Published in final edited form as:

Adv Chronic Kidney Dis. 2015 September ; 22(5): 404–411. doi:10.1053/j.ackd.2015.06.001.

Chronic Kidney Disease and Related Long-term Complications Following Liver Transplantation

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Abstract

Liver transplantation (LT) is the standard of care for patients with decompensated cirrhosis. LT recipients have excellent short-term and long-term outcomes including patient and graft survival. Since the adoption of model for end-stage liver disease (MELD) - based allocation policy, the incidence of post-transplant end stage renal disease has risen significantly. Occurrence of stage 4 chronic kidney disease and end stage renal disease substantially increase the risk of post-transplant deaths. Since majority of late post-transplant mortality is due to non-hepatic post-transplant comorbidities, personalized care directed towards risk factor modification may further improve post-transplant survival.

Introduction

Liver transplantation (LT) has evolved from an experimental therapy to the standard of care for patients with decompensated cirrhosis. As of December 12th, 2014, there were approximately 17,000 candidates awaiting LT. There were just over 6000 LT performed in 2013.¹ The overall 1-year and 5-year patient survival is 90% and 75%, respectively.² While early post-transplant deaths are due to allograft-related causes, the late deaths are mainly due to post-transplant comorbidities.^{3, 4}

Model for end-stage liver disease (MELD) score and renal function

MELD-based liver allocation policy was adopted in February of 2002 to achieve the goals of the Final Rule issued by Institute of Medicine in 1999 to transplant the 'sickest person first' based upon objective and measurable medical criteria for urgency⁵. The MELD score, originally developed to predict the mortality after elective transjugular intrahepatic portosystemic shunt (TIPS) procedure for refractory ascites or gastrointestinal bleeding, was validated and adopted as the measure of waitlist mortality for candidates awaiting LT.^{6, 7}

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Serum creatinine, bilirubin and International Normalized Ratio (INR) of prothrombin time are the components of MELD score. It can be calculated as follows:

$$\text{MELD} = 10 * (0.957 \log_e \text{creatinine} + 0.378 \log_e \text{bilirubin} + 1.12 \log_e \text{INR} + 0.643)$$

MELD score does not differentiate between candidates with acute kidney injury (AKI) secondary to hepatorenal syndrome and those with chronic kidney disease (CKD). In examining the MELD equation, serum creatinine has the greatest impact on the overall score, reflecting the influence of renal dysfunction on waitlist mortality among LT candidates.⁸

MELD Allocation and Simultaneous Liver and Kidney Transplant (SLKT)

As an unintended consequence of MELD allocation, a significantly higher proportion of candidates with renal dysfunction at LT in the MELD era are receiving LT compared to the pre-MELD era.⁹ The rate of simultaneous liver-kidney transplant (SLKT) has also increased significantly in the MELD era (Figure 1).^{9, 10} Candidates who meet the specific criteria for SLKT can be listed for kidney transplant at or subsequent to the time of initial listing for LT. Such patients are allocated both organs from the same deceased donor based upon their MELD score.

SLKT listing criteria are straightforward for LT candidates with ESRD and stage 4 CKD. However, these listing criteria are not very clear for candidates with AKI. Over the last decade the listing criteria for SLKT for AKI have evolved.^{10–12} In 2006, SLKT was not recommended for candidates with AKI who were not on renal replacement therapy (RRT).¹² In the most recent consensus statement, the threshold duration of AKI (with RRT) recommended for SLKT listing has been decreased from 8 weeks to 4 weeks, even though the evidence behind these recommendations is lacking. There is wide variation in SLKT rates across all 11 Organ Procurement and Transplant Network regions.¹⁰

Some centers have pursued SLKT to maximize the outcomes of their patients who have pre-transplant renal dysfunction. The data regarding favorable outcomes for SLKT recipients over LT alone (LTA) among patients with pre-LT renal dysfunction is conflicting in the current literature with some studies showing advantage and some showing no survival advantage of SLKT over LTA.^{13–15} Furthermore, the good quality donor kidneys are allocated to the multi-organ transplant recipients resulting in driving away this scarce resource from high risk kidney transplant alone candidates.^{15, 16}

