ERAS RECOMMENDATIONS

1 PREOPERATIVE COUNSELLING

The unpredictable time spent on the waiting list, the progressive decline in physical function and daily life activities, together with the new "chronic" condition after LT requiring life-long treatments are well-known sources of anxiety, stress and depression among patients on waiting list.[1–4] Moreover, insufficient knowledge about the disease or transplantation seems to be associated with a lower therapeutic compliance.[5]

Current trends on patient education in surgery[6] suggest the scheduling of early preoperative education, with increased frequency of message exposure through several interventions and/or reinforcements, focusing content on the postoperative period and management. The information need on this latter point was ranked higher than the intra-operative and preoperative period by a sample of patients on a LT waiting list and their families.[7]

Multidisciplinary educational strategies should involve a surgeon, anaesthesiologist and most importantly a nurse or an allied-health professional, as a link between the patient and the team, establishing attitudes of trust and allowing the exchange of supplementary information.[4,6] Interestingly, the information needed is reported to be higher for the family or caregivers, compared with the LT candidates themselves and when the cares are present, their involvement can be of considerable value in the patient's adherence to the complex therapeutic process of LT.[8] Regular refreshing of information (e.g. yearly), individual or grouped, may be considered.

Combining oral and written information was preferred by a sample of 42 patients and caregivers[7]: listening to explanations, reading and individual guidance, followed by internet searches, and group discussion,[7] with booklets, leaflets or DVDs as message-reinforcement support.[6]

Regarding information on graft quality, decisions in the case of a deceased donor LT have to be made quickly, and the risks and benefits are difficult to fully explain at the time of an organ offer.

A study inquiring on patients' preferences while waiting for LT[9] revealed how an involvement in shared decision should be consistent with patient preferences: for this reason information on risks related to standard or extended criteria donors may be provided in detail to all patients listed for transplantation. Those patients who want to be informed and involved in shared decision making at the time of the organ offer should be identified at the time of listing, and receive additional information and potentially decision aids.

In this sense, a specific pilot study highlighted how an online decision aid could improve patient's knowledge on organ quality, mitigating the unwillingness to accept donor-specific risks or an extended donor graft.[10]

Recommendations: Patients on a waiting list should receive dedicated, multidisciplinary educational counselling.

Evidence level Low

Recommendation grade Strong

2 PREHABILITATION

Malnutrition and protein depletion are highly prevalent in patients waiting for liver transplantation, and represent a major risk factor for post-transplant morbidity.[11,12] Similarly, the progressive decline in functional capacity and physical inactivity is a primary contributor to frailty,[13,14] which is associated with a major risk of death on waiting list, postoperative infection and early death after liver transplantation.[13,15–17]

As an alternative to the recommended imaging-based methods to assess sarcopenia,[11,16] 6 minutes walking test (6MWT) or liver-specific frailty index[14] better captures the frail phenotype than subjective assessments in pretransplant patients.[15]

Prehabilitation is intended as a proactive process of preoperative optimization, from the diagnosis of the disease until surgery to improve functional reserve, and potentially decrease the incidence of postoperative complications and hasten recovery.[18–20] Several studies on colorectal surgery showed an improvement in preoperative baseline functional capacity with targeted trimodal prehabilitation, including exercise, nutritional and psychological interventions.[21,22] Similar results are not observed in liver surgery, probably due to small sampled trials.[23]

Adapted Physical therapy

Two meta-analyses focussed on physical therapy on patients affected by cirrhosis: 1 from 2017 including 4 RCT[24] and 89 patients, and a Cochrane review from 2018 including 2 supplementary randomized studies[25] and 173 patients. The intervention groups participated in 8-14 weeks of home-based or supervised physical exercise (aerobic, resistance or both) compared to relaxation or no intervention. The included studies were small sampled, with high risk of biases and heterogeneity of measured outcomes and endpoints across the trials.

Both meta-analyses concluded on the absence of a clear beneficial or detrimental effect of physical exercise on mortality, morbidity, or health-related quality of life of patients affected by cirrhosis. Since none of the included trials followed the patients until LT, no conclusion can be made on the impact of physical exercise on liver transplantation outcomes.

Results are expected from 2 ongoing trials (PRIMER trial[26] and FAPA trial[27]), exploring the impact of supervised physical exercises in patients on waiting list on the length of stay in ICU, and mortality rate after LT.

Recommendations: There is no evidence yet of the benefit or harm of physical exercise in cirrhotic patients before liver transplantation.

Evidence level Low

Recommendation grade Weak

Preoperative nutritional screening

Among the available screening tools for malnutrition, none has been rigorously validated in patients affected by cirrhosis, leaving Royal Free Hospital Nutrition Prioritizing Tool (RFH-NPT) as the best option currently available.[28] Patients with a high risk of malnutrition (score 2-7), should be referred for nutritional intervention: counselling involving a multidisciplinary team (physicians, nurses, pharmacists and dieticians) is associated with better survival than counselling by just 1 profession.[29]

Resting energy expenditure (REE) in cirrhosis is usually increased: as an example, patients with chronic liver disease and a sedentary lifestyle should receive a total energy supply of 1.3 x REE.[11] To easily measure REE at bedside, instruments like hand-held calorimetry[30] are available on the market.

Recommendations: Patients with cirrhosis should be screened for malnutrition, using a validated tool, and addressed to a multidisciplinary team for nutritional intervention.

Evidence level Moderate

Recommendation grade Strong

Preoperative nutrition

The unpredictable character of deceased donor liver transplantation reduces the application of classical preoperative nutrition programs. This does not apply to living donor liver transplantation (LDLT), which is a scheduled or semi-scheduled intervention.

