Indications for Liver Transplantation
When to Refer to a LT centre

CIRRHOSIS - END STAGE LIVER DISEASE
WHEN TO REFER TO A LIVER TRANSPLANTATION CENTER

Luis Tomé
CHUC, Portugal

A. DISMAL PROGNOSIS AFTER DECOMPENSATION

The ominous prognosis of cirrhotic patients after decompensation is very well known. The appearance of ascites for example is associated with a mortality of 20% at 12 months. The mortality at 12 months after variceal haemorrhage is greater than 50%. Greater than 50% is also the mortality at the same time point after an episode of severe hepatic encephalopathy. When acute on chronic liver failure occurs then mortality greater than 40% is anticipated at 3 months. The comparison of these results with the survival observed after liver transplantation let us understand that all these patients could benefit from the procedure.

B. ALLOCATION OF DONATED LIVERS

1. In the early 90s the allocation of donated livers depended on blood type compatibility, location of the patient (as surrogate for severity) and time on waiting list. From 1997 patients in acute critical situation (Status 1A) received the highest level of priorization. For other cases Child-Pugh scale defined the allocation sequence. Child-Pugh includes subjective parameters. A ceiling effect was associated to the quantitative variables. The Child Pugh has limited amplitude. When patients corresponded to the same score time in waiting list was the tie-breaker. Time in waiting list does not correlate with mortality.

2. Those days, a model able to predict survival after TIPS has been developed at Mayo Clinic. The final model included INR, bilirubin, creatinine and the nature of liver disease. The model could anticipate the survival at several moments being more accurate than Child-Pugh. This model has been validated for survival of end stage liver disease. It was adopted in the allocation of donated livers in 2002 in the US and in 2006 in the civilized Europe. Clearly the model was superior to clinical judgment in identifying patients at risk of death.

3.1. MELD raises several questions. First of all, it turned clear that a minimum MELD exists (between 18 and 20) so that a patient could take advantage from liver transplantation.

3.2. Secondly, the variables in the formula are not as objective as desired. INR is a normalization of prothrombin. This normalization involves the use of ISI (International Sensivity Index) a constant that depends on the reagent and the apparatus used. ISI depends also on the population to be analysed. Currently ISI has been developed for patients receiving VKAs and was never designed nor validated for patients with liver disease. When the INR in the patients with liver disease was calculated using ISIwarfarin the discrepancies to the value obtained with ISI liver were very large especially in patients with a prolonged prothrombin time. It was suggested to replace INR for another parameter that reflects the synthetic function of the liver. INR could also be removed from the score (MELD XI) but this alternative implies a correction in the original formula.

4.1. Creatinine an indirect marker of the severity of renal disease raises also several questions. Creatinine underestimates renal compromise in mal nourished subjects or in people with decreased muscle mass. For patients with high serum bilirubin, serum creatinine can be overestimated by use of traditional colorimetric method. In cirrhotic patients, Glomerular filtration rate has a more precise relationship with mortality than creatinine. Replacing GFR for creatinine in MELD a much more accurate score could be obtained. Formulas to estimate GFR are not precise and underestimate the value in cirrhosis. It does not take in account renal dysfunction independent of liver disease.

4.2. In the assumptions of MELD, creatinine less than 1 mg% is equated to this last value. The range of GFR of these patients is very large but only 14% has a GFR inferior to 70 ml.min. Creatinine is capped at 4 mg%. The support for the assumption is not clear. Being other parameters constant, MELD begins to increase when creatinine exceed 1.3 mg% to stabilize between 4 and 5.5 mg%.

5. The impact of hyponatremia on the survival of end stage liver disease was acknowledged at Mayo Clinic. For patients with serum sodium concentrations above 135 the MELD-Na score was essentially identical to the MELD score. For patients with MELD scores above 30, the effect of hyponatremia was quiet small. For patients with moderate MELD scores, the effect could be substantial. A patient with a MELD score of 10 and serum Na of 125 would have a MELD-Na of 21.

C. FUTILITY IN LIVER TRANSPLANTATION

Allocation of donor livers should be prioritized to the sickest patients but futile transplantation needs to be avoided. Scores to anticipate survival after liver transplantation have been developed. Donor risk index uses six parameters that define the quality of the liver to be implanted. The index has a clear relationship to the survival in the first 3 years after transplantation but

does not takes in consideration the characteristics of the receptor. The Soft Score developed in 2008 by Rana et al uses 5 donor parameters from donor, 15 from receptor and the cold ischemic time. A score greater than 40 (3 months survival 38%) defines futility but the high number of covariates limits the applicability. The D-Meld uses donor age and Meld score. It is suggested that donor/recipient matches with D-Meld > 1600 should be eliminated. From Zirich came the Balance of Risk, abbreviated as BAR. The score involves the age of the donor, 3 parameters from the receptor (age, previous life support, MELD) and 2 parameters related to the procedure (re-transplantation and cold ischemic time). A threshold at 18 was used for unacceptable patient mortality in standard grafts. It must be said that the comparison by independent authorities does not show that the existent scores can precisely predict the outcome of liver transplantation.

REFERENCES

1. Francoz C, Prié ; Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. ; Liver Transpl. 2010 Oct;16(10):1169-77
2. Jalan, R.; Saliba, F. et al ; Development and validation of a prognostic score to predict mortality in patients with acute on chronic liver failure ; J.Hepatol.2014.61.1038
3. Ma, Y.; Wang, Q et al ; Comparison of differenet scoring systems based on both donor and recipient characteristics for predicting outcome after living donor liver transplantation ; PLOS.2015. DOI 10.1371/journal.pone.0136604
4. Machicao, V. ; MELD-sodium score. The evolution in the prioritization of liver transplantation ; Clin.Liver Dis.2017.21.275-87
5. Merion, R.; Scauble, D. et al ; The survival benefit of liver transplantation ; Am.J.transpl.2005.5.307
6. Porte, R.; Lisman, T. et al ; The INR in the MELD score: problems and solutions ; Am.J.Transpl.2010.10.1349-1353
7. Wiesner, R.; Edwards, E. et al ; MELD and allocation of donor livers ; Gastroenterology.2003.124.91-6

ACUTE LIVER FAILURE

Kenneth Simpson

Edinburgh

ACUTE LIVER FAILURE: WHEN TO TRANSFER TO A TRANSPLANT UNIT?

Acute liver failure (ALF) is characterised by severe acute liver injury leading to the development of coagulopathy and hepatic encephalopathy (HE). Other extra-hepatic organ failures are also common, especially acute kidney injury. The development of this clinical syndrome can be very rapid requiring prompt, comprehensive, initial assessment of the patient, coordination with a potentially geographically removed transplant unit and safe and secure transfer to maximise the potential for patient survival. Emergency liver transplantation remains an accepted treatment for ALF. But over time the clinical management of such rare patients has improved, with increases in non-transplant patient survival reported from many centres. Although the onset of hepatic encephalopathy defines the clinical syndrome of ALF, its development considerably impairs the ability of those in the transplant centres to carefully and comprehensively assess the need or appropriateness of emergency transplantation. More over the safe transfer of patients with hepatic encephalopathy requires more resource, with intubation and ventilation, possible inotropic support and anaesthetic support. Often patients will deteriorate 1 or 2 grades of hepatic encephalopathy during transfer, with increased risks of cerebral oedema. Ideally patients with ALF are therefore selected for transfer to liver transplant centres before the onset of HE.

The causes of ALF vary around the world. The most common cause in the USA and United Kingdom is paracetamol overdose. In India and the Far East, viral hepatitis is more common. The speed of onset of HE is more rapid following paracetamol overdose and the evolution of other organ failures, complications and indications for emergency liver transplantation are different form other causes. Therefore, when assessing when patients should be transferred the aetiology of the ALF should be considered.

WHEN TO TRANSFER A PATIENT WITH PARACETAMOL INDUCED ALF?

Currently in the UK about 50% of cases of paracetamol induced ALF have presented following a single time point suicidal overdose. However, in the USA many more cases present with inadvertent excess paracetamol

consumption over a number of days. This pattern on paracetamol liver toxicity is becoming more common in the UK. Such cases present to medical attention because they are unwell, not because they have taken an overdose. These patients may be difficult recognise presenting with confusion, hypotension, acidosis and in renal failure. Only once the grossly abnormal liver function tests and coagulopathy are return is the correct aetiological diagnosis considered. Although these patients have considerable logistical challenges to safe transfer, they should always be discussed with a liver transplant centre. In contrast, cases with single time point ingestions present with liver injury evolving over a period of 2-3 days following overdose. Rapid increases in prothrombin time may be observed; increases over 50 seconds or a prolonged prothrombin time greater than the number of hours after the overdose are often used to trigger transfer. Paracetamol induced kidney injury is likely multifactorial in pathogenesis, this kidney injury evolves slower than the liver injury, but is an important adverse prognostic indicator. Developing renal failure in the presence of a significant liver injury should prompt discussion regards transfer. Acidosis, hyperlactic acidaemia (especially when unresponsive to fluid resuscitation) and hypoglycaemia are also often associated with poor prognosis after paracetamol overdose and are also indicators to discuss cases with the local transplant centre. We have published on the utility of the SOFA score in deciding which patients with paracetamol induced ALF should be referred for transplantation, but these studies have not been externally validated.

WHEN TO TRANSFER A PATIENT WITH NON-PARACETAMOL INDUCED ALF?

The evolution of liver failure in patients with non-paracetamol causes of ALF is generally less rapid. Some cases may present with features suggestive of chronic liver disease, such as ascites and portal hypertension. A high index of suspicion is necessary to identify these patients: A liver biopsy should be considered in all patients with short or no history of liver disease on initial presentation. Otherwise an evolving coagulopathy, the development of hypoglycaemia or renal failure and HE should prompt discussion regards transfer. Dynamic assessment of liver volume has been used in some units

EASL PRACTICE GUIDELINE ALF: SUGGESTED CLINICAL FEATURES TO PROMPT REFERRAL

HYPERACUTE / PARACETAMOL
Arterial pH <7.3 or HCO3 <18
INR >3.0 D2 or >4.0 thereafter
Oliguria, anuria or established renal failure
HE
Hypoglycemia
Elevated lactate unresponsive to fluid

NON-PARACETAMOL
Arterial pH <7.3 or HCO3 <18
INR >1.8
Oliguria, renal failure or Na <130mmol/L
HE
Bilirubin >300umol/L
Shrinking liver volume

REFERENCES

1. EASL practice Guidelines ALF: https://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-acute-fulminant-liver-failure
2. AASLD Guideline ALF: https://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf
3. Germani G(1), Theocharidou E, Adam R, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol. 2012 Aug;57(2):288-96. doi: 10.1016/j.jhep.2012.03.017.
4. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2014 Mar 20;370(12):1170-1. doi: 10.1056/NEJMc1400974.
5. Donnelly MC, Hayes PC, Simpson KJ. The changing face of liver transplantation for acute liver failure: Assessment of current status and implications for future practice. Liver Transpl. 2016 Apr;22(4):527-35. doi: 10.1002/lt.24403.

