at 5 years), up-to-seven criteria (71% survival at 5 years), total tumour volume (75% survival at 4 years), extended Toronto criteria (68% survival at 5 years), Kyoto criteria (65% survival at 5 years), Metroticket 2.0,[188] and the French alpha-fetoprotein (AFP) system.[189–195] Each proposal expands the selection criteria, allowing more patients to be considered for LT, while showing reduced but excellent long-term outcomes after transplantation. While size and number of lesions have remained an essential surrogate for tumour biology since the introduction of the Milan criteria, more recent systems such as the French AFP model, the Kyoto criteria, or the extended Toronto criteria incorporate additional components to estimate tumour biology such as AFP which is the most widely available and is used in the current French allocation model, des-gamma carboxyprothrombin used in the Kyoto criteria, or exclusion of poorly differentiated tumour histology in the Toronto selection criteria. Recommending the AFP be <1,000 ng/ml represents a minimum biologic assessment, recognising that individual allocation systems may adopt more rigorous biologic selection criteria.[196] Recently, a randomised-controlled trial demonstrated that patients beyond Milan criteria who were downstaged with liver-directed therapies and underwent

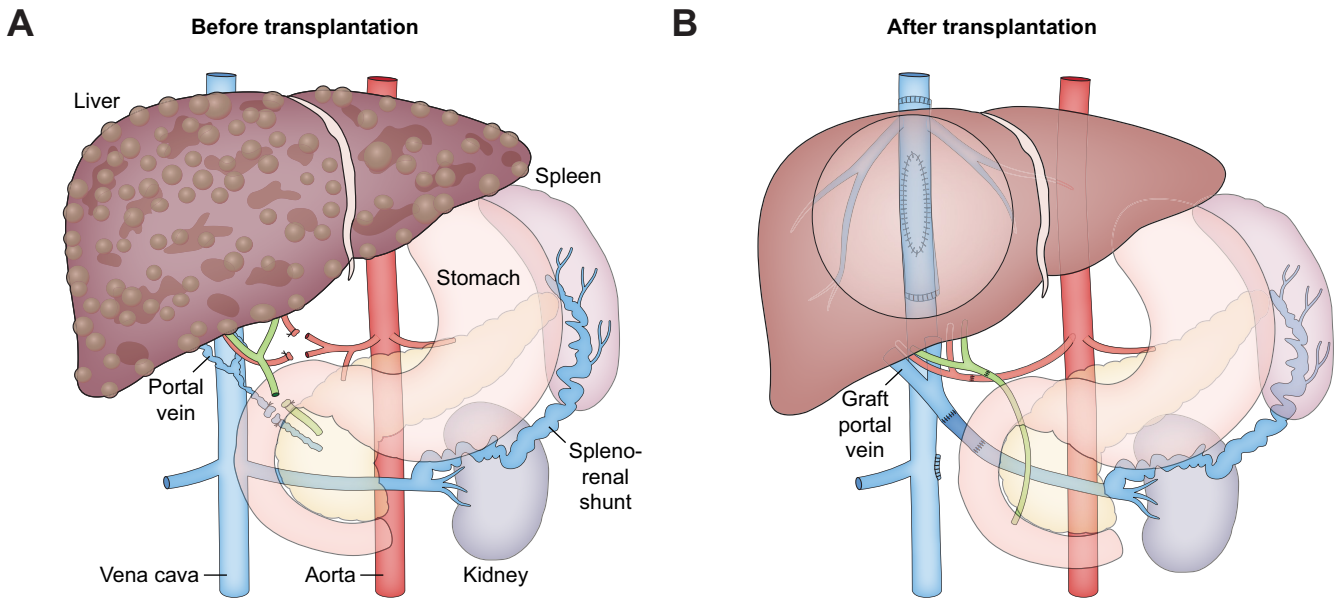

Fig. 4. Reno-portal anastomosis. This reconstruction is physiological because it directs the large spleno-renal shunt into the graft portal vein via the left renal vein (with interposed vein graft). (A) Before transplantation; (B) after transplantation. *Adapted from Bhangui et al., Journal of Hepatology 2019.*[186]

transplant (n = 23) achieved a 5-year tumour event-free survival of 77% compared to 18% in the control group who received continued liver-directed therapy (n = 22) (HR 0.20, 95% CI 0.07–0.57; $p = 0.003$).[1] Overall survival was also superior for the transplanted patients. Due to limitations in available studies on the preferred use of liver-directed therapies for patients awaiting LT, such as including the therapies used for both bridging and downstaging, no specific type of liver-directed therapy can be recommended over another,[197–199] though emerging data shows that radioembolisation may lead to superior tumour control compared to transarterial chemoembolisation.[200]

How should patients with HCC treated with immunotherapy be managed before LT?

Recommendation

- Immunotherapy may be given with caution to patients with HCC who are on the transplant waiting list and whenever feasible, immunotherapy should be stopped to allow for a period of washout prior to transplantation to reduce the risk of refractory rejection, though the optimal interval between completion of therapy and LT is not known and may be impacted by the pharmacokinetics of the immunotherapy agent **(LoE 4, weak recommendation, consensus).**

The recent approval of atezolizumab (an anti-programmed cell death ligand-1 monoclonal antibody) plus bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody), as well as tremelimumab (an anti-cytotoxic T lymphocyte–associated antigen 4 antibody) plus durvalumab (an anti-PD-L1 antibody), as first-line treatment for advanced HCC has led to questions about whether those who are successfully downstaged using immunotherapy may subsequently be considered for LT. If those treated or downstaged with immunotherapy are considered eligible for LT, an additional question is whether there is an optimal interval between treatment and LT to avoid an adverse immunologic outcome. To date, there are several case reports,[121,123,201] as well as two case series describing the use of immunotherapy for downstaging in patients who subsequently received LT,[125,202] which are well-summarised in a review.[126] Duration of treatment, which included multiple different agents ranged from 6 weeks to 2 years, with washout periods ranging from 1 day to 253 days. Two of the case reports, with 8 days and 263 days of washout, detail patients with early graft failure due to suspected refractory rejection, with histology demonstrating massive hepatic necrosis and dense lymphocytic infiltrate, with the remainder having a satisfactory recovery post-LT, including two patients reported to have mild rejection. Long-term oncologic outcomes are not yet available. While most patients were treated with a period of washout that was based on the immune checkpoint inhibitor's half-life, the largest case series from Tabrizian *et al.* included two patients with 1–2-day washout period following the last dose of nivolumab (notably both patients required massive transfusions during transplant which may have accelerated the washout). Recently published reviews identified 42 days[203] and 90 days[204] before the transplant as the safest washout period for rejection-free survival. The 3-months washout was also suggested in a multicentre US study.[205] Thus, the limited available data to date consists of case reports and case series, and prospective data are needed to further illustrate the risks and benefits of immunotherapy for HCC downstaging, as well as the optimal washout period to prevent refractory immunologic graft loss. Given challenges in predicting the timing for DDLT, LDLT may offer an advantage in those patients with HCC who are being treated with immunotherapy.

How should patients with unresectable colorectal liver metastasis be managed?

Recommendation

- Well-selected patients with unresectable liver-only colorectal metastasis may experience improved survival following LT, and thus may be considered for transplantation within the setting of a clinical trial given that results to date are limited by length of follow-up, relatively small numbers of patients, and uncertainty regarding survival outcomes for the comparative group treated with contemporary systemic and surgical therapies. **(LoE 3, weak recommendation, strong consensus).**

Colorectal cancer is one of the most common malignancies worldwide, and nearly 50% of patients with colorectal cancer develop metastatic disease, with the liver being the most common site.[206,207] Though resection of colorectal liver metastases is the standard of care and has an associated survival benefit, many patients present with unresectable disease. In the era of improved systemic therapy and advanced imaging techniques which can provide more accurate staging, the role of LT for highly selected patients with isolated, unresectable colorectal metastases which are responsive to chemotherapy is being reconsidered. The most recent analysis from the Oslo group (SECA II) reports outcomes for 15 patients with liver-only metastasis.[207,208] With a median follow-up of 36 months, overall survival at 1, 3, and 5 years by Kaplan-Meier analysis was 100%, 83%, and 83%, while disease-free survival at 1, 2, and 3 years was 53%, 44%, and 35%, respectively. Those with recurrence following LT typically presented with pulmonary metastases, which were amenable to further resection and, importantly, LT in patients with a Fong clinical risk score of 1-2 resulted in longer disease-free survival than for those with scores of 3-4 (p = 0.044).[208,209] This series with more refined selection criteria, including the role of nodal metastasis and the impact of right sided primary *vs.* left sided primary colon cancer, demonstrates improved outcomes compared to their first series of 21 patients, wherein they reported a 5-year survival rate of 60% with recurrence in 20/21 patients.[210] The benefit of patient selection was also reported in a multicentre series from Toso *et al.*.[211] While the selection criteria for patients who may benefit from LT have now been identified, currently recruiting randomised trials comparing transplantation to chemotherapy (Transmet study, NCT02597348; SECA-III study; NCT03494946; and COLT study, NCT03803436)[212] will be able to provide a contemporary survival analysis and a clearer delineation of the survival benefit of LT for patients with unresectable colorectal liver metastases.[213,214] Standardisation of the definition of resectability remains an area in need of further refinement. A recent multicentre study of LDLT in the setting of colorectal liver metastasis has also demonstrated efficacy and may represent a more realistic option considering the critical shortage of deceased donor liver allografts which are available.[215]

How should patients with unresectable liver metastasis from neuroendocrine tumours be managed?

Recommendation

- Selected patients with unresectable liver-only G1-2 neuroendocrine tumour metastases who have had the primary tumour resected, followed by a period of disease stability, may be considered for LT in centres which are experienced in treating neuroendocrine tumours **(LoE 4, weak recommendation, strong consensus).**

Neuroendocrine tumours (NETs) of the gastroenteropancreatic system are a rare and heterogenous group of malignant tumours, which often present with metastatic disease.[216] Surgical resection of the primary tumour as well as the metastases is the standard of care, though complete resection is feasible only in a minority of patients. Overall survival at 5 years ranges from 40% to 90%, and the use of strict selection criteria (such as <50% of the liver replaced by tumour, stable disease >6 months following resection of primary tumour, low KI-67 index) are associated with the most favourable outcomes. However, it is important to recognise that due to variability in the natural history of the disease, the optimal role of LT for this population remains unknown due to uncertainty in defining the survival outcomes for this selected population without transplantation.[217–221] Recurrence is common following LT, though patients still have prolonged survival.[222] Under current guidelines, selected patients with G1-2 gastroenteropancreatic NETs and non-resectable metastases confined to the liver (KI-67/MIB ≤10%) with portal venous drainage and stable disease for >6 months after resection of the primary tumour may be evaluated for LT.

How should patients with unresectable intrahepatic cholangiocarcinoma be managed?

Recommendation

- Patients with cirrhosis and small, unresectable intrahepatic cholangiocarcinoma (<2-3 cm) may be considered for LT, ideally within the setting of a clinical trial (given that the evidence to date is limited) and ideally treated on the waiting list with liver-directed therapies such as ablation, transarterial radioembolisation or transarterial chemoembolisation, depending on anticipated waiting time **(LoE 4, weak recommendation, consensus).**

Intrahepatic cholangiocarcinoma (iCCA) arises from intrahepatic bile ducts beyond the second-order biliary division and comprises up to 20% of all CCA cases. The standard treatment for iCCA is resection with a regional lymphadenectomy, though many patients present with unresectable or metastatic disease, and thus overall survival remains poor (<10%). The low resectability and high recurrence rates, combined with success of LT for other oncologic indications have renewed interest in consideration of LT for selected patients with iCCA. Following

up on success with an initial multicentre retrospective series from Spain for LT in patients with cirrhosis incidentally found to have a small iCCA <2 cm, Sapisochin *et al.* analysed outcomes for a larger multicentre international cohort. The 1-, 3-, and 5-year survival rates were 93%, 84%, and 65% in the very early iCCA group (<2 cm).[223,224] A recent multicentre report from France reported on outcomes for patients with iCCA <5 cm who underwent LT (n = 49) or liver resection (LR) (n = 26), and found that LT was associated with a higher 5-year recurrence-free survival rate than LR (75% *vs.* 36%; p = 0.004).[225] Several others have reported on LT in the setting of iCCA with mixed results and a recent meta-analysis identified 18 studies comprising 355 patients together with a registry-based study of 385 patients and found pooled 1-, 3-, and 5-year overall survival rates of 75% (95% CI 64–84), 56% (95% CI 46-67), and 42% (95% CI 29–55).[226–228] Importantly, the retrospective data gathered to date generally represent patients transplanted for what was thought to be HCC or in whom iCCA was an incidental finding in the explant. iCCA has thus far not been a standard accepted indication for LT. LT for large, locally advanced, unresectable iCCA is generally contra-indicated, given high recurrence due to lymph node metastasis and low survival rates, though whether the addition of neo-adjuvant chemoradiotherapy and careful patient selection may result in acceptable outcomes has been an area of renewed interest following the report of a prospective series of six patients with locally advanced iCCA treated with neoadjuvant chemoradiotherapy and subsequent LT. Patients were selected based on at least 6 months of disease stability following neo-adjuvant therapy, and survival was 100% (95% CI 100–100) at 1 year and 83.3% (27.3–97.5) at 3 years, though 3 of 6 patients developed recurrence at a median of 7 months post-LT.[229] This same group recently reported an updated series of 18 patients undergoing neoadjuvant therapy followed by LT for locally advanced iCCA and demonstrated overall survival rates at 1-, 3-, and 5-years of 100%, 71%, and 57%, with 7 out of 18 (39%) developing recurrence.[230] Nearly all patients received gemcitabine-based systemic therapy pre-operatively, though those that had started alternative therapies were continued on them. Adjuvant therapy was used in the majority. Though this data is preliminary, larger multicentre analyses are anticipated.

Are patients with early-stage unresectable perihilar CCA treated with neoadjuvant chemoradiotherapy suitable candidates for LT?

Recommendation

- Highly selected patients with unresectable early-stage perihilar cholangiocarcinoma may be considered for treatment with neoadjuvant chemoradiotherapy followed by LT **(LoE 3, weak recommendation, consensus).**

While LT alone for perihilar CCA is associated with a high risk of recurrence, neoadjuvant chemoradiotherapy followed by LT for selected patients with early-stage, unresectable perihilar CCA is associated with 5-year survival rates of 60-70%. Based on a multicentre study from 12 US transplant centres including 214 patients which reported a 5-year disease-free survival rate of 65%, this treatment strategy has been adopted as a standard indication for LT in the US.[231,232] Patients with early-stage unresectable perihilar CCA (mass <3 cm in radial diameter and no metastasis) who are treated with an approved neoadjuvant chemoradiotherapy protocol are eligible for a MELD score exception similar to patients with HCC. The most recent single-centre series from the Mayo Clinic summarised outcomes for 211 patients who underwent LT and demonstrated a 5-year survival rate of 69%, and a 10-year survival rate of 62%.[233] A recent single-centre analysis from Dublin also demonstrated the potential benefit of LT, with a 5-year overall survival rate of 55% in a series which did include four peri-operative deaths, demonstrating the potential for a learning curve,[234] a concept which was also supported by a recent analysis of OPTN data which also showed superior survival and lower recurrence rates in centres with more experience.[235] Specific technical factors that may improve outcomes include avoidance of transperitoneal biopsy of the primary tumour, use of endoscopic ultrasound with biopsy of regional lymph nodes regardless of nodal appearance prior to enrolllment,[236] formal operative staging including routine biopsy of perihilar nodes prior to proceeding to LT, limiting hilar dissection during transplant, and careful assessment for radiation injury to vessels with consideration of arterial aortic jump graft to replace the native hepatic artery.[237–239]

Liver donors

What is the approach to the transplantation of hepatitis virus-positive organs into uninfected recipients and to the transplantation of organs from SARS-CoV-2-positive donors?