According to the ESPEN guidelines,[11] oral diet of cirrhotic patients in the preoperative period should provide 30-35 Kcal x kg^{-1} x d^{-1} with a protein intake of 1.5 g x kg^{-1} x d^{-1}, and minimizing periods of starvation by consuming 3 to 5 meals a day with a late evening snack. Of note, protein intake should not be restricted in cirrhotic patients with hepatic encephalopathy (HE) as it increases protein catabolism.[31,32] Last, a low sodium (unpalatable) diet present an increased risk of even lower food consumption, which should be balanced against its moderate advantage in the treatment of ascites.[11]

A Cochrane systematic review[12] explored the effect of nutritional supplements and enteral nutrition before liver transplantation, but given the clinical heterogeneity between the trials (interventions and measured outcomes) the results could not be meta- analysed. For this reason, standard preoperative nutrition regimens should be used (Grade of recommendation A).[11,12]

In cirrhotic patients who cannot be fed adequately orally, enteral nutrition is recommended, with oesophageal varices not being an absolute contraindication for positioning a nasogastric tube.[11] On the other hand, the placement of a percutaneous endoscopic gastrostomy (PEG) is associated with a higher risk of complications (ascites or varices), and can only be used in selected cases.[11] When a nutritional intervention is introduced, its efficacy could be measured by the handgrip strength tool.[11]

Recommendations cirrhotic patients malnourished or in the preoperative period should receive 30-35 Kcal x kg^{-1} x d^{-1} and a protein intake of 1.5 g x kg^{-1} x d^{-1}, through a standard nutrition regimen minimizing periods of starvation, with no need of protein restriction in case of HE.

Evidence level High

Recommendation grade Strong

Probiotics

A meta-analysis on 246 participants from 3 RCTs and a prospective trial, explored the impact of probiotics administration before liver transplantation.[33] The probiotics used in the studies were different in terms of combinations and concentrations, with *lactobacillus species* being the main component used in all the studies. The authors observed how the use of combination of probiotics and prebiotics prior to, or on the day of liver transplantation, was associated to a decreased rate of postoperative infection, shorter hospital stay, ICU stay and a reduced duration of antibiotic use.

A supplementary RCT[34] not included in the previous meta-analysis observed a reduced 30-days and 90-days infection rate after LT, in patients after receiving 4-strain probiotic preparation daily from enrolment until LT, compared to placebo. Despite the mitigation of the conclusions (study underpowered and interrupted for slow accrual, with n=55 randomized patients instead of an expected sample of n=200) the findings of this trial were in accordance with those of the previous meta-analysis, suggesting that preoperative probiotic administration is associated with decreased rate of postoperative infection.

Recommendations Some evidence supports the use of probiotics, prior to, or on the day of liver transplantation. However, the duration of the treatment and the number of strains included cannot be precisely defined given their variability across the studies.

Evidence level High

Recommendation grade Weak

Preoperative immunonutrition

Pre- and perioperative supplementation with immunomodulating nutrients (IN) in patients undergoing major elective surgery seems to offer some clinical benefit.[35] Waiting for the results of a double blind ongoing trial,[36] there is limited evidence for their use in liver surgery.[37]

The strongest evidence for the perioperative use of IN in liver transplantation arises from a recent meta-analysis.[38] suggesting a reduction in the infectious complications rate and length of hospital stay. This meta-analysis, however, included 7 RCTs with low sample size, mixing different types of immunonutrition (Glutamine dipeptide, Arginine, nucleotides and ω-3 fish oil, in different combination or alone), with moderate risk of bias and high heterogeneity of the results. Among the included trials, only 1 RCT with low risk of bias and narrow confidence intervals provided oral IN administration in the preoperative period[39]: in this trial no improvement of nutritional status of patients on waiting list, nor any reduction in early infectious complication rates posttransplant was observed.

Results are waited for an ongoing, double-blind, single-center trial[40] exploring the benefit of perioperative or postoperative administration of Omega 3 enriched lipid emulsions in LDLT.

Recommendations: the available evidence is nonconclusive, and no recommendation can be given for systematic IN before LT.

Evidence level Moderate

Recommendation grade Weak

3 PERIOPERATIVE FASTING AND CARBOHYDRATE LOADING

Liver glycogen is depleted in cirrhotic patients and it is therefore advisable to take great care to shorten periods without nutrient intake, to avoid gluconeogenesis from muscle protein in malnourished patients.[11]

Preoperative fasting

Preoperative fasting no more than 2 h for liquids and 6 h for solid food has proven to be safe and is recommended for digestive surgery,[41,42] but there is no direct evidence in LT.

ESPEN guidelines[11] suggest that during the immediate period before LT, cirrhotic patients should be managed according to the ERAS approach in order to prevent unnecessary starvation. ERAS recommendations on liver,[37] pancreas[43] and colorectal surgery,[44] agree on the fact that intake of clear fluids up to 2 h before anaesthesia does not increase gastric residual volume, while solid food should be avoided 6 h before surgery.

However, a mitigation should be considered: prolonged gastric emptying due to tense ascites, diabetes or autonomic dysfunction are common among patients affected by end-stage liver disease,[45] increasing therefore the risk for inhalation during intubation.

Recommendations: Preoperative fasting does not need to exceed 6 h for solids and 2 h for liquids. Caution should be considered in case of risk factors for delayed gastric emptying (tense ascites, diabetes or autonomic dysfunction).

Evidence level Low

Recommendation grade Strong

Carbohydrate loading

Preoperative fasting worsen catabolic stress and increases insulin resistance after abdominal surgery,[46] which in LT can be enhanced by the graft quality[47] and can result in postoperative acute kidney injury[48] and late postoperative complications.[49]

To date 3 meta-analyses,[50–52] including a Cochrane systematic review,[51] with significant overlap across included studies, suggest that carbohydrate supplementation before surgery is safe but with little clinical benefit on length of stay, complication rate or patient discomfort.

Preoperative carbohydrate loading is recommended in colorectal[44] and liver surgery[37] guidelines, but no evidence is available in the domain of liver transplantation.

