http://www.revistanefrologia.com

Perioperative renal protection strategies in liver transplantation

Rosana Guerrero-Domínguez, Daniel López-Herrera Rodríguez, Jesús Acosta-Martínez, María Bueno-Pérez, Ignacio Jiménez

Servicio de Anestesiología. Reanimación y Terapéutica del Dolor. Hospital Universitario Virgen del Rocío. Sevilla (Spain)

Nefrologia 2014;34(3):276-84

doi:10.3265/Nefrologia.pre2014.Feb.12409

ABSTRACT

Renal failure is one of the most common and major complications in liver transplant recipients. It has been reported to occur at an incidence of 17% to 95%. This complication is associated with prolonged hospital stay in the intensive care unit, the need for postoperative dialysis, infectious complications, acute rejection, and increased mortality. The causes of renal function deterioration differ in the preoperative and postoperative periods. By identifying patients at risk of developing chronic renal failure and by implementing strategies for renal protection at an early stage, it is possible to slow down the progression of renal failure and improve the long-term outcomes in liver transplant recipients.

Keywords: Liver transplant, Acute renal damage, Calcineurin inhibitor toxicity. Renal failure. Renal biomarkers. Renal protection therapies.

Estrategias perioperatorias de protección renal en el trasplante hepático

RESUMEN

La insuficiencia renal es una de las complicaciones más comunes e importantes en los receptores de trasplante hepático. Se ha descrito que ocurre con una incidencia del 17 % al 95 %. Esta complicación se asocia a una estancia prolongada en la unidad de cuidados intensivos, necesidad de diálisis posoperatoria, complicaciones infecciosas, rechazo agudo y aumento de la mortalidad. Las causas de deterioro de la función renal difieren entre los períodos pre y posoperatorio. Mediante la identificación de los pacientes con riesgo de desarrollo de una insuficiencia renal aguda y la implantación precoz de estrategias de protección renal es posible frenar la progresión de disfunción renal y mejorar los resultados a largo plazo de los receptores de trasplante hepático.

Palabras clave: *Trasplante hepático. Lesión renal aguda. Toxicidad por los inhibidores de la calcineurina. Fallo renal. Biomarcadores renales. Terapias de protección renal.*

INTRODUCTION

The development of chronic renal failure (CRF) and chronic kidney disease (CKD) after an orthotopic liver transplantation (OLT) is associated with prolonged hospital stay[1]. The requirement for renal replacement therapy in the postoperative period, acute rejection and infectious complications lead to decreased survival. An analysis by the Scientific Registry of Transplant Recipients showed that CKD after non-renal organ transplantation was associated with a more than four times greater risk of mortality[1]. According to Charlton et al.[2], post-transplant kidney injury, both acute and chronic, is associated with lower short- and long-term survival[2].

Kidney injury is defined as the clinical and analytical deterioration of renal function if an increase in creatinine levels above 2mg/dl is detected, while an increase creatinine above 3mg/dl or 50% of the baseline value of already established renal dysfunction is considered to be renal failure. Oliguria may be present in both cases, with anuria being exclusive to renal failure[3].

Classically, the RIFLE (Risk-Injury-Failure-Loss-Endstage) criteria were used to stratify risk in acute renal dysfunction, although it has been acknowledged that it

Correspondence: Rosana Guerrero Domínguez
Servicio de Anestesiología, Reanimación y Terapéutica del Dolor.
Hospital Universitario Virgen del Rocío.
Avenida Manuel Siurot S/N. 41013 Sevilla. (Spain).
rosanabixi7@hotmail.com
rosana.guerrero.dominguez@hotmail.com

had major limitations, and as such, in 2007[4,5], the Chronic renal failure Network (CRFN) revised these diagnostic criteria and proposed the classification of severity based on a modification of RIFLE criteria, which stratified the degree of renal dysfunction into five stages and reduced them to three stages in accordance with the increase in serum creatinine values and the decrease in cardiac and urine output[4-6] (Table 1).

The estimated incidence of CRF following OLT ranges between 17% and 95%[1]. The main risk factors include hepatorenal syndrome (HRS), prolonged vena cava clamping time, low blood pressure in the intraoperative period and multiple transfusions.