EXCEPTIONS TO THE MELD SCORE

François Durand
Hepatology & Liver Intensive Care, Hospital Beaujon
University Paris Diderot
INSERM U1149
Clichy, France

1. ALLOCATION POLICIES IN LIVER TRANSPLANTATION

The long-term survival benefit of liver transplantation (LT) in patients with end stage liver diseases and/or small hepatocellular carcinoma (HCC) is considerable [1]. However, the main limitation in LT is the imbalance between the number of patients who could be transplanted and the number of available donors. It is generally considered that only patients with a probability of survival exceeding 50% 5 years after transplantation should considered. Practically, the vast majority of patients who are eventually considered suitable candidates have a much higher probability of survival. The objectives of allocation policies are equity, justice, transparency and utility. During the last 15 years, in an attempt to meet these objectives, most Western countries have adopted sickest first allocation policies based on the MELD score or derivates [2]. The MELD score which includes the 3 objective laboratory values of serum creatinine, bilirubin and INR is a robust prognostic tool in cirrhosis [3]. The principle of MELD score-based allocation systems is to prioritize (maximum score) the patients with the highest MELD score, those with the highest mortality risk without transplantation. It has been argued that transplanting patients with more advanced liver diseases and higher MELD score would result in lower post-transplant survival rates. However, several series have shown that implementation of MELD score-based allocation policies have been associated in a reduction in waiting list mortality without affecting post-transplant outcome, except for extreme values. The MELD-Na score [4] which incorporates serum sodium in addition to the three laboratory variables of the MELD score has been adopted recently in the United States while organ allocation in the United Kingdom is based on a slightly different score termed UKELD [5].

Even though the MELD score proved to be effective at prioritizing patients for liver transplantation, not all patients are adequately prioritized which raises the issue of MELD exceptions.

2. LIMITATIONS OF MELD SCORE-BASED ALLOCATION POLICY

Besides decompensated cirrhosis, liver transplantation is the best option in selected patients with HCC. Not only liver transplantation allows to remove the tumor but it cures the underlying chronic liver disease that promotes malignancy. Excellent results have been reported in selected patients with small HCC and compensated cirrhosis [6, 7]. Most candidates with HCC have a low MELD score that would allow them to be transplanted if not given extra points. Different policies are used in different countries to prioritize these patients and give them an access to transplantation similar to that of patients with decompensated cirrhosis provided the risk of death or dropout as well as post-transplant survival are similar to those of patients with decompensated cirrhosis. Currently, the most widely used variable to select and prioritize patients with HCC are tumor size, number of nodules, serum alphafoetoprotein, the MELD score and waiting time [6]. Since HCC represents 25 to 30% of all indications for liver transplantation, it should not be considered a MELD exception. However, HCC patients with compensated cirrhosis who can receive adjuvant therapy during waiting time to slow tumor progression should not receive a score similar to that of patients with decompensated cirrhosis who are not eligible to adjuvant therapy. Indeed, these latter patients are at higher risk of death or drop out on the waiting list. They may represent MELD exceptions justifying specific prioritization.

In patients with cirrhosis, the MELD score is inaccurate at predicting the outcome in a number of uncommon situations including hepatopulmonary syndrome, severe encephalopathy and recurrent episodes of cholangitis. The MELD score is also relatively inaccurate to categorize patients with preserved liver functions and refractory ascites. In the United States, the MELD-Na score has been adopted to better stratify patients with refractory ascites [4]. However, the accuracy of the MELD-Na score in this population is not optimal. In addition, the MELD-Na score can be manipulated by diuretics. Muscle mass seems to be a strong predictor of mortality in these patients but further validation is needed [8]. Overall, some complications of cirrhosis that represent good indications for transplantation are too uncommon or too variable to derive specific prognostic scores. Finally, the MELD score is not suitable for indications other than cirrhosis. Each of these indications represent MELD exceptions which should be discussed case by case and prospectively evaluated.

3. MELD EXCEPTIONS

MELD exceptions include (i) uncommon complications of cirrhosis which prognosis is not adequately predicted by the MELD score, (ii) uncommon tumors (other than HCC) that represent reasonable indications for transplantation and (iii) miscellaneous conditions unrelated to cirrhosis (Table 1). The objective of MELD

exceptions is to give the patients a reasonable access to transplantation with extra points. Waiting list mortality and post-transplant survival should be similar to those of patients with cirrhosis and a high MELD score. Importantly, a very limited number of MELD exceptions are not necessarily life threatening conditions in the short term (refractory pruritus, polycystic liver disease). They are considered acceptable indications because they are highly debilitating, there is not alternative to transplantation and the results are excellent.

Extra points and time to reach a maximum score are based on expert's opinion. However, experts should reach consensus, at least at a national level to provide criteria as objective as possible to select the patients and guidelines for prioritization [9]. MELD exceptions should be evaluated at regular intervals and prioritization should be adjusted whenever needed.

MELD exceptions related to cirrhosis are most often life threatening conditions [9]. Firstly, the absence of alternative to transplantation should be clearly documented. For instance, in patients with refractory ascites and a low MELD score, TIPS should be the first line option in order to save organs. Transplantation should be restricted to patients with a contraindication to TIPS due previous episodes of encephalopathy and/intermediate MELD score that preclude TIPS insertion. Hepatopulmonary syndrome is an excellent indication for transplantation with recovery in virtually all patients. For years, moderate portopulmonary hypertension was also considered a good indication although post-transplant recovery was not constant. Major improvements in medical management have been achieved in recent years with the advent of new pharmacological agents (endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors and prostanoids) [10]. Thus, indications for transplantation should be reassessed. Polycystic liver disease with a major liver enlargement is an excellent indication for transplantation. In the majority, patients have liver and kidney polycystic disease and a substantial proportion need combined liver and kidney transplantation. A stable creatinine clearance of less than 30-40 mL/min/1.73m2 justifies combined transplantation.

MELD Exceptions	
	Life threatening condition
Complications of cirrhosis and biliary diseases	
Refractory ascites and low MELD score	- Yes
Chronic encephalopathy	- No
Recurrent digestive bleeding	- Yes
Hepatopulmonary syndrome	- Yes
Portopulmonary hypertension	- Yes
Recurrent bacterial cholangitis	- Yes
Refractory pruritus	- No
Uncommon malignancies	
Unresectable liver metastases of endocrine tumors	- Yes
Unresectable epithelioïd hemangioendothelioma	- Yes
Unresectable hilar cholangiocarcinoma	- Yes
Non-malignant conditions unrelated to cirrhosis	
Hemorrhagic telangiectasia with liver involvement	- Yes
Familial amyloid polyneuropathy	- Yes
Polycystic liver disease	- No

Table 1: List of MELD exceptions

REFERENCES

1. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-313.
2. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42 Suppl:S100-107.
3. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-96.
4. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-1026.
5. Neuberger J. Liver transplantation in the United Kingdom. Liver Transpl 2016;22:1129-1135.
6. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-994 e983; quiz e914-985.
7. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
8. [Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Belghiti J, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol 2014;60:1151-1157.
9. Francoz C, Belghiti J, Castaing D, Chazouilleres O, Duclos-Vallee JC, Duvoux C, et al. Model for end-stage liver disease exceptions in the context of the French model for end-stage liver disease score-based liver allocation system. Liver Transpl 2011;17:1137-1151.
10. Savale L, Sattler C, Coilly A, Conti F, Renard S, Francoz C, et al. Long-term outcome in liver transplantation candidates with portopulmonary hypertension. Hepatology 2016.

Evaluating and optimizing patients for Liver Transplantation

STRATEGIES TO EVALUATE AND MAINTAIN ADHERENCE TO ALCOHOL ABSTINENCE

Helena Cortez-Pinto
Departamento de Gastrenterologia, CHLN, Hospital de Santa Maria
Faculdade de Medicina, Universidade de Lisboa, Portugal

INTRODUCTION

According to WHO 2014 report, an estimated 3.3 million deaths, or 5.9 % of all deaths worldwide, were attributable to alcohol consumption in the year 2012, with about half a million due to liver cirrhosis. Europe is the WHO region with the highest per capita alcohol consumption and the highest prevalence of heavy drinkers, and consequently with more deaths due to liver cirrhosis.

Excessive alcohol consumption as a risk factor for liver disease used to be differentiated in excessive alcohol consumption (abuse) or dependence. However the recently published DSM-5 has replaced the categorical distinction between abuse and dependence with a dimensional approach, based on 11 criteria for alcohol use disorders (AUD); two or three positive symptoms constitute a mild substance use disorder, four or five a moderate one and six or more a severe one. In fact, alcohol use disorders are chronic, severe and sometimes fatal disorders with prevalence in the adult population worldwide estimated to be 4.9% (men: 7.8%, women: 1.5%) [1].

There is evidence that abstinence from alcohol can improve the prognosis of alcoholic liver disease (ALD) [2]. Consequently, the most effective measure on the management of ALD is to implement total abstinence [3].

EVALUATION OF ALCOHOL ABSTINENCE

Evaluation of abstinence is usually done by the physician during interview with the patient, and should be confirmed by one family member, during out-patient visits.

There are several laboratory tests that can be used to monitor alcohol consumption.

Among **indirect biomarkers of alcohol use**, the most used are gama-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV) and Carbohydrate–deficient transferrin (CDT) can be used, but are rather non-specific in general, and more so in the presence of liver disease.

GGT levels typically rise after heavy alcohol intake that has continued for several weeks, and should normalize within 2 to 6 weeks of abstinence. However that is not the case in the presence of established liver disease where normalization often takes much longer and may never normalize. Also, it lacks specificity and sensitivity. Nonetheless, it is still one of the most used biomarkers and when a patients with ALD has a marked increase in his GGT basal levels, it raises a high suspicion of recidivism.

Elevated **MCV** due to a direct effect of alcohol on erythroblasts and to folic acid and /or vitamin B12 deficiency has been considered a useful screening value [4]. However its low sensitivity, and its slow return to reference values (3 -4 months) diminishes its potential as a relapse marker.

CDT results are usually expressed as a % of total transferrin (CDT%). CDT levels appear to elevate following alcohol consumption of 60–80 g/d for 2 or 3 weeks, and they normalize with a mean half–life of 2–4 weeks of abstinence. However short periods of abstinence may remain undetected. Also, in patients with severe liver disease false positives can be found.