Renal Recovery after LT alone

The spectrum of renal dysfunction before LT varies from minimal increase in serum creatinine to full-blown renal failure requiring RRT. Table 1 shows the common types for acute kidney injury (AKI) seen among patients with decompensated cirrhosis. A majority of patients with AKI secondary to hepatorenal syndrome (HRS) recover their renal function after LT. However, a subset of patients with HRS and those with acute tubular necrosis may progress to post-LT ESRD.¹⁷

In one of the largest studies, the cumulative incidence of renal non-recovery within six months of LTA was 8.9% among those who were on acute RRT prior to LT and even a smaller proportion (4%) had Stage 4 CKD at six months after LT.¹⁷ The definition of renal non-recovery in this study was transition to ESRD as evidenced by CMS 2728 form. The overall six month post-transplant mortality in the study cohort of 2112 patients with a median MELD score of 38 was 20%. In another study of 1041 LT recipients, the rate of post-LT ESRD in those who were on dialysis before LT and received LT alone was 32%.¹⁸ Both of these studies examined the renal outcomes among those who were on dialysis before LT. However, the primary outcomes were different in both studies. While Sharma et al.¹⁷ defined renal non-recovery as transition to chronic dialysis or listing/receipt of kidney transplant within six months of LT alone, Northup et al.¹⁸ defined renal non-recovery as those who developed ESRD after LT alone during the entire follow up period. In other words, Sharma et al. evaluated the incidence of renal non-recovery among those who were on acute dialysis and received LT alone, whereas Northup et al. examined the incidence of post-LT ESRD in this group.^{17, 18} Both of these studies were complementary and found a strong effect of duration of pre-LT RRT on renal non-recovery. Each additional day of pre-LT RRT was associated with a 3.6% higher risk of renal non-recovery; however, there was no minimal threshold of pre-LT RRT duration above which the risk of renal non-recovery was especially increased.¹⁷ Diabetes and older age were some of the additional independent risk factors of renal non-recovery.¹⁷⁻¹⁹

Sharma et al. also examined the long-term renal function recovery among patients who were on acute pre-LT dialysis and recovered their renal function after LT alone.¹⁷ In their study, among survivors only 4.0% had stage 4 CKD at 6 months after LT. The cumulative incidence of post-LT ESRD in these stage 4 CKD patients was 6.4% at 1 year.¹⁷ There are no studies to date that have examined renal recovery after LT alone with respect to treatment center.

A retrospective study consisting of a heterogeneous population of LT candidates with CKD and AKI showed that >2 weeks of renal dysfunction defined as serum creatinine >1.5mg/dl was associated with post-LT CKD at 1 year.^{20, 21} Another analysis did not show an association between the duration of serum creatinine >1.5mg/dl before pre-LT RRT and renal non-recovery.¹⁷

Post-LT Chronic Kidney Disease and ESRD

Among all non-renal solid organ transplant recipients, LT recipients have the second highest incidence of post-LT chronic renal failure including ESRD (5-year cumulative incidence of 18%-22%) despite the lowest level of immunosuppression with calcineurin inhibitors compared to heart and lung transplant candidates.²² Incident stage 4 CKD and ESRD after LT is associated with high post-transplant mortality risk (Relative Risk=3.32[2.96–3.71]).^{22, 23}

Several observational studies have shown that risk of post-LT ESRD has increased since the implementation of MELD-based allocation.²³⁻²⁵ One of the studies elegantly depicted how rates of post-LT ESRD decreased significantly from 1995–2001 (HR=0.949, P<0.001), but

then how this trend reversed after implementation of MELD-based allocation (2002), with 7.6% increase in ESRD rates every year after 2002 (Figure 2).²³

Identification of LT recipients at risk for post-LT ESRD at the time of transplant

Several observational cohort studies have identified recipient and donor factors that can clearly identify LT recipients at the highest risk of developing post-LT ESRD.^{23–28} Renal function is already compromised in patients with decompensated cirrhosis secondary to portal hypertension physiology. Our hypothesis is that various recipient-, operative-, donor- and post-LT factors such as immunosuppression may serve as second or third hits resulting in progression to stage 3–4 CKD/ESRD (Figure 3).

