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Renal Dysfunction and Liver Transplantation

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1. Introduction

Liver transplantation, whether living donor (LDLT) or deceased donor (DDLT), is currently the treatment of choice for patients with advanced liver disease. While initially the focus was on acceptable short-term survival, currently the efforts are aimed at improving long-term prognosis. Thus, focus is now on the quality of life after liver transplantation, as well as prediction and management of conditions related to morbidity and mortality in long-term survivors. Renal dysfunction is an important problem in this scenario. Both acute (ARD) and chronic renal dysfunctions (CRD) develop frequently after liver transplantation and can seriously jeopardize postoperative patient survival.

Acute kidney injury is one of the most common complications of liver transplantation. It occurs more frequently in those who have hepatorenal syndrome at the time of liver transplantation. Acute renal dysfunction has been associated with an 8-fold increase in mortality risk, prolonged intensive care unit stay and a greater risk for infectious complications. In the subgroup of patients who develop acute renal failure and survive, 80% to 90% regain some degree of renal function, whereas the rest develop permanent renal dysfunction. Chronic renal dysfunction, not only has implications in terms of an increased demand on resources, but is also significantly associated with a higher patient mortality rate.

In order to minimize the occurrence of ARD and CRD thereafter, it is vital to define the possible preoperative, intraoperative and postoperative risk factors. In this review, we discuss the various definitions, diagnostic tools, predictors of renal dysfunction after liver transplantation together with discussion of specific causes of renal dysfunction. This information will be useful in developing strategies for preventing the development or progression of renal dysfunction in liver transplant recipients, especially in view of the current availability of nonnephrotoxic immunosuppressive drugs.

2. Assessment of renal function prior to transplantation

With broadening of the inclusion criteria for liver transplantation, the majority of liver transplant recipients have some impairment of renal function prior to transplantation and most have clinically apparent renal insufficiency at some time in the posttransplant period. Among those with renal impairment at the time of transplant are patients whose renal failure is due to the same underlying process that caused the liver disease (hepatitis B, hepatitis C, analgesic overdose, amyloidosis, autoimmune disease), patients with underlying

parenchymal renal disease from diseases such as diabetes and hypertension, and other patients in whom the functional renal impairment is caused by the liver failure itself and its complications. The latter group may have manifestations ranging from mild sodium retention to oliguric renal failure termed hepatorenal syndrome (HRS) (Smith, 2006).

For both prognostic and therapeutic reasons it is important to *assess the level of renal function* in patients being considered for liver transplantation and to determine if there is any reversible component. Also given organ shortage it should be essential to determine which patients will experience progressive and severe renal dysfunction after liver transplantation (Burra et al., 2009).

2.1 Methods of measurement of renal function

The most commonly used markers of glomerular filtration rate (GFR), blood urea nitrogen (BUN) and serum creatinine (Scr), have limitations that should be kept in mind, especially in the setting of liver transplantation. Because **urea** is generated by the liver from the metabolism of protein and ammonia, both malnutrition and poor hepatic function may cause a falsely low BUN that can lead to an overestimation of GFR. Conversely, corticosteroids, bleeding (particularly in the gastrointestinal tract), and renal hypoperfusion cause higher BUN levels than one would expect for a given level of GFR (Cholongitas et al., 2007 a).

Also current diagnostic paradigms for acute kidney injury are limited by reliance on **serum creatinine (Scr)**, which is affected by age, gender, nutrition and the amount of muscle mass which may render the values inaccurate. Thus, most patients with endstage liver disease with decreased muscle mass may have a misleadingly low Scr. In addition, elevations in Scr may occur several days after the actual injury (Fieghen et al., 2009). Also, a number of medications (including trimethoprim) inhibit the secretion of creatinine, so that when these medications are used, Scr may rise without any true change in GFR (Cholongitas et al., 2007). Furthermore, creatinine is both filtered and secreted by the nephron, so that its clearance is an overestimate of GFR. It should also be noted that the relationship between the serum creatinine and GFR is not linear; at high levels of GFR, the Scr is insensitive to large changes in GFR, while at low levels of GFR, small changes in GFR cause large changes in serum creatinine (Mariat et al., 2004). A problem, not often recognized is that measurement of Scr suffers from a variety of interferences (Cholongitas et al., 2007 b) and absence of international standard for measurement (Seronie-Vivien et al., 2005). Serum creatinine is usually measured by the Jaffè method, but this is prone to interference, for example, from protein, ketones and bilirubin. Hence, hyperbilirubinemia often impacts on the measurement of Scr in endstage liver disease population (Owen et al., 2006). These findings can result in an underestimation of renal function.

Despite the above limitations, the endogenous creatinine clearance from a timed urine collection or as calculated from the Cockcroft–Gault formula {(140- age)/Cr × (weight in kg/72) (× 0.85 for females)} (Cockcroft and Gault, 1976) remains the most common measure of GFR (Lewandowska & Matuszkiewicz-Rowinska, 2011). If a timed urine collection is performed, the amount of creatinine excreted in 24 hours should be 12–25 mg/kg body weight as a crude test for completeness of the collection. Because of the variability in the accuracy of timed collections performed by outpatients, and the excellent correlation of the Cockcroft–Gault calculation with timed creatinine clearance measurements under controlled

conditions, a timed collection may be necessary only for a baseline creatinine clearance and to measure protein excretion. It can then be repeated only as necessary to confirm abrupt or unexpected changes in the serum creatinine (Smith, 2006). However, it should be noted that there is some debate concerning the use of the Cockcroft–Gault equation to estimate GFR (Gonwa et al., 2004). This formula may be inaccurate and pick up small differences in GFR that are statistically significant but clinically irrelevant. Although GFR calculations often overestimate GFR measurements (Poge et al., 2005), even using the best formulas available, the Cockcroft–Gault equation has been used in many published studies and was widely used in clinical practice (Burra et al., 2009).

Modification of diet in renal disease (MDRD) equation (Levey et al., 1999) is another method that is considered more accurate than other formulas to measure GFR in patients with intact kidney function. MDRD equation: GFR = 170 x [Serum creatinine]-0.999 x [Age]-0.176 x [0.762 if patient is female] x [1.180 if patient is black] x [BUN]-0.170 x [Albumin] + 0.318. Most often, the formula, excluding urea and albumin (four variables), is used to calculate GFR, as it is as accurate as the original six-variable formula (Levey et al., 2006). Neither these formulas nor calculation of creatinine clearance from a 24-hour urine collection has been well studied or validated in patients with decompensated cirrhosis. Preliminary data suggest that the MDRD equation is more precise in liver transplant (LT) patients than other renal formulas, but the MDRD equation actually underestimates GFR measured by the gold standard of iothalamate clearance. There are now online calculators that provide a convenient way to estimate GFR (e.g. http://nephron.com/gi-bin/MDRDSIdefault.cgi) (Fabrizi et al., 2010). However, in LT recipients, even the best performing equation, the six-variable MDRD equation, provides an estimate that is within 30% of the actual GFR only two-thirds of the time (Gonwa et al., 2004).

Ideally, renal function can be estimated through the use of inulin, (125I) iothalamate, or 51Cr-EDTA clearance methods, but these are costly and often impractical. Many nuclear medicine departments perform isotopic GFR measurements based on the decay of the plasma level of an injected radiolabeled GFR marker over a few hours (Mariat et al., 2004). However the cost of the radiolabeled GFR markers and the precautions needed in handling them make these tests expensive.

2.2 Diagnosis of pre-transplant kidney dysfunction

Patients with cirrhosis are candidates to develop acute renal failure from different causes; each of them requiring specific treatments. In cirrhotic patients with ascites, pre-renal failure (42%) and acute tubular necrosis (ATN) (38%) represent the most common forms of acute renal failure while hepatorenal syndrome (HRS) is somewhat less frequent (20%) **(**Fasolato et al., 2007). Approximately 18% will develop HRS at 1 year and 39% at 5 years (Terra et al., 2005). However, it may be difficult to identify the cause and start the appropriate treatment (Moreau and Lebrec, 2003). The different causes of acute renal failure in cirrhotics are discussed below. Table 1 shows the differential diagnosis of the causes that are most commonly encountered during preparation for liver transplant.

2.2.1 Hepatorenal syndrome

Patients with end-stage liver disease may exhibit a spectrum of functional renal impairment from mild sodium retention and clinically inapparent reduction in GFR, to an oliguric state

with severe intrarenal vasoconstriction, avid sodium conservation, and very low GFR referred to as hepatorenal syndrome (Eckardt, 1999). In almost half the cases of HRS, one or more precipitating factors may be identified, including bacterial infections (57%), gastrointestinal hemorrhage (36%), and large volume paracentesis (7%) (Fasolato et al., 2007). The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Kidney histology is normal (Wadei et al., 2006).

HRS is a diagnosis of exclusion, requiring the absence of sepsis and nephrotoxic agents, less than 500 mg/day of protein excretion and no microhaematuria, an ultrasound showing no evidence of obstruction or parenchymal renal disease, and a lack of improvement of serum creatinine (<1.5mg/dl) with cessation of diuretic therapy and plasma volume expansion (albumin 1 g/kg upto max. of 100g/day) (*New International Ascites Club's diagnostic criteria of hepatorenal syndrome* (Salerno et al., 2007). If the syndrome persists, acute tubular necrosis may result. Thus, the urine sodium concentration is less than 10 meq/L early in the process, but as tubular ischemia occurs, the urine sodium rises, clouding the diagnostic issue.

2.2.2 Volume depletion induced renal dysfunction

Prerenal failure usually occurs in patients with decompensated cirrhosis. These patients already have significant circulatory dysfunction characterized by low arterial pressure, renal vasoconstriction and decreased renal blood flow; but they have no or only mild reduction in GFR. Volume depletion further decreases renal blood flow and induces a marked decline in GFR which may be rapidly reversible if the underlying cause is corrected (Moreau and Lebrec, 2003). Ten to twenty percent of patients with gastrointestinal hemorrhage have hypovolemic shock on admission. This true hypovolemia is one cause of prerenal azotemia. A retrospective study showed that 5% of patients with cirrhosis hospitalised for acute upper gastrointestinal hemorrhage had early renal failure that lasted less than 7 days after index bleeding (Cardenas et al., 2001). Patients admitted for hemorrhage may also develop prerenal failure due to other causes such as bacterial infection (Cardenas et al, 2001).