Besides the living donor setting, deceased donor LT is similar to emergency surgery, in that it has unpredictable timing. This characteristic may limit the applicability of a carbohydrate loading drink the evening before surgery and 2h before anaesthesia. In a pilot study comparing enhanced recovery versus standard care in liver transplantation, a shorter hospital stay but not complications rate was observed in the enhanced care group.[53] However, it was of note that compliance with preoperative carbohydrate loading was only 50 % in the enhanced recovery group.[53]

Last, similarly to the preoperative fasting, a mitigation should be considered in case of risk factors for prolonged gastric emptying including tense ascites, diabetes or autonomic dysfunction,[45] which are known to increase the risk for inhalation during intubation.

Recommendations: Carbohydrate loading may be recommended at patient admission for liver transplantation, at least 2 h before induction of anaesthesia. Caution should be considered in case of risk factors for delayed gastric emptying (tense ascites, diabetes or autonomic dysfunction).

Evidence level Low

Recommendation grade Weak

4 ANTIMICROBIAL PROPHYLAXIS

Bacterial sepsis, surgical site infections (SSI) and wound complications after liver transplantation increase mortality, morbidity, or hospital stay and are likely to increase overall transplant costs.[54–57] The major surgical procedure and concomitant administration of immunosuppressive treatment are 2 major reasons explaining why LT recipients receive antibiotic prophylaxis; however, its modalities can vary widely from 1 center to another. As emerging bacterial resistance continues to spread worldwide, the question of the broad spectrum of antibiotics to be used in this antibiotic prophylaxis arises.

Recently, an open-label RCT on 102 LT showed how an extended duration of antibiotic prophylaxis (72h) did not provide any advantage in terms of SSI, mortality or length of ICU or hospital stay, when

compared to an intraoperative prophylaxis only.[58] To be noted, despite the low risk of bias, the study was set with 60% power and a type I error rate of 0.10.

A Cochrane systematic review and meta-analysis[59] of 7 randomized controlled trials and 614 LT patients concluded on the absence of clear evidence for any intervention offering significant benefits in the reduction of bacterial infections or wound complications in liver transplantation. Selective bowel decontamination may even increase the rate of infections compared with prebiotics with probiotics.

Three supplementary single-center studies[60–62] cumulatively including 435 patients, suggested that(i) systematic administration of vancomycin led to reduce postoperative infections with enterococcus species at the cost of an increased rate of renal replacement after LT[60]; (ii) a reduction SSI rate with a combination of intraoperative antibiotic prophylaxis, skin preparation with 2% chlorexidine and adhesive surgical field[61]; (iii) the absence of advantage of selective bowel decontamination in terms of infectious complications or length of stay.[62] The cumulative level of evidence was low.

To date, no recommendation can be made to standardize the antibiotic regimen: neither the specific drug to be administered nor the redosing interval. However, the working group favors taking into account local microbiological data in order to best adjust the spectrum of the antibiotic being used. Future studies should seek to define the role of donor's cultures on antibiotic prophylaxis as well as preliver transplantation screening for complex drugs resistance among LT-candidates.

Recommendations It is recommended to administer antibiotic prophylaxis only during the intraoperative period. Extending the duration of prophylaxis does not provide any advantages. Systematic selective digestive decontamination is not recommended.

Evidence level Moderate

Recommendation grade Strong

5 ANTITHROMBOTIC PROPHYLAXIS

Since cirrhosis is associated with an increased risk of bleeding (decreased prothrombin time and platelet count), patients are presumed to be "naturally" anticoagulated. Moreover, given the high incidence of haemorrhagic complications, pharmacologic thrombo-prophylaxis following LT is not routinely used. This dogma is increasingly being challenged by the new evidence-based paradigm of "rebalanced haemostasis": patients with liver disease may be in an unstable haemostatic balance

because of concomitant changes in both pro- and anti-haemostatic pathways, as suggested by the occurrence of both bleeding and thrombotic complications.[63]

Antithrombotic prophylaxis

A systematic review and meta-analysis[64] reported a significant increase in the absolute risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with cirrhosis, compared to those without. Retrospective data found veno-venous bypass, antifibrinolytic medication and pulmonary artery hypertension as risk factors for PE during or early after LT.[65,66] To date there is no direct evidence in favour or against thrombotic prophylaxis early after LT. Evidence derived from liver surgery[37,67,68] suggest that the use of compressive stockings and intermittent pneumatic compression devices may be effective and safe against DVT. Early ambulation and optimal hydration can be safely recommended as general measures against DVT,[69] being therefore part of ERAS recommendations.

Recommendations There is no evidence in favour or against thrombotic prophylaxis, but compressive stockings and intermittent pneumatic compression devices during LT may be recommended.

Evidence level Very Low

Recommendation grade Weak

Anticoagulation prophylaxis

Often LT teams are as concerned by hepatic artery (1-5%) or portal vein thrombosis (4%-24%), both associated with the risk of re-LT or death,[70,71] as they are with DVT and PE. As suggested by some retrospective cohort studies and expert opinion,[72–77] anti-aggregation or anticoagulation may be carefully used:

- Anti-platelet may be offered in high-risk situations as aorto-hepatic graft, trans-arterial chemoembolization, complex vascular reconstruction, once post-LT platelet count is above 25 000 to 50 000.
- Anticoagulation may be offered in high-risk situations (as small portal vein size or pretransplant thrombosis) once post-LT INR is below 1.5 to 2, or according to viscoelastic coagulation monitoring.

Recommendations There is insufficient evidence to provide any formal recommendation on anti-aggregation or anticoagulation. When available, the viscoelastic coagulation monitoring may be used to guide the therapeutic decision.

Evidence level Very Low

Recommendation grade Weak

6 ANESTHETIC PREMEDICATION

While some critically-ill patients may live the upcoming transplant as the last life-saving opportunity, those in better condition may face an intense psychological stress in the hours preceding surgery.[1,4,8] Despite, anxiolytic premedication is seldom prescribed and usually not recommended before LT.[78]

In noncirrhotic patients, oral anxiolytics are associated to psychomotor function impairment after surgery, with a reduction in patient's ability to mobilize, eat and drink.[79] In the specific setting of cirrhosis the high prevalence of minimal/covert hepatic encephalopathy[80] and the impaired metabolism of benzodiazepines and opioids[81] are associated to an increase risk of falls.[82] Moreover, a meta-analysis showed how midazolam has a longer recovery profile compared to propofol in cirrhotic patient undergoing upper GI endoscopy.[83]

No direct evidence is available in the setting of LT, but ERAS guidelines in liver surgery[37] discourage the use of long-acting anxiolytic drugs.