The identification of risk factors[2,7,8] and the development of renal protection strategies that minimise renal damage or its progression in patients with pre-existing CKD increase long-term survival and should be borne in mind as a priority in the management of OLT recipients.

The MELD (Model for end-stage Liver Disease) scale is a scoring system used to determine the severity of chronic liver disease, on the basis of which patients are prioritised on the OLT waiting list. This scale is useful for predicting survival of patients with liver disease and is calculated according to serum creatinine, bilirubin and the INR (International Normalized Ratio)[9]. Patients with high creatinine levels are considered a greater priority for OLT than those with normal renal function[2,7,10,11]. This has influenced a significant increase in the number of patients with renal dysfunction who receive transplants[9]. A comprehensive assessment of OLT candidates with renal dysfunction is required in order to determine who will benefit from a combined liver and kidney transplantation and in whom it is very likely that there will be a spontaneous recovery of renal dysfunction after transplantation[10].

FACTORS ASSOCIATED WITH RENAL DYSFUNCTION IN THE PERIOPERATIVE PERIOD

CRF incidence following OLT is extremely variable, with values that range from 17%-95 %[1,12], as a result of the disparity of criteria for defining this condition, with more than 35 different definitions having been published[13,14]. However, severe CRF, which is likely to require renal replacement therapy, has been documented in 5%-35% of cases[1,15].

Post-OLT CRF has a multifactorial aetiology that is difficult to establish, and three different stages can be determined in relation to OLT: pre-transplant, intraoperative and post-transplant (Table 2). Below, we describe the risk factors associated with each and the strategies that may be employed for a management that optimises renal protection and decreases the incidence of kidney injury in OLT.

RISK FACTORS IN THE PRE-TRANSPLANT PERIOD

There is an association between various kidney disorders and liver disease; thus, for example, membranoproliferative glomerulonephritis is associated with α1-antitrypsin deficiency and hepatitis B and C, immune complex glomerulonephritis[16] is associated with autoimmune hepatitis, and polycystic kidney disease is associated with polycystic liver disease[3]. Other causes of renal dysfunction include diabetes mellitus and hypertensive nephropathy[4,17].

The traditional liver and kidney dysfunction model is pathophysiologically based on hyperaemia and splanchnic arterial vasodilation and increased cardiac output[4,18] with compensatory activation of the renin-angiotensin-aldosterone axis[13]. This results in increased levels of catecholamine and angiotensin, causing intrarenal vasoconstriction and a decreased glomerular filtration rate (GFR), along with hyponatraemia. Recent studies have demonstrated the role of the renin-angiotensin-aldosterone system (RAAS) in the deterioration of liver function[13] such that high levels of angiotensin are related to accelerated fibrosis development in animal research[13]. The progression of this situation leads to a situation of chronic renal failure and the resulting HRS[3,19].

HRS is defined as the development of chronic renal failure in patients with advanced liver disease in the absence of an identifiable cause of renal failure[20], which evolves to a clinical situation with major renal function deterioration, abnormalities in blood circulation and in the activity of endogenous vasoactive systems. All of this leads to renal vasoconstriction with a decrease in the GFR and arterial vasodilation with a decrease in peripheral vascular resistance and low blood pressure[3]. It is characterised by oliguria, hyponatraemia, hyperkalaemia, acid-base imbalance, increased serum urea, creatinine levels higher than 1.5mg/dl and creatinine clearance lower than 40ml/min, low levels of sodium in urine and increased osmolarity[3].

HRS can be triggered spontaneously or as a result of infections, gastrointestinal bleeding, paracentesis or surgery[3], and as such, all of these factors should be treated as early as possible to avoid its occurrence[11].

HRS is classified according to its chronological course[4], with there being two subtypes: type I, with rapidly and aggressively developing renal dysfunction, doubling of

baseline serum creatinine values to 2.5mg/dl in less than two weeks and with mean survival of two weeks[21,22]. In type II, there is a more progressive deterioration of renal function, with a gradual increase[23] in creatinine values above 1.5mg/dl and a 35% patient survival rate beyond one year[4,21,24].