DIRECT BIOMARKERS

These biomarkers are usually the minor ethanol metabolites, such as ethylglucoronide (EtG), ethyl sulfate (EtS), phosphatidyenol species (PEths) or fatty acid ethyl esters (PEths) resulting from biochemical reactions of alcohol. Those biomarkers can be measured in “alternative sampling strategies” such as dried blood spots or hair. This strategies have the advantage of evaluating consumption in the past few months, with cut-offs for abstinence and excessive alcohol consumption, respectively at 7 pg/mg and 30 pg/mg.

Hair EtG was recently compared with serum CDT and it was found that HEtG was more sensitive than serum %CDT to assess relapse in alcohol-dependent patients and was positively correlated with the amounts of alcohol consumed, although serum %CDT was more specific for assessing abstinence. It is of note that these measurements are more reliable if done in repeated measurements [5].

ALCOHOL ABSTINENCE AND LIVER TRANSPLANTATION

In the evaluation previous to liver transplantation in patients with ALD, psychiatric and psychologist consultation are mandatory. Most centres require abstinence for at least 6-months. This 6-months rule has been questioned, mostly in the setting of alcoholic hepatitis, where many centres no longer apply it. Also, it seems that that the risk of recidivism is more related to psychosocial factors than to the duration of abstinence, and there is evidence that liver function recovery is mostly observed in the first three months of abstinence. Although questionable this rule has mainly two advantages, one is that abstinence can so

much improve liver function that liver transplantation no longer is needed, the other being an opportunity to evaluate patient compliance to abstinence. The risk of recurrence of alcohol consumption increases with the duration of follow-up and is estimated between 15 to 40%.

MAINTENANCE OF ABSTINENCE

Alcohol use disorders primarily manifest as impaired control over drinking. Total abstinence of alcohol is the primary goal recommended by most clinicians. However, there is growing interest in harm-reduction strategies that aim to reduce heavy drinking [6].

The most widely used treatments for AUDs are **psychosocial treatments** that can also increase patients' motivation for abstinence, enhance non-alcohol- related outcomes and increase adherence to pharmacological treatment of AUDs. Basically, these treatments usually involve family, community and a therapist encouraging patients to reduce their alcohol use. Among those treatments, **motivational interviewing** (MI) is an evidence-based counseling method that aims to enhance intrinsic motivation and induce behavior change by helping patients explore and resolve their ambivalence about change. MI can reduce the use of alcohol compared to no intervention, but overall effect sizes are small [6]. **Brief interventions** that provide advice or behavioral

Counseling, have been show very moderate efficacy in the primary care setting for patients with alcohol misuse. Cognitive-behavioral therapy (CBT), as well as residential treatments are other options. It is important to tailor treatment option according to their individual preferences and needs.

PHARMACOLOGICAL TREATMENT

- **Disulfiram** was the first medication approved specifically by the US Food and Drug Administration to treat alcohol dependence. Disulfiram is an irreversible inhibitor of ALDH, thus preventing the conversion of acetaldehyde to acetate, leading to acetaldehyde accumulation with its unpleasant side-effects, such as nausea, flushing, vomiting, sweating, hypotension and palpitations thus resulting in an aversive effect. Because of side effects, including some potentially very dangerous, as well as poor adherence, disulfiram should be considered a second- line medication in relapse prevention.

- **Acamprosate** modulates glutamatergic - neurotransmission, counteracting hyper-glutamatergic States. All meta-analyses support the efficacy of acamprosate in improving outcomes in treatment of alcoholism, with small-to- moderate effect sizes [6].

- **Naltrexone** is a non-selective opioid antagonist. Several meta-analysis, as well as a Cochrane analysis, found that naltrexone reduced the risk of relapse to heavy drinking or alcohol consumption rather than increasing abstinence rates. There is abundant evidence supporting the use of oral naltrexone for treating alcohol dependence, although optimal dosage and duration of treatment are not yet established. Also, new long-acting formulations may increase the clinical use of the medication.

- **Nalmefene** is not only an antagonist at the mu- and delta-opioid receptors, but also a partial agonist at the kappa opioid receptor. Gual et al. [7] evaluated the as-needed use of nalmefene in 718 patients, showing a significant greater reduction in heavy drinking days. No head to head comparison was done with Naltrexone.

- **Baclofen**, an agonist at the GABA-B receptor, may prolong the time to first drink, reduce the number of drinking days and facilitate maintenance of abstinence. The most common positive effect observed is the reduction of craving, which usually requires a dosage of at least 150 mg/day. It may be a very interesting option on patients with liver disease [8].

REFERENCES

1. Gowing LR, Ali RL, Allsop S, Marsden J, Turf EE, West R, et al. Global statistics on addictive behaviours: 2014 status report. Addiction 2015;110:904- 19.
2. Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease.J Hepatol 2017;66:610-8.
3. EASL clinical practical guidelines: management of alcoholic liver disease.J Hepatol 2012;57:399-420.
4. Mundle G, Munkes J, Ackermann K, Mann K. Sex differences of carbohydrate-deficient transferrin, gamma-glutamyltransferase, and mean corpuscular volume in alcohol-dependent patients. Alcohol Clin Exp Res 2000;24:1400-5.
5. Crunelle CL, Verbeek J, Dom G, Covaci A, Yegles M, Michielsen P, et al. Hair ethyl glucuronide and serum carbohydrate deficient transferrin for the assessment of relapse in alcohol-dependent patients.Clin Biochem 2016;49:554- 9.
6. Soyka M, Kranzler HR, Hesselbrock V, Kasper S, Mutschler J, Moller HJ. Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision.World J Biol Psychiatry 2017;18:86-119.
7. Gual A, He Y, Torup L, van den Brink W, Mann K. A randomised, double- blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence.Eur Neuropsychopharmacol 2013;23:1432-42.
8. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study.Lancet 2007;370:1915-22.

NUTRITIONAL STATUS: FROM ASSESSMENT TOOLS TO MANAGEMENT

Manuela Merli
Sapienza University, Rome, Italy

Liver transplantation candidates need to address a variety of nutritional challenges ranging from malnutrition to sarcopenia to overweight or obesity.

Sarcopenia is recognized as a crucial component of malnutrition in liver cirrhosis. Muscle wasting and decreased muscle functions both are considered as mainstay for a diagnosis of sarcopenia. Sarcopenia may occur also in overweight/obese patients, conditions making it difficult to recognize the depletion in muscle mass if not purposely investigated.

Both sarcopenia and severe obesity have been recognized as conditions that may increase resources utilization, morbidity and even mortality in patients either befor or after liver transplantation.While nutritional disorders should not be considered as absolute contraindication for liver transplantation, they certainly need to be recognized and patient care in this regard needs to be implemented.

Nutritional assessment should be performed in all patients waiting for liver transplantation by means of different tools (subjective global assessment, objective evaluation of body compartments, interview about dietary intake). A CT-scan or MRI is almost universally present in these patients workout, therefore muscle depletion can be evaluated through L3 skeletal muscle index (L3 SMI) or psoas muscle area (PMA). These muscles are less influenced by fluid overload and also allow detecting patients who have sarcopenic obesity. A number of large studies have utilized the measurement of L3 in cirrhotic patients SMI and recently specific prognostic cut offs have been suggested for this population. A possible alternative for follow up measurements is dual energy Xray absorptiometry (DEXA) which allows muscle assessment of peripheral limbs with much lower exposure to radiations. Measurements of muscle function such as hand-grip strength and gate speed have also been utilized to assess patients performance and frailty while waiting for liver transplantation.

A nutritional care process is recommended in patients awaiting liver transplantation. Dietary counseling has been reported to improve survival in a small study in cirrhotic patients. The nutritional care process should be personalized to the specific needs of the individual patient, as nutritional indications need to comply also with the complications of the liver disease. According to international guidelines 30-35 Kcal/kg/ body weight/ day and 1-1.5 gr of protein per Kg weight/day should be provided but the patient's intake can be lower due to a number of obstacles ranging from gastrointestinal symptoms to tense ascites or hepatic encephalopathy. Small divided meals can be a possible approach and a late evening meal is always recommended to shorten the periods of fasting that induce protein catabolism. Vegetable proteins and protein supplements can also be considered in patients who cannot reach an adequate protein intake due to encephalopathy. In those patients who are severely malnourished and are unable to take adequate oral nutrition enteral or parenteral nutrition are advisable. Obesity should be managed by hypo-caloric diet and adequate protein intake to prevent further muscle wasting.

Patients with advanced liver disease experience a decreased physical activity, which may contribute to muscle dysfunction. A personalized program of physical activity can be useful improving aerobic capacity and muscle function and favoring weight loss in obese patients. Large studies showing the results of nutritional and lifestyle intervention in cirrhotic patients waiting for liver transplantation are still lacking. The availability of an adequate time frame, the severity of liver insufficiency and/or frequent hospitalization for disease complications as well as intrinsic anabolic resistance may represent limitations that need to be specifically addressed for nutritional care.

REFERENCES

1. Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology. 2016.
2. Iwasa M, Iwata K, Hara N, Hattori A, Ishidome M, Sekoguchi-Fujikawa N, Mifuji-Moroka R, Sugimoto R, Fujita N, Kobayashi Y, Takei Y. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition. 2013;29:1418-21.
3. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl. 2012;18(10):1209-16.3) A multicenter study to define sarcopenia in patients with end-stage liver disease.
4. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, Dunn MA; Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium.. Liver Transpl. 2017 May;23(5):625-633.
5. Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, Corradini SG, Siciliano M, Farcomeni A, Attili AF, Berloco P, Rossi M. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. Liver Int 2010, 30:208-14
6. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol. 2012;27:430-41.
7. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, Lucidi C, Di Martino M, Catalano C, Merli M. Eur J Gastroenterol Hepatol. 2015 Mar;27(3):328-34
8. Le Cornu KA, McKiernan FJ, Kapadia SA, Neuberger JM. A prospective randomized study of preoperative nutritional supplementation in patients awaiting elective orthotopic liver transplantation. Transplantation 2000, 69:1364-9

INFECTION SCREENING, PROPHYLACTIC MEASURES AND TREATMENTS, VACCINATION

Patrizia Burra
Padua

Patients with cirrhosis are prone to develop bacterial, viral or fungal infections that could result in the development of multiple organ failure and death.

All candidates before LT have to be screened for latent infections, especially for CMV and BK, in order to prevent an exacerbation after LT under immunosuppressive regimens. Vaccination is an important tool before LT against HAV and HBV, varicella, pneumococcus, influenza and tetanus.