Liver donors with active HCV infection

Recommendation

- The use of HCV RNA-positive grafts in HCV-positive or HCV-negative recipients should be considered provided informed consent, appropriate organ quality and a rapid initiation of effective antiviral therapy are guaranteed **(LoE 3, strong recommendation, consensus).**

The advent of highly effective and well-tolerated oral antiviral drugs has led to expansion in the use of organs from HCV-infected donors in uninfected candidates. Results from case series, multicentre collaborations and transplant registries in liver, kidney, heart and lung transplantation have confirmed excellent results defined by high rates of sustained viral response following post-transplant therapy, unimpaired graft and patient survival, increased access to transplantation and shorter waiting times,[240–253] such that this strategy has evolved from experimental to "standard of care" at many centres.[254] In addition to informed consent at the time of listing for LT, there are two prerequisites that need to be considered including universal and timely access to oral antivirals,[255] as well as confirmed graft quality, particularly in LT.[250] In fact, in countries where grafts are mostly recovered from infected young donors in the setting of opioid epidemics, the quality of the grafts is typically good and the number of discarded grafts has significantly decreased over time.[254] In contrast, in countries where organs are mostly recovered from anti-HCV-positive older

donors not actively infected, who have resolved the infection through antiviral treatment, the quality of the organs is generally suboptimal (fibrosis ≥2) due to the long-standing duration of infection.[256] Overall, the utilisation of HCV-positive donors is a feasible strategy to expand the donor pool and reduce waiting list times with excellent post-transplant outcomes (Table 5). Ongoing work is needed to clarify the best therapeutic option (short *vs*. standard courses) and longer-term outcomes with the use of this strategy.

Liver donors with active HBV infection

Recommendations

- Anti-HBc-positive HBsAg-negative organs should be used for transplantation independently of the HBV status of the recipient provided the recipient is adequately vaccinated and/or there is an option of indefinite prophylaxis with a nucleos(t)ide analogue **(LoE 3, strong recommendation, strong consensus).**
- In HBV-uninfected patients with short life expectancy on the waiting list, the use of HBsAg-positive grafts can be considered if there is an option for indefinite treatment with potent nucleos(t)ide analogues (antivirals), HDV is absent in the donor and the recipient, graft quality is adequate, and the recipient provides informed consent **(LoE 4, weak recommendation, consensus).**

The use of donors who test positive for HBV is an attractive strategy to maximise the use of such grafts as approximately one-third of the global population has serological evidence of past or current HBV infection, including 350–400 million people chronically infected with HBV.

In isolated anti-HBc-positive individuals, HBV reactivation can occur in the setting of immunosuppression. Several single-centre and collaborative studies, as well as systematic reviews, have demonstrated the high risk of reactivation, close to 50%, in naïve transplant candidates undergoing LT with organs from anti-HBc-positive donors in the absence of prophylaxis.[257–263] The risk is significantly lower in recipients with markers of prior HBV contact, with *de novo* HBV infection reported in 14-15%, 10-18% and 4% of anti-HBc-positive alone, anti-HBs-positive alone, or anti-HBc/anti-HBs-positive recipients, respectively.[257,259] Using prophylaxis with nucleos(t)ide analogues, the risk is significantly decreased. In treatment-naïve recipients, prophylaxis reduces the risk from 48% to rates closer to 5-10% using first generation drugs (*i.e*. lamivudine) and close to 2-3% using third generation antivirals (*i.e.* entecavir and tenofovir);[260,264–266] rates that do not change with the addition of hepatitis B immunoglobulins.[257,260] In anti-HBc-positive candidates, prophylaxis reduces the risk of *de novo* HBV infection from 15% to 3-4%, while the gain in anti-HBs-positive candidates or in those who are anti-HBc/anti-HBs-positive seems minimal. In a systematic review with meta-analysis, the pooled risk of HBV transmission in anti-HBs-positive patients (vaccinated or resolved) receiving grafts from anti-HBc-positive donors was similar whether or not they were on prophylactic antiviral treatment post-transplantation.[261] In fact, in one case-control study, active immunisation was found to be effective in preventing *de novo* post-LDLT HBV infection if the post-transplant anti-HBs level was maintained above 100 IU/L with vaccination. Antiviral prophylaxis was safely discontinued in patients who obtained this immunity.[267]

While most of the data published to date is based on lamivudine, the selection of the specific nucleoside analogue should be based on cost and availability.[268] The long-term efficacy of this strategy is dependent on availability of nucleos(t)ide analogues and treatment adherence.

The use of HBsAg-positive grafts in either HBV-infected or uninfected recipients is significantly less common. Yet, data from small single-centre reports and LT registries[269–274] show that the use of HBsAg-positive grafts is safe and comparable in outcome, even in terms of long-term survival, to the use of HBsAg-negative grafts.[272] Altogether the studies demonstrate that it is a feasible option to increase the donor pool provided certain measures are considered, including indefinite prophylaxis with potent oral antivirals (*i.e.* entecavir or tenofovir), lack of HDV infection in both donor or recipient and donor and pathology ± donor imaging excluding fibrosis (fibrosis ≤1), significant inflammation, or any morphological sign that might increase risk in the recipient. As with anti-HBc-positive donors, the addition of hepatitis B immunoglobulin prophylaxis does not result in improved outcomes when used in naïve recipients. In addition, despite the lack of signs of HBV-related disease and viral replication, the large majority of patients continue to be HBsAg positive, and thus the risk of HCC development in the long-term cannot be ruled out.

In general, the use of these organs in the literature was done following a priority of allocation: first to HBsAg-positive recipients, then anti-HBc-positive individuals, and last recipients without serological evidence of HBV infection for whom the severity of the liver disease indicated a short life expectancy on the LT waiting list. Interestingly, one Italian case report suggests that the best candidates to receive HBV-infected organs are those with previously controlled HBV infection (anti-HBc-positive or both anti-HBc- and anti-HBs positive) because they are capable of mounting an effective viral control when faced with a new HBV infection leading to spontaneous anti-HBs production and HBsAg loss.[275]

Table 5. Donor-recipient matching according to HCV status.

		Recipient	
		Anti-HCV-	**Anti-HCV+**
Donor (F ≤2)	**Anti-HCV+ HCV RNA-**	Accept	Accept
	Anti-HCV+ HCV RNA +/unknown	Accept (Immediate post-transplant treatment)	Accept (Post-transplant treatment in anti-HCV+/HCV RNA - recipients)

Liver donors with HIV infection

Recommendation

- The use of liver donors with HIV infection can be considered in HIV-infected recipients if there is an option for effective indefinite anti-HIV therapy, and the recipient provides informed consent **(LoE 4, weak recommendation, strong consensus).**

The published experience of LT from HIV-positive donors (D+) to HIV-positive recipients (R+) remains small and includes successful case reports with limited follow-up of recipients.[276–278] Preliminary data suggest that loss of HIV suppression due to donor-derived HIV superinfection might not be a significant clinical concern in carefully monitored antiretroviral treatment-suppressed HIV-positive organ recipients.[279] Early experience was recently published both in the kidney and liver transplant fields. In a multicentre pilot study directly comparing HIV D+/R+ with HIV D-/R+ KTs, overall transplant and HIV outcomes were excellent; a trend toward higher rejection with D+ raised concerns that warrant further investigation.[280] In turn, experience with LT has also recently been published comparing 24 HIV D+/R+ LTs to 21 HIV D-/R+ LTs. Weighted 1-year survival was 83.3% *vs.* 100.0% in D+ *vs.* D-groups ($p = 0.04$). There were no differences in 1-year graft survival (96.0% *vs.* 100.0%), rejection (10.8% *vs.* 18.2%), HIV breakthrough (8% *vs.* 10%), or severe adverse events (all $p > 0.05$). However, HIV D+/R+ was associated with more opportunistic infections, infectious hospitalisations, and cancer, raising concerns that merit further investigation.[281] Informed consent of the recipient is a requisite if these organs are used outside clinical trials. In addition, a thorough evaluation of HIV response to prior treatments is needed to exclude difficult to treat cases. In a recent evaluation of HIV-positive donors in the US, HIV drug resistance mutations were detected in 42%, yet resistance that would compromise integrase strand transfer inhibitor-based regimens was rare, which is reassuring regarding safety.[282] While there are no restrictions regarding donor CD4 T cell count or HIV viremia in the US under the HOPE act, transplant clinicians must exercise caution when accepting organs from donors with active viremia and low CD4 T cell count associated with higher risks of drug resistance mutations or opportunistic infections.

Liver donors with active SARS-CoV-2 infection (+) PCR

Recommendations

- Liver donation from a SARS-CoV-2-positive donor should not be contraindicated **(LoE 3, strong recommendation, consensus).**
- SARS-CoV-2 monitoring of the recipient should be provided and antivirals should be administered in case of SARS-CoV-2 infection, considering drug-drug interactions **(LoE 4, strong recommendation, consensus).**

The risk of transmission of SARS-CoV-2 from liver donors to candidates is unknown but likely low. The probability that a donor may have SARS-CoV-2 infection should be estimated by considering the epidemiologic risk, obtaining a clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection. Considering the good early post-transplant outcomes when transplanting livers from SARS-CoV-2 (+) donors into uninfected recipients, this practice seems safe.[283–291] Aspects to consider include the unknown but likely low transmissibility of SARS-CoV-2 through non-lung organs, the recipients' risk of mortality or drop out from the waiting list due to liver disease progression, the general local donor availability and the recipient prior immunity to SARS-CoV-2. In a first Italian series (n = 10 PCR-positive donors), two were transplanted into PCR-positive recipients. None of eight PCR-negative recipients was found to be SARS-CoV-2 positive during follow-up. At LT, IgG against SARS-CoV-2 were positive in 80% (8/10) of recipients and 71% (5/7) showed neutralising antibodies (evidence of protective immunity related to recent COVID-19). In addition, testing for SARS-CoV-2 RNA on donor liver biopsies at transplantation was negative in 100% (9/9), suggesting a very low risk of transmission with LT.[286] In a systematic review reporting on 69 recipients receiving 48 kidneys, 18 livers and 3 hearts from 57 donors, SARS-CoV-2 viral transmission was not documented among non-lung transplant recipients, irrespective of the presence of symptoms at the time of procurement. Importantly, only 4% of recipients were vaccinated and SARS-CoV-2 RNA was detected (median 32 Cycle threshold) at procurement in 31% of donors.[292] Similar data has recently been reported by other agencies.[293]

Can we use liver donors with a history of non-infectious (FAP, cancer) transmittable diseases?

Liver donors with cancer

Recommendation

- In case of donation from a donor with a known history of cancer, the risk of cancer transmission *vs.* the risk of death on the waiting list before a suitable graft without such risks would become reasonably available should be weighted, and an individual value-based decision and shared-decision for transplantation should be made if the risk of death on the waiting list outweighs the risk of cancer transmission and the recipient provides informed consent **(LoE 3, strong recommendation, strong consensus).**

The rate of donor-transmitted cancer is low (3-6 cases per 10,000 LTs) but may increase with the expansion of the donor pool (elderly individuals, higher frequency of past history of treated malignancy). Currently, about 2-4% of utilised deceased organ donors are known to have a present or past history of malignancy. A detailed donor characterisation is essential to assess the risk of donor-transmitted cancer[294,295] as the consequences can be devastating for the patient, the

professionals involved and the transplant programme. In a recent systematic review, 92 cases of donor-transmitted cancer were reported in 67 studies. Most were lymphomas, melanomas and NETs, and the majority were diagnosed within 2 years from solid organ transplantation. Outcome following diagnosis was generally poor with a 1- and 2-year survival probability of 55.7% and 51.8%, respectively.[296] The estimated risk needs to be balanced against the risk of patients dying or deteriorating on the waiting list. Some cancers are associated with a minimal risk of transmission and hence are suitable for all transplant candidates. These include basal and squamous cell carcinoma of the skin, *in situ* carcinomas (cervix, low-grade breast, vocal cord, PanIn), non-muscle-invasive urinary bladder cancers, *in situ* urothelial (pTis) and intra-epithelial papillary urothelial carcinoma (pTa/G1-2), good prognosis prostate cancer (≤pT2 and Gleason 3+3, ≤pT2 and Gleason grade = 7 after curative treatment and cancer-free period >5 years), renal cell cancer <1 cm (stage T1a) and Fuhrman grade I/II thyroid solitary papillary carcinoma <0.5 cm and minimally invasive follicular carcinoma <1 cm, and central nervous system neoplasia WHO grades I/II. Others are estimated to carry a very high risk of transmission and thus are unacceptable. These include metastasised cancers, choriocarcinoma, Kaposi's sarcoma, Merkel cell carcinoma and skin sarcoma, stages T3/T4 renal cell cancer, sarcoma (and disease-free interval <5 years), thyroid medullary and anaplastic cancers, leukaemia, lymphoma and plasmocytoma (and disease-free interval <10 years), and primary cerebral lymphoma. In between, there are cancers of low to intermediate risk where decisions should be made case by case based on a risk-benefit analysis. Those with high risk can potentially be used only for recipients with an imminent risk of death. In most instances a complete remission greater than 5 years is mandatory. They include invasive breast cancer after full treatment, complete remission and stringent follow-up for >5 years; gastrointestinal stromal tumours from primary sites other than stomach or duodenum, size >2 cm or high mitotic count; treated lung cancer, with complete remission and stringent follow-up for >5 years; treated melanoma, with complete remission and stringent follow-up; successfully treated early oropharyngeal or ovarian, oesophageal, gastric, pancreatic, liver and biliary cancers, with complete remission >5 years; treated neuro-endocrine neoplasms; prostate cancer with a history of extra-prostatic extension; and Fuhrman I/II renal cell carcinoma >7 cm or Fuhrman III/IV renal cell carcinoma.[297–303]

Liver donors with familial amyloidotic polyneuropathy

Recommendations

- Domino LT from donors with familial amyloidotic polyneuropathy can be considered in selected recipients **(LoE 4, weak recommendation, strong consensus).**
- After domino LT for familial amyloidotic polyneuropathy, close monitoring for early detection of *de novo* transthyretin-neuropathy and cardiomyopathy should be performed **(LoE 4, strong recommendation, strong consensus).**

Hereditary amyloid transthyretin (ATTR) amyloidosis (FAP) is a rare, autosomal-dominant inherited disease, characterised by progressive neuropathy and cardiomyopathy that has been treated with LT because the liver produces the circulating unstable transthyretin (TTR). According to the world registry (*Domino Liver Transplant Registry*. *2019*. http://www.fapwtr.org/ram_domino.htm), an average of approximately 120 patients worldwide were transplanted each year for FAP. However, after the introduction of new treatment methods, such as TTR-stabilising agents[304] the number of transplanted patients has decreased to less than 25 per year. The sequential procedure involves the reuse of livers from these patients with ATTR, which are otherwise structurally and functionally normal, in patients with end-stage liver disease (*i.e.* domino LT), generally elderly patients with hepatic malignancy, given that the clinical manifestations derived from tissue deposition of the misfolded TTR variant theoretically take more than 20 years to develop (informed consent is required). Unfortunately, reports of symptomatic ATTR amyloidosis as early as 6 to 7 years after transplantation have been published,[305–313] particularly manifesting with neuropathy (up to a third of patients after a median follow-up of 7 years) and less commonly with cardiomyopathy.[314,315] While domino LT with the specific variant Val30Met seems to be safe in terms of development of ATTR-cardiomyopathy, the same does not hold true for recipients from non-Val30Met livers, especially if significant cardiac involvement was documented in the donor and if the FAP liver is placed into an old male recipient.[310,311] Strict monitoring of these patients allows for the early detection and potential application of new therapies. Patisiran treatment in patients with hereditary TTR-mediated amyloidosis with polyneuropathy after LT has demonstrated its efficacy in reducing serum TTR, and in improving or stabilising key measures of disease impairment.[316] A periodic assessment of specific scores of peripheral neuropathy, quantitative sensory testing, nerve conduction studies, and eventually sural nerve biopsy is suggested to detect *de novo* TTR-neuropathy, while periodic echocardiograms, Holter electrocardiograms and bone scintigraphy can help detect TTR-myocardiopathy.[317,318] Patients with FAP acquired by transplantation are candidates for liver retransplantation to minimise the progression of symptoms but very few series have reported outcomes in this setting.