Recommendations Long-acting anxiolytic drugs should be avoided. Dose-adjusted, short-acting anxiolytics may be considered in selected patients.

Evidence level Very low

Recommendation grade Weak

7 INCISION

The range and shapes of abdominal incisions in liver transplantation are similar to liver surgery.[37] A recent survey[84] indicated how the 2 most popular incisions were inverted-T (bilateral transverse incision with vertical extension) and bilateral subcostal (right subcostal incision extending to the left with or without vertical extension to the xiphoid) in 70% of LT programs. Other alternatives include

right transverse incision with vertical extension to the xiphoid (J- or L- shaped, known as modified Makuuchi) and median incision[85]: the presence of such range of choice suggest that all are practical.

Despite, there is no published data directly comparing different types of incisions in LT.

A recent systematic review[86] on 19 cohort studies reported how the lifetime risk for incisional hernia formation after liver transplantation ranges from 1.7% to 43%. A large retrospective cohort study[87] (n=718) reported that the rates of incisional hernia formation at 1, 5, and 10 years were 4.5, 13.6, and 19.0 % after liver transplantation.

According to the available evidence, Mercedes incision has been recognized – among other predisposing factors as surgical site infections, mTOR inhibitor rapamycin or severe post-transplantation ascites –as risk factor for incisional hernia formation after live transplantation.[86–90]

Patients suffering from an incisional hernia after liver transplantation experience a diminished health related quality of life, and are significantly less satisfied with the body image, compared to patients without hernia.[91]

Recommendations: The choice of incision is at the surgeon's discretion, depending on the graft and patient's morphology. However, Mercedes-type incision may probably be avoided due to higher risk of incisional hernia.

Evidence level Low

Recommendation grade Weak

8 TEMPORARY PORTOCAVAL SHUNT

In order to decrease portal venous stasis during hepatectomy, cava-sparing liver transplantation can be combined with an additional temporary porto-caval surgical shunt (TPCS), supposed to facilitate the dissection of the retro-hepatic vena cava.[92,93]

Two recent surveys[84,94] revealed how 27% (n=22/93) of LT programs used TPCS,[84] with only 7% (n=3/42) using TPCS as a first-line approach.[94]

According to a previous meta-analysis[95] on 1328 LT from 1 RCT and 5 retrospective studies, TPCS was associated to lower red blood cell transfusion requirement, with reduction of aspartate aminotransferase and creatinine values. It is worth reporting that there was a substantial heterogeneity observed among the studies ($I^2 > 75$ %, $p < .05$).

A recent meta-analysis[96] on 1850 LT included 7 studies, with 2 of them[93,97] not included in the previous meta-analysis. After data aggregation, the authors reported a decrease in the length of hospital stay, a lower rate of primary nonfunction (PNF) and mortality in the TPCS group. In contrast with the previous report,[95] no difference was observed on transfusion rate or creatinine values.

The results of the multicenter, single-blind APCext trial[98] on 214 LT are awaited in 2022.

Recommendations: The available evidence suggest that the use of temporary porto-caval surgical shunt may be beneficial in reducing the red blood cell transfusion requirement, length of stay, PNF and mortality rates. Its use is however, dependent on the surgeon and anaesthesiologist's decision during surgery.

Evidence level Low

Recommendation grade Weak

9 SHORT ACTING ANESTHETIC PROTOCOL

The properties of short acting anesthetic agents, including fast onset and offset, avoidance of drug accumulation and the continuous titration allow rapid awakening with minimal residual effects.

Among them, remifentanil looked to be the favorite option during the initial experience of fast track in LT, given its liver-independent metabolism and short half-life.[99,100] However, the occurrence of opioid-induced hyperalgesia after major surgery mitigated its popularity.[101] Of note, the use of conventional intermediate-long acting opioids (fentanyl or sufentanil) did not preclude early extubation and fast track pathway in 2 large cohorts cumulating more than 800 LT patients.[102,103]

The role of bispectral index (BIS) or nociception monitoring (eg. Surgical Pleth Index) devices to guide the administration of anesthetic drug should be mitigated by the electroencephalographic[104] and hemodynamic changes of cirrhotic patients during LT.

Among anesthetic gases, a double blind, single-center RCT[105] found how desflurane was associated with an increased rate of post reperfusion syndrome when compared to sevoflurane, despite a more rapid recovery profile.[106] Some Institutions consider Isoflurane as an alternative, which is significantly cheaper than sevoflurane but has a similar profile. However, despite a small prospective uncontrolled pilot study[107] which reported on the feasibility of a closed loop automated infusion device for short acting drugs, there is no evidence to support the use of either inhalational agents or total intravenous anesthesia (TIVA). Moreover, there are no reliable pharmacokinetic models for the clinical use of TIVA in LT with large fluid shifts and unpredictable blood losses.

Neuromuscular blocking agents with liver and kidney independent metabolism, such as cis-atracurium, offer an easier pharmacological handling compared to aminosteroidcurares. The introduction of sugammadex (a selective antidote for fast rocuronium reversal)[108] may change this trend but, to date, not enough data are available in favour or against its safety in LT. Given the presence of multiple metabolic alterations observed during LT, train-of-four (TOF) monitoring to determine normal muscle function[108,109] reversal is highly recommended.

Recommendations Short-acting anesthetics can be considered in LT, and within anesthetic gases, there is little evidence to suggest that sevoflurane offers advantage over desflurane. Cerebral or nociception monitoring anesthetic titration may be critically used. Neuromuscular monitoring should guide the appropriate level of muscle relaxation and reversal.