Type II HRS originates as a result of haemodynamic changes in the course of hepatic dysfunction, which may even precede the onset of ascites[24]. These haemodynamic changes include: splanchnic vasodilatation, reduction of effective blood volume, hyperdynamic circulation state with increased cardiac output, vasoconstriction of extra-splanchnic systems, including renal and cerebral circulation and increased RAAS activity. Type I HRS has a similar pathophysiology, but it occurs suddenly.

The treatment of choice while waiting for an OLT is vasoconstrictors such as terlipressin and ornipressin, the expansion of plasma volume[4] or the insertion of transjugular intrahepatic portosystemic shunts that decrease portal hypertension, which are useful as a bridge to OLT[3,24-26].

The identification of candidates for a combined liver and kidney transplantation is key, although very difficult. Recently published criteria[27] include:

1. Patients with end-stage renal disease with cirrhosis and symptomatic portal hypertension or an increase in the hepatic venous pressure gradient greater than 10mmHg.
2. Patients with end-stage liver disease and CKD with a GFR lower than 30ml/min.
3. Patients with CRF including HRS with serum creatinine greater than or equal to 2mg/dl and dialysis of more than or equal to 8 weeks.
4. Patients with end-stage liver disease and CKD with a renal biopsy showing more than 30% glomerulosclerosis or 30% fibrosis.

STRATEGIES FOR PREVENTING RISK FACTORS IN THE PRE-TRANSPLANT PERIOD

All necessary precautions must be taken to avoid the development of CRF or HRS. The potential benefits of diuretics, lactulose, exposure to iodinated contrasts, nephrotoxic drugs, non-steroidal anti-inflammatory drugs and selective cyclooxygenase 2 inhibitors must be carefully balanced with the risk of renal function deterioration, since they may accelerate a syndrome similar to SHR[1,11,24,28-30].

Carrying out paracentesis with the extraction of large quantities of ascitic fluid in patients with hypoalbuminaemia and ascites without peripheral oedema increases the risk of excessive volume depletion and factors that accelerate CRF[1], and as such, the need for it must be rigorously assessed. Paracentesis, by a mechanism that is not fully understood, causes a decrease in systemic vascular resistance and excessive activation of the RAAS[1,31]. The risk of post-paracentesis circulatory dysfunction decreases when plasma expanders are used, with human albumin being the treatment of choice[32,33], which is more effective than other plasma expanders, although, it has not been related to increased survival[20]. In paracentesis with the extraction of less than 5l of ascitic fluid, the risk of post-paracentesis circulatory dysfunction is lower and, although colloids can be used, the international guidelines[20] continue to recommend albumin as the treatment of choice, while, from 5l, the administration of 8g/l of extracted ascites is recommended[1,20].

A recent meta-analysis by Salerno et al.[34] confirms that albumin administration in spontaneous bacterial peritonitis (SBP) reduces the risk of kidney injury and mortality. Although the use of albumin in the doses reported by the authors is recommended in all patients with SBP[20], the benefit of this treatment is greater in those with serum creatinine >1mg/dl, urea >30mg/

Table 1. Current CRF stage classification of the Acute Kidney Injury Network (CRFN)[4].

AKI stage	Serum creatinine criteria	Urine output criteria
1	>0.3mg/dl or an increase of 150-200% on the baseline values	<0.5ml/kg/h for >6h
2	>200-300% (an increase greater than 2 or 3 times the baseline values)	<0.5ml/kg/h for >6h
3	>300% (an increase greater than 3 times the baseline values) or serum creatinine greater than 4mg/dl	<0.3ml/kg/h for >24h or anuria for >12h

CRF: chronic renal failure.

Table 2. Factors determining the development of CRF in OLT recipients[1]

Pre-transplant factors	Intraoperative factors	Postoperative factors
Pre-transplant renal dysfunction (creatinine greater than 2mg/ml)	Haemodynamic instability during anaesthetic induction, anhepatic phase or reperfusion	Acute tubular necrosis secondary to ischaemic or toxic lesions
Hepatorenal syndrome	Intraoperative bleeding and multiple transfusions of blood products	Acute graft rejection or primary graft dysfunction
High bilirubin levels	Standard surgical technique versus the piggyback technique	Postperfusion syndrome
Hypoalbuminaemia	Conventional risk factors	Contrast-induced nephropathy
Hypoproteinaemia		Drug-induced interstitial nephritis
APACHE II		Prolonged use of dopamine or vasopressors
Hyponatraemia		Infections
		Relaparotomy
		Transfusions of blood products
		Calcineurin inhibitor immunosuppression
		Antimicrobial agent use

APACHE: Acute Physiology and Chronic Health Evaluation II.

dl or total bilirubin >4mg/dl[20]. Albumin use is only recommended in cases of SBP, and not in the presence of other infections.