True hypovolemia and subsequent renal failure may also result from vomiting, diarrhea, glycosuria or diuretic treatment used to mobilize ascites.

2.2.3 Severe sepsis

Patients with cirrhosis are susceptible to bacterial infections, in particular spontaneous bacterial peritonitis (SBP). Septic shock and subsequent prerenal azotemia occurs in 10% of patients with SBP. At the onset of SBP, 20-40% of patients have renal failure without shock (Moreau and Lebrec, 2006). Thirty percent of those admitted for SBP or for another bacterial infection develop type 1 HRS during hospitalization (Terra et al., 2005).

2.2.4 Drugs

NSAIDS

Cyclo-Oxygenase (COX)-derived vasodilator prostaglandins protect renal perfusion in patients with cirrhosis and ascites. Hence administration of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (i.e., drugs that can inhibit cyclooxygenase-1 (COX-1)) and cyclooxygenase-2) in cirrhotic patients may lead to marked renal hypoperfusion and

subsequent prerenal failure following COX inhibition induced by non-selective NSAIDs. It was also shown that COX-2 inhibitors, like non-selective NSAIDs, may also induce prerenal failure in patients with cirrhosis and ascites (FitzGerald and Patrono, 2001).

Antibiotics

Patients with cirrhosis and ascites are predisposed to aminoglycoside nephrotoxicity, the reported incidence of which (32%) is much higher than that found by other investigators in the general population (3–11%). Aminoglycoside nephrotoxicity is associated with a marked deterioration in renal function (Cabrera et al., 1982). Patients with decompensated cirrhosis are prone to develop this complication, since they frequently have impaired renal blood flow and glomerular filtration rates, and renal accumulation of aminoglycosides is greater with renal impairment (Moore et al., 1984).

2.2.5 Contrast induced nephropathy

This is defined as impairment of renal function subsequent to the administration of contrast media in the absence of any other cause. Contrast induced nephropathy (CIN) is diagnosed when there is an increase in serum creatinine concentration of > 0.5 mg/dl or a relative increase of > 25% from the baseline within 72 hrs after contrast media administration (Barrett and Parfrey, 1994).

Pre-existing renal dysfunction and diabetes mellitus are the two most important risk factors for CIN. The incidence of CIN is less than 2% when basal creatinine is less than 1.6 mg/dl and increases to 12-29% when above 1.6 mg/dl and to 38% when above 2.0 mg/dl. The presence of more than one risk factor increases the risk to develop CIN by many folds (Liu et al., 2005). The incidence of CIN also rises with increase in the volume of the contrast media. It is less than 2% when patients receive less than 125 ml of contrast media compared with 19% in patients receiving more than that volume. Peri-procedural hydration is regarded as a simple and effective means to prevent CIN. Results of a large number of clinical trials go in favour of post-procedural acetylcystine which is a free radical scavenger and precursor of antioxidant glutathione (Tepel et al., 2006). Recovery occurs in the majority of cases within 2–3 weeks; few patients require dialysis for recovery (Barrett & Parfrey, 1994).

2.2.6 Intrinsic renal failure

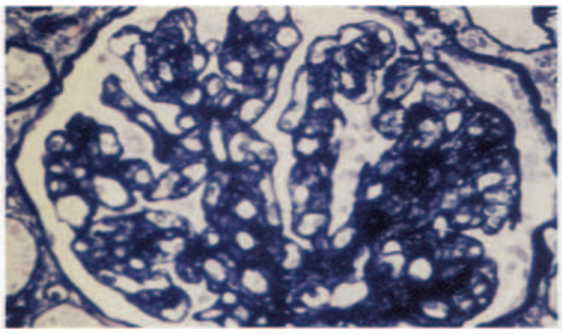
2.2.6.1 Viral hepatitis and associated glomerular diseases

Viral infections such as hepatitis B (HBV) and C (HCV) are well-known to induce concomitant severe hepatic and renal injuries with ultimate endstage renal disease. The most common clinical presentation in both cases is the nephrotic syndrome with a slowly progressive decline in renal function (Lai & Lai, 1991 and Johnson et al., 1994a). The proteinuria remits spontaneously in a minority of patients, but may also recur. The degree of proteinuria appears to correlate with viremia as spontaneous remission of the glomerulopathy is usually associated with clearance of viral antigens from the blood. The mechanisms whereby different viral infections induce distinct glomerular lesions and/or systemic complications have not been fully elucidated. Circulating and most likely in situ immune complexes involving viral antigens and host anti-viral antibodies have been

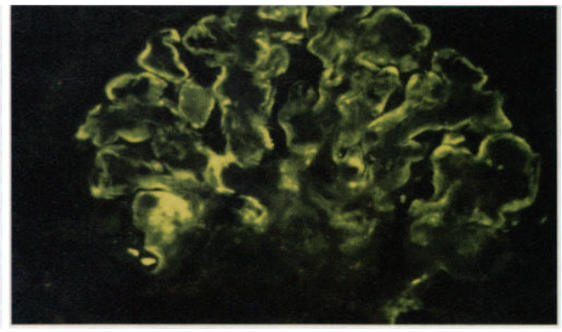
implicated in hepatitis B- associated membranous glomerulonephropathy (Pham et al., 2005).

HCV-related glomerulonephritis

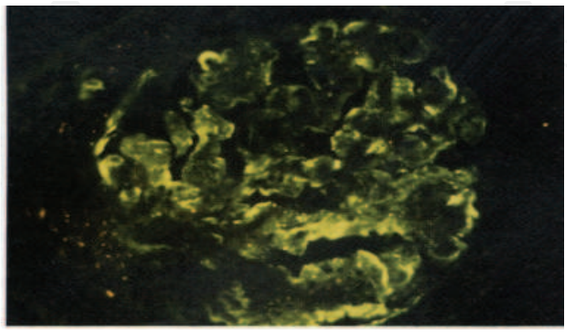
Hepatitis C has been associated most closely with mesangiocapillary glomerulonephritis (Bursten & Rodby, 1993, Johnson et al., 1993 & Johnson et al., 1994b). Many of the patients with chronic HCV and mesangiocapillary glomerulonephritis also have hypocomplementemia, cryoglobulinemia (the cryoprecipitates contain HCV-RNA), and rheumatoid factors (IgM antibodies directed against anti-HCV antibodies). Other symptoms and signs of mixed cryoglobulinemia such as skin lesions, arthritis, and neuropathy may not be present. Indeed, even the hepatitis associated with the renal disease may be asymptomatic and the transaminases may be normal (Johnson et al., 1994b). Less commonly, non-cryoglobulinemic mesangiocapillary glomerulonephritis, focal and segmental glomerulosclerosis, mesangial proliferation with IgA deposition, fibrillary and immunoactoid glomerulopathies occur (Dore et al., 2007). A purely membranous glomerulonephritis has also been reported in patients with HCV, and may have a different pathogenesis (Stehman-Breen et al., 1995). McGuire et al performed kidney biopsies at the time of liver transplantation in 30 patients with HCV-related cirrhosis and a median creatinine of 1.4 mg/dL; immune complex glomerulonephritis was reported in 83% of the patients (McGuire et al., 2006).



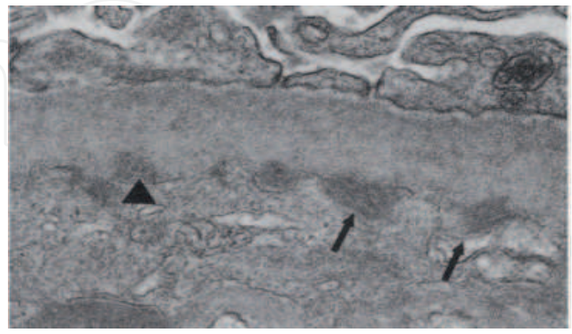
A. Increased cellularity, expansion of mesangium, Thickening & splitting of capillary walls



B. Capillary wall deposits of Ig G



C. Capillary wall deposits of IgM



D. EM of glomerular capillary: subendothelial immune deposits as tactoids (arrows) & microtubules (arrowheads) characteristic of cryoglobuinns

Fig. 1. Renal Biopsy specimen from a patient with Hepatitis C (Johnson et al., 1993)

HBV-related glomerulonephritis

HBV-related glomerulonephritis is more often found in children. Membranous glomerulonephritis is the most common form of HBV-related glomerulonephritis, but mesangiocapillary glomerulonephritis, mesangial proliferative glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy and minimal change disease have all been described. In addition, in patients with HBV-associated polyarteritis nodosa, a variety of histologic patterns have been documented (Lai & Lai, 1991). Immune complexes of hepatitis B surface, core, and e antigens as well as antibodies together with complement components have been demonstrated in glomerular basement membrane and mesangium. HBV antigens have been localized in the glomeruli using immunofluorescent antibodies, electron microscopy, and molecular techniques. HBeAg has been consistently associated with capillary basement membrane deposits (membranous form of glomerulopathy), while HBsAg is more closely associated with deposits in the mesangium (Lai and Lai., 1991; Takekoshi et al., 1991).

Liver disease tends to be mild in patients who present with HBV-related glomerulonephritis. Disease remission is especially evident after HBeAg seroconversion. A significant percent of adults (30%) may progress to renal failure and as many as 10% will require maintenance dialysis (Bhimma et al., 2002).

2.2.6.2 Renal disease associated with poor hepatic function

Patients with poor hepatic function of any cause may develop parenchymal renal disease manifested by nonnephrotic proteinuria, microscopic hematuria, and reduced GFR. The most common histologic picture is a mesangiopathic glomerulonephritis with deposition of IgM and often IgA, perhaps because of impaired clearance by the liver. It has not been proved that these immune complexes are the cause of the renal disease (Smith, 2006).