Evidence level Low

Recommendation grade Strong

10 PERIOPERATIVE ANALGESIA

Although postoperative pain after LT is reported to be less severe than in liver surgery,[110,111] an adequate analgesic regimen should be provided to allow early mobilization and enhanced postoperative recovery.

However, given the role of liver in drug metabolism and excretion, poor graft recovery may contribute to unpredictable drug metabolism, plasma concentration and clearance.

Although indirect, there is a large amount of evidence suggesting the potential benefit of patient controlled analgesia (PCA) in LT. A Cochrane systematic review and meta-analysis of 49 RCT[112] on PCA versus other pain control strategies found that patients with PCA experienced an overall better postoperative pain control, after abdominal, gynaecologic or cardiothoracic surgery. Another noninferiority, parallel substudy[113] of the OSLO-COMET trial (laparoscopic versus open hepatectomy for liver metastases) highlighted the noninferiority of PCA to thoracic epidural analgesia (TEA) for the treatment of postoperative pain, in patients undergoing open liver resection. Moreover, LOS was shorter in the PCA group. A single-center retrospective study[114] reported how patients with higher preoperative MELD, APACHE II scores and reintubation were at high risk of rapid-onset postoperative delirium: in this subgroup of patients PCA should probably be avoided.

A single-center retrospective study reported on the use of TEA in LT[115]: on a 10-year time span, a subgroup of selected patients (n=67 of 279, 24%) showed benefit from TEA performed by

experienced anaesthesiologists, with no adverse events. Besides the challenging technique, its use remains highly controversial because of high risk of severe complications within cirrhotic patients with impaired hemostasis.

Another retrospective study with a small sample size[116] compared bilateral ultrasound-guided *transversus abdominis* plane (TAP) block with levobupivacaine followed by morphine PCA to PCA alone. No difference in pain scores was observed, despite a lower amount of morphine consumption in the TAP+PCA group, compared to PCA alone.

When focussing on patients undergoing liver surgery (and not LT), the use of local anaesthetic wound infiltration was associated with pain scores comparable to those obtained with epidural analgesia.[117–119] However, no published evidence is available on wound catheter infusion, within the target population of LT patients.

A pilot experience with multimodal opioid-sparing management showed a reduction in the average morphine used, compared to standard care.[120] The multimodal pain management included oral gabapentin 600 mg preoperatively, followed by acetaminophen 650 mg every 6 hours, and gabapentin 300 mg every 8 hours as standard, with supplementary opioid prescription at provider's discretion. The retrospective nature and the small sample size of the study (n=13) prevent any reliable conclusion.

The potential hepatotoxicity and nephrotoxicity of Non-Steroidal Anti-Inflammatory drugs (NSAID) brought some experts to avoid their use early after LT, while paracetamol up-to 3g/day seems to be safe even in case of poor graft function.[121] The level of evidence of the previous considerations is however low (expert opinion).

Recommendations We recommend using multimodal and balanced analgesia to manage perioperative analgesia after LT. There is not enough published evidence to state in favor or against an opioid-sparing management: PCA-based morphine may be considered, with caution among patients at high risk for delirium. TAP block may be considered, while TEA cannot be recommended after LT.

Evidence level Low

Recommendation grade Strong

11 EARLY EXTUBATION

Similarly to major surgery, early extubation after LT has gained progressive popularity: after a relative steep learning curve and increasing confidence,[122] some centers[123–125] reported up-to 70 % rate of patients candidate to early extubation after LT, with <8% of adverse event within 72h.[103] Interestingly, there is not a clear-cut definition of "early extubation" with time interval between the end of LT and extubation spanning from few minutes up to 3-8 hours.

A systematic review and meta-analysis of 10 retrospective studies cumulating 3387 patients showed how immediate tracheal extubation after LT was associated to a reduction of lenght of ICU and hospital stay, re-intubation, morbidity and graft dysfunction rate when compared with conventional tracheal extubation.[126] The same review reported pulmonary infection, respiratory failure and surgical complications as the leading reasons for re-intubation. It is worth underlining the absence of RCT, the heterogeneity of data sources and definitions.

Based on predictors of early extubation, 2 large-cohort studies (not included in the previous meta-analysis) proposed a score for safe extubation after LT: the SORELT score[102] (2 major and 3 minor criteria) or a 9-criteria score[127] with blood loss, duration of surgery and vasopressors as common predictors in both scores.

Noteworthy, published studies on early extubation accord similar importance to *where* the patient is assigned immediately after LT. The highest level of evidence in bypassing ICU after LT (fast-tracking) comes from 3 retrospective cohort studies, with some cumulative 1900 LT, where patients were assigned in step-down units with full monitored beds and 1:2 nurse-to-patient-ratio[102,128] or to a surgical ward with 1:1 nurse-to-patient-ratio.[127]

However, given the absence of high-level published evidence (RCT or meta-analysis of RCT) the debate over the adoption of an early extubation policy and fast-tracking is still open,[122,129,130] and despite the potential economy generated from the reduction of ICU-related costs,[131] its implementation relies on local resources and organization.

Recommendations: Each patient undergoing LT should be screened for eligibility for early extubation (< 3-8h). The eligibility should rely on published scores and on local policies and organization for postoperative monitoring.

Evidence level Low

Recommendation grade Strong

12 ABDOMINAL DRAINAGE

A prophylactic abdominal drain after liver transplantation has traditionally been used to monitor postoperative bleeding, bile leaks, drain ascites, and prevent fluid collections. Their use is still largely popular, as revealed by 2 surveys[84,94]: 86%-90% of the responding centres perform a systematic abdominal drainage.