In patients with SBP, the use of albumin infusions at doses of 1.5g/kg of body weight at the time of diagnosis, followed by 1g/kg three days later, has shown to reduce the risk of renal failure and mortality, mainly in patients with kidney injury and hyperbilirubinaemia[1].

Given the high cost and high risk of bacterial resistance, the use of prophylactic antibiotics[20] is controversial and is strictly restricted to patients with a high risk of SBP. Three populations have been identified in which their prophylactic administration is beneficial: patients with acute gastrointestinal bleeding, those with a protein count in ascitic fluid of less than 15g/l and those with previous episodes of SBP[20].

In recent studies, it has been observed that biliary, gastrointestinal and urinary infections and SBP in patients with cirrhosis and ascites[1] who have hyperbilirubinaemia result in a higher risk of CRF. The administration of albumin to prevent CRF when bilirubin values are higher than 4mg/dl is beneficial in these patients even with normal renal function parameters[1].

RISK FACTORS IN THE INTRAOPERATIVE PERIOD

During the intraoperative period, there are often major haemodynamic changes and bleeding associated with different stages of OLT, that occasionally cause low blood pressure which may lead to renal hypoperfusion during transplantation[3]. Bleeding during OLT may occur as a result of a severe coagulopathy or in relation to the surgical techniques employed during liver dissection and in vascular reconstruction. Episodes of renal hypoperfusion have been reported that result from haemodynamic abnormalities associated with post-reperfusion syndrome[3]. There are various surgical techniques that maintain venous return in the anhepatic phase:

- Venovenous bypass.
- Preservation of the inferior vena cava (piggyback).
- Preservation of the inferior vena cava with maintenance of portal vein flow.

Clamping of the portal vein, the hepatic artery and the inferior vena cava during the anhepatic phase interrupts venous return to the lower limbs and to the splanchnic bed, resulting in a decrease in cardiac output, blood pressure, an increase in systemic vascular resistance and a reduction in vital organ perfusion, and could lead to renal

hypoperfusion and potential ischaemic lesion[1]. Although carrying out a venovenous bypass has demonstrated greater haemodynamic stability, thus improving the venous return, it has not consistently been associated with a lower incidence of CRF in the immediate postoperative period[1]. The piggyback technique, with preservation of the inferior vena cava, results in fewer haemodynamic abnormalities than the previous techniques, thus improving venous return during the anhepatic phase, cardiac output and peripheral vascular resistance, and a lower incidence of CRF has been observed in the post-transplant period[1,3] due to less retroperitoneal bleeding, since it is a technique that does not require retrocaval dissection[1].

Other conditions related to the development of CRF during the immediate postoperative period include all non-OLT circumstances present in surgery[1], such as the anaesthetic technique used, which may decrease effective blood volume, severe cardiovascular disease, cardiomyopathy, prolonged episodes of haemodynamic instability, low blood pressure, severe depletion of intravascular volume, the use of drugs that adversely affect intrarenal haemodynamics, advanced age, previous kidney disease and diabetes. An uncommon cause of CRF is obstructive tubulopathy due to pigments, including myoglobin, haemoglobin and bilirubin[35,36].

Moreover, high blood transfusion requirements are associated with an increased incidence of CRF[1].

RISK FACTORS IN THE IMMEDIATE POSTOPERATIVE PERIOD

The predisposing factors for CRF development in OLT recipients may be classified as:

- Drug toxicity.

- Other disorders related to the severity of the patient's condition[3] and allograft dysfunction[29,37].

Nephrotoxic drugs are included in iodinated contrasts, antibiotics (mainly aminoglycosides, amphotericin B and aciclovir), treatment with immunosuppressants such as cyclosporine and tacrolimus, prolonged dopamine or vasopressor[3] administration and multiple transfusions.