Bacterial infections represent a major cause of decompensation in cirrhosis, but also of repeated hospitalizations, impaired health-related quality of life, and increased healthcare costs. Thus, a rapid and epidemiology-oriented evaluation is mandatory in presence of clinical suspicion, even though classic criteria of infection are often missing in cirrhotic patients. Pneumonia, spontaneous bacterial peritonitis, urinary tract infection and soft tissue infections are common types of bacterial infection in cirrhosis. Culture-guided or empiric antibiotic therapies - based on epidemiology, severity of liver disease and site of infection -are mandatory. The presence of invasive fungal infection, such as aspergillosis, represents a contraindication to transplantation and the recipient should be treated at least until there is radiographic, clinical and microbiologic resolution. Long-term antibiotic prophylaxis against spontaneous bacterial peritonitis is debated due to the risk of development of multidrug resistant strains, while other screening tools, as rectal swab, for identification of multidrug resistant bacteria, are useful to assess patient colonization.

Management of particular patients and complications in the waiting list - I

PRURITUS MANAGEMENT IN LIVER DISEASES

Andreas Kremer
Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nürnberg, Ulmenweg 18, 91054 Erlangen, Germany

Chronic pruritus is a common and agonizing symptom of various hepatobiliary disorders, particularly those with cholestatic features. The quality of life of affected patients can dramatically be reduced.[1] In some patients, itching may be mild and tolerable, but in others, it does limit daily life activities, cause severe sleep deprivation resulting in lassitude, fatigue, depressed mood and even suicidal tendencies. In rare cases, intractable pruritus may become a primary indication for liver transplantation.

Pruritus of cholestasis is characterized by a circadian rhythm with patients reporting the highest intensity in the evening and early at night, but it should be mentioned that chronic pruritus in general tends to increase with warmth and at night. A predilection site of pruritus is the limbs and in particular the palms and soles, although generalized pruritus is reported by many patients.[2] Furthermore, female cholestatic patients commonly report pruritus worsening during the progesterone phase of the menstrual cycle, in late pregnancy, and during hormone replacement therapy. Patients may report that scratching barely alleviates itch sensations and that pruritus is accompanied with other sensations such as stinging and burning. In contrast to pruritus in dermatological disorders, primary skin lesions are not detectable in cholestatic patients; however, intense scratching activity may cause secondary skin alterations such as excoriations and prurigo nodularis. Other causes for chronic pruritus should be excluded.

The pathogenesis of hepatic pruritus remains at least in part still elusive. Bile salts, opioids, histamine, and progesterone metabolites have been controversially discussed as causing agents in the past. [1] However, for these substances neither a correlation with itch severity nor a causative link has ever been established. Hepatic pruritus occurs independent of the extent of cholestasis. Pruritus is an adverse event of the semi-synthetic bile salt obeticholic acid (OCA, Ocaliva®) which has been licensed for primary biliary cholangitis. [3] Cholestatic patients do not present with histamine-induced skin alteration such as erythema or urticarial and antihistamines do not improve itching. [4] Thus, histamine is not a major player in the pathogenesis of hepatic pruritus. Recently, we would identify lysophosphatidic acid (LPA) which is synthesized by autotaxin (ATX), as potential pruritogen in liver diseases. [5] ATX levels correlated with itch severity and response to treatment. LPA receptor blocker and ATX inhibitors might therefore represent future causal anti-pruritic treatment strategies.

Current treatment recommendations for pruritus in cholestasis are based on only a few well-designed, randomized, placebo-controlled trials and several cohort studies. The rationale for medical and interventional therapeutic approaches is

- to remove the pruritogen(s) from the enterohepatic cycle by non-absorbable, anion exchange resins such as cholestyramine in mild pruritus or invasive interventions such as nasobiliary and transcutaneous drainage or external biliary diversion in desperate cases,
- to alter the metabolism of the presumed pruritogen(s) in the liver and/or the intestine by inducers of the hepatic biotransformation machinery such as rifampicin,
- to modulate central itch and/or pain signaling by influencing the endogenous opioidergic and serotoninergic system via μ-opioid antagonists and selective serotonin re-uptake inhibitors (SSRI), respectively, or
- to remove the potential pruritogen(s) from the systemic circulation by invasive methods such as anion absorption, plasmapheresis or extracorporeal albumin dialysis (MARS®, Prometheus®) if pruritus is intractable.

Due to its anti-cholestatic properties UDCA is used as baseline treatment for various cholestatic diseases such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP), cystic liver fibrosis and pediatric cholestasis syndromes.6 In randomized placebo-controlled trials in UDCA did not significantly improve itch intensity. However, UDCA is a safe and effective drug for pruritus in women suffering from ICP. [7]

Independent of drug treatment patients should be advised to use rehydrating emollients or cooling (menthol-containing) creams, to shorten their finger nails and wear loose-fitting cotton clothes.

According to the European Guideline treatment of hepatic pruritus should be started using the bile acid resin cholestyramine. Cholestyramine is recommended as a 4-gram sachet 1 h before and after breakfast and may be extended to 16 g/day. Resins should be taken at least 4 h prior to any other medication as they may interfere with their intestinal absorption. In a recent randomized, placebo-controlled trial colesevelam which has a higher binding affinity for bile salts than cholestyramine, failed to be superior to placebo. Rifampicin is regarded as second-line treatment. It is a safe short-term therapy of hepatic pruritus; however,

hepatotoxicity may occur in up to 10% of patients after treatment for several weeks or months requiring the monitoring of serum transaminase levels at regular intervals. If rifampicin is ineffective within 2 weeks, the μ-opioid antagonist naltrexone is recommended as third-line treatment. Naltrexone moderately improved pruritus at doses of 25–50 mg/day. Adverse effects may include withdrawal-like reactions, particularly during the first days of therapy. Therefore, naltrexone should be administered at low doses of 12.5 mg/day or intravenous infusion of naloxone followed by a stepwise dose increase. The selective serotonin uptake inhibitor sertraline (75–100 mg/day) can be administered as fourth-line therapy. [8,9] If these drugs are ineffective bezafibrate (400 mg/day) may represent an alternative drug with a good safety profile. Alternatively, gabapentin and pregabalin may be given. Future therapies may include inhibitors of the apical bile salt transporter (IBAT) which are currently investigated in placebo-controlled trials. The most promising compound represents GSK672 which had a strong effect within a two week treatment period. [10]

REFERENCES

1. Beuers U, Kremer AE, Bolier R, Elferink RP. Pruritus in cholestasis: facts and fiction. Hepatology 2014;60:399-407.
2. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol. 2000;14:643-655.
3. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. The New England journal of medicine 2016;375:631-643.
4. Jones EA, Bergasa NV. Evolving concepts of the pathogenesis and treatment of the pruritus of cholestasis. Can J Gastroenterol. 2000;14:33-40.
5. Kremer AE, Martens JJ, Kulik W, Rueff F, Kuiper EM, van Buuren HR, et al. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. Gastroenterology 2010;139:1008-1018.
6. Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol 2006;3:318-328.
7. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009;15:2049-2066.
8. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol 2009;51:237-267.
9. Kremer AE, Bolier R, van Dijk R, Oude Elferink RP, Beuers U. Advances in pathogenesis and management of pruritus in cholestasis. Digestive diseases 2014;32:637-645.
10. Hegade VS, Kendrick SF, Dobbins RL, Miller SR, Thompson D, Richards D, et al. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. Lancet 2017. Epub

HIV-INFECTED PATIENTS

Sofia Ferreira

Unidade de Transplante Hepato-Pancreática – Centro Hospitalar do Porto

Combination of antiretroviral drugs (ART), introduced in clinical practice from the mid-nineties, is able to reduce HIV-RNA viremia under the limit of detectability in the great majority of HIV-infected patients. The suppression of HIV replication resulted in improvement of cellular immune function, patient's clinical status in any stage of HIV disease, and in a dramatic decrease of HIV/AIDS-related mortality. The life expectancy of people with HIV is now approaching that seen in the general population. Consequently, the relative importance of other traditionally non-AIDS-related morbidities has increased [1, 2].

Liver disease is now the second most common non-AIDS-related cause of mortality in HIV- infected patients, accounting for a greater proportion of deaths than cardiovascular disease, composing 13% of mortality cases between 1999-2001, the majority of which in the context of viral hepatitis co-infection [1]. The number of liver-related deaths in individuals not co-infected with either hepatitis B (HBV) or hepatitis C virus (HCV) is very small, accounting for less than 5% of all liver related deaths [2]. Taking into account, these two aspects- better HIV control and high prevalence and mortality of liver disease - an increasing number of co-infected people are being referred for liver transplantation.

Several authors observed that the prevalence of extensive liver fibrosis and moderate or severe activity were higher in HIV/ HCV co-infected than in mono-infected patients as was the median fibrosis progression rate. HIV seropositivity, alcohol consumption, age at HCV infection and severe immunosuppression were associated with an increase in the fibrosis progression rate [3,4,5].

Some studies suggested a benefit of ART in reducing the incidence or slowing the progression of liver disease, fibrosis and cirrhosis, while others showed no evidence of benefit or harm, compared with no antiretroviral therapy. A recent meta-analysis found that the risk of liver-related mortality was reduced by approximately 70% in patients receiving ART when compared to untreated patients [6].

The incidence of clinical liver events in HIV/ HCV co-infected patients with Child-Pugh class (CP) A compensated cirrhosis is close to that reported in HCV mono-infected patients, with a low 3-year risk of first liver decompensation. However, time to next

decompensation is critically reduced. Lower baseline CD4 cell counts, lack of therapy against HCV, higher CP score, permanent ART interruption during follow-up and time since HCV infection diagnosis are the factors related to the occurrence of clinical liver events. Minimal changes in CP score have strong impact in the prognosis of this population [7,8].

Gelu- Simeon et al [9] followed prospectively 77 HIV/ HCV coinfected- patients experiencing an initial decompensation. They reported a 78% survival rate at 12months after a first decompensation. The probability of experiencing at least a second episode of decompensation after the initial one was 46% and 63% at 1 and 2 years, respectively. The univariate analysis showed that a higher MELD score at initial decompensation was significantly associated with poorer survival as was the occurrence of further episodes of decompensation during follow-up. Under multivariate analysis, the MELD score remained significantly associated with surviving after an initial episode of decompensation. The presence of ascites during initial decompensation tended to predict a poorer prognosis compared with jaundice alone. It was found that a cut-off MELD of 20 was able to discriminate HIV/HCV coinfected patients with good survival from those with poor survival. The kinetics of MELD score after the initial decompensation episode differed significantly between deceased and non-deceased patients. The mean MELD score of patients who remained alive during the study period fell significantly during the first 6 months, while it remained stable in deceased patients. After 6 months, the mean MELD score increased significantly by +0.32/month ($P<0.0001$) in patients who die during follow-up, while it did not change significantly among those who remained alive. The authors suggest that the kinetic of MELD score may help us not only to refer but also to manage patients on the waiting list for liver transplant. This is particularly important in HIV/ HCV co-infected patients who are a high-risk population with a more rapid liver disease progression.

