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Minireview

Protecting the Kidney in Liver Transplant Recipients: *Practice-Based Recommendations From the American Society of Transplantation Liver and Intestine Community of Practice*

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Both acute and chronic kidney disease are common after liver transplantation and result in significant morbidity and mortality. The introduction of the Model for End-stage Liver Disease score has directly correlated with an increased prevalence of perioperative renal dysfunction and the number of simultaneous liver–kidney transplantations performed. Kidney dysfunction in this population is typically multifactorial and related to preexisting conditions, pretransplantation renal injury, perioperative events, and posttransplantation nephrotoxic immunosuppressive therapies. The management of kidney disease after liver transplantation is challenging, as by the time the serum creatinine level is significantly elevated, few interventions affect the course of progression. Also, immunological factors such as antibody-mediated kidney rejection have become of greater interest given the rising liver–kidney transplant population. Therefore, this review, assembled by experts in the field and endorsed by the American Society of Transplantation Liver and Intestine Community of Practice, provides a critical assessment of measures of renal function and interventions aimed at preserving renal function early and late after liver and simultaneous liver–kidney transplantation. Key points and practice-based recommendations for the prevention and management of kidney injury in this population are provided to offer guidance for clinicians and identify gaps in knowledge for future investigations.

Abbreviations: AR, acute rejection; BAS, basiliximab; BELA, belatacept; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CsA, cyclosporine; CS, corticosteroids; DAC, daclizumab; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EVR, everolimus; FDA, Food and Drug Administration; GFR, glomerular filtration rate; HES, hydroxyethyl starch; KDIGO, Kidney Disease Improving Global Outcomes; LT, liver transplantation; MDRD, Modification of Diet in Renal Disease; MELD, Model for End-stage Liver Disease; mGFR, measured glomerular filtration rate; MMF, mycophenolate mofetil; mTOR-I, molecular target of rapamycin inhibitor; NAC, *N*-acetylcysteine; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine; SLKT, simultaneous liver–kidney transplantation; SRL, sirolimus; TAC, tacrolimus

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Introduction

The burden of end-stage renal disease (ESRD) following liver transplantation (LT) has substantially increased in the Model for End-stage Liver Disease (MELD) era (1,2). In combination with pretransplantation renal injury, perioperative insults can result in acute kidney injury (AKI) that is associated with increased short-term mortality and a higher incidence of ESRD (3–7). The cumulative incidence of stage $\geq$ 4 chronic kidney disease (CKD) (<30 mL/min) within 5 years of LT is approximately 15–25%, depending on whether estimated or measured glomerular filtration rate (eGFR or mGFR) is used (8). Subjects at higher risk of ESRD are also at a higher risk of overall mortality (58% 5-year survival) (9). Lesser degrees of CKD (stage 2–3) occur in approximately 50–60% of LT recipients by 5 years. However, most of these percentages

come from pre-MELD era data, and the current risk of ESRD may now be significantly higher (1,6,10–15). Even with these data, it is still difficult to discern the relative contribution of preexisting comorbidities, unrecognized intrinsic renal disease, perioperative events, and immunosuppression to the overall burden renal dysfunction following LT (16,17). This review will critically analyze the diagnosis, monitoring, and protection of renal function both early and late after LT. All authors reviewed the available data and practice-based recommendations were graded according to the GRADE system (Table S1) (18).

Assessment of Renal Function After LT

The current standard approach is to use blood-based equations to approximate mGFR in LT recipients (Table 1). However, the use of creatinine-based equations may lead to both overestimation and underestimation of renal function, especially in malnourished recipients with low GFR (8). Furthermore, chromogens such as bilirubin at high levels may interfere with serum creatinine measurements by the traditional Jaffe method, although this issue has more clinical relevance in pre-LT patients with high MELD scores (19). In a meta-analysis of solid organ transplant recipients (35% liver), the CKD-EPI-creatinine and the MDRD-4 equations, while imperfect, were the most accurate compared with mGFR (20). Rather than an absolute value, an acute change in eGFR may provide the most prognostic value in AKI.