Other factors that may occur in liver transplant patients are similar to those of any other patient who remains in a critical care unit. We can include prolonged periods of low blood pressure, septic conditions, pre-renal kidney injury or clinical conditions typical of OLT, such as acute graft rejection or its primary dysfunction[1].

STRATEGIES FOR REDUCING RISK FACTORS IN THE INTRAOPERATIVE AND IMMEDIATE POSTOPERATIVE PERIOD

In relation to the surgical technique

Certain surgical techniques previously discussed improve the haemodynamic state, mainly in the anhepatic phase, and have shown to be considerably beneficial against CRF development in the postoperative period (piggyback).

Plasma volume replacement and maintenance of renal perfusion

It is widely known that volume depletion is the most important risk factor for the development of post-transplant CRF[38]. There is controversy over most appropriate choice of fluid to resuscitate these patients. 0.9% NaCl or other potassium-free fluids are recommended in patients with renal dysfunction[4]. However, the use of large amounts of 0.9% NaCl is associated with hyperchloremic metabolic acidosis, which may lead to hyperkalaemia[4]. It is common for cirrhotic patients with a liver transplant to have varying degrees of hyponatraemia and its sudden correction with 0.9% NaCl increases the risk of post-transplant central pontine myelinolysis, and this factor must be borne in mind. Moreover, the administration of large volumes of potassium-containing solution, such as Lactated Ringer's (LR) solution, may cause hyperkalaemia in CRF patients.

In OLT, volume replacement is beneficial for maintaining mean arterial pressure (MAP) figures greater than 65mmHg, since lower figures are associated with renal hypoperfusion[4]. A hyperdynamic state due to vasodilation in liver failure may require the addition of noradrenaline to increase MAP and therefore optimise renal perfusion[3].

There is controversy as regards the use of crystalloids or colloids as resuscitation fluids. Although the use of colloids will restore intravascular volume most effectively, there are studies in patients with OLT during their hospitalisation in the critical care unit that show a greater incidence of renal dysfunction and requirement for renal replacement therapies in patients resuscitated with colloids, with respect to those resuscitated with LR[4].

Pharmacological interventions

Oliguria is determined by tubular obstruction with the accumulation of detritus during renal ischaemia. It is assumed that non-oliguric CRF has a better outcome and spontaneous recovery than oliguria[4]. Various drugs have been used to optimise renal function:

- Loop[3] or osmotic diuretics: although early diuretic use improves diuresis and may transform oliguric CRF into non-oliguric CRF, a lower incidence of CRF or renal replacement therapy techniques has not been demonstrated after their use. They are recommended in cases of volume overload with cardiorespiratory compromise.

- Vasodilators that counteract renal vasoconstriction: dopamine, calcium channel blockers, prostaglandins and atrial natriuretic peptides have been used, amongst others, without positive results having been observed after their use[3]. In various meta-analyses[4], it has been demonstrated that dopamine does not prevent the development of CRF in patients with OLT[4], and is associated with increased mortality and arrhythmogenic events in studies carried out on septic shock that compare dopamine with noradrenaline[4]. Fenoldopam is a selective dopamine-1 receptor agonist that may prevent the development of CRF, although there are mixed results with regard to this premise[4].

- Immunosuppressants: calcineurin inhibitors are the most nephrotoxic immunosuppressants and as such, several strategies have been developed in an attempt to preserve renal function, which include the use of low doses and/or the delay in their introduction via combination with anti-interleukin-2 (IL-2) receptor antibodies and/or mycophenolate (MMF). If there is previous kidney injury, we recommend delaying treatment with calcineurin inhibitors (cyclosporine and tacrolimus) by 3 to 7 days[1], and instead using anti-lymphocyte antibodies or MMF. Whenever they are introduced, blood levels must be monitored and it must be borne in mind that they can be altered by the use of other drugs, such as various antimicrobial agents[3]. There are currently new non-nephrotoxic immunosuppressant agents with immunosuppressant action demonstrated, such as IL-2 receptor antagonists, mTOR *(*target of rapamycin molecule) inhibitors, sirolimus and everolimus[10,39], or antilymphocyte preparations that may delay or replace the administration of calcineurin inhibitors in patients at risk of developing CRF or with previous renal function deterioration[1]. The risk of graft rejection must be assessed before this is determined[1].