Is there a need to expand living donor programmes due to lack of sufficient deceased donors?

Recommendations

- To reduce mortality on the LT waiting list, countries should optimise the allocation of deceased donor livers for transplantation. If there is ongoing avoidable waiting list mortality, implementation or expansion of LDLT programmes should be considered **(LoE 2, strong recommendation, strong consensus).**
- In all settings, LDLT experience should be concentrated in high-volume centres with sufficient training and experience, in order to minimise risks and optimise outcomes for all stakeholders **(LoE 2, strong recommendation, strong consensus).**

LDLT is an important alternative to DDLT to expand the pool of available organs for transplant. In some settings, based on cultural and ethical considerations, LDLT is the primary or only source of livers to treat end-stage liver disease or otherwise unresectable neoplastic processes limited to the liver or the hepatic hilum. In Europe in recent years, application of LDLT in adult recipients has declined.[319,320] Potential reasons include not only concerns about donor safety but also the declining number of LT indications based on successful treatment of HCV and increasing expansion of donation after circulatory determination of death (DCD) in combination with broader clinical application of advanced forms of perfusion preservation. In general, while LDLT offers good results for recipients, it is a procedure that requires subjecting an otherwise healthy individual – the donor – to a major medical procedure, with associated risk for morbidity and mortality.[321–325] For this reason, the decision to expand LDLT programmes needs to be made at the local level, considering waiting list needs and LT candidate mortality while awaiting a graft. Depending on the setting, expansion of LDLT can shorten transplant waiting times, allowing recipients in some cases to be transplanted in a less decompensated state, which can have implications for subsequent post-transplant recipient survival.[319,326–328] LDLT also offers the advantage of offering a good-quality liver arising from a thoroughly evaluated donor, subject to less ischaemia-reperfusion injury in relation to shorter cold ischaemia, and with potentially less risk for rejection in cases of related donation. In addition, there is the potential advantage of a size-matched graft for a small adult or paediatric recipient. Potential disadvantages associated with LDLT include not only donor risk and more recipient biliary complications but also inadequate opportunity to assess aggressive tumour biology among recipients with HCC and cytokine and growth factor release during the process of liver regeneration, both of which might favour post-transplant HCC recurrence. The latter two risks are largely theoretical, however, as comparable post-transplant HCC recurrence and disease-free survival rates have been observed between LDLT and DDLT recipients.[327] It is difficult to provide cut-off wait times or MELD scores beyond which LDLT should universally be considered, as neither consistently captures the individual degree of disease severity or likelihood of waiting list dropout or death.[319] From a systems perspective, LT waiting list dropout may be a useful measure for determining when to expand LDLT. While some degree of dropout is unavoidable, ongoing rates in a certain area or patient population >10% even after optimisation of DDLT might prompt consideration of LDLT.[320,329] It is important to note that LDLT outcomes are highly dependent on centre experience, and LDLT should not be performed anecdotally. Concentrating LDLT experience in fewer centres to increase volume (at least 10 LDLT procedures per year) is important in all settings but is particularly important in countries or areas where LDLT in general is uncommon.[8]

Box 1. Risk factors for adverse post-transplant outcomes after cDCD liver transplantation

Independent risk factors in cDCD liver transplantation

- Donor age >60 years
- Donor warm ischaemia >30 minutes
- Graft cold ischaemia >6 hours
- Recipient MELD >25
- Recipient re-transplantation

cDCD, controlled donation after circulatory determination of death; MELD, model for end-stage liver disease.

What are risk factors for an adverse outcome in controlled DCD LT? Does the evidence to date support the use of uncontrolled DCD livers for transplant? Should this form of donation (continue to) be actively pursued?

Recommendations

- Both donor and recipient risk factors should be considered in order to optimise controlled DCD LT outcomes, while combining several risk factors should be avoided or else the application of advanced perfusion preservation strategies should be applied **(LoE 2, strong recommendation, strong consensus).**
- Livers from uncontrolled DCD donors recovered with normothermic regional perfusion, should be restricted to recipients in whom the risk of continued waiting outweighs the risk of an adverse post-transplant outcome **(LoE 3, strong recommendation, strong consensus).**

Given the pre-recovery period of warm ischaemia occurring both prior and during donor cardiac arrest, livers arising from controlled DCD (cDCD) donors present increased risk for adverse post-transplant outcomes. Risk has been assessed by numerous authors and quantified according to at least three different cDCD risk scores. Consistently, donor age, donor warm ischaemia (both pre-preservation as well as hepatectomy time), graft cold ischaemia, and complex recipient (high MELD score, urgent/emergent and/or re-transplantation indication) have been listed as significant, independent risk factors in cDCD LT[330–332] (Box 1). While one or even two of these risk factors should not necessarily prohibit proceeding, accumulation of multiple risk factors, which additionally include high donor BMI/graft macrosteatosis and high recipient BMI, may render outcomes for a particular cDCD LT "futile". Alternatively, accumulation of risk factors may serve as an indication for application of advanced forms of liver maintenance and preservation.[7,10,333] Uncontrolled DCD (uDCD) donors suffer sudden and unexpected cardiac arrest, often outside the hospital setting; resuscitation manoeuvres are initiated but are unsuccessful. Death is declared in accordance with both national and international standards, whereupon organ preservation manoeuvres may be initiated in countries or settings with uDCD protocols. In contrast with cDCD, uDCD is subject to considerably longer periods of pre-preservation donor warm ischaemia (up to 2-2.5 hours in some cases). In spite of near universal application of *in situ* post-mortem normothermic regional perfusion (NRP) to reperfuse and reoxygenate the abdominal organs prior to recovery, applicability of uDCD LT is low, and results, including both graft and patient survival rates, remain inferior to those achieved with donation after brain death livers of comparable characteristics.[334–338] Livers arising from uDCD donors in general should be transplanted with caution, taking into consideration the risk of continued waiting

vs. the risk of an adverse post-transplant outcome in the recipient.

Who is an adequate candidate for live liver donation? What are the anatomical limitations to donation? What are the physiological limitations to donation? What are the expected complication rates for live liver donors? Is anonymous/altruistic liver donation a reasonable/viable option? If so, with what caveats?

Recommendations

- Evaluation of live liver donor candidates should be performed according to an established protocol and include liver anatomical, parenchymal, and volumetric assessment; age- and sex-appropriate screening for clinically relevant as well as silent co-morbid conditions, including procoagulant conditions; MASLD, cardiovascular disease, cancer, infectious, and other potentially transmissible diseases; and psychosocial risk factors **(LoE 2, strong recommendation, strong consensus).**
- Live donor liver remnant should be at least 30% of pre-donation volume or mass **(LoE 2, strong recommendation, strong consensus).**

Live liver donation is a major surgical procedure applied to healthy individuals, to whom it does not provide any direct therapeutic advantage. Liver donor evaluation and surgery need to uphold the fundamental principles of ensuring donor safety while simultaneously providing a suitable graft for the recipient. Over 20 donor deaths have been reported to date, and donors themselves have required LT after developing post-hepatectomy liver failure.[325] After years of international experience and assessment, it has been seen that liver donor morbidity rates are primarily in the range of 15-25%, and donor mortality is 0.2-0.5%.[321–325] For LDLT recipients, while rates of biliary complications are higher relative to DDLT with a whole graft, graft and patient survival rates are comparable for the two procedures.[319,339]

Potential live liver donors should be thoroughly vetted in the context of an established protocol (Box 2). An essential prerequisite of LDLT is explicit willingness of the donor to donate and full understanding of the entire donation process, including the associated risks for perioperative complications and death. Liver donors are healthy individuals, aged between 18 to 55-60 years, with no chronic illnesses, including latent infections or other diseases that might be transmitted with the transplant graft. Donors should not only have normal liver but also cardiovascular, pulmonary, and renal function, as well. Donors should be at least ABO compatible if not identical to the recipient. ABO-incompatible LDLT is only an option when the institution is familiar with desensitisation using rituximab and when no identical or compatible donor is available. Donor BMI should be <30, and hepatic steatosis should be absent or minimal (5-10%). In some settings, donors with higher BMI have been re-considered after successful completion of weight loss programmes. Estimated remnant liver mass in the donor should be >30-35% (higher end when donors are older and/or have minimal hepatic steatosis detected on imaging or biopsy).[340] Liver donors need to offer a graft representing at least 0.8% of recipient lean body mass, and donor anatomy should be such that it may be reconstructed in the recipient without leaving the donor with any issues of insufficient remnant inflow or outflow, including biliary outflow problems. Potential donors also need to be screened for anxiety and other mood problems in order to avoid or mitigate adverse psychological outcomes following donation.

If potential donors with pre-existing medical conditions and/or psychiatric disorders are ultimately considered eligible to donate, prompt treatment of their conditions is necessary to optimise control and stability prior to surgery.[341] An individualised assessment is performed in cases of extended living donor criteria not meeting the aforementioned limits, taking into consideration not only medical but also ethical aspects associated with a riskier procedure for both stakeholders.

In general, liver donors have a direct personal and often consanguineous relationship with their recipients. In some settings, unrelated/altruistic donation has been performed, with adequate postoperative results for both donors and recipients,[339] though experience with this approach remains anecdotal.

Box 2. Live liver donor assessment and prerequisites

- Healthy adult, aged 18-60 years
- Freely willing to donate
- Understands entire donation process and associated risks, including up to 0.5% risk of death
- No co-morbid conditions, including obesity and psychiatric and mood disorders
- Up-to-date cancer screening, performed in accordance with age, sex, and history of known exposures
- Screening for infectious and other transmissible diseases, performed in accordance with area of origin and history of known exposures
- ABO-compatible with intended recipient
- Minimal-to-no hepatic steatosis (<10%)
- Liver remnant >30% of pre-donation liver mass

What evidence is there to support donor-recipient matching? Does donor-recipient matching improve post-transplant outcomes? Does donor-recipient matching impact organ utilisation rates and allocation systems?

Recommendation

- Although novel liver allocation systems, including ones of donor-recipient matching, may offer certain advantages relative to MELD, their use cannot be recommended as of yet due to the lack of robust clinical data **(LoE 3, weak recommendation, strong consensus).**

LT allocation systems are created with the objective of reducing disparities and optimising outcomes in the face of scarce resources (*i.e.*, suitable deceased donation liver grafts). Currently, most DDLT allocation systems are based on MELD or MELD-Na, which is focused on transplant necessity by treating the "sickest first" in order to reduce waiting list mortality and improve outcomes according to intention-to-treat.

While MELD has advantages, it does not adequately capture all aspects related to waiting list dropout and disease severity. In this regard, MELD add-ons and exception points are necessary to maintain equity and access to transplant for an increasing number of LT candidates. Other allocation systems have been proposed to optimise survival benefit (*i.e.*, maximise differences between life expectancy after transplant and life expectancy without transplantation) or life-year gains for the population in general.[342] Donor-recipient matching is an example of a utility-based system whereby a graft is allocated to its "preferred recipient" based on likelihood of offering the best possible outcome for a particular graft-recipient pair.[343] While promising in theory, an optimal match may require shipping a graft a long distance, thereby reducing its suitability and increasing logistical complexity and cost. While novel organ preservation technologies may help overcome this last obstacle, the fact remains that there is still no effective artificial liver support system that allows recipients to wait for a best possible match, and transplant urgency remains a key factor in determining who should receive an otherwise compatible liver in most settings.

Perfusion preservation strategies

What are the different perfusion preservation strategies? What evidence is there to support their application over static cold preservation? What are associated costs and/or other drawbacks? Are costs outweighed by clinical benefits?

Recommendations

- Perfusion preservation strategies should be considered at different points in the donation and transplantation process to reduce adverse post-transplant outcomes, including biliary complications, in particular when using extended criteria and DCD grafts **(LoE 2, strong recommendation, strong consensus).**
- Machine perfusion strategies should be used to increase the donor organ pool and organ utilisation **(LoE 1, strong recommendation, strong consensus).**

Compared with immediate application of static cold storage following cessation of donor blood flow, perfusion preservation provides a continuous supply of oxygen and other metabolic substrates and allows for removal of graft waste products and some degree of allograft viability assessment prior to transplantation or definitive graft discard. Perfusion preservation may be applied either *in situ* in the donor or *ex situ* following allograft recovery. *In situ* perfusion preservation comprises normothermic regional perfusion (NRP) applied in DCD donors[344] (Fig. 5). NRP is initiated after declaration of death to reverse warm ischaemic injury occurring in the period surrounding donor cardiac arrest. Data supporting the use of NRP in DCD is provided by observational studies, primarily arising from Europe.[333,345–347] A recent systematic review and meta-analysis on these studies determined that the use of postmortem NRP in cDCD LT was associated with a 71% reduction in the development of any form of biliary stricture(s) (relative risk [RR] 0.29, 95% CI 0.15-0.57) and 85% reduction in ischaemic-type biliary lesions (RR 0.15, 95% CI 0.105-0.45) relative to immediate static cold storage.[338] Decreased risk of liver graft loss (adjusted HR 0.39, 95% CI 0.20-0.78) has also been described in the context of a propensity-adjusted multicentre study. While[348] no formal cost analysis has been performed, it should be kept in mind that effects of *in situ* NRP extend to up to four organs in the abdomen (two kidneys, liver, pancreas). A recent cost simulation suggests that the additional cost associated with applying *in situ* NRP (roughly €3,000 per case) may be offset by curing more patients of end-stage kidney and liver disease and type I diabetes mellitus and achieving better allograft function and fewer complications and graft failures among DCD kidney and liver recipients.[349] *Ex situ* machine perfusion preservation may be applied over a range of temperatures: hypothermic 0-12 °C, midthermic 13-24 °C, subnormothermic 25-34 °C, or normothermic 35-38 °C.[350] To date, clinical application of *ex situ* machine perfusion preservation prior to transplantation has almost exclusively been performed at hypothermic (portal only Hypothermic Oxygenated Perfusion – HOPE; Dual portal and arterial Hypothermic Oxygenated Perfusion – D-HOPE) or normothermic (normothermic machine perfusion, NMP) temperatures, or via controlled rewarming, raising temperature progressively from the hypothermic range[351] (Table 6). Randomised clinical trials that have been performed to date have demonstrated significantly lower peak hepatic transaminases arising among recipients of livers treated with *ex situ* NMP[12,352] and significantly fewer complications, including ischaemic-type biliary lesions, arising among recipients of marginal quality livers (extended criteria and DCD) treated with *ex situ* HOPE and D-HOPE.[10,353] Additionally, both NMP and D-HOPE+controlled rewarming+NMP have been used to evaluate and ultimately transplant livers initially declined for transplantation.[11,354,355] Regarding the cost-effectiveness of *ex situ* machine perfusion strategies, there is promising preliminary data coming from cost estimates and simulations to suggest an overall favourable economic profile for their utilisation in clinical LT.[353,356–359] More robust evidence is still needed, however, to definitively confirm the cost-effectiveness and utility of using any *in situ* or *ex situ* liver perfusion preservation strategy.