Duration of elevated serum creatinine prior to LT is one of the simplest ways of identifying patients with chronic parenchymal renal disease. However, serum creatinine is not a very reliable indicator of renal function among patients with cirrhosis because of decreased muscle mass and decreased synthesis of creatinine in these patients. For the same reasons, creatinine based equations for calculating estimated glomerular filtration rate (eGFR) are also unreliable and tend to overestimate the renal function.^{29, 30}

O’Riordan et al. analyzed 368 patients before and after LT using the following variables to predict post-LT chronic renal failure defined as eGFR <30 ml/min: serum creatinine, history of hypertension, degree of proteinuria and the duration of renal impairment. The risk score can be calculated using the following equation:

$$\begin{aligned} \text{Risk of progression to eGFR} < 30 \text{ ml/min at 1 year post-LT} = & -1.8 + (0.001 \times \text{duration of renal impairment in days}) \\ & + (0.64 \times \text{proteinuria in g/24 hr}) + (0.013 \times \text{serum creatinine in } \mu\text{mol/L}) \\ & + (1.5 \text{ if a history of hypertension}) \end{aligned} \quad 27$$

All the variables were determined at pre-LT assessment with the exception of duration of AKI which was determined at the time of transplant assessment or at any point up to the LT. For patients with a score above 2.16, this equation had a high sensitivity (99.2%) and specificity (100%) for predicting post-LT chronic renal failure.²⁷ This study lacked a validation cohort.

Israni and colleagues in their elegant analyses of national data showed that the hazard of ESRD was highest within 6 months of LT and stabilized after 6 months of LT.²⁵ The independent predictors of post-LT ESRD within 6 months of LT were recipient age, history of diabetes, history of malignancy, body mass index (BMI), dialysis in the week prior to LT, serum creatinine and liver donor risk index (DRI).²⁵ There were only 5.6% of patients with history of malignancy, however, and the type, timing and stage (active or remission) of malignancy was not specified. The information on DRI is not readily available all the time because of the missing data for various DRI components (donor age, donor cause of death, donor race, donation after cardiac death, partial vs. split liver, height of donor, local vs. regional vs. national and cold ischemia time³¹). Although this model had a C-statistic of 0.78, the practical utility of this model is not known. This study also examined the predictors

of late ESRD (ESRD after 6 months of LT); however, their outcome of late ESRD was conditional on 6 months ESRD-free survival.²⁵ The predictors of late ESRD were diabetes at LT, hepatitis C, African American race, albumin, bilirubin and creatinine at LT. Furthermore, the late model used the patient characteristics from the time of transplant and did not include the occurrence of AKI in the peri-operative and early post-operative period in the model.

Sharma et al. developed and validated a patient-specific post-LT ESRD risk score called renal risk index (RRI) using national data.²⁸ RRI is a risk calculator that predicts the post-LT ESRD risk based upon recipient factors. RRI was derived from a cohort of 43,514 LT recipients. It consists of 14 recipient risk factors – age at LT, African American race, cholestatic disease, hepatitis C, BMI, pre-LT diabetes, serum creatinine, serum albumin, serum bilirubin, serum sodium, Status-1 listing, re-transplantation, history of transjugular intrahepatic porto-systemic shunt, and pre-LT dialysis - independently associated with new onset post-LT ESRD.²⁵ RRI score represents the relative risk of developing incident post-LT ESRD compared to the reference patient. RRI was stratified into decile based upon the risk of post-LT ESRD. Risk of post-LT ESRD increased with the increase in RRI decile (Figure 4). Increase in RRI decile was also associated with increased post-transplant mortality. RRI can be calculated using a web-based calculator at <https://rri.med.umich.edu> (Figure 5) for post-LT ESRD risk stratification and risk-based management.³²

Peri-operative and Post-LT strategies to attenuate post-LT CKD and ESRD

A recent large single center retrospective study examined the impact of intraoperative dialysis on dialysis-free survival among 155 LTA and 83 SLKT recipients with a mean calculated MELD score of 37. Before LT, 61% were in the intensive care unit, 19% were mechanically ventilated, 43% required vasopressor support, and 80% were on some form of renal replacement therapy at the time of transplantation. The 1-year survival was 80% and 90-day dialysis-free survival was 99%³³. While these results are promising, the role of intraoperative dialysis needs to be further studied prospectively.