A Cochrane systematic review published in 2011[132] found no RCT on the topic and included 2 nonrandomized studies. The first is a well-designed, prospective, case-control study[133] on 35 patients with "no-drain policy" and matched 1:2 with historical controls. The Authors observed no difference in complications rate but longer ICU and hospital stay in the no-drain group (explained by the higher percentage of marginal grafts and renal failure). Interestingly, abdominal drainage did not affect any type of complication and its presence did not help in detecting early complications. The second is a prospective case-series[134] compared with unmatched historical controls. The Authors found no difference in length of ICU or hospital stay, but a higher rate of secondary abdominal drainage among patients with refractory ascites in the "no-drain" group. The same Authors published a similar study with similar conclusions within a larger series.[135]

In contrast, a third retrospective cohort study[136] with unmatched historical controls observed a reduced rate of postoperative morbidity and length of stay in the "no-drain" group, but this design is prone to selection bias.

No difference in mortality or graft dysfunction rate was observed in any of the previous studies.

Two supplementary[53,137] studies reported a low rate of drain use within a pilot enhanced recovery program after liver transplantation, but the direct impact of the drain policy was not addressed.

Recommendations: There is insufficient evidence to recommend no routine drain policy in liver transplantation. Whenever a drain is used, it may be advisable to remove as soon as possible. It can be considered to systematically drain the peritoneal cavity of patients affected by refractory ascites.

Evidence level Low

Recommendation grade Weak

13 FLUID MANAGEMENT

Fluid restrictive strategies are part of ERAS guidelines,[46] to fasten gastrointestinal recovery[43,44] and reduce blood loss.[37] However, available evidence from high-quality RCTs[138,139] is not clearly in favor or against the risk for postoperative acute kidney injury (AKI) with restrictive fluid therapy compared to a liberal management. The best evidence in LT comes from a recently published metanalysis[140]

focusing on liberal versus restrictive fluid management strategy. Pooled data from 7 RCT and 29 observational studies suggest that an intra operative restrictive strategy is associated with reduced pulmonary complications, duration of mechanical ventilation and blood loss with neither an increase in AKI rate nor LOS in ICU. The impact of these results should be mitigated by the critical risk of bias of most observational studies and the overall low quality of evidence from included RCT.

Hence, given the variations in responsiveness to fluid boluses depending on the severity of cirrhosis,[141] and wide range of hemodynamic variations across the 3 different phases of LT (hepatectomy, anhepatic and neohepatic),[142,143] a fixed-strategy may not be the best option. A systematic review and meta-analysis[144] comparing goal directed fluid therapy (GDFT) to conventional therapy in 23 RCT and 2099 patients undergoing to major abdominal surgery, found a significant reduction in morbidity and hospital LOS. A multicenter trial on GDFT for optimizing postoperative cardiac output after LT[145] has been set up, but results are not yet available.

Transesophageal echocardiography (TEE) may be considered to target fluid therapy.[146,147]

Recommendations a restrictive fluid management strategy may carefully be considered during LT over a more liberal one. Indirect evidence from other major surgery population suggest that a goal-directed fluid therapy may provide better outcomes than standard of care. TEE may be considered to target fluid therapy.

Evidence level Low

Recommendation grade Weak

Intraoperative blood product management

The choice of the transfusion strategy has also implications on fluid management, and to address the intraoperative management of blood products and factor concentrates during LT, dedicated guidelines[148] recommend the use of viscoelastic tests as Thromboelastography (TEG) or Rotational Thromboelastometry (ROTEM): available data[149–151] suggest that their use is associated to a reduction in blood, fresh frozen plasma and platelet transfusion, compared to standard laboratory tests. These conclusions should be however mitigated given the before-after study design, biased by secular change in practice and reported co-interventions of the coagulation system.

Viscoelastic tests seems moreover to be cost-effective in LT.[152]

Results from the PROTON trial, exploring the impact of preoperative administration of prothrombin complex concentrate before LT on perioperative blood loss and transfusion, are still pending.[153]

Recommendations When available, Viscoelastic tests as Thromboelastography (TEG) or Rotational Thromboelastometry (ROTEM) might be used to drive the management of blood products and factor concentrates during LT.

Evidence level Low

Recommendation grade Weak

14 PERIOPERATIVE NORMOTHERMIA

Patients undergoing LT are exposed to a high risk of hypothermia (<36°C) given the extent of visceral exposure, duration of surgery, infusion of large volumes of fluids and transfusion, liver exclusion (highly metabolic organ) and replacement by a graft preserved in cold solutions. The main consequences of perioperative hypothermia are an increased risk of cardiac arrhythmias, coagulopathy, wound infections and altered drug metabolism.[154]

Two small-sampled RCT investigated the impact of a new humidification device[155] or warming garments[156] compared to standard forced air warming during LT. Both devices seems to offer a better thermic homeostasis during the different phases of LT, with an absolute increase of 0.5°C. These conclusions should be mitigated by the small sample and high risk of biases of both studies.

The benefit of therapeutic hypothermia in acute liver failure is still debated,[157] but may be considered in selected cases.

Recommendation: Perioperative normothermia should be maintained during liver transplantation.

Evidence level: Low

Grade of recommendation: Strong

15 PROPHYLACTIC NASOGASTRIC TUBE

There are no studies evaluating the effect of the prophylactic use of a nasogastric tube in LT.
ERAS Recommendations after liver,[37] pancreatic,[43] bariatric[158] or colorectal[44] surgery, based on the best available evidence, suggest avoiding the systematic use of a prophylactic nasogastric tube: their omission is associated to an earlier return of bowel function and a decrease in pulmonary complications. Indeed, nasogastric tube expose patients to an increased risk of fever, atelectasis and pneumonia, with no protective role against complications like anastomotic leakage.

Recommendations: Indirect evidence suggests that routine postoperative nasogastric tube after liver transplantation is not indicated. Nasogastric tubes placed during surgery should be removed before reversal of anaesthesia.