In general, mTOR inhibitors are not used during the first three months after transplantation, since they worsen scarring and increase the risk of hepatic artery thrombosis. Numerous studies[39] have shown that early use of these strategies (during the first year after transplantation), such as the administration of mTOR inhibitors with low doses of calcineurin inhibitors or their total withdrawal, significantly improves medium-long term renal function, with a low incidence of rejection.

Anti-thymocyte globulin is practically restricted to steroid-resistant acute rejection in the context of liver transplantation and is not administered as a general rule, since its use has only been approved by the Food and Drug Administration in renal transplantation and aplastic anaemia.

MMF is not nephrotoxic, but it may be less effective as an immunosuppressant, with a higher risk of late graft rejection[11].

Renal replacement therapies

In various multicentre studies[4] where fluid balance in patients with CRF has been analysed, it has been observed that this balance was more positive in non-surviving patient groups with oliguric CRF or those who required renal replacement therapy[4]. The requirement for pre-transplant dialysis may be associated with higher mortality than the MELD scale[19]. Narayanan Menon et al.[40] found mortality to be five times higher in this patient subgroup.

Current results indicate that early renal replacement therapy after OLT improves survival in CRF patients. We require randomised clinical trials that confirm this hypothesis, which is currently based on prospective studies[4].

Currently, renal replacement techniques allow ultrafiltration to be carried out with preferential fluid loss if urea and creatinine levels are moderately high, continuous haemodiafiltration if there is greater metabolic involvement or conventional haemodialysis. Continuous techniques are preferred, due to their better haemodynamic tolerance, lower increase in intracranial pressure and better control of circulating volume, although the risk of bleeding is greater, given the permanent anti-clotting of the circuit[4]. These patients are likely to be treated with conventional anti-clotting agents by heparinisation of the circuit, although a small number are resistant to this treatment and require alternatives such as anti-clotting with citrates or prostacyclins.

New biomarkers for the early detection of renal dysfunction

Although renal function deterioration in severe liver disease has been related to haemodynamic abnormalities that compromise renal blood flow, in recent studies, it has been discovered that the intestines play an important

role[13] as mediators between the kidneys and liver, with high values of interleukin 17A (IL-17A) being secreted by intestinal Paneth cells[13], which is related to renal dysfunction mainly during the reperfusion phase[13,41].

Classically, the increase in serum creatinine levels has been used for the diagnosis of renal dysfunction, but it is a highly insensitive marker of renal function deterioration[13,17]. Creatinine may be lower as a result of low muscle mass (which is very common in cirrhotic patients) or an increase in the GFR due to drugs that are often prescribed in these patients[19]. As such, the diagnosis of CRF based on plasma urea is complicated due to the great variability in its levels, since high levels may be found in episodes of digestive bleeding or in situations with increased protein catabolism, relative hypovolaemia and HRS, amongst others, and lower levels may be found due to insufficient synthesis in severe liver disease.

Many more sensitive and earlier biomarkers than increased creatinine in liver disease[42] have been developed to predict renal function deterioration[13]. One of those most studied is called serum or urinary[9] neutrophil gelatinase-associated lipocalin (NGAL)[13,42], a 25 KDa protein whose levels rapidly change in renal dysfunction. It can be determined both in the pre- and post-transplant period, and it is considered to be the earliest marker of renal failure, allowing strategies that prevent major complications to be established. Although more studies are required to corroborate the above[13,43-45], it is a promising biomarker in this context[42].

Cystatin C is a peptide produced by nucleated cells and it is an ideal marker of renal dysfunction in cirrhosis of the liver. Its values are not changed by muscle mass, diet or inflammatory conditions. However, it is an expensive method that is not universally available[19].

Numerous biomarkers are currently being researched.