Surgical techniques

What type of partial liver graft is optimal in a child?

Recommendation

- In the absence of a size-matched whole liver graft, both split and living donor transplantation should be performed in small children **(LoE 3, strong recommendation, consensus).**

The availability of paediatric size-matched whole liver grafts cannot respond to the demand, and the use of partial grafts from live and/or split donors is mandatory. The choice between the two options is guided by centre experience and cultural factors, explaining diverging strategies between the East and the West.[360] LDLT is associated with excellent post-transplant

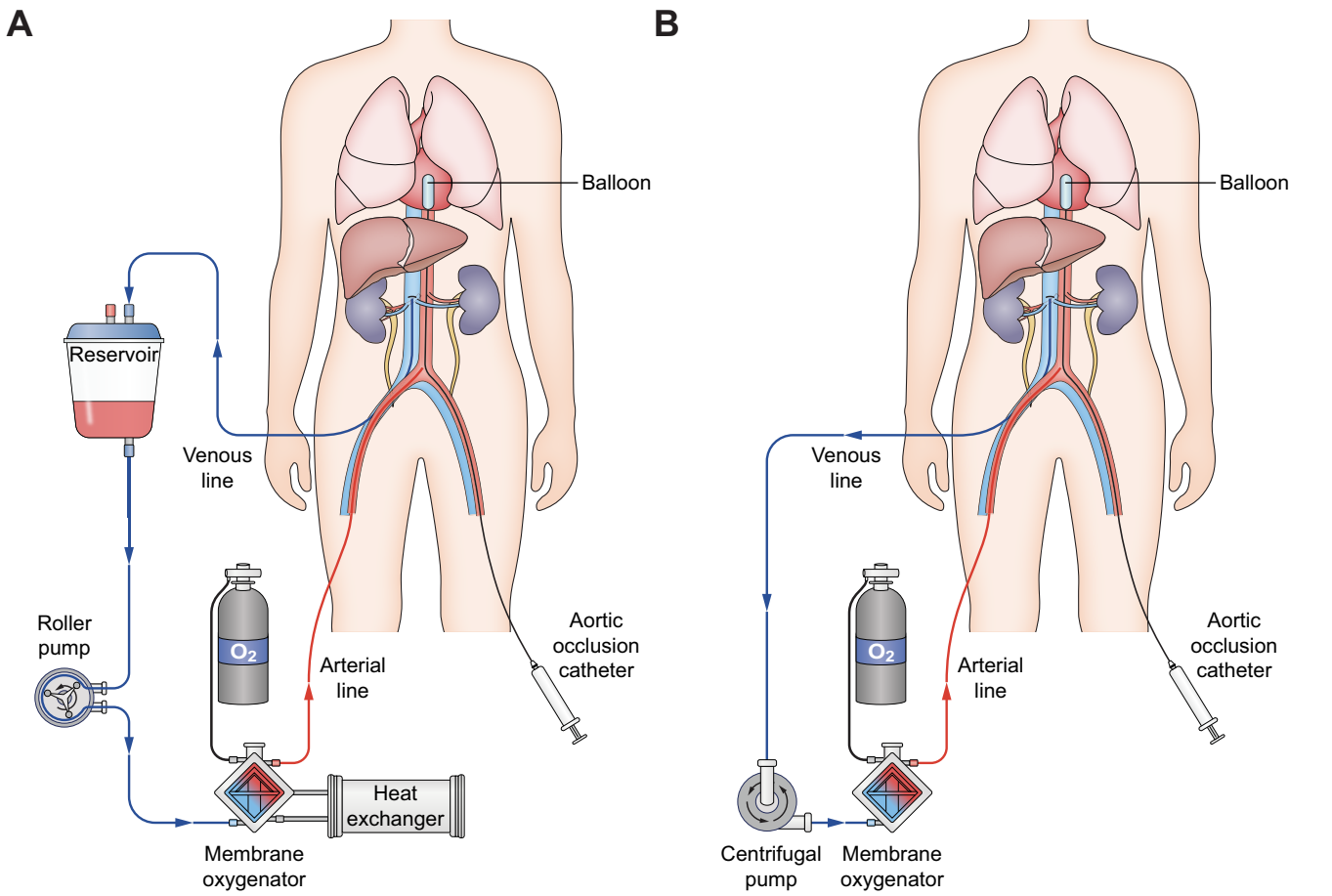

Fig. 5. Arrangements for A-NRP in donation after circulatory determination of death. According to (A) the original set-up, the A-NRP circuit includes a reservoir, roller pump, and heat exchanger to maintain perfusate temperature 37 °C. (B) Current set-ups typically include a centrifugal pump, which induces less hemolysis, and excludes the reservoir, thereby minimising priming solution volume. Additionally, the heat exchange unit may be removed to simplify the circuit and travel logistics and to maintain mild subnormothermia during donor reperfusion, which may offer additional cytoprotective effects. *Adapted Fondevila et al. Transplantation 2023*[344]. A-NRP, abdominal normothermic regional perfusion.

Table 6. Liver perfusion preservation techniques.

Liver perfusion preservation techniques	
***In situ* (inside donor, prior to organ recovery)**	
Normothermic regional perfusion (NRP)	Recirculation of oxygenated blood to abdomen (A-NRP) or chest and abdomen (TA-NRP) at 35-38 °C following declaration of death in DCD
***Ex situ* (following organ recovery, on a device)**	
Hypothermic machine perfusion (HMP)	Pumping of perfusate to graft at 0-12 °C
Hypothermic oxygenated perfusion (HOPE)	Pumping of actively oxygenated perfusate to graft portal vein at 0-12 °C
Dual hypothermic oxygenated perfusion (D-HOPE)	Pumping of actively oxygenated perfusate to graft portal vein and hepatic artery at 0-12 °C
Normothermic machine perfusion (NMP)	Pumping of actively oxygenated perfusate containing red blood cells or another oxygen carrier to graft portal vein and hepatic artery at 35-38 °C
Controlled rewarming (COR)	Pumping of actively oxygenated perfusate to graft portal vein and hepatic artery, progressively raising temperature from 10 to 20 °C

function. The use of split liver grafts is globally underused, and may be promoted, especially over the use of reduced liver grafts. It allows for the transplantation of two recipients, and a global decrease in waiting time and waiting list mortality.[361,362] In addition, split liver grafts are associated with similar outcomes as whole LT both in paediatric (left lateral segments) and adult (extended right lobe) recipients, as long as ischaemia time is short and recipient MELD is low.[361,363,364] Further prospective assessment of split liver transplantation is needed.

Is one type of vena cava anastomosis (piggy-back vs. caval replacement) superior to others?

Recommendations

- Both the piggy-back and the total caval replacement techniques are viable options, with no clear preference for one over the other. Selection should be based on local expertise, prevailing practice, and individual patient anatomy **(LoE 3, weak recommendation, consensus).**
- Selective use of temporary portocaval shunt or veno-venous bypass may be considered **(LoE 3, weak recommendation, consensus).**

Technical aspects of LT vary greatly between centres. In Europe, 50% of centres report using the piggy-back technique, and 40.5% total caval replacement as their standard techniques[365,366] (Fig. 6). In the piggy-back approach, the recipient inferior vena cava (IVC) is preserved. The donor supra- or intrahepatic IVC is anastomosed to the recipient vena cava in an end-to-side or side-to-side fashion to the recipient vena cava. This technique can be performed with a partial clamping of the IVC, maintaining part of the caval blood flow. Alternatively, total caval replacement involves a complete clamping of the IVC above and below the explant liver with excision of the recipient intrahepatic IVC. Total clamping impacts renal blood outflow and cardiac return, and may require use of veno-venous bypass to diminish haemodynamic impact. Thanks to the partial caval clamping, the piggy-back technique may be associated with less blood loss, improved haemodynamic stability during implantation of the liver graft and a decreased risk of post-transplant acute kidney failure.[367,368]

However, using both techniques, the haemodynamic impact varies greatly from one patient to another, probably reflecting the extent of pre-existing porto-systemic shunts.[369] This suggests the need for veno-venous bypass or temporary porto-caval shunt at least in selected patients, independently of the anastomosis technique. A meta-analysis of six retrospective and randomised studies has shown that the use of temporary portocaval shunt during piggy-back transplantation is associated with less ischaemia-reperfusion injury, less blood transfusion, and improved postoperative renal function.[370] Currently, techniques preserving caval and/or portal flow are used in most centres either as the first approach (14%) or on demand (38%).[365] Overall, one may recommend using the piggy-back technique with the addition of temporary porto-caval shunt in selected patients. The use of total caval replacement with on demand veno-venous bypass may also be appropriate. High quality data is lacking in the field, and prospective/randomised data are needed.

Immunosuppression strategies

Is there a demonstrably preferable combination of immunosuppressive drugs and blood levels that optimises the balance between rejection and post-transplant renal dysfunction?

Recommendations

- Tacrolimus trough levels should be kept at 6-10 ng/ml during the first month followed by 4-8 ng/ml thereafter **(LoE 1, strong recommendation, consensus).**
- It is recommended to combine tacrolimus with other immunosuppressive drugs (MMF, AZA or mTORi) to allow for a lower range of tacrolimus trough levels than recommended for monotherapy and to help preserve renal function **(LoE 2, strong recommendation, strong consensus).**
- The administration of basiliximab induction with delayed introduction of tacrolimus is strongly recommended in patients at risk of developing post-transplant renal dysfunction **(LoE 2, strong recommendation, strong consensus).**

A systematic review and meta-analysis published in 2012[371] indicates that administration of tacrolimus at doses required to reach levels of 6-10 ng/ml during the first month followed by 4-8 ng/ml thereafter, in combination with a short course of corticosteroids (3 months), results in improved renal function without increased rejection rates, compared to the target trough levels of 10-15 ng/ml originally recommended by regulatory authorities. The need to administer induction therapies and/or to add other agents in order to keep rejection at bay when targeting these trough levels has not been demonstrated. Post-transplant renal function can be optimised/preserved in all patients by using renal sparing immunosuppression regimens

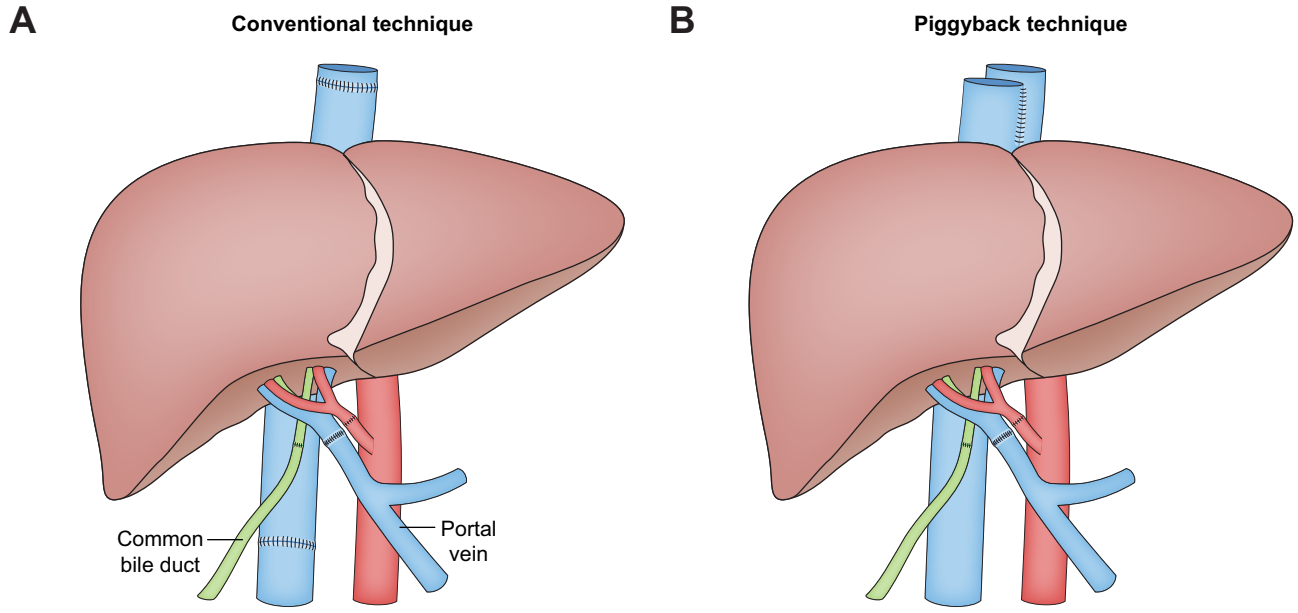

Fig. 6. Conventional *vs.* piggyback anastomosis. (A) Before transplantation. (B) after transplantation. *Adapted from Zarrinpar & Busuttil, Nature Reviews Gastroenterology & Hepatology 2013.*[366]

that target lower tacrolimus trough levels than those outlined above. Renal sparing regimens include tacrolimus combined with either basiliximab induction and/or additional immunosuppressants (*e.g.* mycophenolate mofetil [MMF], azathioprine [AZA] or mammalian target of rapamycin inhibitors [mTORi]).[372] The superiority of renal sparing regimens has not been formally proven, given that in all RCTs demonstrating a benefit on renal function, patients enrolled in the control groups were exposed to tacrolimus trough levels above of what is recommended here.[373–377] Although the optimal tacrolimus levels when using combination regimens are not well established, trough levels should be below the range recommended for tacrolimus monotherapy to preserve renal function (*e.g.* 4-7 ng/ml during the first month, followed by 3-5 ng/ml). The use of basiliximab and MMF or AZA to allow for a 5-day delay in the introduction of tacrolimus is strongly recommended in patients at risk of post-transplant renal dysfunction, as assessed by the pre-existence of kidney dysfunction, advanced liver failure, hyponatremia or high BMI.[378] Although the majority of countries use MMF, AZA, initially used in the LT setting, can be maintained as an alternative. Beyond the first year after transplant, most patients can be maintained on tacrolimus levels of 4-6 ng/ml (monotherapy) or lower if tacrolimus is combined with other immunosuppressants. Conversion to a calcineurin inhibitor (CNI)-free everolimus-based regimen can be achieved in more than 50% of patients, but the benefit of this strategy as a means to improve/stabilise renal function substantially decreases beyond 12 months post-transplant.[379] Many long-term survivors can maintain normal liver tests with tacrolimus levels substantially lower than the thresholds recommended above.[15] The benefits of managing patients on such low levels in terms of reduced immunosuppression-related side effects have not been formally demonstrated and could be counteracted by the development of subclinical rejection, which should be investigated by monitoring donor-specific antibodies (DSAs) and transient elastography values, or by performing surveillance liver biopsies.[16] Among mTORi, everolimus can be used from day 7 after LT but sirolimus should be avoided during the first month post-transplant. Patients in poor clinical condition and/or requiring prolonged intensive care stay post-transplantation are typically maintained on lower immunosuppressive doses than those recommended above.