Cystatin-C is a nonglycosylated low molecular weight basic protein produced at a constant rate by nucleated cells and less influenced by factors that may influence serum creatinine (SCr), such as muscle mass and gender. Cystatin-based eGFR is associated with improved mortality risk stratification in the general population and better renal function assessment in cirrhotic individuals (21,22). Thus, given the limitations of creatinine-based eGFR measures, GFR may be better estimated by using cystatin-C–based equations (cystatin-C, CKD-EPI-CystC) or both (CKD-EPI-Cr-CystC). Among LT recipients, cystatin-C–based equations had somewhat superior performance (r^2 = 0.78–0.83) in estimating mGFR compared with creatinine-based estimations (MDRD-4, MDRD-6, CKD-EPI-Cr, r^2 = 0.76–0.77) (15). However, it still underestimated

Table 1: Common methods for measuring glomerular filtration rates

Measure	Formula	Calculation
Estimated		
Creatinine	MDRD4	$175 \times (Scr)^{-1.154} \times (age)^{-0.203} \times (0.742$ if female$) \times (1.212$ if African American$)$
	MDRD6	$198 \times [SCr\ (mg/dL)]^{-0.858} \times [age]^{-0.1678} \times [0.822$ if patient is female$] \times [1.178$ if patient is black$] \times [$serum urea nitrogen concentration $(mg/dL)]^{-0.293} \times [$urine urea nitrogen excretion $(g/d)]^{0.249}$
	2009 CKD-EPI creatinine equation	$141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] where: SCr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.
Cystatin C	2012 CKD-EPI Cystatin C equation	$133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [$\times 0.932$ if female] where: SCysC is serum cystatin C (in mg/L), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.
	2012 CKD-EPI creatinine–cystatin C equation	$135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age}$ [$\times 0.969$ if female] [$\times 1.08$ if black] where: SCr is serum creatinine (in mg/dL), SCysC is serum cystatin C (in mg/L), κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, min(SCr/k, 1) indicates the minimum of SCr/k or 1, and max(SCr/k, 1) indicates the maximum of SCr/k or 1; min(SCysC/0.8, 1) indicates the minimum of SCysC/0.8 or 1 and max(SCysC/0.8, 1) indicates the maximum of SCysC/0.8 or 1.
Radioisotope		
Measured		
Iothalamate		Iothalamate clearance (volume of plasma cleared of the marker per unit time): UV/P where: U = urinary concentration of the substance, V = urine flow rate (urinary volume), P = average plasma concentration)
Iohexol		Blood specimens are obtained after subcutaneous injection of non-radiolabeled iohexol and results are analyzed via liquid chromatography–tandem mass spectrometry

S_{Cr}, serum creatinine; SCys, serum cystatin C.

mGFR by approximately 12%, particularly in low-GFR groups.

Direct measurements of GFR represent the gold standard to assess renal function, although they are onerous to perform, costly, and inconvenient for repeated testing (23–25). Measurement relies on clearance of exogenous markers (e.g. inulin, iohexol, and iothalamate) that are filtered without secretion or reabsorption by the renal tubule and exclusively eliminated by the kidneys unbound to proteins. Filtration and clearance of tagged radioisotopes can also be used to estimate GFR, particularly among simultaneous liver–kidney transplantation (SLKT) recipients to assess the relative contribution of native versus transplanted kidneys to overall renal function (26,27). However, these tests involve radiation exposure and are expensive and impractical for serial monitoring.

Key Points and Recommendations

- Of the creatinine-based equations, CKD-EPI-creatinine and the MDRD-4 study equations provide the most accurate estimate of mGFR after liver transplantation (1C).
- Of all blood-based estimates of GFR, equations with cystatin-C are the most accurate in liver transplant recipients (2C).
- Direct measures of GFR are the most accurate tests available but are expensive, labor-intensive and impractical in clinical monitoring (1C).