In conclusion, renal dysfunction in the context of OLT is associated with longer hospital stay[46,47], higher costs[46-48], post-transplant sepsis and mortality. We must determine CRF development risk factors in the pre-transplant period, the intraoperative period and the immediate postoperative period, and develop renal protection strategies that minimise renal damage or its progression in order to improve long-term survival. These strategies should be carried out as a priority in patients with OLT who develop CRF or in those with pre-existing renal function deterioration, in an attempt to avoid its progression, and we recommend a multidisciplinary approach that includes all professionals involved in the OLT process.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

KEY CONCEPTS

1. The development of ARF in liver transplant recipients is one of the most common problems (with an incidence of 17-95%) and which increases hospital stay most.
2. Various strategies for renal protection can be carried out during the pre-transplant, intra-operatory and post-operatory phase, with the aim of preserving renal function.
3. A pre-operative exhaustive evaluation is recommended to determine which patients will benefit from hepatorenal transplant and in which patients a spontaneous recovery of renal function after OLT is predicted.
4. Renal replacement therapy prior to OLT is associated with an increase in mortality five times greater in the post-operatory period.
5. Episodes of bleeding, infections, hypotension and hypovolaemia in the pre-operatory period are closely related with ARF development and must be treated aggressively.
6. The new biomarkers predict deterioration of renal function early on, providing promising NGAL results.
7. Calcineurin inhibitors used as immunosuppressive treatment in the post-transplant period play a significant role in the development of renal failure due to their considerable nephrotoxicity.

REFERENCES

1. Pham PT, Pham PC, Wilkinson AH. Management of renal dysfunction in the liver transplant recipient. Curr Opin Organ Transplant 2009;14(3):231-9.
2. Charlton MR, Wall WJ, Ojo AO, Gines P, Textor S, Shihab FS, et al. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. Liver Transpl 2009;15:S1-34.
3. Galán Torres JBM. Insuficiencia renal en el trasplante hepático. In: Montero Benzo R, Vicente Guillén R, eds. Tratado de trasplante de órganos. Madrid: Arán; 2006. p 1265-71.
4. Saner FH, Cicinnati VR, Sotiropoulos G, Beckebaum S. Strategies to prevent or reduce acute and chronic kidney injury in liver transplantation. Liver Int 2012;32(2):179-88.
5. Barrio V. Usefulness and need for standardized criteria in diagnosing acute renal dysfunction in critical patients. Med Intensiva 2012;36(4):247-9.
6. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al.; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
7. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279-90.
8. Paramesh AS, Roayaie S, Doan Y, Schwartz ME, Emre S, Fishbein T, et al. Post-liver transplant acute renal failure: factors predicting development of end-stage renal disease. Clin Transplant 2004;18:94-9.
9. Machicao VI, Srinivas TR, Hemming AW, Soldevila-Pico C, Firpi RJ, Reed AI, et al. Impact of implementation of the MELD scoring system on the prevalence and incidence of chronic renal disease following liver transplantation. Liver Transpl 2006;12(5):754-61.
10. Trotter J, Kahn B. Renal dysfunction and the liver transplant recipient; novel strategies for determination of reversibility and renal protective therapies pretransplant and posttransplant. Curr Opin Organ Transplant 2012;17(3):225-9.
11. Rimola A. Insuficiencia renal en el trasplante hepático. Nefrologia 2002;22 Suppl 5:69-71.
12. Pham PT, Pham PC, Wilkinson AH. Renal failure in adult liver transplant recipients. In: Busuttil RW, Klintmalm GB, eds. Transplantation of the liver. 2nd ed. Philadelphia, Pennsylvania: Elsevier Saunders; 2005. pp. 891-914.
13. Verna EC, Wagener G. Renal interactions in liver dysfunction and failure. Curr Opin Crit Care 2013;19(2):133-41.
14. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? J Am Soc Nephrol 2003;14:2178-87.
15. Contreras G, Garces G, Quartin AA, Cely C, LaGatta MA, Barreto GA, et al. An epidemiology study of early renal replacement therapy after orthotopic liver transplantation. J Am Soc Nephrol 2002;13:228-33.
16. Trawale JM, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int 2010;30:725-32.
17. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19(1):3-26.
18. Saner F, Kavuk I, Lang H, Biglarnia R, Frühauf NR, Schäfers RF, et al. Terlipressin and gelafundin: safe therapy of hepatorenal syndrome. Eur J Med Res 2004;9:78-82.
19. Weber ML, Ibrahim HN, Lake JR. Renal dysfunction in liver transplant recipients: evaluation of the critical issues. Liver Transpl 2012;18(11):1290-301.
20. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53(3):397-417.
21. Lau C, Martin P, Bunnapradist S. Management of renal dysfunction in patients receiving a liver transplant. Clin Liver Dis 2011;15(4):807-20.
22. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48:2064-77.
23. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-40.
24. Wadei HM. Hepatorenal syndrome: a critical update. Semin Respir Crit Care Med 2012;33(1):55-69.
25. Wong F, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. Ann Intern Med 1995;122(11):816-22.
26. Jalan R, Forrest EH, Redhead DN, Dillon JF, Hayes PC. Reduction in renal blood flow following acute increase in the portal pressure: evidence for the existence of a hepatorenal reflex in man? Gut 1997;40(5):664-70.
27. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). Am J Transplant 2008;8(11):2243-51.
28. Boyer TD, Zia P, Reynolds TB. Effect of indomethacin and prostaglandin A1 on renal function and plasma renin activity in alcoholic liver disease. Gastroenterology 1979;77(2):215-22.
29. Koo M, Sabaté A, Ramos E, Dalmau A, León E, Fabregat J, et al. Factors related to renal dysfunction after liver transplantation in patients with normal preoperative function. Rev Esp Anestesiol Reanim 2006;53(9):538-44.
30. Pham PTT, Pham PCT, Rastogi A, Wilkinson AH. Review article: current management of renal dysfunction in the cirrhotic patient. Aliment Pharmacol Ther 2005;21(8):949-61.
31. Ruiz-del-Arbol L, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997;113(2):579-86.
32. Moreau R, Valla DC, Durand-Zaleski I, Bronowicki JP, Durand F, Chaput JC, et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trail. Liver Int 2006;26(1):46-54.
33. Ginès A, Fernández-Esparrach G, Monescillo A, Vila C, Domènech E, Abecasis R, et al. Randomized trial comparing albumin, dextran 70,