Is there a specific immunosuppressive regimen for patients at high risk of cancer after LT?

Recommendations

- Exposure to CNIs should be minimised by employing combined immunosuppressive regimens, preferably an mTORi in the case of high risk of hepatic or extrahepatic cancer recurrence **(LoE 2, strong recommendation, strong consensus).**
- An mTORi-based immunosuppression regimen is strongly recommended in patients with history of recurrent/*de novo* non-melanoma skin cancer **(LoE 2, strong recommendation, strong consensus).**

Retrospective studies have shown associations between high CNI levels (typically above those recommended previously in the manuscript) and both post-transplant HCC recurrence[380] and *de novo* malignancies.[381–383] The effects of mTORi on HCC recurrence post-transplant remain the subject of intense research. Six systematic meta-analyses of predominantly retrospective studies have concluded that mTORi-based immunosuppression is associated with reduced HCC recurrence and better patient survival (regardless of the mTORi agent employed).[384–389] However, these meta-analyses are difficult to interpret given the marked heterogeneity of the retrospective studies included. Of note, the only large RCT exploring the effects of mTORi-based immunosuppression in the natural history of post-transplant HCC published to date yielded negative results,[390] although a subsequent *ad hoc* analysis concluded that patients with higher tumour activity at the time of transplantation benefited from mTORi use.[391] A recent report suggests that the cumulative exposure to tacrolimus, rather than benefits associated with the use of specific concomitant immunosuppressants (mTORi or MMF), is the main immunosuppression-related factor contributing to increased post-transplant cancer incidence.[381] In KT, there is evidence derived from four RCTs and meta-analyses suggesting that the use of mTORi-based immunosuppression reduces the incidence of non-melanoma skin cancer, but not other malignancies.[392,393] Altogether, with the exclusion of non-melanoma skin cancer, the strongest evidence available support not exceeding the CNI levels recommended for patients at high risk of either HCC recurrence or *de novo* cancer post-transplant, rather than any specific immunosuppressive regimen.

Is there a role for immunological risk stratification either before and/or after LT (both paediatric and adult)?

Recommendations

- Screening for preformed DSAs should be performed in recipients at risk of humoral sensitisation (previous transplantation, previous transfusions, previous pregnancies). Patients with a high level of preformed DSAs should receive more intensive follow-up than those who do not have detectable pre-formed DSAs **(LoE 4, strong recommendation, strong consensus).**
- Monitoring for *de novo* DSAs in combination with alanine aminotransferase and other non-invasive tests such as transient elastography may be recommended to identify LT recipients at risk of exhibiting sub-clinical rejection in whom aggressive immunosuppression minimisation would not be advisable. In the presence of high mean fluorescence intensity DSAs, minimisation is not advisable unless allograft damage has been excluded by performing a liver biopsy **(LoE 3, weak recommendation, consensus).**

Patients with humoral sensitisation and high levels of preformed DSAs at the time of LT (cumulative mean fluorescence intensity >10,000) are at risk of acute antibody-mediated rejection (AMR) early post-transplantation. Although this is a rare event, it can be difficult to diagnose and can result in graft loss.[394] The presence of pre-formed DSAs is also known to increase the risk of T cell-mediated rejection (both in adult and paediatric recipients), and it has been associated with graft failure and/or recipient mortality in at least five studies including

both HCV-positive and HCV-negative recipients.[395–399] Despite these reports, there is currently no evidence to recommend stratifying patients and adjusting their immunosuppressive treatment on the basis of pre-formed DSAs alone. DSAs should be considered in combination with various clinical/demographic parameters previously described to be linked to increased risk of rejection (*e.g.* recipient and donor age, history of autoimmune liver disease). In the minority of patients with high levels of pre-formed DSAs in whom DSAs persist post-transplant,[396] a low threshold for performing liver biopsies in cases of abnormal liver tests is recommended.

Development of *de novo* DSAs after transplantation has been associated with increased risk of both clinical and sub-clinical rejection, worse allograft fibrosis and graft loss (both in adult and paediatric recipients; see meta-analysis by Beyzaei *et al.*).[400] However, whether *de novo* DSAs are directly pathogenic or constitute a marker of under-immunosuppression remains a matter of debate. Furthermore, the benefits of strengthening immunosuppression levels on the basis of the development of *de novo* DSAs have not been investigated. On this basis, a recommendation for universal post-transplant DSA monitoring cannot be made. On the other hand, in patients in whom immunosuppression minimisation is being considered, screening for DSAs in combination with alanine aminotransferase (and/or using transient elastography and/or surveillance liver biopsies) is advisable as a means to exclude patients at high risk of exhibiting sub-clinical rejection.[16] In patients with high mean fluorescence intensity DSAs, immunosuppression minimisation is not recommended in the absence of a liver biopsy excluding liver allograft damage. The introduction of molecular HLA typing has enabled the implementation of novel strategies to quantify the liver allograft's immunogenicity, some of which have been shown to be associated with clinical outcomes (*e.g.* eplet mismatch or HLA evolutionary divergence).[16,401] However, further research is needed before any of these strategies can be recommended for patient management.

Is there a recommended treatment for acute and chronic AMR diagnosed on the basis of the recent Banff criteria?

Recommendations

- In patients with combined acute T cell-mediated rejection and AMR, the T cell-mediated component may be treated first according to each unit's standard of care (*e.g.* steroid boluses). Treatment with plasmapheresis +/- intravenous immunoglobulin is suggested in patients who do not respond to this approach or in those with 'pure' acute AMR (as per Banff criteria) **(LoE 4, open recommendation, strong consensus).**
- In patients with persistent signs of AMR who do not respond to the regimens outlined above, a second-line therapy can be considered (*e.g.* rituximab, to deplete B cells or eculizumab to inhibit complement activation) **(LoE 5, weak recommendation, consensus).**
- Patients with a diagnosis of probable chronic AMR according to current Banff criteria, exhibiting raised transaminases and/or at least moderate inflammatory infiltrates, may be treated by intensifying the conventional immunosuppression regimens **(LoE 5, weak recommendation, strong consensus).**

Given the frequent co-existence of acute AMR and T cell-mediated rejection, initial treatment should concentrate on treating the T cell-mediated component. This may involve high-dose corticosteroid boluses and, if needed, second-line treatments such as polyclonal lymphocyte-depleting antibodies. If moderate-to-severe allograft dysfunction and/or histological abnormalities persist following this, the recommended next step is plasmapheresis and intravenous immunoglobulin to remove circulating IgG. This recommendation is based on what has now become standard of care in KT,[402] although there is not a high level of evidence to recommend this strategy even in KT. Only anecdotal evidence exists on the use of anti-CD20 monoclonal antibodies (which deplete circulating B cells but do not influence circulating DSA levels) and/or other second-line treatment strategies such as proteasome inhibitors or eculizumab, and no specific recommendations can be made in this regard other than proposing to employ them as second-line agents in cases when persistent AMR has been demonstrated in a follow-up liver biopsy.

The current Banff criteria for chronic AMR[403] lack specificity and are not backed up by mechanistic studies supporting a direct pathogenic role of DSAs (in contrast to what has been described in KT). Therefore, treatments focused on removing circulating IgG or targeting B/plasma cells cannot be recommended in this setting. In patients exhibiting chronic AMR according to Banff criteria with significantly raised transaminases and/or at least moderate inflammatory damage, assessing patient medication compliance and strengthening of the baseline immunosuppression regimen (*e.g.* higher tacrolimus levels and/or addition of corticosteroids or MMF/everolimus/AZA) is recommended. Of note, the same recommendation applies to patients with similar histological findings but in the absence of circulating DSAs and/or C4d deposition.

Are induction of operational tolerance and attempts at immunosuppression discontinuation feasible?

Recommendations

- Complete withdrawal of immunosuppression should not be an aim of standard of care, even in the case of an extended rejection-free postoperative course **(LoE 2, strong recommendation, strong consensus).**
- If immunosuppression is completely discontinued for individual reasons, close monitoring of rejection that includes histological assessments should be guaranteed **(LoE 2/3, strong recommendation, strong consensus).**

Attempts at immunosuppression withdrawal can be successful in a small proportion of selected long-term surviving adult and paediatric LT recipients, referred to as operationally tolerant (approximately 20% and 30%, respectively). Although attempts at complete immunosuppression withdrawal result in a high incidence of allograft rejection, when performed under very close biochemical and histological monitoring they have shown to be safe, as rejection episodes tend to be mild and easily respond to transient increases in immunosuppression. However, there is no evidence indicating that successful immunosuppression withdrawal results in improved clinical outcomes. Although a multiplicity of biomarkers of operational

tolerance have been reported, none of them have been successfully validated in prospective trials. Therefore, immunosuppression withdrawal cannot be recommended outside of closely monitored clinical trials. The use of immunoregulatory cell therapy to intentionally induce tolerance early after LT has proven successful in a small clinical trial that involved splenectomy in LDLT recipients[404] but these results will need to be confirmed in ongoing trials. Patients who are off immunosuppression need to have at minimum a liver biopsy performed 1 and 3 years after immunosuppression discontinuation and continue to undergo monitoring of routine liver tests indefinitely.

Disease recurrence after LT

What are the best strategies to prevent and treat relapse to alcohol use following LT?

Recommendations

- To prevent alcohol relapse after LT, a multidisciplinary team including transplant hepatologist, transplant surgeon, psychologist, psychiatrist and addiction specialist should be involved in all stages of the transplant procedure, including the assessment during the evaluation process and in long-term follow-up **(LoE 3, strong recommendation, strong consensus).**
- The pattern of alcohol consumption should be included in the multidisciplinary evaluation. If the patient fulfils criteria for alcohol use disorder, pharmacological treatment and behavioural therapy either before or after LT should be considered as part of the multidisciplinary management approach **(LoE 3, strong recommendation, strong consensus).**
- If there is a discrepancy between a patient's self-reported alcohol consumption and clinical suspicion of alcohol intake, routine screening for alcohol biomarkers should be performed. This can be done using ethyl glucuronide in urine or possibly hair, phosphatidylethanol in blood or another appropriate test depending on local availability **(LoE 3, strong recommendation, strong consensus).**
- The treatment of alcohol relapse after LT should involve a multidisciplinary team including a transplant hepatologist, a psychologist, a psychiatrist and an addiction specialist. Pharmacological interventions to mitigate cravings should also be integrated into the therapeutic strategy **(LoE 3, strong recommendation, strong consensus).**

The natural history of alcohol-related problems often encompasses a relapsing-remitting pattern of alcohol use, which means that a thorough assessment of the disease before listing for a LT and follow-up after the procedure are crucial to achieving success. For alcohol-related liver disease, prolonged abstinence (3–6 months) is a key criterion for acceptance to the European liver transplant waiting lists. The notion that LT for patients who did not remain abstinent during the pre-transplant period does not appear to affect long-term survival despite the higher risk of relapse[405] has to be balanced against donor perceptions and local availability of management programmes for avoiding relapse to harmful alcohol use after transplantation.[406] A multidisciplinary assessment involving several stakeholders, such as a transplant hepatologist, a transplant surgeon, a psychologist, a psychiatrist and an addiction specialist, is becoming mandatory to robustly evaluate candidates with alcohol-related liver disease or severe acute alcohol-related hepatitis for LT.[407] The psychosocial assessment of transplant candidates and the evaluation of social background, including active support from family, are essential parts of the pre-transplant evaluation process. Available data confirm that in addition to the usual medical factors, psychosocial and behavioural issues may affect the ultimate transplant outcome. In fact, the data suggest that pre-transplant psychiatric history can predict post-transplant psychological outcomes, and that these, in turn, may predict physical morbidity and mortality.[408] After LT, during the regular follow-up, ideally all patients, but at least patients at high risk of relapse, should undergo a multidisciplinary assessment involving a transplant hepatologist, a psychologist, an addiction specialist, a psychiatrist, and when necessary, a social worker. The caregiver should be involved in the process. The psychologist should plan support of the patient with the caregiver, while the addiction specialist and/or the psychiatrist should prescribe medical treatment when necessary. The transplant hepatologist should evaluate the risk of alcohol-related liver damage and its severity. In fact, in patients at risk of relapse into alcohol consumption, liver function tests are used to evaluate the alcohol-induced liver injury. The urine or hair concentrations of ethyl glucuronide or the blood phosphatidylethanol should be used to detect the relapse of alcohol use after LT.

Combined cognitive behavioural therapy and pharmacotherapy seem more effective than usual care and pharmacotherapy alone in patients with alcohol use disorder.[409] Several pharmacological therapies have been approved for alcohol use disorder[410] and can be used by expert hepatologists or addiction specialists in the post-transplant setting, after careful evaluation of liver function, and drug-drug interactions with immunosuppression.[411] Ideally, the implementation of a transplant care model (system of care) that focuses on addressing psychosocial and behavioural issues and supporting self-management throughout the transplantation phases should be developed. Research in other transplant populations has shown that transplant centres with a higher level of chronic illness care, integrating the building blocks of a care model that include continuity of care, focus on self-management support and decision support for clinicians among others, have more favourable outcomes than those with a low level of chronic illness management.[412]

What are the best strategies to prevent and diagnose recurrent and de novo MASLD following LT?

Recommendations

- To prevent recurrent or *de novo* MASH, metabolic risk factors should be addressed and treated according to current standards **(LoE 3, strong recommendation, strong consensus).**
- Healthy lifestyle (appropriate diet, avoiding alcohol consumption, physical activity to avoid weight gain) and pharmacological treatment of complications (arterial hypertension, dyslipidaemia, diabetes, *etc.*) should be aggressively pursued in the post-transplant setting **(LoE 3, strong recommendation, strong consensus).**
- When there is uncertainty in diagnosing recurrent or *de novo* MASH *vs.* other causes of liver disease, a liver biopsy is suggested **(LoE 3, weak recommendation, consensus).**
- Adjustment of immunosuppression should be considered according to the kind of associated complication but should be balanced against the risk of rejection **(LoE 2, strong recommendation, strong consensus).**

MASLD and MASH,[413] either *de novo* or recurrent, are commonly seen after LT.[414,415] BMI prior to and following LT, diabetes mellitus, arterial hypertension and hyperlipidaemia are the major risk factors for post-LT MASLD/MASH. Considering all the metabolic complications potentially affecting patients after LT, the risk of developing post-transplant MASLD/MASH can be considered high, although studies published on this topic are based on small sample sizes, with heterogeneous definitions of disease recurrence.[416] Despite these data highlighting the importance of the early diagnosis of MASLD/MASH post-LT, it is still unclear if this population needs specific follow-up, in terms of frequency and type of screening, to detect recurrent and *de novo* MASLD/MASH early.[417] When abnormal liver function tests are reported, other causes of liver disease should be evaluated. In cases where MASH either recurrent or *de novo* may overlap with another liver injury/disease, a liver biopsy should be considered. To distinguish recurrent or *de novo* MASH, histological information is combined with the history of the patient, and the information regarding donor and recipient steatosis. Appropriate counselling before and immediately after LT is important to prevent post-transplant obesity and its related complications, such as the development of diabetes mellitus, graft steatosis, and *de novo* malignancies. Lifestyle modifications and a low-calorie diet represent the cornerstone of weight gain prevention after LT. Moreover, supervised physical activity is considered safe after LT in stable patients[418] and effective for glucose homeostasis,[419] which could be particularly beneficial in patients transplanted for MASLD-related liver disease. After LT, patients should be evaluated regarding their diet, alcohol intake and physical activity. The evaluation by a dietician and by a physical activity specialist are requested in specific cases. Ideally, this should be managed as part of the transplant care model.[412] In cases in whom there is a need for integrated intensified management, consultation with a cardiologist, a diabetologist/endocrinologist, and obesity treatment team is performed, and this is done in all patients with metabolic risk factors after LT, not only in those transplanted for MASH.