Evidence level Low

Recommendation grade Strong

16 POSTOPERATIVE NAUSEA AND VOMITING

Postoperative nausea and vomiting (PONV) is relatively uncommon after LT, and no direct evidence nor recommendations for prevention are available. Hence, female gender, history of PONV or motion sickness, nonsmoking status, age and postoperative opioids are considered as strong risk factors for PONV after surgeries under general anesthesia.[159]

Recently the Cochrane collaboration published an updated systematic review and meta-analysis[160] focussing on the topic, with droperidol, metoclopramide and ondansetron being the most studied drugs among the 60 different analysed. Given the publication biases and poor methodological quality of smaller included studies, no conclusion as to whether these drugs differ in their ability to prevent PONV could be done. Ondasetron administration is associated to a lower rate of nausea and vomiting if administered at induction rather than intraoperatively. However, limited evidence suggested how the combination of dexamethasone and ondansetron might be more effective than each drug alone.

ERAS guidelines for liver surgery[37] follow the recommendations from the international consensus group on PONV: 2 antiemetic drugs are advocated to reduce postoperative PONV.[161] It should be noted that often patients undergoing LT already receive steroids during the perioperative period, and therefore 1 single additional agent (as a 5-HT3 antagonist) need to be supplemented.

Recommendations: Indirect evidence suggest the use of a multimodal approach to PONV, with 2 antiemetic drugs as prophylaxis (e.g. 5-HT3 antagonist and steroids).

Evidence level Low

Recommendation grade Strong

17 EARLY POST OPERATIVE ORAL NUTRITION

There is no direct evidence on early oral nutrition, compared to enteral nutrition (EN) or parenteral nutrition (PN) in the setting of LT. ESPEN guidelines recommend starting normal food and/or EN within 12-24 h after LT to reduce infection rate (Grade of recommendation B).[11] After the acute postoperative phase, the energy intake requirement should be of 30-35 kcal x kg^{-1} x d^{-1} (e.g. for a 70kg patient: 2100-2450 Kcal per day).[11] Indirect evidence from ERAS recommendations in liver surgery[37] suggest that most patients can eat normal food at day 1, even in case of hepatico-jejunostomy, as confirmed by 2 pilot studies on ERAS and LT.[53,137] The quality and volume should be modulated according to patient's tolerance.

In the specific setting of LT, a pilot, open-label RCT[162] on 36 patients undergoing LDLT, compared EN via a naso-gastric tube within 12h versus control: the authors reported a reduction of biliary complications and infection rate in the experimental group, but the interpretation should be cautious given the small sample and high risk of bias. Another small sampled retrospective study[163] reported how EN via jejunostomy within 12h after LDLT was associated to a reduced length of stay and infection rate, when added to PN alone. However, the long time to extubation (4-5 days) and the hospital of stay longer than to 1 month in both groups, prevent from any relevant conclusion.

If feeding tubes for EN may be inserted even after LT, with fluoroscopic assistance, endoscopic assistance, or transperitoneal jejunostomy,[164] their benefit over PN is unclear: a Cochrane review found no strong evidence for significant differences for EN vs PN.[12]

PN should be considered as the very last option, in alternative to no feeding at all: in case of patients with unprotected airways and compromised cough and swallow reflexes the nasogastric route (via feeding tubes) or jejunostomy should be discussed and considered before deciding of PN.[11]

Recommendations: normal food oral intake and/or enteral nutrition (nasogastric tube or jejunostomy) should be started 12-24h after liver transplantation, according to patient's tolerance. Parenteral nutrition should be considered as the very last option, when the use of oral route (enteral feeding tubes or jejunostomy) is not possible.

Evidence level Very Low

Recommendation grade Strong

Nutritional supplements

A Cochrane review on nutritional interventions after LT including 6 RCT, found no evidence for significant differences between different interventions (e.g. enteral plus parenteral glutamine-

dipeptide, parenteral nutrition with alanyl-glutamine, protein, fat, branched-chain amino acids, carbohydrates, in different combinations).[12]

A single-center, retrospective, unmatched study compared 2 groups of patients undergoing LDLT and both receiving PN and early EN via jejunostomy[165]: 1 received immunomodulating diet (IMD) enriched with hydrolyzed whey peptide (HWP), and the control group standard EN. The rate of post-transplant bacteremia was significantly lower in the IMD-HWP compared to control.

A small sample, double blind trial is ongoing, to compare the impact of a 5-strains symbiotic composition for 15 days after LT, compared to maltodextrine alone, after the beginning of oral diet.[166]

Recommendations: There is no clear evidence of the benefit of nutritional supplements after liver transplantation.

Evidence level Low

Recommendation grade Weak

18 EARLY MOBILISATION

Prolonged bed rest is associated with muscle atrophy, acquired muscle weakness[167] and adverse outcomes in surgical intensive care unit.[168] Recently a multicenter, international, double-blind trial on 200 patients in ICU after surgery (including 2 LT) reported how patients in the early goal-directed intervention group improved mobilisation, had a shortened length of stay, and improved functional mobility at discharge.[168] The intervention arm included basic manoeuvres such as sitting and standing or stepping in place at the bedside.

If the applicability of these findings to well-fit patients with few limitations for mobility is uncertain,[44] sicker patients are those who can benefit the most of such interventions.

In the setting of LT, an open-label RCT[169] reported how the implementation of an intense rehabilitation program in ICU was associated to a shorter time to first flatus and an earlier ability to sit on the edge of the bed. However, no difference on the length of stay nor in morbidity rate were observed.

Nursing staff or allied-health professional are directly involved in patient mobilisation: for this reason ERAS team and nurse managers should promote the role of physical activity as a nursing staff priority,[170] by implementing a mobilisation protocol.

Patients should be encouraged to continue mobilisation and physical activity even after discharge. A retrospective study on a large-scale administrative database and 3072 patients after LT,[171] revealed how the discharge in inpatient rehabilitation, skilled nursing facility or long-term acute care were associated to a reduced risk of 30-days readmission, when compared to home or home-health. These results are consistent with previous small-scale trials.[172,173]

Recommendations: Early mobilization after LT should be encouraged with early-goal directed interventions, from the morning after LT until hospital discharge. Physical rehabilitation may be continued after discharge.