Most recipient risk factors of post-LT ESRD such as age, race/ethnicity, history of malignancy, and donor factors are non-modifiable. Optimization of modifiable recipient risk factors such as hepatitis C, diabetes, BMI, pre-transplant renal function and serum sodium in the pre-transplant setting of worsening liver failure is very challenging and difficult because of narrow window of opportunity for LT. Furthermore, approximately, 45–60% of LT recipients experience peri-operative acute renal failure, with 20% to 25% requiring RRT.^{34, 35} This AKI during peri- and postoperative period may serve as second or third hit for the patients with already compromised renal function (Figure 3). Strategies to avoid second and third hits to the kidneys during the peri- and immediate post-operative period may avoid AKI and improve renal outcomes.

There are no standard practice guidelines with respect to CKD care and immunosuppression management among LT recipients. There are no data on referral to nephrology and CKD care coordination among solid organ transplant recipients. A multidisciplinary care model should be implemented at the level of the transplant center partnering with community-

based providers to better serve solid organ transplant recipients. Early intervention and risk factor modification may improve renal outcomes in this unique population.

Immunosuppression

Calcineurin inhibitors (CNI) are known to cause nephrotoxicity and can present as acute and chronic nephrotoxicity. Acute CNI nephrotoxicity, less commonly seen in LT recipients, is reversible with the cessation of CNI therapy. The mechanism is unclear; however, role of endothelin resulting in vasoconstriction of afferent and efferent glomerular arterioles has been implicated.³⁶ Chronic CNI nephrotoxicity is more frequently seen in LT recipients. It is due to irreversible severe arteriolar hyalinosis, glomerulosclerosis and interstitial fibrosis.

Strategies to limit post-LT CNI exposure, such as use of induction immunosuppression with delayed introduction of CNI, have been shown to improve and maintain renal function among those with pre-existing renal dysfunction.^{37–41} More recently, a combination of everolimus and low dose tacrolimus regimen one month after LT has shown promise in preserving renal function one year after LT.⁴⁰ However, the two year data from this registration trial did not show any further improvement in the renal function compared to standard immunosuppression.⁴² Applying these strategies in patients who are at high risk for developing post-LT ESRD along with modification of other risk factors may improve renal outcomes.

Hypertension

Hypertension is a known risk factor for CKD and cardiovascular disease in the post-transplant setting. Prevalence of post-LT hypertension is up to 70% as compared to 10–15% prior to LT.⁴ The majority of patients with cirrhosis before LT have decreased systemic vascular resistance (SVR), low blood pressures and hyper-dynamic circulation due to systemic vasodilation, hepato-renal interaction and activation of renin angiotensin aldosterone system. These changes are reversed after a successful LT. Moreover, immunosuppression medications play a major role in development of hypertension.

Steroid induced hypertension is generally secondary to mineralocorticoid effects but it also increases SVR. CNIs contribute to hypertension via increased sympathetic activity, renal (and systemic) vasoconstriction, renal insufficiency and sodium retention. Multiple studies have shown lower incidence of hypertension with tacrolimus as compared to cyclosporine.⁴³ Sirolimus is not a common cause of hypertension, unlike CNIs. However, it can cause proteinuria or renal dysfunction in a fair proportion of patients.⁴¹

There are no randomized controlled trials in the transplant setting evaluating the comparative effectiveness of various antihypertensive regimens. Due to direct vasodilator effect, calcium channel blockers are the first line of treatment for post-LT hypertension. However, up to 30% of patients may require more than one anti-hypertensive agent. Selective beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blocker and loop diuretics are good second line options.

Diabetes Mellitus

New onset diabetes (NOD) after LT is an important long term complication affecting graft and patient survival. The prevalence of diabetes in pre-LT patient is 10–15% with significant increase after LT. Studies have shown that the majority of NOD occurs within the first six months of LT due to high doses of corticosteroids in addition to other immune suppression and physical inactivity. A fraction of these patients achieve improved glycemic control. However, 20–40% of LT recipients end up having long-term diabetes.⁴⁴ Based on an analysis of more than 15,000 LT recipients in SRTR database, independent risk factors for NOD include recipient age >49 years, African American race, BMI >24, hepatitis C infection, recipient cirrhosis history, donor age >59, diabetic donor and use of corticosteroids at discharge.⁴⁵