In patients transplanted for MASLD/MASH-related cirrhosis, immunosuppressive protocols need to be optimised in order to minimise the risk of metabolic complications. Steroids should be minimised or even withdrawn. This is essential not only to reduce the cardiovascular risk, but also to decrease the risk of developing graft steatosis, and consequently MASLD/MASH recurrence.[54] In general, the management of immunosuppressive regimens should be combined with an evaluation of medication adherence as this is one of the most important risks for acute and chronic rejection.[420,421] However, a recently published prospective study failed to demonstrate a direct association between the development of *de novo* metabolic syndrome and immunosuppressive therapy, probably due to the overlap of immunosuppressive regimens.[422] Therapeutic changes over time should be taken into account but there is no evidence to recommend a CNI-free regimen in patients who develop diabetes after transplant.

After LT, a multidisciplinary approach is mandatory to promote lifestyle modifications, such as a balanced diet and adequate physical activity, starting in the early post-LT period.[423] Patients should be involved in their management. Recently a patient guideline has been developed by patients, patient representatives, clinicians and scientists and is based on current scientific recommendations, intended to support patients in making informed decisions.[424]

Lifestyle intervention, however, is not effective at achieving significant weight loss in all LT recipients.[425] In recent years, novel therapeutic drugs (*e.g.*, GLP-1 receptor agonists) have proven effective as anti-obesity medications in non-transplanted patients.[136,426] Promising data have also been published in the post-LT setting, but they need to be confirmed in larger cohorts with longer follow-up periods to describe long-standing weight loss[427,428]. Bariatric surgery after LT may be considered in patients who do not sufficiently lose weight despite lifestyle (and perhaps medical treatment). To date, there are few studies reporting outcomes of post-LT bariatric surgery (Roux-en-Y gastric bypass and sleeve gastrectomy). Even though these procedures were described as safe, with similar post-operative times and morbidity, they should be performed in expert, high-volume centres.[137]

In summary, the transplant hepatologist should regularly perform liver and renal function tests, lipid and glucose metabolism tests, and assess body weight. When there is a suspicion of metabolic syndrome with liver involvement, the patient should undergo ultrasound of the liver and in selected cases, liver biopsy might be indicated or at least a liver elastography and other non-invasive biomarkers should be used and when metabolic syndrome has already developed there might be a need for consultation with a metabolic specialist[429] (Fig. 7).

However, more research is needed in this field before confirming a common management of these patients.

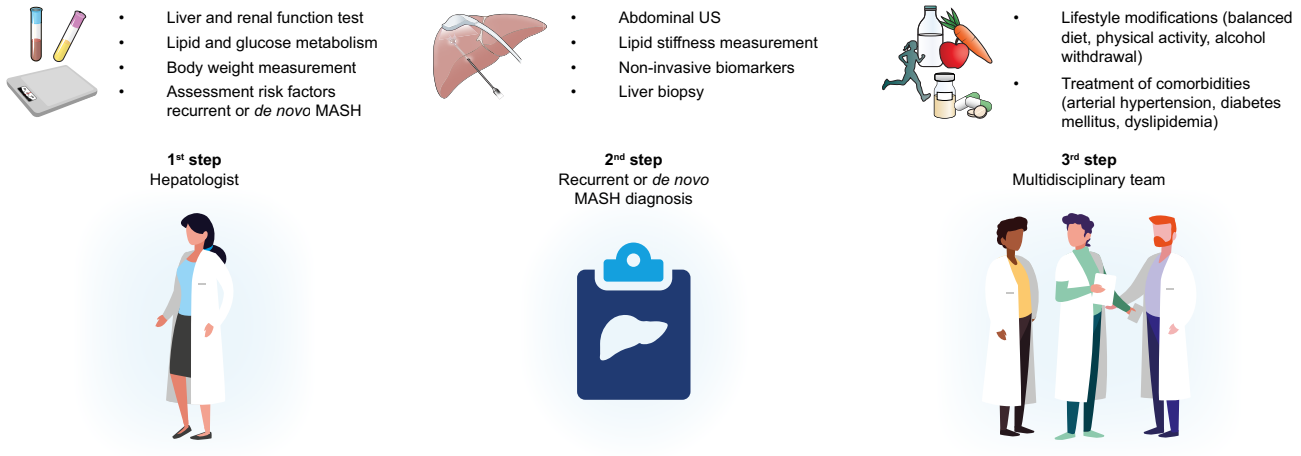

Fig. 7. Strategy for the prevention, diagnosis and management of *de novo* or recurrent MASH. MASH, metabolic dysfunction-associated steatohepatitis.

What are the best strategies to prevent autoimmune liver disease recurrence?

Recommendations

- Ursodeoxycholic acid should be given lifelong after LT to all patients with primary biliary cholangitis to prevent recurrence **(LoE 2, strong recommendation, strong consensus).**
- For transplant recipients with primary biliary cholangitis no immunosuppressive regimen (in particular cyclosporine over tacrolimus) should be recommended in order to prevent disease recurrence **(LoE 2/3, strong recommendation, strong consensus).**
- In transplant recipients with AIH, corticosteroid withdrawal to avoid long-term steroid-associated side effects, should be performed cautiously due to the risk of disease recurrence **(LoE 2/3, strong recommendation, consensus).**
- There is no specific immunosuppressive regimen or treatment effective in preventing primary sclerosing cholangitis recurrence **(LoE 3, strong recommendation, strong consensus).**

The recurrence rates of autoimmune liver diseases, including AIH, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are highly variable, at between 10% and 50%. This variability is due to the heterogeneity in recurrence definition (histologically proven *vs.* clinically suspected). Preventive administration of ursodeoxycholic acid (UDCA) at a dose of 10 to 15 mg/kg/day in two divided doses in patients transplanted for PBC was associated with lower risk of PBC recurrence.[430] This was further confirmed in a larger study of the PBC Global Study Group that showed that UDCA was not only associated with a lower risk of PBC recurrence but also with a reduction in the long-term risk of graft loss, liver-related death and all-cause death.[17] In this study, as previously shown,[431,432] the use of cyclosporine A added a protective effect to UDCA. In contrast, a Japanese report focusing on LDLT showed that cyclosporine A for initial immunosuppression was a statistically significant risk factor for PBC recurrence. In a subgroup analysis, it was shown that initiation with tacrolimus as the first immunosuppressant, followed by a switch to cyclosporine A, minimised PBC recurrence. No differences were observed in patients treated solely with tacrolimus or cyclosporine A without transitioning.[433] Therefore, the data are not robust enough to recommend one immunosuppressive regimen over another to prevent disease recurrence. Of note, PBC is associated with a higher risk of late acute rejection.[434] No medical intervention has demonstrated its efficacy in preventing PSC recurrence after LT.[435] Higher inflammatory activity of inflammatory bowel disease after LT has also been shown to increase the risk for recurrent PSC and colorectal cancer.[436] Several studies showed an association between colectomy before the transplant and decreased risk of PSC[437,438] but a recent EASL guideline on PSC advises against doing this routinely.[439] In a recently published analysis from the ELTR, LDLT was associated with a higher mortality rate due to disease recurrence compared to donation after brain death.[440] On the contrary, a US study based on the Adult to Adult Living Donor Liver Transplantation Cohort found no difference between LDLT and DDLT regarding PSC recurrence.[441] Similar results were published in a Canadian study[442]: recurrence rates, time to recurrence, recurrence-related graft failure, graft survival, and patient survival were not significantly different between first-degree living-related, living-unrelated, or deceased donors. Treatment with tacrolimus has been reported as an independent risk factor for PSC recurrence[437]; however, this finding was not confirmed by later studies. More recently a large study from ELTR and SRTR (the Scientific Registry of Transplant Recipients) showed that tacrolimus is associated with better patient and graft survival rates than cyclosporine.[443] Multiple acute cellular rejection episodes are associated with PSC recurrence,[444] suggesting that the primary aim of the immunosuppressive regimen is to avoid rejection. According to EASL PSC guidelines the use of UDCA can be considered in patients retransplanted for recurrent PSC.[439] Currently the type of biliary anastomosis (duct-to-duct bile duct anastomosis *vs.* hepaticojejunostomy) has not been associated with the risk of disease recurrence.[19,445,446] A meta-analysis found no statistically significant difference in AIH recurrence rate between

tacrolimus and cyclosporine, even if publication biases were acknowledged.[447] A large multicentre, international, retrospective study found that younger age at transplant, use of MMF post-LT and sex mismatch and high IgG levels pre-LT are associated with disease recurrence.[18] Patients with AIH recurrence are less likely to be on triple immunosuppressive therapy compared to patients without recurrence.[448] The use of long-term low-dose corticosteroids in order to prevent AIH recurrence after LT is controversial.[449,450] It has been shown that this strategy in combination with other immunosuppressive agents reduce AIH recurrence without jeopardising graft and patient survival, and without increased sepsis or osteoporosis rates.[451] On the other hand, dual immunosuppressive regimens, without corticosteroids, in LT recipients were associated with acceptable rates of survival and acute cellular rejection.[132] This was also confirmed by a previous report which found that corticosteroids could be safely withdrawn in 50% of AIH LT recipients.[452] In accordance, AASLD guidelines advise to discontinue corticosteroids and monitor patients for AIH recurrence.[99] The choice of immunosuppressive regimen should consider medication adherence as this is one of the most important risks for acute rejection.[420] Adherence is significantly lower in young adults (<40 years) on prednisolone.[453] A double immunosuppressive regimen combining tacrolimus with an anti-metabolite (AZA or MMF) may allow for safe corticosteroid withdrawal.

Long-term follow-up lifestyle

How can quality of life and adherence be improved in adult and adolescent LT recipients? How can employment and schooling be improved in adult, adolescent, and young LT recipients?

Recommendations

- Quality of life after LT should always be considered as an outcome measure. Strategies to improve post-LT health-related quality of life are: trusted relationship with medical team; optimisation of mental health through prescription of psychologic therapies when needed; physical activity **(LoE 2, strong recommendation, strong consensus).**
- Adherence to medical prescriptions and particularly to immunosuppressive therapy should be regularly evaluated after LT. Strategies to improve post-LT non-adherence include targeted education strategies, simplified drug regimens, psychological behavioural support **(LoE 3, strong recommendation, strong consensus).**
- Special attention should be dedicated to adolescents, since they are at high risk of poor adherence, poor school performance and difficulties in social relationships. These issues should be addressed by a multidisciplinary team **(LoE 2, strong recommendation, strong consensus).**

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 quality of life.[423,454] Unfortunately, the measurement of quality of life in LT recipients has not been rigorously studied and is not standardised as reported by a recent review of instruments used to assess quality of life after LT. Including relevant patient-reported outcomes (PROs) after transplantation – including quality of life – provides a more complete evaluation of transplant outcome. According to previous studies, post-LT quality of life is worse than that measured in the general population but similar to that experienced by other solid organ transplant patients or cohorts with chronic diseases. A trusted relationship with the medical team during the post-operative follow-up improves patients' perception of their own clinical condition. Mental health should be screened, and psychological therapies should be provided to patients experiencing common feelings such as reactive depression or anxiety.[455] Several studies have reported an improvement in quality of life after engaging in physical activity.[456]

Adherence can be defined as the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider.[457–459] Assessing patient adherence to medical regimens and lifestyle recommendations is the first step towards understanding the reasons for poor adherence or non-adherence.[460,461] Adherence to medical prescriptions is crucial to avoid complications such as acute and chronic rejection, meaning that assessing adherence includes evaluating the regular intake of immunosuppression.[420,421] It is crucial to consider easy to use, acceptable measures of adherence by both clinicians and patients, despite it being well known that the combination of different methods provides the highest sensitivity.[462–464] Therefore, healthcare providers dealing with LT recipients 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.[465] Targeted educational strategies, simplified drug regimens, psychological behavioural support represent valuable options to reduce non-adherence, especially for patients deemed at high risk.[420] The experience based on an educational pilot study to implement the management of poor adherence has been shown to be effective.[421]

While the results of LT are typically presented in terms of graft and patient survival, medical and surgical complications, and quality of life, these conventional metrics fall short in capturing the entirety of transplanted adolescents' experiences with their new liver. Their transition from adolescence to adulthood represents a notably vulnerable period. School performance is an important aspect of functional outcomes in the adolescent population. The high risk of non-adherence in adolescents is linked to their developmental and specific care models need to be considered especially during the transition phase.[466] The percentage of LT 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.[37] Patient-reported outcomes that assess relevant parameters from a patient perspective, such as return to work, should be considered. More generally, patients should be involved in determining the relevant patient-reported outcome dataset and patient-reported outcomes, including symptom distress, psychological status *etc*, should only be reported by patients.

Which is the best transition programme from paediatric to adult healthcare services?

Recommendation

- A transition programme should be developed in all centres (especially where there is an active paediatric transplant programme), in order to ensure a smooth transfer of care for transplant recipients reaching adulthood, and global care thereafter **(LoE 3, strong recommendation, strong consensus).**

The transition from childhood to adolescence and adulthood may be complicated in LT recipients.[467] The higher incidence of graft loss in adolescents has consistently been linked to their non-adherence to their prescribed medication,[468,469] considered a potential explanation for acute rejection during their transition to adulthood. All care providers (including transplant experts (hepatologists)) involved in the transition process need to have a proper knowledge about paediatric diseases. Non-adherence to medical prescriptions is associated with a poor medical outcomes in adolescents after LT.[465] During the transition from paediatric age to adulthood, transplant recipients seem to become particularly vulnerable to this problem. Specific programmes for adolescents should therefore be available at all specialised transplant centres, especially during the transition from adolescence to adulthood. These programmes should be based on multidisciplinary measures developed by professional educators, supported by psychologists and co-ordinated by transplant physicians (Fig. 8). For consistency, this should ideally occur in the same centre as the paediatric programme. The absolute key to the success of the process is an interested and capable adult service that is willing to continue the transition process. Building a local network of interested and committed professionals is critical to the success of any transition programme.[470] It would be much easier to teach patients strict adherence to medical prescriptions during their childhood, when patients are less likely to see these requirements as an imposition. It becomes more difficult for adolescents to be compliant as they begin to experience a desire for independence and self-management.[421] Transition programmes may be developed in close cooperation with adolescents. Adolescents could design their own individual transition instead of participating in a predetermined programme. Best clinical practices for transition should consider local circumstances, gender and location of medical follow-up after transition.