	Prerenal Azotemia	**Acute tubular Necrosis**	**Hepatorenal Syndrome**	**Primary Nephropathy**
Urine sodium	<10 mEq/L	>30 mmol/L	<10 mmol/L	>30 mmol/L
Urine to plasma creatinine ratio	>30:1	<20:1	>30:1	<20:1
Proteinuria	<100mg	<500mg	<500mg	Variable

Table 1. Differential Diagnosis of Acute renal failure in advanced liver disease. (Eckardt, 1999)

Renal failure post liver transplantation

Renal insufficiency, whether acute renal failure (ARF) or chronic kidney disease (CKD), is a common complication after liver transplantation and represents a major cause of morbidity and mortality following LT (Yalavarthy et al., 2007).

3. Acute renal failure

3.1 Epidemiology

Acute renal failure (ARF) is one of the most common complications of liver transplantation (LT), with a variable incidence rate in different studies. The incidence of acute kidney injury (AKI) has been reported to vary between 17% to 95% post-liver transplantation (Bilbao et al.,

1998, Lima et al., 2003). The difference in the incidence reported may be due in part to the large difference in the criteria used to define ARF.

Campbell et al., 2005 and Lebrón Gallardo et al., 2004 used a value of serum creatinine above 1.5 mg/dl as diagnostic of acute Kidney injury (AKI) and reported an incidence as high as 64%. On the other hand, Junge et al, 2006, reported a relatively low incidence of 11.9% and defined AKI post-LT as serum creatinine of 2.5 mg/dl in the first week only. Actually the incidence rate of post-LT ARD differs even in the same center when variable definitions are used. Barri and colleagues, 2009 conducted a study on 1050 patients who underwent LT, using changes in serum creatinine from baseline as the main marker for acute kidney injury (AKI). They used three different definitions to diagnose post-LT AKI. Defining AKI as a rise in serum creatinine of >0.5 mg/dL resulted in the highest incidence of AKI (78%). The second definition of AKI was a rise in serum creatinine of >1 mg/dl and this resulted in an incidence of AKI 46%. When AKI was defined as a rise of serum creatinine of >50% from baseline to above 2 mg/dl, the lowest incidence of AKI (14%) was found (Barri et al., 2009). Hence, these variations in definitions cause difficulties in comparing different studies and demonstrate the need for a consensus in the diagnosis of acute renal disease after LT.

3.2 Definition of acute renal failure

Several researchers have evaluated the problem of renal impairment post-LT but it is difficult to meaningfully compare these studies as a series of different definitions are used (Cabezuelo et al., 2002).

To address this issue, RIFLE classification was introduced in 2002. RIFLE is an acronym for *risk* of renal dysfunction, injury to the kidney (ARI), *failure* of the kidney (ARF), *loss* of kidney function and *end-stage kidney disease* (Table 2). It was later modified and is functioning as AKIN (Acute Kidney Injury Network) classification since 2005 (Table 3). The AKI term includes a wide range of renal dysfunction, starting with a very early and discrete renal failure with minimal changes in the serum creatinine level (*stage 1, Risk*), through moderate changes (*stage 2, Injury*), to an advanced renal failure (*stage 3, Failure*), often requiring renal replacement therapy (Bellomo et al., 2004 & Mehta et al., 2007). Two additional stages (*Loss of function* and *Endstage- renal-disease*) were introduced in order to classify cases of a partial or total and permanent loss of renal function. Some studies used these criteria to determine the incidence of ARF post-LT. Kundakci reported that AKD occurred in more than half of LTs postoperatively. AKI occurred in 64 (57%) LTs with risk, injury, and failure frequencies of 19%, 11%, and 28%, respectively (Kundakci et al., 2010). Zhu et al reported that postoperatively, AKI was found in 60% of patients. According to the AKIN criteria, it was: stage 1 – in 30%, stage 2 – in 13%, and stage 3 – in 17% of the individuals (Zhu et al., 2010).

AKIN classification was introduced with great enthusiasm, but soon proved to be of little use. Its main disadvantages include undersensitivity and no reference to aetiology or pathophysiology of AKI. Thus, it does not distinguish between the prerenal azotemia and a real injury of the renal parenchyma. Serum creatinine level and eGFR based on it are not useful parameters in the early diagnostics of AKI. First of all, the increase in creatinine level occurs late, after a few days, with an injury of more than 50% of the renal parenchyma.

Moreover, it is influenced by too many factors of creatinine synthesis and secretion in the renal tubules. In patients with graft dysfunction, these indicators are even less reliable, because of malnutrition and – frequently observed in these patients – high levels of serum bilirubin which interferes with creatinine measurements and causes a significant reduction in serum creatinine level (Cholongitas et al., 2007a).

Risk	Increase of serum creatinine 1.5-2 times baseline	Less than 0.5ml/kg/hr for >6hrs
Injury	Increase of serum creatinine 2-3 times baseline	Less < 0.5ml/kg/hr for >12hrs
Failure	Increase of serum creatinine of > 3 times baseline	<0. <0.3ml/kg/hr for >24hrs or anuria>12hrs
Loss	Persistent need for RRT for >4 weeks	
End-stage	Persistent need for RRT for >3 months	

Table 2. Risk, Injury, Failure, Loss of Kidney Function, End-stage (RIFLE) Kidney Disease classification (Mehta et al., 2007)

Acute Kidney Injury			Recovery
Stage1	**Stage 2**	**Stage 3**	Loss of function>4 weeks but <3 months
Rise in serum creatinine ≥0.3 mg/dl or Increase to ≥150% to 200% (1.5-fold to 2-fold) from baseline.	Increase in serum creatinine to > 200%- 300% (> 2-fold to 3-fold) from baseline.	Increase in serum creatinine to > 300% (> 3-fold) from baseline, or serum creatinine ≥4.0 mg/dl with an acute increase of at least 0.5 mg/dl.	End-stage renal failure >3 months
Urine output < 0.5 ml/kg/hour for > 6 hrs.	Urine output < 0.5 ml/kg/hour for > 12 hrs.	Urine output < 0.3 ml/kg/hr for 24 hrs, or anuria for 12 hrs.	Death

Table 3. Classification/staging system for acute kidney injury modified from RIFLE criteria. (Bellomo et al., 2004)

3.3 Aetiology and risk factors of acute kidney injury after liver transplantation

In order to apply protective strategies to minimize the occurrence of acute renal dysfunction (ARD) and chronic renal dysfunction thereafter, it is vital to define risk factors for ARD and manage properly as early as possible (Barri et al., 2009).

The evaluation of predictive factors for renal failure that occurs postoperatively has been the matter of several investigations. Clinical studies evaluating these risk factors have yielded variable results. Although the risk factors for AKI are often multifactorial and difficult to establish, they can be linked to three distinct time frames in relation to the liver transplant: the pretransplant (pre-LT), intraoperative, and post-LT periods as follows: pre-transplant (HRS, pre-transplant kidney dysfunction, high bilirubin concentrations), intra-operative

(hemodynamic instability, intraoperative bleeding), and postoperative factors (contrast nephropathy, acute tubular necrosis secondary to ischemic or toxic agents, liver allograft dysfunction, multiple antibiotic use, reoperations especially re-transplantation). Actually the most common cause of ARF early after LTx is ischemic acute tubular necrosis, followed later by cyclosporine toxicity and sepsis (Fabrizi et al., 2010).

Preoperative	Intraoperative	Postoperative
Pretransplant renal dysfunction	Hemodynamic instability during anesthesia	Hypovolemia
Hepatorenal syndrome	Longer anhepatic phase	Need for pressor amines
High MELD score	Intraoperative bleeding	Haemodynamic instability
Preexisting Diabetes mellitus	Volume of transfused blood products	Perioperative volume of transfused blood products.
Hypertension	Intraoperative acidosis	Sepsis.
Hyponatremia		Relaparotomy.
		Contrast nephropathy
		Delayed liver graft function or primary graft nonfunction
		Calcineurin inhibitors
		Drug-induced interstitial nephritis.
		HCV recurrence

Table 4. Risk factors for Post liver transplant Acute Renal Dysfunction (Lewandowska & Matuszkiewicz-Rowinska, 2011)

3.3.1 Pretransplant renal dysfunction

The rate of renal failure among patients awaiting liver transplantation (LT) and the waiting time for LT have increased in recent years. The introduction of the Model for End-Stage Liver Disease (MELD) score will likely further enrich the proportion of LT candidates who have renal dysfunction, as creatinine is a key component of MELD calculation. The decision to perform combined kidney/liver transplantation (CKLT) as opposed to liver transplantation alone can be difficult in patients with end-stage liver disease and recent onset renal insufficiency. Because of scarce organ resources, it is important to predict accurately which patients with pretransplant renal dysfunction will recover after LT and who will have persistent or progressive kidney disease.

**Pretransplantation serum creatinine level:* is an important predictor of post-LT survival and renal dysfunction (Brown et al., 1996, Lafayette et al.,1997, Bilbao et al., 1998, Markmann et al., 2001, Nair et al., 2002, Pawarode et al., 2003 and Campbell et al., 2005). Even relatively mild elevations in preoperative creatinine (>1.0-1.5 mg/dL) may portend poor renal function

postoperatively (Lafayette et al., 1997, Bilbao et al., 1998 and Pawarode et al., 2003). Bilbao (1998), Sanchez (2004) and Yalavarthy (2007) observed that preoperative creatinine >1.5 mg/dl was predictive of the need for postoperative renal replacement therapy (RRT) and also the risk of postoperative infection. Contreras et al reported that preoperative blood urea nitrogen was also an important predictive factor for the need for renal replacement therapy post-transplant (Contreras et al., 2002). Nair et al, (2002) demonstrated that patients with an average preoperative serum creatinine of 0.8 mg/dl had a 5-year patient survival of 62% compared to a 5-year survival of only 42% in patients with a preoperative serum creatinine of 2.7 mg/dL. Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data from 1988 to 1995 demonstrated that patients with a preoperative serum creatinine >2 mg/dl had a 5-year survival of only 50%. Furthermore, patients requiring preoperative RRT had worse outcomes compared to those not requiring RRT (Jeyarajah et al., 1997).