Immunosuppression medications, both corticosteroids and CNI play a major role in NOD. Corticosteroids increase the risk of diabetes through decreasing insulin production and peripheral sensitivity and increasing hepatic gluconeogenesis. CNI, both cyclosporine and tacrolimus, can decrease insulin synthesis and secretion via pancreatic beta cell toxicity in addition to causing insulin resistance and hyperinsulinemia. Between the two agents, tacrolimus is associated with higher rates of NOD as compared to cyclosporine [hazard ratio (HR) 1.24, 95% confidence interval: 1.07–1.43].⁴⁵ Among the different immune suppression strategies studied to reduce the risk of NOD, steroid free regimens, use of induction therapy and switching of CNI from tacrolimus to cyclosporine have shown promising results⁴⁶.

LT recipients with long-term diabetes have higher rates of death due to infection, chronic comorbidities such as CKD and cardiovascular disease as well as graft failure due to chronic rejection and late onset hepatic artery thrombosis.^{44, 46} Even patients with transient NOD after LT have increased mortality and graft loss as compared to non-diabetic patients. Goals of management of NOD patients in regards to glycemic control, cardiovascular risk optimization, renal risk, serum lipid profile, ophthalmologic and urinary protein screening should be the same as that of the general population.

Metabolic Syndrome, Dyslipidemia and Obesity

Immunosuppression is the major risk factor for metabolic syndrome, dyslipidemia and obesity. All three can further potentiate the progression of CKD. Metabolic syndrome is common after LT. A study of 252 LT recipients found that 52% had metabolic syndrome following LT, compared with only 5% before LT.⁴⁷ Prevalence of dyslipidemia is 24 to 70% in LT recipients based on different studies and definitions.

Among CNI, cyclosporine is associated with higher rates of hyperlipidemia and hypertriglyceridemia as compared to tacrolimus. The exact reason is unknown but could be related to decreased bile acid synthesis by cyclosporine. Switching from cyclosporine to tacrolimus is associated with improved lipid profile.⁴⁸ Sirolimus and everolimus can cause significant hyperlipidemia specially when used in combination with cyclosporine. Strategies directed towards diet and weight management may improve the metabolic syndrome and obesity. HMG CoA inhibitors are considered as first line agents to treat dyslipidemia

whereas patients with normal cholesterol and isolated hypertriglyceridemia might benefit more from Omega 3 fish oil.

Treatment of Hepatitis C

Hepatitis C has been shown to be an independent risk factor for post-LT ESRD.^{22, 24–26, 28} Direct acting antiviral agents (DAA) have revolutionized the treatment of hepatitis C over the last four years, especially in post-LT setting.^{49–51} Prior to approval of these DAA's, the sustained virological response of antiviral therapy with pegylated interferon and ribavirin varied from 20%–45%.^{52, 53} The drug discontinuation rates were very high because of serious and life threatening adverse effects with 48 weeks of pegylated interferon and ribavirin.⁵³

With the approval of sofosbuvir^{54–57}, simeprevir and ledipasvir^{54–56} and many more DAA's in phase 2 and 3 of drug development^{58, 59}, the myth of interferon-free treatment with superior efficacy and safety is turning into a reality for all genotypes. However, the pharmacokinetics of sofosbuvir in patients with eGFR <30 ml/min are not very well elucidated.

The hepatitis C treatment recommendations after LT are based upon the studies available to date. Table 2 shows the recommended treatment regimen based upon hepatitis C genotype. The regimens for decompensated cirrhosis based upon genotype are also available; however, they are beyond the scope of this review and can be found at www.hcvguidelines.org.

Conclusion

Post-transplant renal dysfunction is one of the most important and common complications experienced by LT recipients leading to increased morbidity and mortality. Major risk factors contributing to post-LT ESRD include recipient factors at LT as well as immunosuppression related side effects. Many of the risk factors that predict CKD/ESRD after LT are associations, and not always causative. Specific risk equations have been developed to identify patients at risk for post-LT ESRD. Modification of risk factors before LT is challenging because of narrow window of opportunity.

There is a need for implementation of multidisciplinary approach at the level of transplant centers partnering with community physicians to provide CKD care to solid organ transplant recipients. Identification of patients' high risk for developing ESRD using RRI, early intervention directed at risk factor modification and immunosuppression management with minimization of CNI in conjunction with agents such as mycophenolates and everolimus may improve renal outcomes in this unique population.