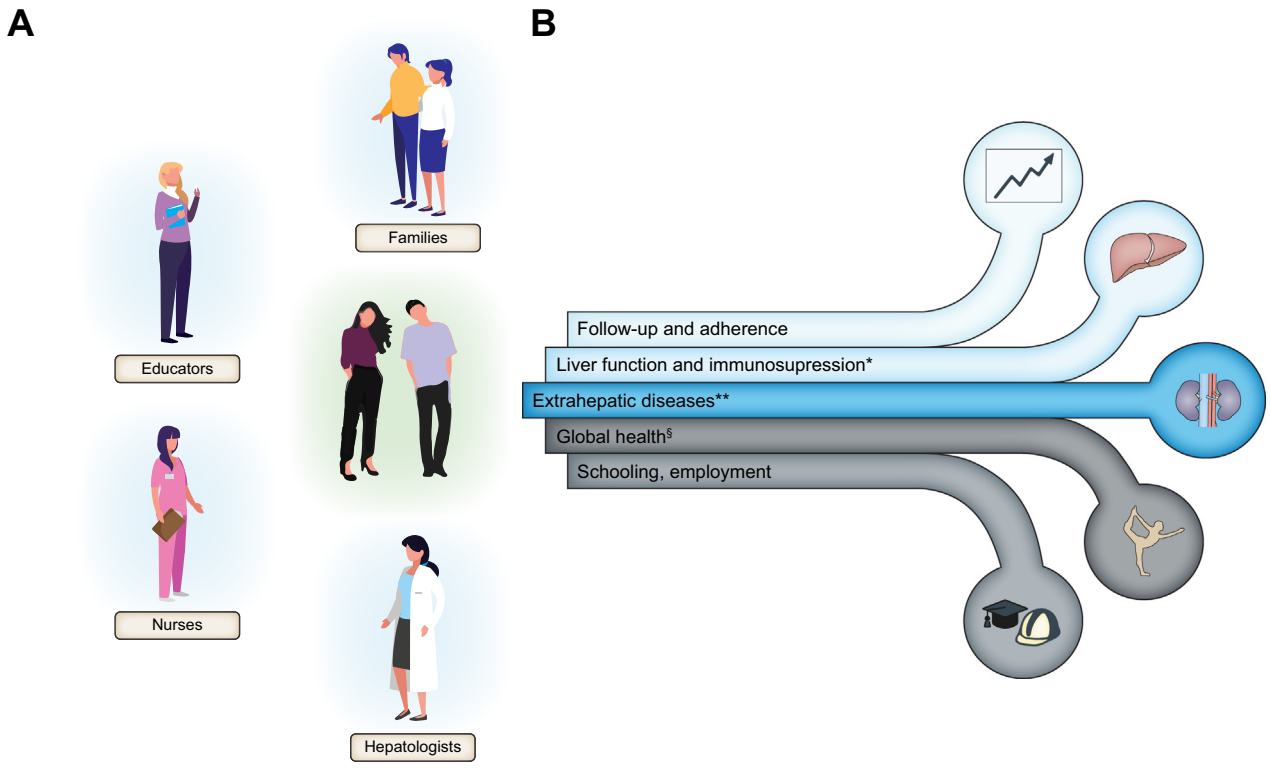

Fig. 8. Transition programme from paediatric to adult healthcare service. (A) Transplant patients reaching adulthood are ready to undergo transition to the adult healthcare service. A dedicated team involving nurses, paediatric hepatologists, transplant hepatologists, health educators will help them during this active process and will follow them up henceforth. The family play an active role. (B) Main goals to be pursued after transition; *wise minimisation of immunosuppression and surveillance against primary disease recurrence; **renal dysfunction, metabolic diseases need prevention, surveillance and/or early treatment; §including mental health, quality of life.

How can sexual function and safe pregnancy be improved in LT recipients?

Recommendations

- Transplant care providers should address sexual dysfunction in both male and female recipients. Patients with sexual dysfunction have to undergo thorough diagnostic evaluation and to determine the appropriate pharmacologic and/or non-pharmacological therapies **(LoE 3, strong recommendation, strong consensus).**
- Pre-conceptional counselling is recommended for LT recipients, in order to assess graft function, rule out risk of drug-related teratogenic effects, and perform genetic tests if needed. Obstetricians and transplant hepatologists should ensure a combined, strict follow-up during pregnancy, and immediately after delivery **(LoE 3, strong recommendation, strong consensus).**

Successful LT leads to improvements in sex hormone disturbances in both men and women, but post-LT medication (including immunosuppressants) can interfere with hormone metabolism.[471] Since sexual function after transplant in both male and female patients is poorly evaluated, it is mandatory for the transplant care providers to learn how to address male and female recipients to highlight the presence of urological and gynaecological disorders, in collaboration with the urologist and gynaecologist, according to patients' wishes. Among the types of medication that may be involved in the pathogenesis of erectile dysfunction in male patients, antihypertensives and corticosteroids should also be borne in mind. The pathogenesis of erectile dysfunction is multifactorial and causes include hypogonadism as well as treatment with calcineurin inhibitors.[471] Women achieve normal menstrual function and fertility a few months after LT, and the recommendation for women of reproductive age who undergo LT is to monitor their menstrual function and use of contraception. Women currently account for one in three LT recipients, and approximately a third of them are of reproductive age (18–49 years old).[472] There is also a stronger suggestion that pregnancy is not recommended within 2 years after LT. The most important factors for the good outcome of a subsequent pregnancy are stable graft function, stable immunosuppression, and no hypertension prior to conception. The pregnancy must be planned, and the physician should optimise the woman's immunosuppression and check for good graft function.[472,473] Although there is no specific mention of the recommended timing of a conception after LT, waiting a year or two is generally considered a good idea.[472] Cyclosporine and tacrolimus have not been definitively associated with teratogenesis. Steroids can complicate pregnancy, with the side effects observable in any patient (high risk of infection, osteopenia, hypertension, hyperglycaemia, cataracts). Steroids can also exacerbate gestational diabetes.[474] Azathioprine apparently has no teratogenic effects. It crosses the placenta, but the fetus does not have the enzyme needed to convert it into its active form. The issue with this drug mainly concerns the associated oncogenic risk.[475] Few data are available about the role of MMF and its use during pregnancy is not advisable. Breastfeeding is strongly recommended by paediatric associations as the sole diet for the newborn until they are 6 months old at least. The doses of immunosuppressants taken during breastfeeding are lower than during gestation, so it is important to adjust a new mother's immunosuppressant therapy after delivery to allow for breastfeeding, if possible.[472] In the transplant centre there should be multidisciplinary counselling between the transplant team, obstetricians and neonatologists to plan the pregnancy and also the follow-up after pregnancy. Where appropriate, a clinical genetics referral may be appropriate.

Special topics: Management of pre-transplant existing pronounced hypersplenism in LT candidates

Hypersplenism is common in patients with advanced cirrhosis. It can affect all haematological cell lines, but thrombopenia is the most common feature.[476] Its origin is multifactorial, linked to portal hypertension with intra-splenic sequestration, myeloid toxicity (including alcohol, anti-viral, chemotherapy), antiplatelet antibody, and/or low levels of thrombopoietin.[476] The presence of a low platelet count should be integrated in the broader picture of cirrhosis affecting both pro- and anticoagulant factors and creating a new homeostasis.[477] To illustrate, a low platelet count *per se* is not suggested to predict the risk of bleeding in patients with cirrhosis.[478,479] In this setting, rotational thromboelastometry may be superior to routine coagulation laboratory tests, and may accurately predict the risk of bleeding during high-risk procedures, including during LT.[480–482]

As a rule, the correction of a low platelet count is not recommended before low-risk procedures.[477] Blood products should be used sparingly in order to avoid side effects, including fluid overload. Also, the management of platelets should integrate correction of coagulation factors.

Before a high-risk procedure (including transplantation) or in the presence of bleeding, platelet transfusion can work synergistically with local haemostatic means. As an alternative, avatrombopag and lusutrombopag, two thrombopoietin receptor agonists should be considered. As demonstrated by a meta-analysis, and despite the absence of cost-effectiveness, they are superior to no treatment in avoiding platelet transfusion and rescue therapy.[483] They need a few days to work, and their use is more suited for planned live donation than deceased donor transplantations. Other means such as splenectomy, and less invasive alternatives such as partial splenic vein embolization, and spleen parenchyma ablation by radio-frequency or microwave have been described but are currently not part of standard management strategies.[484–486]

After transplantation, portal pressure decreases rapidly, and thrombopoietin levels increase starting from day 1. As a consequence, platelet count usually reaches normal values with 2 weeks.[487] However, in the presence of pre-transplant splenomegaly, subclinical hypersplenism may persist in some patients.[488]

Conclusion

Several achievements have been made in the LT field, however there are still multiple unmet needs that should be addressed in

the near future. LT indications are expanding, pushing the limits for oncological patients, patients with ACLF and rare liver diseases and requiring objective selection criteria. An adequate donor pool is needed in order to respond to an increased demand and will require the expanded use of DCD, LDLT (even from anonymous donors), and poor quality livers improved as a result of machine perfusion systems. Equity in the access to LT should be offered to all transplant candidates and outcome measures should not be limited to graft and patient survival but aim to improve quality of life. Long-term outcomes of LT recipients, especially considering young adults transplanted as children, represent a new challenge for transplant care providers. Management of rejection and balance between efficacy and side effects of immunosuppression remains the object of many trials. Machine learning systems may help in solving some of these issues.

Appendix. Delphi round agreement on the recommendations of the present clinical practice guidelines.

Recommendation	Consensus
A potential candidate for LT should not be disqualified based on age alone **(LoE 2, strong recommendation).**	94%
The assessment of candidacy for LT in the elderly population should include cardiopulmonary, frailty-sarcopenia and nutritional status, anatomical and surgical factors, as well as age- and risk factor-based screening for asymptomatic malignancies **(LoE 3, strong recommendation).**	97%
New allocation systems should be implemented to address the compromised access of women to LT **(LoE 3, strong recommendation).**	93%
Patients with ACLF grade 3 (and CLIF-C ACLF score ≤64) should be evaluated for LT **(LoE 3, strong recommendation).**	100%
Patients with ACLF and more than three organ failures according to the CLIF-C organ failure score or CLIF-C ACLF score >64 should be re-evaluated daily and only listed for LT when organ failures and/or ACLF grade improves to ≤3 (or CLIF-C ACLF score ≤64). In cases of acute respiratory distress syndrome and/or high lactate levels, the indication for transplantation should be a cautious decision as this is associated with increased postoperative mortality **(LoE 3, strong recommendation).**	91%
Selected patients with severe acute alcohol-related hepatitis not responding to medical treatment should be considered for early LT if they present with favourable predictors for post-LT sobriety **(LoE 3, strong recommendation**	94%
Patients with acute severe autoimmune hepatitis should be considered for early corticosteroid therapy before hepatic encephalopathy onset **(LoE 3, strong recommendation).**	100%
Patients with acute severe autoimmune hepatitis with severe coagulopathy and hepatic encephalopathy III-IV should not be treated with corticosteroids but considered for early LT **(LoE 3, strong recommendation).**	94%
Patients with severe autoimmune hepatitis not responding to corticosteroids (no improvement or worsening in liver biochemistry and liver synthetic function parameters or development or worsening of hepatic encephalopathy) should be considered for early LT **(LoE 3, strong recommendation**	100%
In patients with Wilson's disease and end-stage liver failure, neuropsychiatric manifestations should not preclude referral, evaluation and waitlisting for LT **(LoE 4, strong recommendation).**	100%
Patients with Wilson's disease and isolated neuropsychiatric manifestations should ideally be referred for evaluation by a multidisciplinary team at a LT centre. The decision to proceed with LT screening needs to be taken on a case-by-case basis after careful discussion **(LoE 4, strong recommendation).**	100%
Patients with a history of a recently treated non-hepatic cancer, who have undergone a curative therapy and are tumour free/in remission, should undergo a multidisciplinary assessment for suitability and timing of LT that includes detailed cancer- and treatment-specific information, including "recurrence-free survival" estimates, and therapeutic options for potential post-LT cancer recurrence **(LoE 3, strong recommendation).**	97%
Patients with active malignancy should be excluded from the LT waiting list except those with selected indolent or very low-grade cancers **(LoE 3, strong recommendation).**	100%
Coronary imaging, invasive or non-invasive, should be considered as the initial strategy in LT candidates who are at high risk of significant coronary artery disease **(LoE 3, strong recommendation).**	100%
In LT candidates, unrevascularisable significant coronary artery disease (defined by ≥50% stenosis in ≥1 segment of the three major coronary arteries, or ≥70% stenosis in moderate-size branch vessels) should be considered a contraindication to LT **(LoE 3, strong recommendation).**	100%
In patients with obesity with compensated cirrhosis and a BMI >35 without clinically significant portal hypertension, bariatric surgery may be considered in centres with experience in both LT and bariatric surgery **(LoE 4, weak recommendation).**	90%
In patients with obesitywith decompensated cirrhosis and a BMI >35, bariatric surgery should be considered only at the time of LT or thereafter **(LoE 3, strong recommendation).**	91%
Sleeve gastrectomy should be proposed as the technique of choice in selected patients with obesity with well-compensated cirrhosis, or in the setting of LT **(LoE 3, strong recommendation).**	97%
In patients with compensated liver disease, portopulmonary hypertension alone is not an indication for LT **(LoE 2, strong recommendation).**	97%
Vasomodulator therapy should be offered to all LT candidates with porto-pulmonary hypertension and mean pulmonary arterial pressure ≥35 mmHg and pulmonary vascular resistance ≥3 Wood units **(LoE 2, strong recommendation).**	100%
A mean pulmonary arterial pressure >45 mmHg despite vasomodulator treatment should be considered as an absolute contraindication to LT **(LoE 2, strong recommendation).**	100%
In patients with porto-pulmonary hypertension in need of LT, an adequate haemodynamic response to vasomodulator therapy is required to proceed to transplant and should be defined as mean pulmonary arterial pressure <35 mmHg and portal vascular resistance <5 Wood units or mean pulmonary arterial pressure of 35 to 45 mmHg and portal vascular resistance <3 Wood units **(LoE 2, strong recommendation).**	94%
In the situation of cirrhosis with chronic kidney disease, combined liver-kidney transplantation is recommended in patients who are on dialysis for end-stage renal disease or have a most recent eGFR/creatinine clearance value of ≤30 ml/min. **(LoE 2, strong recommendation).**	97%
In the situation of cirrhosis with chronic kidney disease for which reversibility is uncertain, both simultaneous or sequential liver-kidney transplantation is recommended **(LoE 2, strong recommendation).**	86%