In preliminary studies, Ragni et al demonstrated significantly shorter pre-transplantation survival, mainly due to infections, in HIV-infected patients listed for liver transplantation when compared with HIV negative patients, despite equivalent MELD scores at the time of listing [11]. In another study, Stock et al reported that MELD score did not accurately predict survival of HIV coinfected patients in waiting list for LT [12]. Moreover, survival of HIV-infected patients with decompensated cirrhosis is significantly shorter than that in HIV-negative patients. Pineda et al demonstrated in a multicenter Spanish case-control study that the outcome of cirrhosis after the first decompensation in HIV/HCV coinfected patients is significantly worse than that observed in the mono HCV-infected population: survival at 1, 2 and 5 years for HIV/HCV co-infected and HCV monoinfected populations was 54%/74%, 40%/61% and 25%/44%, respectively [13]. Murrillas et al (14), observed that the mortality in each category of MELD in HIV-infected patients was approximately 2 to 4 times higher than the mortality reported for the corresponding categories of non–HIV-infected patients with cirrhosis, indicating yet again that HIV-infected patients with cirrhosis have a poorer survival than non HIV-infected patients, regardless of their similar baseline severity of chronic liver disease. They suggested that according to the survival curves calculated for the different MELD categories, liver transplantation should be recommended in HIV-infected patients with cirrhosis with a MELD score greater than 10 because the probability of survival observed in these patients was clearly lower than that currently expected following liver transplantation. However, this cannot be implemented in the majority of centers. Taken together, these data suggest that HIV-infected patients reaching the minimal MELD score requested for activating the waiting list (i.e. a MELD score not inferior to 15) should be listed and transplanted as soon as possible. Currently, the general and hepatologic criteria for patients' selection are based on the experience coming from the non-HIV-infected population where the scoring of severity of hepatic failure is based on MELD and Child-TurcottePugh (CTP) scores; these scores and the relative thresholds are reliably used as minimal listing criteria and to assess the severity of liver disease also for HIV-infected candidates. Although the MELD score correlated with death on the waiting list for the HIV-infected patients, the absolute value of the MELD score is associated with poorer survival rates in comparison with HIV-negative monoinfected patients. Currently available data support the inclusion of MELD score in the standard HIV medical management for early identification of patients to be referred and listed for LT, but the optimal score to hierarchize HIV patients in the waiting list is yet to be described. The kinetics of MELD could be an added value [10]. Probably some prioritization for HIV-positive recipients might be indicated, but it is unlikely that additional MELD points for HIV-positive patients could become part of the standardized point system analogously to the additional points given for localized hepatocellular cancers (HCCs) [14].

Of note, most of the above studies and observations were in HIV/ HCV co-infected patients, so possibly all these issues will be of less importance and almost nonsense in the era of directly acting antivirals. Finally, we must take in account that HIV-monoinfected patients are not spared from end stage liver disease-alcohol, NASH, drug toxicity- and their natural history is not as well characterized.

REFERENCES

1. Colette J Smith, Lene Ryom, Rainer Weber, Philippe Morlat, Christian Pradier, Peter Reiss, Justyna D Kowalska, Stephane de Wit, Matthew Law, Wafaa el Sadr, Ole Kirk, Nina Friis-Moller, Antonella d'Arminio Monforte, Andrew N Phillips, Caroline A Sabin, Jens D Lundgren, for the D:A:D Study Group. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet 2014; 384: 241–48
2. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodefi ciency virus: the D:A:D study. Arch Intern Med 2006; 166: 1632–41
3. Pineda JA et al. Clinical progression of hepatitis C virus- related chronic liver disease in human immunodeficiency virus – infected patients undergoing highly active antiretroviral therapy. Hepatology. 2007; 46: 622- 630
4. Salmon- Ceron D. et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol. 2005; 42: 799-805
5. Yves Benhamou, Marie Bochet, Vincent Di Martino, Frederic Charlotte, Felipe Azria, Anne Coutellier, Michel Vidaud, François Bricaire, Pierre Opolon, Christine Katlama, and Thierry Poynard for the Multivirc Group. Liver Fibrosis Progression in Human Immunodeficiency Virus and Hepatitis C Virus Coinfected Patients. Hepatology. 1999;30: 1054-1058.
6. Llewellyn A, Simmonds M, Irving WL, Brunton G, Swoden AJ. Antiretroviral therapy and liver disease progression in HIV and hepatitis C co-infected patients: a systematic review and meta-analysis. Hepatology, Medicina and Policy. 2016: 1-10
7. Pineda JA, Aguilar- Guisado M, Rivero A et al. Natural history of compensated hepatitis C virus- related cirrhosis in HIV-infected patients. Clin Infect Dis 2009; 49: 1274- 1282.
8. López-Diéguez M, Montes M, Pascual-Pareja JF, Quereda C et al. The natural history of liver cirrosis in HIV- hepatits C virus-coinfected patients. AIDS 2011; 899-904.
9. Moana Gelu-Simeon, Tatiana Bayan, Maria Ostos. MELD score kinetics decompensated HIV+/HCV+ patients. Medicine. 2015; 30.
10. Ragni M, Eghtesad B, Schlesinger K, et al. Pre-transplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. Liver Transpl 2005; 11: 1425-30.
11. Stock P. Rapid deterioration of HIV coinfected patients waiting for liver transplantation is not predicted by MELD. Liver Transpl 2005; 11: 1315-7.
12. Pineda JA, Romero-Gomez M, Diaz-Garcia F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatol 2005; 41: 779-89.
13. Javier Murillas, Antonio Rimola, Montserrat Laguno, Elisa de Lazzari, Javier Rascón, Fernando Aguero, José L.Blanco, Eduardo Moitinho, Asunción Moreno, José M.Miró and the ESLD-HIV Working Group Investigators. The Model for End-Stage Liver Disease Score Is the Best Prognostic Factor in Human Immunodeficiency Virus 1–Infected Patients with End-Stage Liver Disease: A Prospective Cohort Study. Liver Transplantation 15:1133-1141, 2009

Management of particular patients and complications in the waiting list - II

CONCOMITANT RENAL FAILURE: WHEN TO CONSIDER SIMULTANEOUS LIVER AND KIDNEY TRANSPLANTATION?

Claire Francoz

Intensive Care Unit and Liver Transplantation, Hepatology, Hopital Beaujon, Clichy, France

INTRODUCTION

Simultaneous liver and kidney transplantation (SLKT) is usually proposed in patients with both end-stage liver and kidney diseases. Indeed, the results of either kidney transplantation in patients with decompensated cirrhosis or those of liver transplantation (LT) in patients with end-stage kidney disease are poor. In contrast, several studies report an excellent outcome after SLKT.

While kidney transplantation is unquestionable in candidates for LT on chronic dialysis, the indication of kidney transplantation remains challenging in cases of prolonged acute kidney injury (AKI) and/or underlying chronic kidney disease (CKD). In one hand, post transplant kidney failure alters the results of LT at both short and long-terms and, in other hand, in a context of organ shortage, unnecessary kidney transplantation in patients with a high potential for renal recovery has to be avoided. In addition, current immunosuppressive regimens are mainly based on nephrotoxic agents (calcineurin inhibitors) and may further deteriorate renal dysfunction after LT, increasing thus morbidity and mortality. Therefore identifying the reversibility and the irreversibility of renal impairment after LT is a key issue.

RENAL IMPAIRMENT IN PATIENTS WITH CIRRHOSIS

For many years, it has been clearly established that kidney function plays a major role in the prognosis of cirrhosis [1, 2]. Renal dysfunction includes both acute and chronic dysfunction [3].

AKI is a common complication of decompensated cirrhosis and has been reported to occur in up to 50% of hospitalized patients with cirrhosis[4, 5]. AKI is thought to be due to the combination of an impaired effective arterial blood volume secondary to arterial vasodilation, with increased intra-renal vasoconstriction and impaired renal autoregulation [6]. AKI can be precipitated by factors that further impair circulatory status and reduce renal perfusion, such as gastrointestinal bleeding and bacterial infections [7-10], very common in candidates for LT (Figure 1) [11, 12].

Classical phenotypes of AKI include prerenal failure, hepatorenal syndrome (HRS) and intrarenal failure, mainly due to acute tubular necrosis (ATN) [13]. Recent data suggest that AKI may represent a *continuum*, from prerenal to ATN, rather than distinct categories, with overlap between phenotypes. In patients with decompensated cirrhosis, precipitating factors such as hypovolemia, administration of nephrotoxic agents, infection and/or SIRS may precipitate renal hypoperfusion that is a central mechanism, whatever the phenotype of AKI. In addition, the most recent *International Club* of Ascites (ICA) concludes that tubular lesions may be found in patients with HRS [14].