Nephroprotective Strategies Based on the Liver Transplantation Time Period

Perioperative renal protection

Real-time AKI diagnosis and renal protection during the LT perioperative period remain significant challenges. Various intraoperative events such as hemodynamic instability, volume depletion, and bleeding have been associated with postoperative AKI (3,28). Nephroprotective strategies during LT are sparse and follow generally accepted surgical practice guidelines, such as maintenance of intravascular volume and mean arterial pressure. In prospective randomized trials, *N*-acetylcysteine, dopamine, and fenoldopam have demonstrated inconsistent nephroprotective effects (Table 2) (29–31). Two recent retrospective studies demonstrated that hydroxyethyl starch ([HES] 130/0.4) and chloride-liberal fluid protocols are actually associated with an increased risk for postoperative AKI (32,33), in contrast to findings from an earlier study (34). Of note, the US Food and Drug Administration (FDA) issued a black box warning for HES use in critically ill patients, which includes LT recipients. In addition, pathological tubular changes related to early HES administration have been seen in LT recipients with late CKD (35). Surgical technique involving the approach to the IVC anastomosis may be important, but the data are mixed in terms of whether piggyback or bicaval replacement with or without veno–veno bypass affect AKI development (36,37). Ultimately, no data are currently available to suggest a perioperative intervention that reliably demonstrates renal protection, as described in a recent Cochrane review (38). These negative findings may in part be due to study methodology, heterogeneous populations, lack of randomized trials, and evolving AKI definitions.

Despite that lack of substantial data to support perioperative renal protective strategies, there have been recent data supporting the role of novel biomarkers as perioperative surrogates to detect early AKI before significant deterioration of renal function (39). The most commonly studied biomarker in LT-associated AKI is neutrophil gelatinase-associated lipocalin (NGAL) (36,40–43). However, most of the data regarding biomarkers in detecting early AKI are based on investigative research and have not yet realized sufficient positive data to become predictive in the clinical arena. Additional proteins that have been validated immediately before, during, or late after LT have been shown to correlate with AKI and CKD in the LT setting, but their clinical application is in its infancy. Future investigations as to the relevance and use of these biomarkers are currently in the pipeline.

Key Points and Recommendations

- There is no high-quality evidence supporting any renal protective intraoperative interventions (1C).
- Resuscitation with HES and chloride-liberal fluids should be avoided in liver transplant recipients (1C).
- There are promising biomarkers of renal injury available for study for detecting early AKI, which may ultimately lead to targeted strategies to avert significant postoperative renal injury and CKD (2C).

Renal protection early (0–12 months) after LT

Deterioration in renal function after LT is multifactorial (44). Simple calculations of renal function at the time of transplantation may provide a reasonable accurate assessment of the long-term mortality and ESRD risk and may help guide such modifications of immunosuppression protocols, such as calcineurin inhibitor (CNI) therapies (9,45). CNI-induced nephrotoxicity contributes to short- and long-term renal deterioration, presumably mediated by renal arteriolar vasoconstriction (46). Within the first few weeks, these effects can be reversed or minimized with reduced exposure to CNI agents. Another early complication is thrombotic microangiopathy, which occurs in approximately 4% of LT recipients and may be caused by CNI therapy (particularly tacrolimus) in the setting of a reduced von Willebrand factor–cleaving protease (ADAMTS13) (47,48). Short- and long-term survival is clearly diminished in LT recipients with thrombotic microangiopathy, and

Table 2: Randomized trials of perioperative renal protection in liver transplant recipients