Cause of renal disease

May also help predict posttransplantation creatinine. Certainly patients with underlying chronic kidney diseases such as *glomerulonephritis, diabetic nephropathy* would be expected to have persistently poor or worsening renal function after LT alone, particularly in the setting of calcineurin inhibitor–based immunosuppression. Sezer et al., reported that microalbuminuria is a main risk for renal function deterioration (Sezer et al., 2011). Many transplant centers have reported that a large majority of their CKLT patients underwent transplantation for chronic kidney disease. In contrast, hepatorenal syndrome (in studies from the early 1990s) demonstrated a good post-LT alone renal outcome and hence concomitant renal transplantation may be avoided. Of patients with ARF due to the hepatorenal syndrome, approximately two-thirds will recover, although recovery may be delayed 3 months or longer after LT (Yalavarthy et al., 2007). Because waiting times for liver transplantation and duration of renal dysfunction prior to transplantation have increased since then, it is possible that renal outcomes after LT alone in patients with HRS may be less favorable now.

Duration of pretransplant renal dysfunction

Bahirwani et al., 2008 showed that patients with preexisting renal dysfunction, especially if the duration is more than 12 weeks, experience a significant fall in eGFR after liver transplantation alone.

Most studies agreed on reporting the negative impact of pretransplant renal dysfunction on posttransplant renal function, regardless of the criteria that they depended upon to define the dysfunction. Lebrón Gallardo (2004), Faenza (2006) and Burra (2009), used serum creatinine; Gonwa et al., 2004 used pre-LT GFR & Kim et al., 2004 used creatinine clearance. Indeed mortality after LT is affected modestly by the presence of pretransplant acute renal failure (<2-fold increase), but increases markedly (up to 8-fold) in the face of acute renal failure posttransplant (Yalavarthy et al., 2007).

3.3.2 MELD score

The proportion of patients undergoing liver transplantation (LT) with renal insufficiency has significantly increased after the MELD era due to the fact that more patients with high

serum creatinine are being transplanted and hence affecting the posttransplant kidney function (Sharma et al., 2009). An association was observed between postoperative ARF and a higher Model for End-Stage Liver Disease (MELD) score (Sanchez et al., 2004, Campbell et al., 2005, Tinti et al., 2010 and Sezer et al., 2011) and between ARF and a reduced pre-LT serum albumin (Tinti et al., 2010). No association was noted between ARF and other pre-LT parameters. The association of ARF with MELD and hypoalbuminemia may be the result of a close relationship between renal and hepatic functions among cirrhotic patients (Tinti et al., 2010). Schnitzbauer reported that time on the waiting list with endstage hepatic disease is a major risk factor associated with early posttransplant renal impairment (Schnitzbauer et al., 2010).

3.3.3 Early liver allograft dysfunction

Several studies reported that early liver allograft dysfunction is among the major risk factors associated with early posttransplant renal impairment (Fraley et al.,1998, Gainza et al., 2002, Ojo et al., 2003, Lebrón Gallardo et al., 2004, Cabezuolo et al., 2006, Yalavarthy et al., 2007 and Schnitzbauer et al., 2010). *Small-for-size (SFS) grafts*, which may lead to specific problems of delayed function or SFS syndrome (characterized by prolonged cholestasis, ascites or coagulopathy) may also aggravate the problem of post-transplant renal dysfunction. Lee et al., 2007 in their study on 248 adult patients who underwent LDLT reported a significant relationship between small-for-size grafts (GRWR < 0.8) and early postoperative renal dysfunction. Yamamoto et al., 2004 also demonstrated this relationship.

3.3.4 CNI nephrotxicity

Acute, reversible nephrotoxicity accompanying CNI therapy results from the imbalance in vasoactive substance release. The administration of CNI causes vasoconstriction of both the afferent and, to a greater degree, the efferent arterioles, which leads to a decrease in renal blood flow and glomerular filtration rate (GFR), and an increase in renal vascular resistance. In its most extreme form, there is tubular damage and a clinical picture of acute tubular necrosis, perhaps on the basis of ischemia. Kidney biopsy histopathology shows characteristic isometric vacuoles in proximal and distal tubular cells. Calcineurin inhibitors can also cause an acute form of nephrotoxicity manifested by acute renal failure in the early posttransplant period. Renal biopsy in these patients shows endothelial damage, formation of fibrin thrombi in capillary loops (Fig. 2), eosinophilic material in the walls of arterioles and small arteries, with patchy necrosis of smooth muscle cells. This lesion is histologically similar to that seen in malignant hypertension and thrombotic thrombocytopenic purpura. Indeed, thrombocytopenia sometimes accompanies this syndrome in transplanted patients (Remuzzi & Bertani, 1989).

Diagnosis of ARF

Vigilant postoperative care including not only monitoring of renal parameters, but also a thorough analysis of risk factors of renal dysfunction is vital.

3.4 Postoperative monitoring of renal parameters

At present, monitoring of the renal function bases mostly on the results of the serum creatinine level and the estimated glomerular filtration rate (eGFR rate) calculated with the

use of MDRD and Cockcroft-Gault formula and on monitoring of diuresis (Cockcroft & Gault, 1976 and Levey et al., 1999).

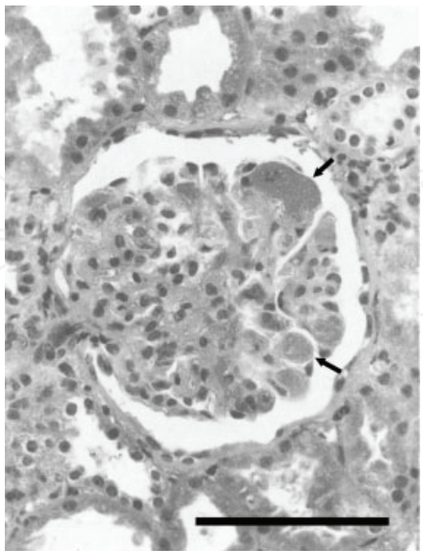


Fig. 2. Thrombotic angiopathy of cyclosporine toxicity. The arrowheads point to fibrin thrombi in the capillary loops of a glomerulus from a patient with acute cyclosporine toxicity. (Smith, 2006: Photomicrograph courtesy of David Howell)

Because of the above-mentioned limitations of AKIN criteria, it is now attempted to find new biomarkers released by the renal tubules, which (if increased in urine or blood serum) would allow for an early diagnosis of AKI or identification of a group at increased risk of AKI. The most frequently mentioned indicators of this type include: cystatin C (Biancofiore et al., 2006), NGAL (*neutrophil gelatinase-associated lipocalin*) (Portal et al., 2010), KIM-1 (*kidney injury molecule-1*) or interleukin-18 (Lewandowska & Matuszkiewicz-Rowinska, 2011).

Recently, there have been a few reports published that evaluated the usefulness of the latest methods of an early AKI assessment in post-LT patients. Portal et al. evaluated the usefulness of serum and urine NGAL level measurements in patients immediately after liver transplantation, in prognosing the risk of AKI development within the next 48 hours. A multivariate regression analysis showed two independent risk factors of AKI development: APACHE II (OR 1.64/point; 95% CI, 1.22–2.21, P=0.001) and serum NGAL level (OR 1.01/ng/ml, 95% CI, 1.00–1.02, P=0.002). When combined together (so called renal risk index), these two factors revealed the highest predictive value. Index with APACHE II score of >13 and serum NGAL level of >258 ng/ml, calculated at ≥1, showed a sensitivity of 100% and a specificity of 76% in the prediction of severe AKI [Portal et al., 2010].

3.4.1 Analysis of risk factors

Xu and colleagues, on the basis of the analysis of data from 102 patients subjected to LT, developed a predictive model of AKI incidence following LT. A multivariate analysis showed that independent risk factors of this complication included: preoperative creatinine level of >1.2 mg/dl, intraoperative diuresis of ≤60 ml/hour, intraoperative hypotension, and use of noradrenaline. They calculated the risk score as follows: [–2.128 + 1.109×

(preoperative creatinine level of >1.2 mg/dl) + 2.243 × (intraoperative diuresis of ≤60 ml/hr) + 1.542 × (intraoperative hypotension) – 2.463 × (intraoperative use of noradrenaline)]. Next, the authors studied the usefulness and predictive value of the developed formula in a prospective study including 44 patients after LT, assuming that the probability of AKI = EXP (risk score)/ [1 + EXP (risk score)]. Aiming to achieve the highest sensitivity and specificity of the indicator (75% and 93.8%, respectively), a cut-off value of –0.2 was assumed as optimal in determining the prognosis of AKI. This meant that among patients with an index value of ≥–0.2, the risk of AKI development was significantly higher than in patients with an index value of <–0.2. The model developed by the authors proved to be reliable: AKI occurred in 9 out of 11 patients from the group of high risk, and only in 3 individuals out of 33 from the low-risk group (Xu et al., 2010).

3.5 Prevention of acute renal dysfunction

To prevent acute kidney injury effectively, it is necessary to know its risk factors, to evaluate the patient in detail before liver transplantation, and to obey the rules of conduct, characteristic for all clinical situations that could lead to AKI development.

3.5.1 General measures

- thorough monitoring of the water and electrolyte balance,
- avoidance of nephrotoxic drugs,
- discontinuation of preparations inhibiting the effect of angiotensin II,
- careful dosing of other medicines, with adjustments of doses to the current renal function.

Unfortunately, despite promising results of *in vitro* and experimental studies, it was impossible to prove the protective effect of N-acetylcysteine on kidneys in that population (Hilmi et al., 2010, Sagias et al., 2010 and Jegatheeswaran & Siriwardena, 2011).