Apart from specific conditions such as IgA nephropathy and glomerulonephritis associated with viral hepatitis,

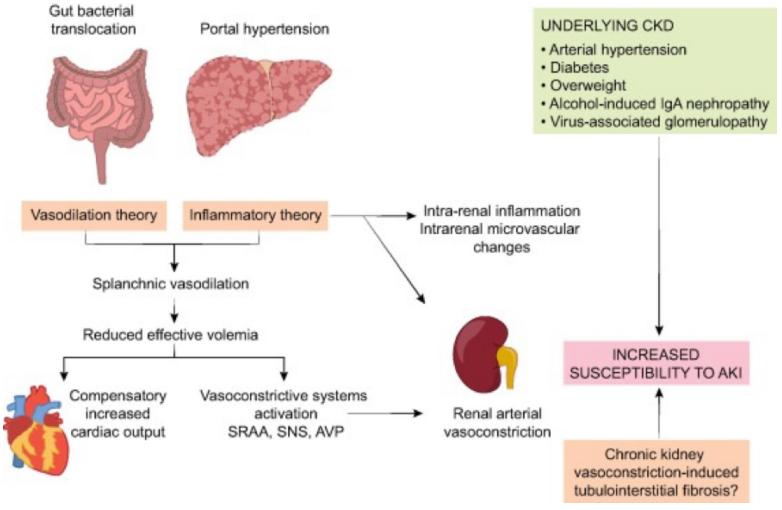


Figure 1: Mechanisms contributing to impaired renal function in cirrhosis [12]

In end-stage liver diseases, several factors contribute to increase susceptibility of the kidney to AKI. Both vasodilation secondary to portal hypertension and systemic inflammation induced by gut bacterial translocation tend to induce renal arterial vasoconstriction, due to the activation of vasoconstrictive systems (SRAA, SNS and AVP) in response to decreased effective blood volume. Intra-renal inflammation induce intra-renal microvascular changes resulting in decreased GFR with an imbalance between preglomerular and postglomerular resistance (which corresponds to both preglomerular and post glomerular vascular tone) as well as impaired renal microcirculation affecting tubular and glomerular function Underlying CKD due to associated comorbidities eventually increases the risk for AKI. Consequences of prolonged kidney vasoconstriction are not clearly elucidated but may induce tubular interstitial fibrosis and further increase the risk of AKI.

the pathophysiology of chronic kidney disease (CKD) in patients with cirrhosis has been poorly explored. Due to the high prevalence of comorbidities including diabetes, past history of hypertension and atherosclerosis, it can be assumed that chronic kidney changes are more common in patients with cirrhosis than in the general population, especially in patients with non-alcoholic steatohepatitis (NASH)-related cirrhosis [15]. In addition, with the growing incidence of NASH-related cirrhosis [15], metabolic-syndrome-associated CKD will certainly increase in the future. Finally, parenchymal consequences of chronic vasoconstriction associated with the so called type 2 HRS are not known. Kidney biopsies of patients with type 2 HRS show various histological changes [16, 17]. These results suggest that in the long term, chronic vasoconstriction may promote inflammation and fibrosis as shown in several models.

Finally, there is a growing evidence suggesting close interconnexions between AKI and CKD [18]. In general population, large recent studies have demonstrated that about 20% of patients who survive an episode of AKI are at high risk for progressing to advanced stages of CKD [19]. Risk factors associate ageing, diabetes, arterial hypertension and overweight. In addition, repeated and/or severe episodes of AKI increase the risk for developing CKD. These results, observed in general population, may be transposed in patients with cirrhosis.

EVALUATION OF AKI IN CANDIDATES FOR LT, MANAGEMENT AND INDICATION FOR SLKT

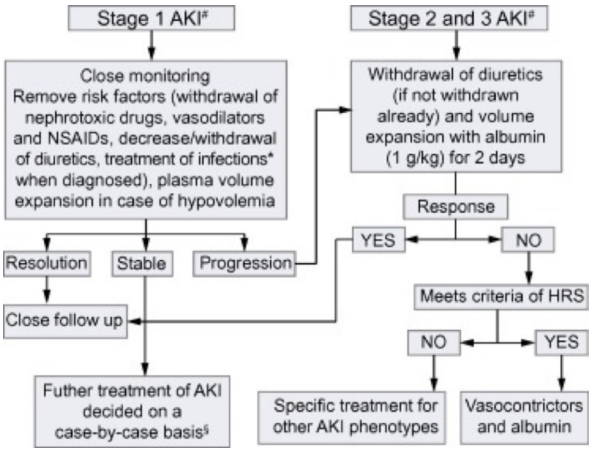
By definition, AKI corresponds to an abrupt reduction of GFR that occurs during a short time interval (less than one week). In recent years, a new classification of AKI integrating a dynamic definition consisting in a rise in serum creatinine level, rather than a single value, has been proposed in the general population, then adapted (removal urinary output, which is highly variable) and applied in cirrhosis (Table 1). AKI includes all conditions leading to acute renal dysfunction, from impairment, without any structural lesion, to severe kidney damage. Interestingly, although type-1 HRS has been deemed to be a functional injury, it has been incorporated under the general definition of AKI in 2015 [14]. Based on this classification, an algorithm for the management has been proposed (Figure 2).

Table 1: Classification of AKI in cirrhosis, International Club of Ascites [14]

Stages	Criteria
1	Increase in SCr*> 0.3mg/dL within 48h or >150-200% from baseline[$]
2	Increase in SCr* 200-300% from baseline[$]
3	Increase in SCr * >300% from baseline$ or SCr*>4 mg/dL or renal replacement therapy

SCr: serum creatinine; [$]value of SCr obtained in the previous 3 months when available, if more than one value of Scr, consider the closest to the admission to the hospital, if no previous value, consider SCr at admission.

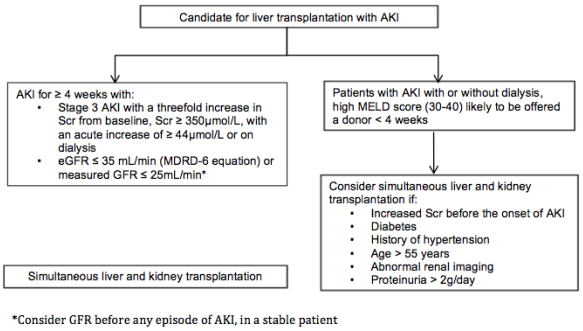
Figure 2: Proposed algorithm for the management of acute kidney injury (AKI) according to International Club of Ascites—AKI (ICA-AKI) [14]



"Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria. §No global consensus was reached on this point. HRS, hepatorenal syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; sCr, serum creatinine.

Criteria to perform SLKT rather than liver transplantation alone have been recently proposed. They are based on a high probability of non-renal recovery post transplantation [20]. Whatever patients are on dialysis or not, these criteria rely on the progression of AKI over a period of 4 weeks or more and only patients with AKI stage 3 have to be considered. However, patients with a high model for end-stage liver disease (MELD) score (35-40) may be offered an organ less than 4 weeks after being placed on the waiting list. In these patients, increased baseline creatinine or, even better, glomerular filtration rate measured by clearance of exogenous marker below 35 mL/min, in stable condition and before the onset of AKI, diabetes, history of hypertension, advanced age, abnormal renal imaging [21] and proteinuria >2 g/day, all suggesting underlying CKD, argue for SLK transplantation (Figure 3). However, no clear-cut algorithm has been validated yet and further studies evaluating biomarkers of reversibility or irreversibility of renal failure are needed. Objective markers of maladaptative repair after tubular cell injury, the key mechanism associated with « irreversible AKI » (progression from AKI to CKD), as well as non invasive markers of kidney fibrosis represent an attractive perspective [22, 23].

Figure 3: decision of simultaneous liver and kidney transplantation versus liver transplantation alone in candidates with acute kidney injury [12]



AKI, acute kidney injury; eGFR, estimates of glomerular filtration rate;

EVALUATION OF CKD IN CANDIDATES FOR LT, MANAGEMENT AND INDICATION FOR SLKT

Identifying CKD and the cause of CKD remains a challenging issue in patients with cirrhosis.

CKD is defined by a decreased in GFR, the most accurate surrogate marker of renal function. According to the KDIGO classification, 5 stages of CKD have been described, of increasing severity. From a GFR of 60 mL/min (corresponding to stage 3), CKD may be considered as significant [24].

The reference for the assessment of GFR is the measured clearance of an exogenous marker (inulin, iothalamate, iohexol), however this technique is time-consuming, costly and difficult to perform in routine [3]. Several estimates of GFR, proposed in general population, have been assessed in cirrhosis. While Cockcroft, modification of diet in renal disease 4 (MDRD-4) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations) tend to overestimate GFR, MDRD-6 may be more accurate in cirrhosis[25-27]. Table 2 summarizes the variables included in current equations. Other estimates incorporating Cystatin C have been proposed but need further evaluations [28].

As in general population, current biomarkers aiming at defining the cause of CKD (leucocyturia, hematuria, proteinuria, imaging) have a poor accuracy. Kidney biopsy remains the gold standard however it is difficult to perform in this population due to abnormal coagulation and thrombocytopenia [29].

The management of CKD in patients with cirrhosis does not differ from those without cirrhosis. However, in decompensated cirrhosis, nephroprotective strategies currently used in nephrology cannot be used, especially angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers which are poorly tolerated.

SLKT should be proposed in patients who would not recover renal function after LT or will rapidly deteriorate in the 2 first years after LT. Current recommendations for SLKT are CKD for, at least, 6 months with one of the following: (a) eGFR ≤ 40 mL/min (MDRD-6 equation) or GFR ≤ 30 mL/min (iothalamate clearance), (b) Proteinuria ≥ 2 g a day, (c) Kidney biopsy showing > 30% global glomerulosclerosis or > 30% interstitial fibrosis or (d) Metabolic disease [20]. However, using these recommendations based on expert opinion, there are still some "futile" kidney transplantations. For instance, we have shown that using CKD for more than 6 months and eGFR ≤ 40 mL/min by MDRD-6 equation, the risk of unnecessary kidney transplantation was of 8% [27]. In the future, biomarkers evaluating the irreversibility of renal dysfunction should be developed and markers of fibrosis represent an attractive persepective.

CONCLUSION AND PERSPECTIVES

SLKT should be proposed in candidates for LT who have either pre LT AKI that would not recover after transplantation or pre LT CKD at high risk of developing end-stage kidney failure within 2 years post LT. Accurate tools are lacking to predict recovery of renal function after LT and tools have to be developed in the future, including both biomarkers and imaging techniques.