Author	N	Study design	Major findings
Zacharias (38)	4378	Cochrane database systematic review: Only randomized controlled trials – 72 studies included in analysis	• No reliable evidence that interventions during surgery can provide protection from renal injury • Methodology of trials and definitions for renal failure/AKI not consistent and at times of low quality
Mukhtar (34)	40	Prospective randomized (living donor transplantation): 6% HES 130/0.4 versus albumin 5% intraoperatively and first 4 post-LT days	• No difference in CrCl in both groups • Cystatin C levels trended toward higher in the HES group
Hilmi (29)	100	Prospective randomized double-blind placebo-controlled: 140 mg/kg of NAC bolus after induction anesthesia followed by 70 mg/kg q4h × 12 doses versus 0.9% IV saline given similarly	• No difference in AKI between NAC and placebo at day 14
Grande (37)	77	Prospective randomized nonblinded: Intraoperative veno–veno bypass versus no bypass	• No statistical difference was found in renal function or need for hemodialysis
Della Rocca (30)	43	Prospective randomized nonblinded: Fenoldopam 0.1 $\mu g \cdot kg^{-1}$ min^{-1} versus dopamine 2 $\mu g \cdot kg^{-1}$ during and until 48 h post-LT	• Significantly less AKI and requirement for diuretics at day 3 post-LT in fenoldepam group
Biancofiore (31)	140	Prospective randomized nonblinded: Fenoldopam 0.1 $\mu g \cdot kg^{-1}$ min^{-1} versus dopamine 3 $\mu g \cdot kg^{-1}$ versus placebo during and until 96 h post-LT	• No change in CrCl with fenoldopam but significantly less drop in CrCl with dopamine versus placebo

AKI, acute kidney injury; CrCL, creatinine clearance; HES, hydroxyethyl starch; IV, intravenous; LT, liver transplantation; NAC, *N*-acetylcysteine.

management includes conversion to alternate CNI therapy (cyclosporine [CsA]) or even CNI withdrawal if severe and/or nonresponsive.

In the immediate postoperative phase (< 1 month), one approach to sparing renal function has been to administer short-term induction therapy (polyclonal or monoclonal antibodies) with delayed CNI introduction (Table 3). This approach avoids the synergistic vasoconstrictive effects of CNI with known perioperative risk factors associated with AKI (49). Two studies have demonstrated a renal benefit not only of delayed TAC introduction but also of lower maintenance TAC levels. The first was a multicenter, randomized trial comparing daclizumab (DAC) + mycophenolate mofetil (MMF) + corticosteroids (CS) + delayed low-dose TAC (target tacrolimus trough level 4–8 ng/mL, starting day 4–6) versus MMF + CS + standard TAC dosing (target trough level 10–15 ng/mL for first month, thereafter 4–8 ng/mL) (50). Statistically significant differences in median eGFR were found in favor of the DAC + delayed low-dose TAC at 1 and 6 months post-LT, with no difference in AR (23.2% versus 27.7%). This was validated in a European multicenter, prospective, randomized, open-label trial, of standard dose TAC (target trough levels > 10 ng/mL) + CS versus MMF, reduced-dose TAC (target trough levels ≤ 8 ng/mL) + CS versus DAC induction + MMF + reduced-dose TAC (delayed until day 5) + CS (51). The decrease in eGFR was significantly less in the DAC + delayed/reduced TAC + MMF compared with standard TAC. In addition, there was less AR in DAC + delayed/reduced TAC + MMF versus reduced TAC + MMF versus standard TAC (19.0% versus 29.2% versus 27.6%). In contrast, another study showed similar AR rates (17.5% versus 18.75%) but no renal benefit of DAC + delayed TAC versus standard TAC (52), stressing the importance of both delaying TAC and aiming for lower target trough levels (51). The strategy of using MMF to minimize CNI without induction therapy was tested in a multicenter prospective study that randomized *de novo* LT patients to standard TAC or reduced TAC + MMF (53). One-year eGFR was higher in the reduced versus standard TAC group, with a lower risk of AR (30% versus 46%).