3.5.2 Modification of nephrotoxic immunosuppressive regimens

To avoid postoperative acute renal failure and/or chronic renal failure has met with variable results (Fabrizi et al., 2010). There are no data to suggest that switching from one calcineurin inhibitor to another at equipotent doses will result in less nephrotoxicity. However, as trough tacrolimus levels correlate more closely with the area under the curve of drug exposure than do trough cyclosporine levels, it may be easier to avoid calcineurin inhibitor toxicity using tacrolimus. If cyclosporine is used, the blood level drawn 2hrs post dose (C2 level) should be used to monitor therapy.

Strategies to limit CNI exposure include CNI minimization, avoidance, and withdrawal

Candidates for such a treatment would be first of all patients with impaired renal function found before transplantation. There is no well-defined protocol to prevent or minimize cyclosporine or tacrolimus nephrotoxicity.

Some centers advocate *Calcineurin inhibitor minimization* using mycophenolate mofetil or sirolimus. This may be associated with a modest increase in creatinine clearance (CrCl) and a decrease in serum creatinine (SCr) in the short term. Mycophenolate mofetil may improve renal outcomes during CNI minimization more than sirolimus. Despite improvement in

CrCl or SCr, CNI nephrotoxicity is progressive over time when CNI exposure is maintained. Persistent damage is observed on biopsies as long as the CNIs are continued.

CNI withdrawal

May be the best option by delivering CNIs during the early period of immunologic graft injury and then converting them to less nephrotoxic agents before significant renal damage occurs (Flechner et al., 2008). Late CNI withdrawal has achieved variable results, possibly because withdrawal was attempted after the kidney damage was too extensive. In a case report on 3 patients with renal function impairment who switched from CNI to sirolimus, 2 improved substantially and came off dialysis, while in 1 (whose renal dysfunction was initially milder, not severe enough to require dialysis) serum creatinine levels remained altered after switching to sirolimus (Kamar et al., 2007). Early CNI withdrawal, prior to significant kidney damage, has generally improved CrCl and markers of fibrosis, a finding also observed with sirolimus in most studies. Successful withdrawal appears to be more effective than CNI minimization. Lam et al stressed that sirolimus conversion should be initiated early since late conversion rarely improves chronic renal dysfunction (Lam et al., 2004). In fact, several studies have shown that in patients with pre-existing renal disease, sirolimus can even worsen nephrotoxicity and promote proteinuria (Bumbea et al., 2005, Letavarnier et al., 2005 and Diekmann et al., 2007).

Antibody induction with delayed CNI initiation

It has been suggested that in case of high serum creatinine levels at the time of grafting, it may be wise to delay the use of calcineurin inhibitor based immunosuppression in the immediate post-operative period (Distant & Gonwa, 1993). Polyclonal antibody (thymoglobulin) induction was used to delay CNI use and avoid renal toxicity without increasing the risk of rejection or HCV recurrence. However side-effects such as "first dose reaction" have been reported in 80% of patients. This can often be ameliorated by premedication with antipyretics and steroids. Other side-effects include thrombocytopenia, CMV infection, posttransplant lymphoproliferative disease (PTLD), serum sickness and anaphylaxis (Pillai & Levitsky, 2009).

Later, monoclonal antibody induction using basiliximab (anti-CD25 monoclonal anti-body) and alemtuzumab (anti-CD 52 antibody) was used. These antibodies remain in the circulatory system for weeks after initiation of therapy and have been used successfully with low-dose CNIs. Neuhaus (2002) and Liu (2004) reported successful use of basiliximab with less nephrotoxicity and fewer side-effects compared to the antithymocyte globulins. Also, Tzakis (2004) and Marcos (2004) showed that liver transplant recipients who received alemtuzumab induction with low dose tacrolimus had less renal toxicity than those who received standard doses of tacrolimus. The use of these antibodies may be effective to limit CNI exposure, but longer-term follow-up data are required (Flechner et al., 2008). Actually a recent study showed that induction with basiliximab resulted in 30-day and 1-year patient, graft and renal outcomes comparable with a control group receiving standard CNI-based immunosuppression. The authors concluded that antibody induction with delayed CNI should be further studied prospectively (Verna et al., 2011).Also a recent study showed that steroid-free alemtuzumab induction regimen was associated with less hypertension and rejection but with more infectious complications. Thus, the overall benefit of alemtuzumab induction in LT recipients is called into question (Levitsky et al., 2011).

CNI avoidance

The use of the so-called renal-sparing agents is still debatable. Avoidance is hampered by lack of experience and possible sirolimus-induced side effects (delay in surgical wound repair because it inhibits fibrogenesis (Montalbano et al., 2004), inducing proteinuria, anaemia, thrombocytopenia, peripheral swelling, hypercholesterolemia and gastrointestinal disorders (Vivarelli et al., 2006). Use of sirolimus with mycophenolate mofetil to avoid CNI exposure de novo has improved glomerular filtration rate for at least two years in most studies in kidney transplantation; however, experience is limited in liver and heart transplantation, and reports of delayed graft function and wound healing with sirolimus may have dampened enthusiasm for *de novo* use. There is hardly published evidence for CNI-free de novo approaches with mTOR-inhibitors in liver transplant collectives. Schnitzbauer et al are conducting a prospective, noncontrolled, two-stage study (PATRON07) on patients with serum creatinine >1.5mg/dl or eGFR < 50 ml/min at the time of transplantation. Its objective is to evaluate the feasibility of a de novo CNI-free immunosuppressive regimen based on induction therapy with basiliximab (20 mg IV day 0 and day 4 after transplantation), prednisolone 500mg during reperfusion then 1mg/kg and tapered by month 6 after LT, mycophenolate mofetil (2g/d bid), and mTOR-inhibition with sirolimus after day 10 after LT aiming at trough-levels of 4 to 10 ng/ml. The primary endpoint is defined as the incidence of steroid-resistant acute rejection within the first 30 days after liver transplantation. The authors hope that the results of PATRON07 may be the basis for a large multicenter randomized controlled trial in patients with poor renal function at the time-point of liver transplant (Schnitzbauer et al., 2010).

If CNI-free-"bottom-up" immunosuppression strategies are safe and effective, this may be an innovative concept that could improve the patient short and long-time outcome with regards to renal function, infectious complications and avoidance of over-immunosuppression after LT.

Future direction of immunosuppression: Costimulation blockade (Belatacept)

Belatacept is a soluble cytotoxic T-lymphocyte antigen-4 (CTLA-4) agent which binds CD80 and CD86 and inhibits T cell activation. Belatacept competes with the CD28 receptor on T cells which normally binds CD80 and CD86 on the antigen presenting cell as a co-stimulatory signal required for T cell activation. Belatacept is administered intravenously once a month and does not carry the renal toxicity of CNIs. Clinical trials in liver transplant patients are currently ongoing with this agent (Pillai & Levitsky, 2009).

3.5.3 Surgical technique of 'piggy back'

It is necessary to conduct further studies in order to answer the question whether the new surgical technique of 'piggy back' type will allow for a reduction of AKI incidence (Cabezuelo et al., 2003 and 2006).

3.6 Dialysis in the liver transplant patient

Around 8-17% of the patients with AKI after LT require renal replacement therapy (Lewandowska & Matuszkiewicz-Rowinska, 2011). Dialytic therapy in the immediate postoperative period requires close attention to hemodynamics and coagulation parameters.

(Smith, 2006 and Lewandowska & Matuszkiewicz-Rowinska, 2011).The most frequently used perioperative treatment methods include continuous techniques in 75% of cases, such as continuous veno-venous haemo(dia)filtration (CVVHD), dialysis of SLED type (slow low efficiency dialysis), and intermittent haemodialysis in 25% of cases. Continuous techniques are preferred for two main reasons: the patients are frequently haemodynamically unstable and remain at a significant risk of brain oedema. However, the real advantage of these methods over the applied standard haemodialysis has not been proven so far.

In the liver transplant patient with impaired hepatic clearance and renal failure, attention should be paid to the route of excretion of all pharmacologic agents given and doses adjusted accordingly. Cyclosporine, tacrolimus, prednisone, and mycophenolate mofetil are not removed by hemodialysis to any significant extent, while methylprednisolone and azathioprine (and its active metabolite mercaptopurine) are cleared partially during dialysis. Most angiotensin-converting enzyme inhibitors are dialyzable, with benazepril and quinapril being exceptions. Calcium channel blockers are generally not cleared by hemodialysis, while many of the beta-blockers (atenolol, acebutalol, metoprolol, nadalol, sotalol) are cleared. Because atenolol is primarily cleared by the kidneys, the dose to achieve a desired effect is much lower in patients with poor renal function. Metoprolol on the other hand is primarily metabolized by the liver. Metabolites of verapamil with atrioventricular (AV) node-blocking properties, but little antihypertensive effect can accumulate in patients on hemodialysis. This agent is thus best avoided in end-stage renal disease (Smith, 2006).

In some of the cases, there may appear a need for renal replacement therapy during LT procedure mostly due to hypervolemia and the risk of brain oedema (Lewandowska & Matuszkiewicz-Rowinska, 2011). Townsend et al. used intraoperative CVVHD in 41 out of 636 patients (6.4%) that they operated on. A mean time of dialysis was 258 minutes and a mean filtration rate was 1–1.5 l/h. No significant complications were observed apart from blood clotting in the dialyser (no anticoagulation was used in most of the patients) in 40% of cases. Indications included either typical, life threatening symptoms of AKI, such as overhydration or hyperkalemia, or disorders typical for this group of patients: lactic acidosis, hyponatremia, risk of brain oedema or necessity of transfusion of large volumes of blood preparations. In 78% of cases, CVVHD procedures were continued after OLT for 3–11 days (Townsend et al., 2009).