and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996;111(4):1002-10.
34. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol 2013;11(2):123-30.
35. Mesa L, Bolaños L, Vázquez C, Lavilla J, Errasti P, Purroy A. Nefropatía obstructiva intrarrenal aguda. Nefrologia 1992;12(4):199-204.
36. Rosado Rubio C, Fraile Gómez P, García Cosmes P, Díaz Bandera R, González Álvarez C. Hemólisis intravascular y fracaso renal. Nefrologia 2011;31(5):621-2.
37. Monge E, Fernández-Quero L, Navía J. Complicaciones médicas postoperatorias precoces del trasplante hepático ortotópico en adultos (I). Rev Esp Anestesiol Reanim 2002;49(10):529-40.
38. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416-20.
39. De Simone P, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, Saliba F, et al. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. Am J Transplant 2012;12(11):3008-20.
40. Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation 1995;59:361-5.
41. Park SW, Kim M, Brown KM, D'Agati VD, Lee HT. Paneth cell-derived interleukin-17A causes multiorgan dysfunction after hepatic ischemia and reperfusion injury. Hepatology 2011;53:1662-75.
42. Dedeoglu B, de Geus HR, Fortrie G, Betjes MG. Novel biomarkers for the prediction of acute kidney injury in patients undergoing liver transplantation. Biomark Med 2013;7(6):947-57.
43. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008;52:425-33.
44. McIlroy DR, Wagener G, Lee HT. Biomarkers of acute kidney injury: an evolving domain. Anesthesiology 2010;112:998-1004.
45. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002;40:221-6.
46. McGuire BM, Julian BA, Bynon JS Jr, Cook WJ, King SJ, Curtis JJ, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Intern Med 2006;144:735-41.
47. Brown RS Jr, Lake JR, Ascher NL, Emond JC, Roberts JP. Predictors of the cost of liver transplantation. Liver Transpl Surg 1998;4:170-6.
48. Brown RS Jr, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. Transplantation 1996;62:1788-93.

Sent to review: 18 Dec. 2013 | Accepted: 18 Dec. 2014