Table 2: Variables Included into Current Estimates of GFR

Equation	Variables
Cockcroft-Gault [30]	Age, SCr, Gender, Weight
MDRD-4 [31]£	Age, SCr, Gender, Ethnicity*
MDRD-6 [31]	Age, SCr, Gender, Ethnicity, BUN, Albumin
CKD-EPI [32]	Age, SCr, Gender, Ethnicity
CKD-EPI Cystatin C [33]£	Age, Gender, Cystatin C
CKD-EPI Creatinine-Cystatin C [34]	Age, Gender, Cystatin C, SCr, Ethnicity

MDRD: Modification of Diet in Renal Disease equation, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation, *black versus non black ethnicity, BUN: blood Urea Nitrogen. £MRDR-4 and CKD-EPI include same variables but formula are different

REFERENCES

1. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). Hepatology 2007;45:797-805.
2. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42 Suppl:S100-107.
3. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605-613.
4. Cardenas A, Gines P, Uriz J, Bessa X, Salmeron JM, Mas A, Ortega R, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001;34:671-676.
5. Terra C, Guevara M, Torre A, Gilabert R, Fernandez J, Martin-Llahi M, Baccaro ME, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology 2005;129:1944-1953.
6. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272-1284.
7. Durand F, Graupera I, Gines P, Olson JC, Nadim MK. Pathogenesis of Hepatorenal Syndrome: Implications for Therapy. Am J Kidney Dis 2016;67:318-328.
8. Adebayo D, Morabito V, Davenport A, Jalan R. Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. Kidney Int 2015;87:509-515.
9. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279-1290.
10. Stadlbauer V, Wright GA, Banaji M, Mukhopadhya A, Mookerjee RP, Moore K, Jalan R. Relationship between activation of the sympathetic nervous system and renal blood flow autoregulation in cirrhosis. Gastroenterology 2008;134:111-119.
11. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12:711-719.
12. Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. J Hepatol 2016;65:809-824.
13. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003;37:233-243.
14. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968-974.
15. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013;10:686-690.
16. Trawale JM, Paradis V, Rautou PE, Francoz C, Escolano S, Sallee M, Durand F, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int 2010;30:725-732.
17. Calmus Y, Conti F, Cluzel P, Hill G, Antoine C, Scatton O, Soubrane O, et al. Prospective assessment of renal histopathological lesions in patients with end-stage liver disease: effects on long-term renal function after liver transplantation. J Hepatol 2012;57:572-576.
18. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58-66.
19. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int 2009;76:1089-1097.
20. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, Feng S, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant 2012;12:2901-2908.
21. Levitsky J, Baker T, Ahya SN, Levin ML, Friedewald J, Gallon L, Ho B, et al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. Am J Transplant 2012;12:2949-2957.
22. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest 2011;121:4210-4221.
23. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 2015;11:264-276.
24. 5 NKFKDCPGfCKDP. Evaluation of Laboratory Measurements for Clinical Assessment of Kidney Disease. Guideline 4. Estimation of GFR. Am J Kidney Dis 2002;39:S76-S110.
25. Cholongitas E, Shusang V, Marelli L, Nair D, Thomas M, Patch D, Burns A, et al. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. Aliment Pharmacol Ther 2007;26:969-978.
26. Francoz C, Prie D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl 2010;16:1169-1177.
27. Francoz C, Nadim MK, Baron A, Prie D, Antoine C, Belghiti J, Valla D, et al. Glomerular filtration rate equations for liver-kidney transplantation in patients with cirrhosis: validation of current recommendations. Hepatology 2014;59:1514-1521.
28. De Souza V, Hadj-Aissa A, Dolomanova O, Rabilloud M, Rognant N, Lemoine S, Radenne S, et al. Creatinine- versus cystatine C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. Hepatology 2014;59:1522-1531.
29. Wadei HM, Geiger XJ, Cortese C, Mai ML, Kramer DJ, Rosser BG, Keaveny AP, et al. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. Am J Transplant 2008;8:2618-2626.
30. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
31. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-470.
32. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-612.
33. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-29.
34. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 2008;51:395-406.

PORTAL VEIN THROMBOSIS

Filipe Nery
Centro Hospitalar do Porto – Hospital Sto António
EpiUnit – Instituto de Saúde Pública da Universidade do Porto
Instituto de Ciências Biomédicas de Abel Salazar – UP

Portal vein thrombosis (PVT) refers to the presence of a clot in the lumen of the portal vein trunk or one or two of its branches, which can partially or totally occlude the lumen. Some risk factors to its development in cirrhosis (and out of the hepatocellular carcinoma context) have been recognized so far, as the presence of at least medium sized esophageal varices, a diminished portal vein flow velocity, the severity of liver insufficiency/ liver disease, the "procoagulant" environment and some genetic prothrombotic conditions. [1-5]

In severe patients (most commonly the ones that are in a waiting list for liver transplantation – LT), PVT prevalence may be as high as 26%. [6] That's why BAVENO VI recommends PVT screening to all patients that shall enter a list for LT and with a periodicity of every 6 months while on list. [7]

Probably the most recognized PVT classification is the one described by Yerdel in 2000. It relies in an anatomical strict classification. [8] Recently, Sarin et al proposed an anatomic-functional classification, which may, if validated, aid in a near future not only to select patients to start anticoagulation treatment but also to establish a more reliable prognosis. [9]

Classically, PVT has been recognized to have a negative impact in morbi-mortality, leading to liver decompensation and death. Yet, recent longitudinal studies haven't shown any deleterious effect of PVT in liver decompensation or death. [2, 10-12] But there is a subset of patients that seems to have lower survival rates when PVT occur, and are those who are submitted to LT. [13] So, this is clearly the subset of patients that may benefit of PVT treatment.

Anticoagulation, either with low molecular weight heparin (LMWH) or Vitamin K Antagonists (VKA) is the standard therapy to PVT treatment. [14] Francoz et al. have well documented more than a decade ago the benefit of PVT treatment with complete recanalization being achieved in 42% of the patients. [15] Other authors also have documented this positive effect of anticoagulation treatment. (16-18) As aforementioned, anticoagulation is not only efficacious but also doesn't seem to induce severe bleeding events, since patients undergo esophageal varices eradication prior its start. The Non-VKA oral anticoagulants (NOAC), either direct thrombin or FXa inhibitors are a new class of anticoagulants that don't need either daily subcutaneous injections nor regular blood controls, and are currently in use for prophylaxis and treatment of venous thromboembolic events. To date, there are only 4 case reports considering the use of rivaroxaban and regression of PVT, which favours its efficacy [19-22] and 2 retrospective studies that show its safety when used in cirrhotic patients irrespective of the cause that led to its administration. [23, 24]

So, once a diagnosis of PVT is done in a patient on the waiting list for LT, an immediate screening for esophageal varices shall be done and eradication treatment started whenever necessary. Anticoagulation treatment shall then be started, nowadays still with LMWH or VKA anticoagulants, but probably that in a near future NOACs will be the best choice. It is important to note that the aim to start anticoagulation is to achieve recanalization, but if this goal is not achieved, further extension of PVT shall be prevented, in order to avoid the surgical procedure harder or even impossible. Once LT is achieved, some details should be thought, namely when considering the donor, as it is expectable a more prolonged cold and warm ischemia times. Donor with "lower qualities", which are more prone to ischemia and heart-stopping donor, shall not be used. [25] Other issue to be addressed is anticoagulation treatment after LT, as PVT may frequently relapse, and its relapse and extension may induce graft dyfunction. [26] Yet, this is still a matter of debate.

Overall, PVT has been considered a formal contra-indication to liver transplantation till 1985, mainly due to technical issues and dismal outcome. [27] Nowadays, PVT, when recognized in a patient in a waiting list for LT shall be proposed to anticoagulation treatment in order to reverse thrombosis or prevent its extension. The decision to proceed for transplantation must be multidisciplinary with the involvement of the radiologists and surgeons.

REFERENCES

1. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. The New England journal of medicine. 2011;365(2):147-56.
2. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660-7.
3. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. Journal of hepatology. 2009;51(4):682-9.
4. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. Journal of hepatology. 2004;40(5):736-41.
5. Erkan O, Bozdayi AM, Disibeyaz S, Oguz D, Ozcan M, Bahar K, et al. Thrombophilic gene mutations in cirrhotic patients with portal vein thrombosis. European journal of gastroenterology & hepatology. 2005;17(3):339-43.
6. Gayowski TJ, Marino IR, Doyle HR, Echeverri L, Mieles L, Todo S, et al. A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. The Journal of surgical research. 1996;60(2):333-8.
7. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. Journal of hepatology. 2015;63(3):743-52.

8. Yerdel MA, Gunson B, Mirza D, Karayalcin K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. Transplantation. 2000;69(9):1873-81.
9. Sarin SK, Philips CA, Kamath PS, Choudhury A, Maruyama H, Nery FG, et al. Toward a Comprehensive New Classification of Portal Vein Thrombosis in Patients With Cirrhosis. Gastroenterology. 2016;151(4):574-7 e3.
10. Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crino F, et al. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012;265(1):124-32.
11. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. The American journal of gastroenterology. 2013;108(4):568-74.
12. John BV, Konjeti R, Aggarwal A, Lopez R, Atreja A, Miller C, et al. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. Annals of hepatology. 2013;12(6):952-8.
13. Nery F, Valla D. Splanchnic and extrasplanchnic thrombosis in cirrhosis: prophylaxis vs treatment. Curr Hepatology Rep 2014;13:224-34.
14. European Association for the Study of the Liver. Electronic address eee. EASL Clinical Practice Guidelines: Vascular diseases of the liver. Journal of hepatology. 2016;64(1):179-202.
15. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54(5):691-7.
16. Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. Journal of clinical gastroenterology. 2010;44(6):448-51.
17. Senzolo M, T MS, Rossetto V, Burra P, Cillo U, Boccagni P, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver international : official journal of the International Association for the Study of the Liver. 2012;32(6):919-27.
18. Delgado MG, Seijo S, Yepes I, Achecar L, Catalina MV, Garcia-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012;10(7):776-83.
19. Pannach S, Babatz J, Beyer-Westendorf J. Successful treatment of acute portal vein thrombosis with rivaroxaban. Thrombosis and haemostasis. 2013;110(4):626-7.
20. Martinez M, Tandra A, Vuppalanchi R. Treatment of acute portal vein thrombosis by nontraditional anticoagulation. Hepatology. 2014;60(1):425-6.
21. Lenz K, Dieplinger B, Buder R, Piringer P, Rauch M, Voglmayr M. Successful treatment of partial portal vein thrombosis (PVT) with low dose rivaroxaban. Zeitschrift fur Gastroenterologie. 2014;52(10):1175-7.
22. Yang H, Kim SR, Song MJ. Recurrent acute portal vein thrombosis in liver cirrhosis treated by rivaroxaban. Clinical and molecular hepatology. 2016;22(4):499-502.
23. Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, et al. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. Digestive diseases and sciences. 2016.
24. De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver international : official journal of the International Association for the Study of the Liver. 2017;37(5):694-9.
25. Ponziani FR, Zocco MA, Senzolo M, Pompili M, Gasbarrini A, Avolio AW. Portal vein thrombosis and liver transplantation: implications for waiting list period, surgical approach, early and late follow-up. Transplantation reviews. 2014;28(2):92-101.
26. Manzanet G, Sanjuan F, Orbis P, Lopez R, Moya A, Juan M, et al. Liver transplantation in patients with portal vein thrombosis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2001;7(2):125-31.
27. Shaw BW, Jr., Iwatsuki S, Bron K, Starzl TE. Portal vein grafts in hepatic transplantation. Surgery, gynecology & obstetrics. 1985;161(1):66-8.