Another immediate post-LT nephroprotective regimen using the costimulation blockade agent belatacept (BELA) and avoidance of CNI therapy was evaluated in a multicenter trial (54). This study enrolled 250 LT patients who were randomized into five groups: three BELA-containing groups (BAS [basiliximab] + BELA more intensive + MMF; BELA more intensive + MMF; BELA less intensive + MMF); TAC + MMF; TAC alone (trough 6–12 ng/mL for both TAC groups). In the intent-to-treat analysis, the mean eGFR was 89–93 mL/min/1.73 m^2 in the BELA groups and 71–75 mL/min/1.73 m^2 in the TAC groups by month 12, validating the benefit of a CNI-free regimen. However, all BELA groups experienced higher rates of AR (44%, 33%, 33% versus 13% and 30%,

Table 3: Randomized trials of calcineurin-inhibitor minimization within the first year post-liver transplantation

Author	N	Study design	Major findings
Early (< 1 month) CNI minimization studies			
Yoshida (50)	148	Immediate post-LT: DAC + reduced TAC delayed 6 days versus standard TAC	• Improved GFR in reduced, delayed TAC • No difference in AR rates
Neuberger (51)	525	Immediate post-LT: standard TAC versus reduced-dose TAC + MMF versus DAC + reduced TAC delayed 5 days plus MMF	• Significantly less drop in GFR in reduced, delayed TAC • Less AR in reduced, delayed TAC
Calmus (52)	199	Immediate post-LT: DAC + standard TAC delayed 5 days versus standard TAC	• No difference in month 12 SCr > 1.43 mg/dL • No difference in AR rates
Boudjema (53)	195	Immediate post-LT: reduced TAC + MMF versus standard TAC	• Significantly better GFR at month 12 in reduced TAC + MMF • Significantly less AR in reduced TAC + MMF
Klintmalm (54)	250	Immediate post-LT: BAS + BELA more intensive + MMF versus BELA more intensive + MMF versus BELA less intensive + MMF versus TAC + MMF versus TAC	• Significantly better month 12 GFR in all BELA groups • Significantly higher AR rates in all BELA groups • Significantly diminished month 12 survival in BELA less intensive + MMF
Asrani (55)	222	Immediate post-LT: standard TAC versus reduced TAC + SRL	• No difference in GFR • Graft loss, death, vascular thrombosis, and sepsis higher in reduced TAC + SRL
Delayed (1–12 month) CNI minimization studies			
Teperman (56)	293	Week 4–12 post-LT: CNI + MMF versus CNI to SRL + MMF	• Significant month 12 eGFR increase in SRL + MMF • High side effects and discontinuation in SRL + MMF • Higher rejection rate in SRL + MMF
De Simone (57) Saliba (58) Fischer (59)	719	Week 4 post-LT: TAC elimination + EVR versus reduced TAC + EVR versus standard TAC	• Month 12/24/36 eGFR superior for reduced TAC + EVR • Reduced incidence and severity of AR in reduced TAC + EVR • TAC elimination arm stopped due to high AR rates
Fischer (60)	203	Week 4 post-LT: BAS induction for all; CNI to EVR versus CNI continuation	• Significant improvement in GFR with EVR conversion • No difference in AR rates
Abdelmalek (70)	607	Month 6–144: CNI to SRL versus CNI continuation	• No improvement in GFR with SRL conversion • Higher AR rates with SRL conversion

AR, acute rejection; BAS, basiliximab; BELA, belatacept; CNI, calcineurin inhibitor; DAC, daclizumab; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; EVR, everolimus; eGFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTOR-I, molecular target of rapamycin inhibitor; NAC, *N*-acetylcysteine; SRL, sirolimus; TAC, tacrolimus.

respectively). In addition, the study was halted due to an unexplained higher death rate in the BELA groups during follow-up, leading to a FDA black box warning for use in LT recipients.

Development of the mammalian target of rapamycin inhibitors (mTOR-Is) has generated considerable interest, especially in view of their potential to reduce or eliminate CNIs and the associated renal toxicity. The use of sirolimus (SRL) in the immediate postoperative phase (< 1 month) in *de novo* LT was assessed in a phase 2 prospective randomized open-label active-controlled trial (56). Patients were randomized to conventional-dose TAC (trough 7–15 ng/mL) or SRL (loading dose 15 mg, initial dose 5 mg titrated to a trough of 4–11 ng/mL) + reduced-dose TAC (trough 3–7 ng/mL). There was no

observed nephroprotective benefit or difference in AR (30.4% versus 26.4%), and the incidences of graft loss (26.4% versus 12.5%), death (20% versus 8%), hepatic artery/portal vein thrombosis (8% versus 3%), and sepsis (20.4% versus 7.2%) were significantly higher in the SRL + TAC arm. As a result, SRL carries a FDA black box warning for use in *de novo* LT recipients.