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Recommendation	Consensus
In the situation of cirrhosis associated with sustained acute kidney injury, simultaneous liver-kidney transplantation is recommended in patients with GFR ≤25 ml/min and/or on haemodialysis for at least the last 6 weeks **(LoE 2, strong recommendation).**	97%
In patients with compensated cirrhosis who are candidates for kidney transplantation, KT alone can only be proposed in the absence of clinically significant portal hypertension. The diagnosis of clinically significant portal hypertension in this situation warrants specific studies **(LoE 5, open recommendation).**	93%
During pre-transplant evaluation, all patients with cirrhosis should be assessed for frailty **(LoE 3, strong recommendation).**	100%
Frailty *per se* should not be a contraindication to LT **(LoE 3, strong recommendation).**	97%
Any frail patient should be evaluated for rehabilitation and nutritional support **(LoE 4, strong recommendation).**	97%
Anticoagulation is recommended in LT candidates with cirrhosis and a newly diagnosed bland portal vein thrombosis **(LoE 3, strong recommendation).**	100%
A transjugular intrahepatic portosystemic shunt procedure should be considered in selected transplant candidates with portal vein thrombosis **(LoE 3, strong recommendation).**	75%
Selected patients with HCC beyond the Milan criteria (without macrovascular tumour invasion and extrahepatic spread) should be considered for LT if downstaged to within Milan criteria or other criteria (*i.e.* UCSF and AFP score) according to country allocation system criteria **(LoE 2, strong recommendation).**	97%
Patients with unresectable HCC who present with an AFP level >1,000 ng/ml should not be considered for transplantation (regardless of whether they are within or beyond Milan criteria) except when treated with liver-directed therapy resulting in a significant sustained and persistent decline in AFP levels **(LoE 2, strong recommendation).**	100%
Immunotherapy may be given with caution to patients with HCC who are on the transplant waiting list and whenever feasible, immunotherapy should be stopped to allow for a period of washout prior to transplantation to reduce the risk of refractory rejection, though the optimal interval between completion of therapy and LT is not known and may be impacted by the pharmacokinetics of the immunotherapy agent **(LoE 4, weak recommendation).**	94%
Well-selected patients with unresectable liver-only colorectal metastasis may experience improved survival following LT, and thus may be considered for transplantation within the setting of a clinical trial given that results to date are limited by length of follow-up, relatively small numbers of patients, and uncertainty regarding survival outcomes for the comparative group treated with contemporary systemic and surgical therapies. **(LoE 3, weak recommendation).**	97%
Selected patients with unresectable liver-only G1-2 neuroendocrine tumour metastases who have had the primary tumour resected, followed by a period of disease stability, may be considered for LT in centres which are experienced in treating neuroendocrine tumours **(LoE 4, weak recommendation**	97%
Patients with cirrhosis and small, unresectable intrahepatic cholangiocarcinoma (<2-3 cm) may be considered for LT, ideally within the setting of a clinical trial (given that the evidence to date is limited) and ideally treated on the waiting list with liver-directed therapies such as ablation, transarterial radioembolisation or transarterial chemoembolisation, depending on anticipated waiting time **(LoE 4, weak recommendation).**	83%
Highly selected patients with unresectable early-stage perihilar cholangiocarcinoma may be considered for treatment with neoadjuvant chemoradiotherapy followed by LT **(LoE 3, weak recommendation).**	89%
The use of HCV RNA-positive grafts in HCV-positive or HCV-negative recipients should be considered provided informed consent, appropriate organ quality and a rapid initiation of effective antiviral therapy are guaranteed **(LoE 3, strong recommendation).**	100%
Anti-HBc-positive HBsAg-negative organs should be used for transplantation independently of the HBV status of the recipient provided the recipient is adequately vaccinated and/or there is an option of indefinite prophylaxis with a nucleos(t)ide analogue **(LoE 3, strong recommendation).**	100%
In HBV-uninfected patients with short life expectancy on the waiting list, the use of HBsAg-positive grafts can be considered if there is an option for indefinite treatment with potent nucleos(t)ide analogues (antivirals), HDV is absent in the donor and the recipient, graft quality is adequate, and the recipient provides informed consent **(LoE 4, weak recommendation).**	85%
The use of liver donors with HIV infection can be considered in HIV-infected recipients if there is an option for effective indefinite anti-HIV therapy, and the recipient provides informed consent **(LoE 4, weak recommendation).**	97%
Liver donation from a SARS-CoV-2-positive donor should not be contraindicated **(LoE 3, strong recommendation).**	93%
SARS-CoV-2 monitoring of the recipient should be provided and antivirals should be administered in case of SARS-CoV-2 infection, considering drug-drug interactions **(LoE 4, strong recommendation).**	89%
In case of donation from a donor with a known history of cancer, the risk of cancer transmission *vs.* the risk of death on the waiting list before a suitable graft without such risks would become reasonably available should be weighted, and an individual value-based decision and shared-decision for transplantation should be made if the risk of death on the waiting list outweighs the risk of cancer transmission and the recipient provides informed consent **(LoE 3, strong recommendation).**	97%
Domino LT from donors with familial amyloidotic polyneuropathy can be considered in selected recipients **(LoE 4, weak recommendation).**	97%
After domino LT for familial amyloidotic polyneuropathy, close monitoring for early detection of *de novo* TTR-neuropathy and cardiomyopathy should be performed **(LoE 4, strong recommendation).**	100%
To reduce mortality on the LT waiting list, countries should optimise the allocation of deceased donor livers for transplantation. If there is ongoing avoidable waiting list mortality, implementation or expansion of LDLT programmes should be considered **(LoE 2, strong recommendation).**	97%
In all settings, LDLT experience should be concentrated in high-volume centres with sufficient training and experience, in order to minimise risks and optimise outcomes for all stakeholders **(LoE 2, strong recommendation).**	97%
Both donor and recipient risk factors should be considered in order to optimise controlled DCD LT outcomes, while combining several risk factors should be avoided or else the application of advanced perfusion preservation strategies should be applied **(LoE 2, strong recommendation).**	100%
Livers from uncontrolled DCD donors recovered with normothermic regional perfusion, should be restricted to recipients in whom the risk of continued waiting outweighs the risk of an adverse post-transplant outcome **(LoE 3, strong recommendation).**	97%
Evaluation of live liver donor candidates should be performed according to an established protocol and include liver anatomical, parenchymal, and volumetric assessment; age- and sex-appropriate screening for clinically relevant as well as silent co-morbid conditions, including procoagulant conditions; MASLD, cardiovascular disease, cancer, infectious, and other potentially transmissible diseases; and psychosocial risk factors **(LoE 2, strong recommendation).**	100%

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Recommendation	Consensus
Live donor liver remnant should be at least 30% of pre-donation volume or mass **(LoE 2, strong recommendation).**	100%
Although novel liver allocation systems, including ones of donor-recipient matching, may offer certain advantages relative to MELD, their use cannot be recommended as of yet due to the lack of robust clinical data **(LoE 3, weak recommendation).**	96%
Perfusion preservation strategies should be considered at different points in the donation and transplantation process to reduce adverse post-transplant outcomes, including biliary complications, in particular when using extended criteria and DCD grafts **(LoE 2, strong recommendation).**	100%
Machine perfusion strategies should be used to increase the donor organ pool and organ utilisation **(LoE 1, strong recommendation).**	100%
In the absence of a size-matched whole liver graft, both split and living donor transplantation should be performed in small children **(LoE 3, strong recommendation).**	94%
Both the piggy-back and the total caval replacement techniques are viable options, with no clear preference for one over the other. Selection should be based on local expertise, prevailing practice, and individual patient anatomy **(LoE 3, weak recommendation).**	96%
Selective use of temporary portocaval shunt or veno-venous bypass may be considered **(LoE 3, weak recommendation).**	n.a.
Tacrolimus trough levels should be kept at 6-10 ng/ml during the first month followed by 4-8 ng/ml thereafter **(LoE 1, strong recommendation).**	90%
It is recommended to combine tacrolimus with other immunosuppressive drugs (MMF, AZA or mTORi) to allow for a lower range of tacrolimus trough levels than recommended for monotherapy and to help preserve renal function **(LoE 2, strong recommendation).**	100%
The administration of basiliximab induction with delayed introduction of tacrolimus is strongly recommended in patients at risk of developing post-transplant renal dysfunction **(LoE 2, strong recommendation).**	100%
Exposure to CNIs should be minimised by employing combined immunosuppressive regimens, preferably an mTORi in the case of high risk of hepatic or extrahepatic cancer recurrence **(LoE 2, strong recommendation).**	97%
An mTORi-based immunosuppression regimen is strongly recommended in patients with history of recurrent/*de novo* non-melanoma skin cancer **(LoE 2, strong recommendation).**	97%
Screening for preformed DSAs should be performed in recipients at risk of humoral sensitisation (previous transplantation, previous transfusions, previous pregnancies). Patients with a high level of preformed DSAs should receive more intensive follow-up in terms of transaminases and non-invasive fibrosis testing than those who do not have detectable pre-formed DSAs **(LoE 4, strong recommendation).**	97%
Monitoring for *de novo* DSAs in combination with alanine aminotransferase and other non-invasive tests such as transient elastography may be recommended to identify LT recipients at risk of exhibiting sub-clinical rejection in whom aggressive immunosuppression minimisation would not be advisable. In the presence of high mean fluorescence intensity DSAs, minimisation is not advisable unless allograft damage has been excluded by performing a liver biopsy **(LoE 3, weak recommendation).**	86%
In patients with combined acute T cell-mediated rejection and AMR, the T cell-mediated component may be treated first according to each unit's standard of care (*e.g.* steroid boluses). Treatment with plasmapheresis +/- intravenous immunoglobulin is suggested in patients who do not respond to this approach or in those with 'pure' acute AMR (as per Banff criteria) **(LoE 4, open recommendation).**	97%
In patients with persistent signs of AMR who do not respond to the regimens outlined above, a second-line therapy can be considered (*e.g.* rituximab, to deplete B cells or eculizumab to inhibit complement activation) **(LoE 5, weak recommendation).**	90%
Patients with a diagnosis of probable chronic AMR according to current Banff criteria, exhibiting raised transaminases and/or at least moderate inflammatory infiltrates, may be treated by intensifying the conventional immunosuppression regimens **(LoE 5, weak recommendation).**	97%
Complete withdrawal of immunosuppression should not be an aim of standard of care, even in the case of an extended rejection-free postoperative course **(LoE 2, strong recommendation).**	100%
If immunosuppression is completely discontinued for individual reasons, close monitoring of rejection that includes histological assessments should be guaranteed **(LoE 2/3, strong recommendation).**	100%
To prevent alcohol relapse after LT, a multidisciplinary team including transplant hepatologist, transplant surgeon, psychologist, psychiatrist and addiction specialist should be involved in all stages of the transplant procedure, including the assessment during the evaluation process and in long-term follow-up **(LoE 3, strong recommendation).**	100%
The pattern of alcohol consumption should be included in the multidisciplinary evaluation. If the patient fulfils criteria for alcohol use disorder, pharmacological treatment and behavioural therapy either before or after LT should be considered as part of the multidisciplinary management approach **(LoE 3, strong recommendation).**	100%
If there is a discrepancy between a patient's self-reported alcohol consumption and clinical suspicion of alcohol intake, routine screening for alcohol biomarkers should be performed. This can be done using ethyl glucuronide in urine or possibly hair, phosphatidylethanol in serum or another appropriate test depending on local availability **(LoE 3, strong recommendation).**	100%
The treatment of alcohol relapse after LT should involve a multidisciplinary team including a transplant hepatologist, a psychologist, a psychiatrist and an addiction specialist. Pharmacological interventions to mitigate cravings should also be integrated into the therapeutic strategy **(LoE 3, strong recommendation).**	100%
To prevent recurrent or *de novo* MASH, metabolic risk factors should be addressed and treated according to current standards **(LoE 3, strong recommendation).**	100%
Healthy lifestyle (appropriate diet, avoiding alcohol consumption, physical activity to avoid weight gain) and pharmacological treatment of complications (arterial hypertension, dyslipidaemia, diabetes, *etc.*) should be aggressively pursued in the post-transplant setting **(LoE 3, strong recommendation).**	100%
When there is uncertainty in diagnosing recurrent or *de novo* MASH *vs.* other causes of liver disease, a liver biopsy is suggested **(LoE 3, weak recommendation).**	93%
Adjustment of immunosuppression should be considered according to the kind of associated complication but should be balanced against the risk of rejection **(LoE 2, strong recommendation).**	97%
Ursodeoxycholic acid should be given lifelong after LT to all patients with primary biliary cholangitis to prevent recurrence **(LoE 2, strong recommendation).**	100%
For transplant recipients with primary biliary cholangitis no immunosuppressive regimen (in particular cyclosporine over tacrolimus) should be recommended in order to prevent disease recurrence **(LoE 2/3, strong recommendation).**	97%
In transplant recipients with AIH, corticosteroid withdrawal to avoid long-term steroid-associated side effects, should be performed cautiously due to the risk of disease recurrence **(LoE 2/3, strong recommendation).**	91%

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Recommendation	Consensus
There is no specific immunosuppressive regimen or treatment effective in preventing primary sclerosing cholangitis recurrence **(LoE 3, strong recommendation).**	100%
Quality of life after LT should always be considered as an outcome measure. Strategies to improve post-LT health-related quality of life are: trusted relationship with medical team; optimisation of mental health through prescription of psychologic therapies when needed; physical activity **(LoE 2, strong recommendation).**	100%
Adherence to medical prescriptions and particularly to immunosuppressive therapy should be regularly evaluated after LT. Strategies to improve post-LT non-adherence include targeted education strategies, simplified drug regimens, psychological behavioural support **(LoE 3, strong recommendation).**	100%
Special attention should be dedicated to adolescents, since they are at high risk of poor adherence, poor school performance and difficulties in social relationships. These issues should be addressed by a multidisciplinary team **(LoE 2, strong recommendation).**	100%
A transition programme should be developed in all centres (especially where there is an active paediatric transplant programme), in order to ensure a smooth transfer of care for transplant recipients reaching adulthood, and global care thereafter **(LoE 3, strong recommendation).**	100%
Transplant care providers should address sexual dysfunction in both male and female recipients. Patients with sexual dysfunction have to undergo thorough diagnostic evaluation and to determine the appropriate pharmacologic and/or non-pharmacological therapies **(LoE 3, strong recommendation).**	97%
Pre-conceptional counselling is recommended for LT recipients, in order to assess graft function, rule out risk of drug-related teratogenic effects, and perform genetic tests if needed. Obstetricians and transplant hepatologists should ensure a combined, strict follow-up during pregnancy, and immediately after delivery **(LoE 3, strong recommendation).**	97%

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; AKI, acute kidney injury; AMR, antibody-mediated rejection; AS-AIH, acute severe AIH; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; cDCD, controlled DCD; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CPG, clinical practice guidelines; DCD, donation after circulatory determination of death; DDLT, deceased donor liver transplantation; DSAs, donor-specific antibodies; EASL, European Association for the Study of the Liver; ELTR, European Liver Transplant Registry; GLP-1, glucagon-like peptide 1; HOPE, hypothermic oxygenated perfusion; HR, hazard ratio; ICA, Invasive coronary imaging; INR, international normalised ratio; IVC, inferior vena cava; LDLT, living donor liver transplantation; LFI, liver frailty index; LoE, level of evidence; LR, liver resection; LT, liver transplant(ation); MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; mPAP, mean pulmonary aterial pressure; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; OPTN, Organ Procurement & Transplantation Network; PBC, primary biliary cholangitis; PoPH, portopulmonary hypertension; PROs, patient-reported outcomes; PSC, primary sclerosing cholangitis; PVR, pulmonary vascular resistance; RCT, randomised-controlled trial; RR, relative risk; RRT, renal replacement therapy; TIPS, transjugular intrahepatic portosystemic shunt; UCSF, University of California, San Francisco; UDCA, ursodeoxycholic acid; uDCD, uncontrolled DCD; UNOS, United Network for Organ Sharing.

Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

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Author names in bold designate shared co-first authorship:

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