3.7 Prognosis of acute kidney injury

Acute renal failure (ARF) has been associated with an 8-fold increase in mortality risk, prolonged ventilation time and intensive care unit (ICU) stay, greater risk for infectious complications, and greater hospital costs. De Simone et al reported an in-hospital mortality rate as high as 41% for patients with ARF versus 5% for those with preserved renal function (De Simone et al., 2009). Mortality of patients who required renal replacement therapy is from 45.1% to 67% (Cabezuelo et al., 2002, Faenza et al., 2006).

Zhu and colleagues analysed retrospectively the influence of the renal function following LT on late clinical outcomes in 193 patients. Among patients with acute kidney injury (AKI), the 28-day and 1-year mortality was significantly higher than in non-AKI patients (15.5% and 25.9% *vs.* 0% and 3.9%, respectively; P<0.5). One-year survival of non-AKI patients was 96%, and of AKI patients in stage 1, 2, and 3– 85.5%, 84%, and 45.3%, respectively. The Cox

regression analysis showed that the independent risk factors of death in the first year following the transplantation included postoperative AKI (HR 12.1; P<0.05), postoperative infection (HR 4.7; P<0.01), postoperative hypertension (HR 4.4; P<0.01), and postoperative APACHE II index of ≥10 (HR 3.6; P<0.05) (Zhu et al., 2010). Similar results were published by Gonwa et al. (2001a) and by Ishitani et al. (1993).

During the later course, renal dysfunction exerts an important influence on the quality of life of transplant recipients (Alessandria et al., 2005, Lewandowska & Matuszkiewicz-Rowinska, 2011). AKI significantly increases the risk of *development of chronic renal failure* in the late post-LT period. The risk of developing chronic renal failure after LT is approximately 20% after 5 years, associated with the use of calcineurin inhibitors and a 4-fold increased mortality risk (Sharma et al., 2009 and Schnitzbauer et al., 2010).

4. Chronic renal dysfunction

With improved survival of liver transplant recipients, chronic kidney disease has emerged as a major long-term complication after OLT (Bahirwani & Reddy, 2009). In fact, liver transplant recipients have the highest five-yr incidence of CRF of any non-renal solid organ transplant recipient; additionally, the risk of death is at least fourfold higher in patients who develop CRF (Ojo et al., 2003). Numerous studies have been performed in the last decade in order to clarify the epidemiology and clinical significance of chronic kidney dysfunction among liver recipients (Fisher et al., 1998, Brown et al., 2001, Cohen et al., 2002 & Herlenius et al., 2008).

4.1 Epidemiology of chronic renal dysfunction

The incidence of chronic kidney disease (CKD) post-Liver transplant varies widely, from 10 to 83%, most likely owing to the *lack of a standard definition* of post-transplantation chronic renal disease, *differences in the methodology* utilised to estimate renal function, and *variable periods of follow-up* (Fabrizi et al., 2010).The frequency of CKD (defined as eGFR <60 ml/min) according to recent series is listed in Table 5. However the incidence of the milder forms of renal dysfunction (GFR between ≥30 mL/min and ≤70 mL/min) is likely to be considerably higher than estimated (Fisher et al., 1998, Randhawa and Shapiro, 2005). Definitely, the incidence of CKD increases with time. The latest report on the epidemiology of CKD after liver transplantation has been offered by Lee et al (2010). A cohort of 431 recipients who underwent liver transplantation between 1997 and 2008 was included. The cumulative incidence of CKD (eGFR <60 ml/min) was 17% at 1 year, 23% at 3 years, and 27% at 5 years. Sharma et al., 2009 reported the cumulative incidence of post-LT CRF at 1, 3, and 5 years was 8%, 17% and 22%, respectively.

Authors	Frequency	Time post-LT
Lee J, et al (2010)	17.6% (76/431)	12 months
Burra P, et al (2009)	35.3% (143/406)	12 months
Kim S, et al (2004)	43.5% (27/62)	17 months
De Boccardo G, et al (2008)	62.3% (144/231)	73 months

Table 5. Epidemiology of chronic kidney disease among liver transplant recipients (CKD = eGFR <60 ml/min)

4.2 Definitions of chronic kidney disease

The most common definition used is eGFR<60ml/min. Other definitions of CKD have been used. Gonwa and colleagues, defined post-LT CRD as sustained serum creatinine >2.5 mg/dl. They reported that the combined incidence of CKD with end-stage renal disease (on RRT), was 4.3% at 5 years and 18% after 13 years of follow-up (Gonwa et al., 2001b). **Ojo et al, 2003** in a larger study analyzed the data from the Scientific Registry of Transplant Recipients for 36,849 adult patients who had LT in the United States between 1990, and 2000. The incidence of post-LT CRD was 18% at 5 years and 26% at 10 years. This study defined post-LT CRD as GFR < 29 mL/minute/1.73 m^2 or the development of end-stage renal disease, which was defined as initiation of RRT or listing for renal transplantation.

Chronic renal dysfunction, not only has implications in terms of an *increased demand on resources*, but is also significantly associated with a *higher patient mortality rate*. Hence identification of the risk factors for its development of chronic renal dysfunction after liver transplantation is crucial.

4.3 Risk factors for posttransplant chronic kidney disease

Although previously attributed largely to calcineurin inhibitor toxicity (Ojo et al., 2003, Pillebout et al., 2005), it has become clear that the onset of chronic renal failure following LT is multifactorial, and reported to be correlated with posttransplant acute renal failure (Lee et al., 2010 and Tinti et al., 2010), pre-transplant renal dysfunction (Kamath et al., 2001; Burra et al., 2009 and Tinti et al., 2011), hepatitis C status, age, female gender, diabetes mellitus, hypertension, Model for End Stage Liver Disease (MELD), pretransplant proteinuria (Lee et al., 2010), pretransplant hepatorenal syndrome, alcohol intake (Hetz et al., 2005, Pillebout et al., 2005 and Randhawa & Shapiro, 2005), smoking and dyslipidemia (Sezer et al.,2011).

4.3.1 Postoperative acute renal failure (ARF) and dialysis requirement in the post-transplantation period

Post-LT ARF was proved to be an early predictor of chronic kidney disease (CKD) in several studies (Ojo et al., 2003; Kim et al., 2004; Burra et al., 2009 and Sharma et al, 2009). Barri and his colleagues, 2009 stated clearly that the high incidence of acute kidney injury post–liver transplantation is an important risk factor for long-term renal dysfunction and its associated morbidity and mortality. Ojo et al., 2003 reported a relative risk of 2.13. In the study by Tinti and colleagues, post-LT CKD was present in 44.4% of patients with ARF in contrast to 6.7% of patients without ARF (Tinti et al., 2010). A multivariate Cox regression analysis revealed that the overall risk of CKD development (eGFR < 60 mL/min/1.73 m^2) was associated with the existence of posttransplant ARF and its severity. In fact, a recent consensus conference on acute kidney injury(AKI) suggested that since AKI is a very strong predictor of CKD, a milder definition for AKI should be used to detect this problem early and to intervene before it is severe and progresses to CRD (Barri et al., 2009).

4.3.2 Abnormal GFR at different intervals posttransplant

Sanchez et al., 2010 in a study conducted on 592 liver transplant recipients also confirmed this finding and showed that patients with GFR less than 60 ml/min per 1.73 m^2 *at month 3*

post-transplant have a higher risk of developing renal failure; however, those who avoid renal failure seem to maintain renal function long-term. Kamar et al. reported the eGFR *after 6 months* was the only risk factor of renal failure for further 60±48 months. This was also a predictor of glomerular sclerosis found in 50% of glomerules in the renal biopsy performed afterwards (Kamar et al., 2011). Other studies have reported that an *abnormal GFR at 1 year* identifies patients at risk of chronic renal dysfunction (Cohen et al., 2002 & O'Riordan et al., 2006).

4.3.3 Pretransplant renal dysfunction

Impaired pre-transplantat kidney function is a prognostic indicator for chronic kidney disease (CKD) following liver transplantation, as recently highlighted by a meta-analysis of clinical, observational studies. A stratified analysis including only studies provided with baseline GFR, revealed that the summary estimate of RR and 95% CIs for occurrence of chronic renal failure after liver transplantation in patients with diminished renal function at transplantation was 2.12 (95% CI, 1.01-4.46, p=0.01) (Fabrizi et al., 2011). Even relatively mild elevations in pre-transplant creatinine >1.5 mg/dL may portend poor long term renal function. This was confirmed by many investigators (Moreno et al., 2003, Kim et al., 2004 and Burra et al., 2009). A multivariate Cox regression analysis performed by Lee et al revealed that the overall risk of CKD development was associated with low pre transplant eGFR in addition to post-transplant acute renal failure (Lee et al., 2010). In fact, Sharma et al., 2009 concluded that the estimated GFR at LT was the most important determinant of post-LT chronic renal failure. Sezer reported that after 5 years, GFR negatively correlated with initial Renal Resistive Index (r=-0.32; P<.01).

Duration of pretransplant dysfunction

Campbell (2005) suggested that duration, rather than the cause, of pretransplant renal dysfunction (pre-LT RD) is the key to predicting creatinine at 12 months after transplantation. ROC analysis among LT alone patients showed that the duration of renal disease by itself had a moderate ability to predict creatinine >1.5 mg/dL at 12 months posttransplantation (area under ROC curve = 0.71). The optimal predictive cutoff was 3.6 weeks. However they stated that they cannot at this time recommend that all patients with duration of renal disease longer than 3.6 weeks undergo combined liver kidney transplantation (CLKT) since creatinine of 1.5 mg/dL 1 year after transplantation is not necessarily high enough to justify concomitant renal transplantation. Instead they recommended that a threshold duration of renal dysfunction in combination with other predictive clinical variables (e.g height of creatinine, requirement for RRT) be prospectively investigated as an aid to clinical decision making.