Evidence level Moderate

Recommendation grade Strong

19 GLYCEMIC CONTROL

Perioperative hyperglycemia is a common finding during LT, driven by an exacerbation of insulin resistance induced by major surgery, and enhanced by hepatogenous diabetes from the cirrhotic native liver, the anhepatic and reperfusion phases, the type of graft, high-dose steroids and immunosuppressants.[174–177]

A cluster of several retrospective studies, based on single-center cohorts[178–184] and 1 national LT registry[185] cumulatively enrolling more than 4900 patients, similarly reported an association between uncontrolled new-onset hyperglycemia (150-200 mg/dL) and poor clinical outcomes including mortality, acute kidney injury, sepsis, graft rejection, length of hospital stay and risk of re-admission after LT.

A single-center, open-label, effectiveness RCT on 164 patients highlighted a lower rate of infections at 30 days and 1 year after LT in the group with target glucose level of 140 mg/dL compared to 180 mg/dL[184] in the early postoperative period. However, no difference was observed in the rejection rate (primary outcome), length of stay, readmission or death.

Supplementary evidence from 1 “before-after,”[182] 2 case-control[179,181] and 2 cohort[176,183] studies with some cumulative 740 LT patients suggest how an intensive insulin protocol in ICU after LT was associated to a reduction in the rates of infection, graft rejection, time to extubation, length of ICU and hospital stay. Despite some heterogeneity in blood glucose targets across these studies, an increased risk of moderate hypoglycemic events is reported,[186] to be carefully monitored as for any critically ill patient.[187]

Closed-loop artificial pancreas seems promising in LT to maintain a stable perioperative glucose level without episodes of hypoglycemia, when compared to the sliding scale method.[176,188] The amount of evidence is however too little to drive any meaningful recommendation.

Recommendations: We recommend a protocolized approach to blood glucose management in LT patients targeting an upper blood glucose level ≤180 mg/dL from the intraoperative period to the early postoperative period (first 24-48 hours postoperatively in the absence of complications and/or organ failure).

Evidence level Moderate

Recommendation grade Strong

20 POSTOPERATIVE ILEUS

The underestimated occurrence of postoperative ileus after LT may prevent early postoperative feeding, thus worsening malnutrition and maintaining frailty. In this line, its prevention should be a key objective of enhanced recovery protocols.
A single-center, open-label randomized trial explored the impact of gum chewing 3 times a day on 64 patients after deceased or living donor LT.[189] The Authors reported no difference neither in time to first flatus, nor in time to sip water, soft bled diet, length of stay in ICU or hospital. Recently, a multicentre, double-blind, RCT evaluated the effects of oral daikenchuto (a traditional Japanese herbal medicine) administration in patients after LT.[190] In this trial was observed that rate of caloric intake in the early period after LT was higher in experimental arm, but not time to first stool, length of hospital stay or patient reported outcomes (quality of life and abdominal discomfort).

If gum chewing and daikenchuto may have little effect on postoperative ileus after digestive surgery, currently available evidence does not support their efficacy in LT.

Results are expected from a 3 arms, double-blind, add-on RCT[191] on 100 LT patients: the study aims to determine if the supplementary use of acupressure bracelets or gum-chewing to stool softener alone has any impact on postoperative ileus or length of stay.

Recommendations: There are no acknowledged strategies to prevent postoperative ileus after LT.

Evidence level Low

Recommendation grade Weak

21 POSTOPERATIVE EDUCATION

Insufficient knowledge about the disease and complexity of medical prescriptions are correlated to a lower therapeutic adherence,[5,192] this latter associated to a major risk of graft rejection and post-transplant complications.[192] For this reason, education programs after liver transplantation are needed.

It has been suggested that patient education programs should include 3 types of intervention: individualized education, behavioural intervention and psychological support.[2] The objectives are to provide information ensuring the patient's safety, suitable knowledge to help the patients to choose methods to manage stress and accept their new chronic condition. The involvement of a clinical pharmacist and group sessions with expert patients may be considered.

A single-center, uncontrolled prospective study[193] explored the impact of a systematic pharmaceutical educational approach on the early postoperative period (early after surgery, the day before discharge and first outpatient consultation). The authors observed how this strategy increased the general knowledge of immunosuppressive therapy, drug monitoring knowledge and the treatment of underlying diseases among patients. The authors suggested how the involvement of multidisciplinary caregivers in the early stage of the program, the use of different educational tools and repeated education allowed emphasizing the importance of immunosuppressive regimen.

However, informational needs on treatment, symptoms, daily activities (including physical activity) and self-management (including weight control) may change over the time after LT, as suggested by a cross-sectional study on 159 LT patients followed in outpatient clinic.[194] For these reasons, time-specific education program after LT should be based on recipients' informational needs, often required for a long period of time, rather than presenting a single educational session.

Recommendations: Systematic educational programs after liver transplantation may increase patient awareness and knowledge on the immunosuppressive therapy and on physical changes after LT. Such multidisciplinary programs could include a clinical pharmacist, and should be continued over a long period after liver transplantation.

Evidence level Low

Recommendation grade Strong

22 AUDIT

Audit and feedback is an important strategy to close the gap between actual and desired clinical practice: a Cochrane systematic review[195] indicated that feedback may be more effective when baseline performance is low, the source is a supervisor or colleague, it is provided more than once, it is delivered in both verbal and written formats, and when it includes both explicit targets and an action plan.

However, although action planning is a familiar activity in clinical practice, health professionals often lack the time, skills or knowledge to interpret feedback and formulate and plan improvement actions: for this reason, an implementation toolbox, with suggested actions and materials linked to specific potential barriers in the care process, may support this action planning process.[196]

As for any other ERAS guideline,[37,43,44,158] strict adherence to the protocol is paramount for the success of its implementation, leading auditing compliance to become *per se* a key element.[46]

Recommendations Systematic audit improves compliance and clinical outcome in healthcare practice.

Evidence level Moderate

Recommendation grade Strong

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