HEPATOCELLULAR CARCINOMA: BRIDGE AND DOWNSTAGING THERAPIES

Christian Toso

Divisions of transplant and abdominal surgery, Department of Surgery, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland
Hepato-pancreato-biliary centre, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

In many countries, hepatocellular carcinoma (HCC) represents a growing indication for transplantation. This observation is both linked to a higher incidence of HCC, and to the use of expended listing criteria. An appropriate waitlist management of patients with HCC has therefore never been as critical as today due to the competition for liver grafts between patients with and without HCC. Waitlist anti-HCC treatments can be used as bridging in patients already within transplant criteria, or as *downstaging* in patients originally not qualifying for transplantation based on local policies [1].

BRIDGING

According to a cost-analysis study, the use of waitlist HCC treatment is generally accepted as being useful in patients with an expected waiting time of at least 6 months [2]. Such a practice appears reasonable although one can wonder whether an HCC treatment should not be planned in all listed patients. The morbidity of loco-regional treatments is low, wait time is not always predictable in advance, and most patients wait more than six months anyway. Overall, waitlist HCC treatments is used more and more liberally, as shown by US data with 62% of patients treated between 2004 and 2009, and 82% between 2009 and 2011 [3]. The type of treatment should be chosen according to the size and location of the HCC, but trans-arterial chemo-embolization (TACE) and radio-frequency ablation (RFA) are most used.

Of note, the use of waitlist HCC treatment should be used even more liberally in centers listing patients outside Milan. Such patients show an increased risk of progressing beyond a transplantable state, and should be monitored and treated with further attention [4].

A debate remains on whether waitlist treatment has an overall impact on post-transplant outcomes. It appears now clear that patients replying well to treatment have better post-transplant outcomes [5, 6]. To illustrate, patients with >90% response after TACE demonstrate virtually no risk of post-transplant recurrence [6]. Such outcomes match the extremely low risk of recurrence after HCC treatment with complete response. These observations suggest that selected patients with complete response may not even be considered for upfront transplantation [1].

DOWNSTAGING

The option of bringing back HCC patients into transplantation criteria has been validated by a number of studies demonstrating similar post-transplant survivals for patients originally within Milan and those downstaged to Milan. The group of Bologna demonstrated that 32 patients with a single ≤8 cm HCC, bifocal HCCs ≤5 cm, or 3-6 HCCs each ≤4 cm (with a total diameter ≤12 cm) could be successfully downstaged to Milan and transplanted. They showed similar post-transplant survivals than 88 patients continuously within Milan [8]. The group of UCSF presented similar outcomes on 64 downstaged patients with a single ≤8 cm HCC, 2-3 HCCs each ≤5 cm (with a total diameter ≤8 cm), or 4-5 HCCs each ≤3 cm (with a total diameter ≤8 cm) (9). In addition, downstaging has also been validated based on AFP. Those with an original AFP>400 ng/ml and a successful waitlist AFP decrease <400 ng/ml demonstrated similar post-transplant survivals than those with an AFP continuously <400 ng/ml [10]. Collectively, these results show the power of selection of downstaging, identifying the best candidate among those who originally look as having bad expected post-transplant outcomes.

A number of points appear important:

- Post-downstaging candidate selection should be based both on morphological and biological (such as AFP) factors. An AFP remaining high despite the efficient treatment of a liver HCC should promote the search for extra-hepatic disease.

- Time is a key factor, and it is advised to wait at least 3-6 months prior to transplanting downstaged patients in order to make sure that their HCC remains stable. A drop-out is better than an early recurrence, as the second option has an impact on two patients: the one with the recurrence, and the other patient who did not receive the organ.

Overall, *bridging* should be used liberally, especially when the expected waiting time is >6 months, and when expended listing criteria are used (due to the increased risk of drop-out). *Bridging* has the potential of improving post-transplant survival and recurrence rates, especially in case of (near-)complete loco-regional HCC response. *Downstaging* allows for the selection of patients with the good biology HCCs among those with bad expected outcomes originally. Any patient can be included in such a strategy (downstaging and palliative HCC treatments are similar), transplantability should be assessed both on morphology and biology (AFP), and a minimum of 3-6 months waiting is advised before transplantation

REFERENCES

1. Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. J Hepatol. 2010;52(6):930-6.
2. Llovet JM, Mas X, Aponte JJ, Fuster J, Navasa M, Christensen E, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. Gut. 2002;50(1):123-8.
3. Toso C, Majno P, Berney T, Morel P, Mentha G, Combescure C. Validation of a dropout assessment model of candidates with/without hepatocellular carcinoma on a common liver transplant waiting list. Transpl Int. 2014;27(7):686-95.
4. Toso C, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, Majno P, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology. 2015;62(1):158-65.
5. Agopian VG, Morshedi MM, McWilliams J, Harlander-Locke MP, Markovic D, Zarrinpar A, et al. Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. Ann Surg. 2015;262(3):536-45; discussion 43-5.
6. Terzi E, Ray Kim W, Sanchez W, Charlton MR, Schmeltzer P, Gores GJ, et al. Impact of multiple transarterial chemoembolization treatments on hepatocellular carcinoma for patients awaiting liver transplantation. Liver Transpl. 2015;21(2):248-57.
7. Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model". Am J Transplant. 2015;15(10):2552-61.
8. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant. 2008;8(12):2547-57.
9. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology. 2015;61(6):1968-77.
10. Merani S, Majno P, Kneteman NM, Berney T, Morel P, Mentha G, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. J Hepatol. 2011;55(4):814-9.

Liver Transplantation

CHOOSING A DONOR IN A SCARCITY LIVER GRAFT ERA: FROM EXTENDED CRITERIA TO DONATION AFTER CIRCULATORY DEATH

Jorge Paulino
Lisbon

The success of liver transplantation has resulted in a demand for grafts that exceeds the number of available organs. Organ donation is therefore crucial. This rate of donation depends on numerous factors, including intensive care capacity, funding for organ donation programmes and public awareness.

During the last decades, several studies have tried to define parameters and cut-off values for extended criteria organs, but there is still no general definition accepted within the transplant community. Several risk factors such as older donor age, prolonged cold ischemic time (CIT) and hypotension, steatosis and high sodium values have been widely accepted, although their impact differs significantly in the reported studies.

Therefore, in the clinical setting, our liver transplantation program has been dealing with the waiting list by successfully using most grafts from expanded criteria donors.

Another donor pool that we still use is the living donor FAP liver, by performing domino transplantation, despite a lower frequency due to the medical therapeutic alternative for that disease. These grafts are by no means considered as extended criteria, because of their intrinsic favorable characteristics, namely a unique molecular expression profile.

The waiting list time has been reduced by an aggressive donation activity, with a substantial rise of the deceased donation, without the need of increasing the living donor program.

The donation after circulatory death is also addressed, in a theoretic way, as our group doesn't have any experience in this field: the pros and cons of DCD donation is reviewed, including the absolute need to avoid a negative influence on the deceased heart beating donor pool, already experienced in other European countries.

The general tendency of the new trends of liver recipients are also commented, obliging to another ways of liver graft allocation policies. This will include the recognition of various donor groups according to their quality and the need for good donor and recipient selection must lead us to define new policies for organ allocation of marginal grafts that may come into conflict with current policies of organ allocation according to the risk of death among patients awaiting a liver transplantation.

HEPATITIS B SPECIFIC PROTOCOLS TO AVOID GRAFT INFECTION - WHERE DO WE STAND?

Paolo De Simone
University of Pisa Medical School Hospital, Pisa, Italy

BACKGROUND

The current practice of post-liver transplant (LT) hepatitis B virus (HBV) reinfection prophylaxis entails use of high-barrier antivirals and anti-HBV immunoglobulin (HBIg). Controversy exists as to duration of HBIg, and recent evidence suggests that low-risk LT recipients (i.e. negative HBV-DNA at transplant) may benefit from a shortened course of immunoglobulins. There is some evidence, though, that immunoglobulins might exert anti-inflammatory activity and thereby prevent immunological graft damage and improve graft and patient survival.

MATERIALS AND METHODS

Systematic review of the available literature on risk of rejection in adult LT patients undergoing post-transplant immunoprophylaxis with HBIg.

RESULTS

Only a limited number of studies have addressed this issue, and due to variations in the type, intensity and duration of treatment regimens it is difficult to draw firm conclusions. Combination therapy of HBIg and antiviral drugs is consistently associated with better graft and patient survival compared to antiviral monotherapy or HBIg alone. Current HBV reinfection rates are below 10% in most series, with higher rates for schedules with limited duration of HBIg, while reinfection is almost nil for patients on lifelong HBIg. There is suggestion that high-dose HBIg administration may reduce the incidence of acute rejection, but these results are challenged by an overall reduction in graft rejection rates over the recent years. Some evidence has highlighted an increased risk of hepatocellular carcinoma (HCC) recurrence in HBIg-free regimens.

CONCLUSIONS

Well-designed, prospective randomized studies with larger patient cohorts are needed to substantiate the evidence for anti-inflammatory benefits of HBIg and their impact on both graft rejection and HCC recurrence.

IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION: LESSONS THAT SHOULD BE LEARNED FROM KIDNEY TRANSPLANTATION.

Christophe Legendre
Hôpital Necker & Université Paris Descartes, Paris, France

Immunosuppression in kidney transplantation is currently homogeneous combining an induction with an anti-CD25 monoclonal antibody in patients with a low immunological risk, Thymoglobuline® if the immunological risk is high together with tacrolimus-MMF/MPA ± steroids.

Due to the strong belief that CNIs were responsible for the majority of graft losses, many attempts have been made during the past ten years to minimize, avoid or convert CNIs to other drugs.

In this presentation we will review the main results of these attempts and we will focus on the major role of donor-specific antibodies (DSA).

Due to novel and sensitive methods to monitor DSAs, it is currently admitted that their presence, either de novo or at time of transplantation, is a major factor of decreased results after kidney transplantation. The current scheme is the following: decreasing immunosuppression is leading to under-immunosuppression that leads to de novo DSAs, the consequence of which is an increased incidence of antibody-mediated rejection, clinical or subclinical and then chronic.

The natural history of antibody-mediated rejection is now well defined. The role of under-immunosuppression is also well defined whether it is induced by patient's non-compliance or doctors decreasing immunosuppression.

It is therefore currently of good practice in kidney transplantation not to decrease immunosuppression without very strong reasons with risk otherwise to induce de novo DSAS that we still not know how to treat!

In contrast, it has been reported in the last years that transplanting a patients with DSAs at time of transplantation may lead to acceptable results even though the treatment is not very well defined yet. As more and more patients waiting for a kidney transplantation are sensitized, this is becoming a real issue.

The main conclusion is that we do not know yet haw to measure immunosuppression in clinical practice !

A ACIM continua a crescer a inovar e a desenvolver.

Para que tudo isto seja possível temos de mudar de "casa"

Agora a nossa nova casa será:

www.acim.pt