Indeed for liver transplant (LT) candidates with pretransplant mild to moderate chronic renal impairment or recent-onset ARF, the decision of whether to perform LT alone or CLKT can be challenging because no single factor has been shown to be predictive of the degree of progression of chronic kidney disease following successful LT. Although Pham et al., 2007 suggested, like Campbell, that the duration of pretransplant renal dysfunction had a negative impact on posttransplant renal function outcome, Marik et al., 2006 and Sharma et al., 2009, in contrast, failed to demonstrate that the duration of pretransplant renal dysfunction was predictive of post-LT renal outcome.

4.3.4 Calcineurin inhibitors (CNI)

Chronic CNI nephrotoxicity is caused by immunological and non-immunological damage. Histopathological examination shows renal tubular atrophy with typical microcalcification, patchy fibrosis and nodular arteriolar hyalinosis. According to Mihatsch, arteriolopathy, the main symptom of CNI nephrotoxicity, is a variant of thrombotic microangiopathy with slow, subclinical course. Differentiation between arteriolar hyalinosis associated with CNI administration and arteriolar sclerosis in hypertension, diabetes, or the elderly poses a challenge. A typical feature of CNI toxicity is substitution of smooth muscle cells by hyaline deposits in the external media layer; while in arteriolar hyalinosis in other clinical situations the smooth muscle cells are intact and hyaline deposits accumulate beneath the endothelium (Mihatsh et al., 1994).

There is no precise classification to assess CNI nephrotoxicity; that is why new scales and classifications are developed in order to enhance the precision of diagnosing CNI nephrotoxicity. The new scales to evaluate CNI nephrotoxicity, like the older ones, show arteriolar hyalinosis as the most typical abnormality (Kambham et al., 2007). One histologic study reported the association of these changes with cyclosporine dose and over time. Mild arteriolar hyalinosis at six months appeared to be associated with high doses and was reversible. By comparison, at three years, irreversible severe arteriolar hyalinosis and glomerosclerosis was observed, despite decreased doses and trough levels (Nankivell et al., 2003**).**

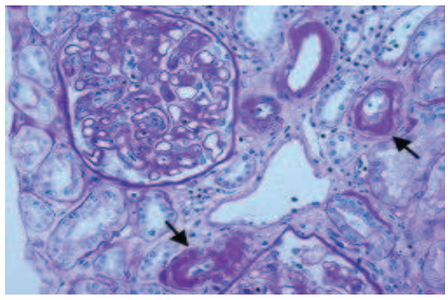


Fig. 3. Nodular hyalinosis typical of CNI (John et al., 2010)

Chronic lesions and acute nephrotoxicity in CNI treatment are caused by various mediators, including renin–angiotensin–aldosterone (RAA) system, which by activating angiotensin type 1 receptor is not only a contributory factor in renal vascular bed constriction, but also influences kidney fibrosis and aldosterone release. Activation of RAA system through CNI may cause harmful hemodynamic (vasoconstriction) and nonhemodynamic changes (via enhanced synthesis of transforming growth factor-β, vascular endothelial growth factor and enhanced renal cell apoptosis) (Friedlander, 2007). The CNI-induced TGF-β formation produces tubulointerstitial fibrosis by increased synthesis and decreased extracellular matrix degradation (Khanna et al., 2002). Administration of losartan, AT1 blocker, in transplant patients leads to a significant decrease in TGF-β serum levels and increased GFR (Campistol et al., 2001).

Recent trials have shown that aldosterone, the final product in the RAA system, may play an important role in CNI nephrotoxicity; therefore, spironolactone administration may be an effective strategy in the prevention of CNI nephrotoxicity (Perez-Rojas et al., 2007). During

CNI treatment, disturbances in nitric oxide (NO) release and NO synthase activity may generate reactive oxygen species; all of them might be involved in tubular epithelial to mesenchymal transition (Sharma et al., 2000 and Han et al., 2006). Protein kinase C (PKC-β) contributes to CNI-dependent fibrosis. It has been proved that cyclosporine administration enhanced PKC-β mRNA and protein expression; adding hispidine, a PKC-β inhibitor, inhibited TGF-β1 synthesis in proximal tubule cells (Liu, 2006).Genetic susceptibility to cyclosporine nephrotoxicity has been suggested. Cyclosporine is a substrate for the transmembrane pump P-glycoprotein. There is some evidence in animals and in vitro that decreased expression of this pump may contribute to increased cyclosporine levels, leading to nephrotoxicity. Altered protein pump expression has also been observed in association with several polymorphisms in its gene. As an example, the TT genotype is associated with decreased P-glycoprotein expression in the kidney. In a case control study of donor and recipient pairs, the TT genotype in the donor directly correlated with chronic cyclosporine nephrotoxicity in the allograft recipient. This suggests that underlying genetic factors that increase cyclosporine concentrations in the kidney may contribute to chronic nephrotoxicity (Hauser et al., 2005).

Progressive obliterative arteriolopathy and chronic interstitial fibrosis with glomerulosclerosis develop in LT recipients in a *dose-dependent* and *time-dependent* fashion and have limited potential for reversibility (Fabrizi et al., 2010).

Manifestations of Chronic calcineurin inhibitor nephrotoxicity: renal insufficiency due to glomerular and vascular disease, abnormalities in tubular function, and an increase in blood pressure (Hauser et al., 2005).

Abnormalities in tubular function include:

- hyperkalemia (due to reducing of potassium excretion both by decreasing the activity of the renin-angiotensin-aldosterone system and by impairing tubular responsiveness to aldosterone) (Tumlin and Sands, 1993).
- hypophosphatemia (due to urinary phosphate wasting) (Moz et al., 2004)
- hypercalciuria (Nijenhuis et al., 2004).
- hypomagnesemia — presumably due to drug effects on magnesium reabsorption. Hypomagnesemia has been implicated as a contributor to the nephrotoxicity associated with cyclosporine (Miura et al., 2002).

Difference between cyclosporine and tacrolimus: There are conflicting views in the literature regarding any difference in the nephrotoxic effect of either cyclosporine or tacrolimus. Many investigators did not identify any difference in the impact of either drug on the immediate postoperative kidney function (Burra et al., 2009, Dehghani et al., 2008, Kim et al., 2004 and Wei et al., 2006). On the other hand, O'Riordan et al., 2006 found a beneficial effect of tacrolimus use, compared with cyclosporine, which retarded the progression of acute renal disease to chronic renal disease. This has been previously noted by Filler et al., 2005 and Lucey et al., 2005. In contrast, a previous long-term trial comparing cyclosporine and tacrolimus in liver transplant recipients found a similar incidence of early acute renal failure and late hypertension, while late renal insufficiency was more prevalent with tacrolimus (Porayko et al., 1994). Recently, Lee and colleagues, 2010 in a multivariate Cox regression analysis revealed that the overall risk of CKD development was associated with cyclosporine more than tacrolimus.

4.3.5 Hepatitis C

Hepatitis C recurrence after transplant is almost universal. Infection with hepatitis C virus (HCV) is the leading indication for LT worldwide and one explanation for the higher incidence of renal failure in LT patients is that HCV per se and the severity of HCV recurrence are risk factors for renal dysfunction (Asfandiyar et al., 2006). The mechanism by which HCV infection may induce early renal failure is not yet fully understood. HCV infection has been associated with mesangiocapillary glomerulonephritis and cryoglobulinemia (Braun et al., 2003), conditions that have been reported in HCV+ve LT recipients (Abrahamian et al., 2000 and Kendrick et al., 1997). Immunosuppressive therapy results in an early and significant increase in HCV replication after LT (Gane et al.., 1996), which may increase the risk of glomerular damage if concurrent renal transplantation is not performed [Pascual et al., 1997]. Moreover in these series, the presence of lower GFR before transplant (although not statistically significant) and the significant higher incidence of diabetes mellitus after transplantation in HCV group, compared to non-HCV group, could be additional factors justifying the worse renal function of HCV+ve liver transplant recipients (Burra et al., 2009).

Studies have reported a different influence of hepatitis C on chronic renal dysfunction after liver transplantation. Pillebout (2005) found a strong association linking HCV infection with end-stage renal disease at biopsy, relating particularly to interferon therapy. In contrast, Burra et al., 2009 found no such association between the onset of chronic renal failure and the use of interferon before or after LT. Instead they stressed that HCV status had a negative impact on the median GFR in the first year of liver transplantation. Later on, HCV may lose this negative impact, while early stage renal failure continues to play a part in impaired renal function. Actually this study stated that HCV status, pre-LT GFR and serum creatinine levels were independent predictors of renal function a year after LT. Asfandiyar and colleagues, 2006 also demonstrated that infection with hepatitis C is an independent risk factor for chronic kidney disease as well as the relation with severity of HCV. Actually, Ojo et al., 2003, found that HCV was an independent risk factor for chronic renal dysfunction after all non-renal solid organ transplants and not just liver transplantation.

4.3.6 Glomerulonephritis

Only a few, small-sized studies on the histological features of chronic kidney disease (CKD) among LT recipients exist. In addition to histological lesions attributable to calcineurin inhibitor toxicity, a large spectrum of glomerular abnormalities was noted. Gonwa et al observed calcineurin inhibitor toxicity (n=33; 73%), non-recovered HRS (n=3; 7%), and focal segmental glomerulosclerosis (n=3; 7%) in their cohort of 45 patients who underwent kidney biopsy post-liver transplantation (Gonwa et al., 2001b). In another study by Pillebout, chronic renal failure was attributed to (i) specific chronic cyclosporine/tacrolimus arteriolopathy; (ii) typical diabetic nephropathy; (iii) acute or chronic thrombotic microangiopathy attributed to cyclosporine/tacrolimus arteriolopathy or alpha-interferon (Pillebout et al., 2005). In hepatitis B, CNI toxicity and focal segmental sclerosis, but not immune-complex disease, were revealed as significant contributors to CKD after LT (Lee et al., 2010). The question whether those cases with glomerular lesions represent de novo glomerulonephritis or progression of pre-existing disease was unanswered; only prospective studies with serial kidney biopsies can address this point (Fabrizi et al., 2010). Pre-transplant proteinuria is a

significant and independent risk factor for CKD after liver transplantation, according to Lee et al., 2007 and O'Riordan et al., 2006.