Acknowledgments

Dr. Sharma is supported by National Institutes of Health (NIH) grant DK-088946.

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Clinical summary bullet points

- Serum creatinine is an over-weighted component of model for end-stage liver disease (MELD) score
- MELD score cannot distinguish between chronic kidney disease (CKD) and acute kidney injury secondary to hepatorenal syndrome
- The relative risk of new onset post-LT end stage renal disease (ESRD) has increased by 15% in the MELD era.
- Post-LT advance CKD and ESRD are associated with high mortality, morbidity and resource utilization
- Optimization of modifiable risk factors of CKD and ESRD may improve outcomes

Figure 1.

Incidence of simultaneous liver and kidney transplant (SLKT): 2000–2014

The incidence of SLKT has increased significantly after implementation of MELD-based liver allocation policy in February of 2002. The incidence of SLKT was less than 3% in the pre-MELD era. This rate has increased to approximately 8% since 2002 (MELD era)

Figure 2.

Risk of post-LT end stage renal disease by year of liver transplantation.

This figure displays trends in covariate-adjusted post-LT ESRD incidence by calendar year of LT. Before 2002 (pre-MELD era), rates of new-onset post-LT ESRD decreased significantly by 5.1% per year ($HR=0.949$; 95% confidence interval 0.924–0.975; $p < 0.0001$). However, the trend sharply reversed in 2002 (MELD era), with ESRD incidence increasing by 7.6% per year after year 2002 ($p < 0.0001$). The risk of post-LT ESRD is increasing by was decreasing in pre-MELD era. Adapted from Sharma et al., AJT 2011;11: 2372–2378 with permission from Wiley.

Figure 3.

Conceptual model for post-LT chronic kidney disease

This figure displays the risk factors and various hits from pre-transplant to post-transplant period resulting in kidney injury and the burden of chronic kidney disease.

Cumulative Incidence of Post-LT ESRD: Stratified by RRI

Sharma et al. 2013, JASN

Figure 4.
Cumulative incidence of post-LT end stage renal disease stratified by renal risk index.
Adapted from Sharma et al., JASN 2013; 24:2045–52 with permission from JASN.

Predicting ESRD after LT: Renal Risk Index

- Renal risk Index (RRI): 14 recipient characters
- RRI Calculator: <http://rri.med.umich.edu>

Reference: Sharma P, Goodrich NP, Schaubel DE, Guidinger MK, Merion RM. Patient Specific Prediction of End Stage Renal Disease Risk after Liver Transplantation. *Journal of American Society of Nephrology*, 2013, doi:10.1681/ASN.2013040436

Figure 5.

Renal Risk Index (RRI) Calculator

This figure displays the RRI calculator website and predicted cumulative incidence of post-LT ESRD based upon RRI score and RRI decile. (<http://rri.med.umich.edu>)

Table 1

Types of Acute Kidney Injury in LT Candidates

Types of Acute Kidney Injury in LT Candidates
Hypovolemia induced Pre-renal <ul style="list-style-type: none">• GI bleed• Infection• Diarrhea• Systemic hypoperfusion
Hepatorenal syndrome <ul style="list-style-type: none">• Pre-renal physiology
Parenchymal disease <ul style="list-style-type: none">• Glomerulonephritis• Acute tubular necrosis• Interstitial nephritis
Drug induced <ul style="list-style-type: none">• NSAIDS• Contrast-induced
Post-obstructive: rare

Table 2

Interferon Free Treatment Regimen for Post-LT Hepatitis C Recurrence*

	Treatment naïve/Treatment experienced*
Genotype 1 and 4 No cirrhosis/Compensated cirrhosis <ul style="list-style-type: none"> Regimen Duration 	Daily fixed dose ledipasvir (90 mg)/sofosbuvir (400 mg) +weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) 12 weeks
Genotype 2 and 3 No cirrhosis/Compensated cirrhosis <ul style="list-style-type: none"> Regimen Duration 	Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) 24 weeks

* Full details of treatment regimen for patients with decompensated cirrhosis, ribavirin intolerance and alternative regimen for genotype 1 can be found at www.hcvguidelines.org