4.3.7 Pre-existing comorbidities such as diabetes mellitus, hypertension

A few studies have looked at the relation between *diabetes mellitus* and *hypertension* and chronic renal dysfunction. Karie-Guigues et al., 2009 reported incidence rates of 10.5% for pre-LT hypertension and 43.4% for new-onset hypertension at one year post-transplantation. Diabetes mellitus was reported in 12.5% of the patients before LT and 19.2% developed new onset diabetes after one year of LT. They showed that neither hypertension nor diabetes (pre-transplant or de novo for both) were significantly associated with a GFR decrease at any time points after LTx. These results are in line with those previously reported by Ojo et al, 2003 for hypertension and by O'Riordan et al, 2006 for diabetes.

4.3.8 Child-pugh score and high model for end-stage renal disease (MELD) score

At 3 years after LT, GFR negatively correlated with initial Child-Pugh score (Sezer et al., 2011) and pretransplantat direct bilirubin. After 5 years, GFR negatively correlated with prothrombin time ($r=-0.29$; $P<.05$). Overall risk of CKD development (eGFR < 60 mL/min/1.73 m^2) was associated with high Child-Pugh score and high Model for End-Stage Renal Disease (MELD) score (Lee et al., 2010). Especially in recipients whose pre-operative eGFR was high (>or=60 mL/min/1.73 m^2), rapid progression of kidney disease was associated with Child-Pugh score (in addition to high tacrolimus level and posttransplant acute renal failure) (Fabrizi et al., 2011).

4.4 Prevention of CKD

Especially patients undergoing LT for HCV may benefit particularly from methods for protecting kidney function, such as:

- an optimal control of glucose metabolism,
- dyslipidemia and proteinuria, and an
- aggressive blood pressure containment treatment (Opelz et al., 1998, Randhawa and Shapiro, 2005 and Pillebout et al., 2005).
- Minimizing CNI exposure. Use of CNIs is an important contributor to CRF after liver transplant, accounting for >73% of the renal diagnoses in those patients, (Gonwa et al., 2001b) and this had led to a number of strategies to minimize CNI exposure (mentioned above).

4.5 Outcome of chronic kidney disease after liver transplantation

4.5.1 CVS morbidity/mortality

Chronic kidney disease is a known risk factor for cardiovascular morbidity/mortality in the non-transplantation setting. The Heart Outcomes and Prevention Evaluation (HOPE) study suggested that even mild renal insufficiency was a significant risk factor for a subsequent cardiovascular event (Mann et al., 2001). The Cooperative Cardiovascular project demonstrated that the mortality risk for patients with moderate renal insufficiency for myocardial infarction was three times higher than that of patients with intact kidney function (Shlipak et al., 2002). These results suggest that renal insufficiency is an

independent risk factor for cardiovascular disease and should be considered in addition to other traditional risk factors. Transplant recipients are at increased risk of cardiovascular disease, and information gained in the last decade suggests that the occurrence of CKD appears to further increase the burden of cardiovascular disease among LT recipients. Therefore, the most common endpoint among LT recipients with CKD is not the need for renal replacement therapy or kidney transplantation but death secondary to cardiovascular disease (Fabrizi et al., 2010).

Calcineurin inhibitors also contribute to the development of diabetes mellitus, dyslipidemia, hypertension, and oxidative stress, all of which contribute to cardiovascular morbidity (Merville, 2005).

4.5.2 Mortality

The occurrence of CKD after liver transplantation has a major impact on post-LT mortality. Many investigators confirmed this observation. Moreno et al evaluated 289 consecutive LT patients with post-transplant follow-up longer than 6 months. Patient survival was significantly lower among LT patients with chronic renal dysfunction than in those without this complication (63% vs. 71%, p=0.024). Ojo (2003) conducted a population-based cohort analysis among 69,321 persons who received non-renal transplants (liver, lung, heart, intestine, heart-lung) in the United States between 1990 and 2000. The occurrence of CRF significantly increased the risk of death (RR, 4.55; 95% CIs, 4.38 to 4.74; P<0.0001). The 13-year survival rate in patients with end-stage renal disease posttransplant in a study performed by Gonwa et al., 2001 was only 28.2% versus 54.6% in those without posttransplant kidney disease.

Sharma (2009) evaluated retrospectively 221 adult LT recipients who had LT in the MELD era (Feb 2002-Feb 2007). In their multivariate analysis, the decrease in GFR during post-LT follow-up was the only independent predictor of post-LT mortality after adjustment for age, etiology, MELD score, and GFR at liver transplantation. The risk of post-LT patient mortality was 2.9 (1.3-6.4; p=0.008) for patients with GFR <30 versus >30-60 ml/min and 3.2 (1.19-8.67; p=0.02) for patients with GFR <30 versus>60 ml/min. Pawarode (2003) studied 172 consecutive LT recipients over a median follow-up of 72.4 months (range, 6.5 to 100.6 months). Severe renal failure was associated with significantly lower survival by Cox regression analysis (p=0.004). O'Riordan (2006) followed 230 patients after liver transplantation over 5.6 years (Irish National Liver Transplant database); the 10-year cumulative incidence of CKD stage 4 (GFR 15-29 ml/min) and 5 (dialysis or GFR <15 ml/min) was 6.1% and 2.6%, respectively. Cox regression analysis of overall patient survival suggested that the post-LT GFR < 30 ml/min was associated with a hazard ratio of 3.05 (95% CI, 1.21-7.7; p=0.02); the other independent risk factors of lower patient survival being fulminant hepatic failure and retransplantation.

Authors	Relative Risk	P
Ojo A, et al (2003)	4.55(4.38;4.74)	0.001
Pawarode A, et al (2003)	NA	0.004
O'Riordan A, et al (2006)	3.05 (1.21;7.70)	0.02
Sharma P, et al (2009)	3.2 (1.19;8.67)	0.02

Table 6. Impact of Posttransplant Chronic renal dysfunction on Mortality

5. Conclusions

- There has been abundant evidence over the last decade on the importance of kidney dysfunction among liver transplant recipients. However, still questions need to be assessed.
- Acute kidney injury (AKI) has significant prognostic implications for long-term outcomes in patients undergoing liver transplantation. Hence, every effort has to be undertaken to preserve renal function throughout all stages of patient care.
- In this review we discussed the important risk factors that negatively affect kidney function. A specially increased risk frequently exists among liver transplant recipients with pretransplant renal dysfunction.
- Diagnosis of *acute kidney injury* was also discussed. To better define acute kidney injury, new markers (e.g. neutrophil gelatinase-associated lipocalin) have become available that help to identify patients at risk for renal injury within hours of a triggering insult. Larger studies are required to validate the results. These newly established markers for injury, such as NGAL, in conjunction with improved markers for renal function will allow us to further delineate the natural course of AKI during liver transplantation.
- The occurrence of *chronic kidney disease* after liver transplantation has a major impact on mortality. Additional studies are needed to understand better the natural history of chronic kidney disease among liver transplant recipients. Strategies need to be put in place for the early detection of these individuals and then preventive measures introduced to retard the progression of chronic kidney disease.
- Hepatitis C appears to be an additional risk factor affecting renal function in the long term in liver transplanted patients. Further dedicated prospective studies aiming to evaluate the possible pathogenetic mechanism of HCV damage on long-term renal function after liver transplantation are needed. For the present time, it would be advisable to avoid combinations of risk factors for renal impairment, at least in the first year after LT in HCV+ve recipients.
- Modification of nephrotoxic immunosuppressive regimens to avoid postoperative acute renal failure and/or chronic renal failure has met with variable results. Although there is no well-defined protocol to prevent or minimize cyclosporine or tacrolimus nephrotoxicity, some centers currently advocate the use of a calcineurin-sparing protocol adjusted for the degree of renal dysfunction. Hence, the clinical evaluation of the presence of multiple risk factors for renal insufficiency and etiology of liver disease would be important to select patients who would benefit from a renal sparing regime of immunosuppression. However, dedicated large studies meticulously evaluating these renal sparing regimes in patients with risk factors for renal dysfunction are still recommended. Also trials on novel agents targeting different sites of the immune cascade and without renal toxicity are on the way. Until then, finding the balance between preserving graft function and optimizing immunosuppression while minimizing renal toxicity remains a challenge.
- Studies that incorporate renal diagnosis and other prognostic indicators (such as proteinuria) to stratify liver transplant candidates according to risk for kidney dysfunction post-liver transplant are in progress.

6. Acknowledgement

The author would like to express her thanks to: Dr Naglaa Ali Zayed, Associate Professor, Endemic Medicine Department, Cairo University. Dr Ayman AL sebaey AL Ghoraieb Assistant lecturer of Hepatology, National Liver Institute.

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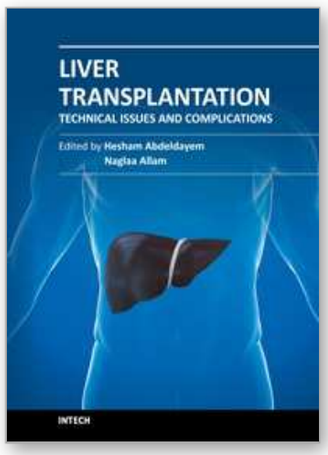

Liver Transplantation - Technical Issues and Complications
Edited by Prof. Hesham Abdeldayem

ISBN 978-953-51-0015-7
Hard cover, 454 pages
Publisher InTech
Published online 10, February, 2012
Published in print edition February, 2012

This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoprolifrative disorders (PTLD), have been covered in more than one chapter.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Naglaa Allam (2012). Renal Dysfunction and Liver Transplantation, Liver Transplantation - Technical Issues and Complications, Prof. Hesham Abdeldayem (Ed.), ISBN: 978-953-51-0015-7, InTech, Available from: http://www.intechopen.com/books/liver-transplantation-technical-issues-and-complications/renal-dysfunction-and-liver-transplantation

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