Despite concerns for immediate post-LT use of mTOR-Is, a number of studies have tested their use later (1–12 months) after LT when their safety profile may be more favorable. In the multicenter Spare the Nephron Liver trial, subjects maintained on CNI and MMF were prospectively randomized 4–12 weeks after LT to be converted from CNI to SRL (trough SRL 5–10 ng/mL) versus maintenance CNI (trough goals: CsA 100–250 ng/mL or TAC 3–10 ng/mL), both in conjunction with continued MMF therapy (2–3 g/d) (56). The SRL + MMF group demonstrated better renal function improvement from baseline than CNI + MMF, although AR (12.2% versus 4.1%) and rates of discontinuation for adverse events (36% versus 27%) were significantly greater. The pivotal phase 3 H2304 trial evaluated everolimus (EVR) in combination with reduced TAC 1 month post-LT, with an arm of later TAC withdrawal, compared with standard-exposure TAC (57–59). Everolimus (trough EVR 3–8 ng/mL) + reduced-exposure TAC (trough TAC 3–5 ng/mL) resulted in less AR episodes (4.1% versus 10.7%) and renal function was significantly improved out to month 36 versus the standard TAC group (trough TAC 6–10 ng/mL). These findings led to FDA approval for use of reduced-dose TAC + EVR > 1 month from LT. However, the complete TAC withdrawal arm was terminated early due to high AR rates, and drug discontinuation for adverse events occurred more often in the EVR + reduced TAC (25.7%) versus TAC controls (14.1%). The PROTECT study was a multicenter, prospective, open-label trial in which LT patients given initial BAS induction were randomized at 4 weeks post-LT to start EVR (trough 5–12 ng/mL) and taper off CNI therapy or continue their current CNI-based regimen (trough TAC 5–12 ng/mL) (60). Although the Cockroff–Gault CrCl formula revealed no significant difference between treatments, eGFR showed superiority for EVR using the MDRD-4 formula (+ 7.8 mL/min/1.73 m^2; $p = 0.02$). Rates of mortality, rejection (17.7% versus 15.3%), and efficacy failure were similar between the two study groups. Importantly, a 24-month extension showed continued renal benefit of EVR versus CNI therapy (61).

Key Points and Recommendations

- Delay and reduction of CNI exposure may lessen or protect against perioperative AKI but typically requires antibody induction (2C).
- CNI therapy is typically required to prevent rejection in the first postoperative year, but can be reduced in this time period to improve renal function (1A).
- Long-term success at renal function maintenance can be achieved by early (1–12 months post-LT) CNI reduction, typically in combination with adjunctive non-nephrotoxic immunosuppressive agents (1A).
- An FDA black box warning exists for the use of sirolimus and belatacept in LT recipients due to an increased risk of mortality (1A).

Renal protection late (>12 months) after LT

Despite evidence of using mTOR-Is and MMF early after LT to minimize CNI nephrotoxicity, this strategy does not seem to apply as well later after LT (62–69). The trials examining these late renal-sparing regimens to date are either prospective uncontrolled trials, controlled trials with small sample sizes or retrospective observational studies. There was a large prospective open-label randomized trial that evaluated late conversion from CNI to SRL for renal function preservation (Tables 3 and 4) (70). Patients who had been maintained on CNI for 6–144 months were randomized 2:1 to conversion from CNI to SRL (loading dose 10–15 mg, trough SRL 8–16 ng/mL) versus CNI continuation (target troughs CsA 50–250 ng/mL, TAC 3–10 ng/mL) for up to 6 years. The SRL conversion group had a higher rate of AR (6.4% versus 1.9%) and discontinuations mainly for adverse events or side effects (49.9% versus 5.7%), without overall GFR improvement. These results were likely due to a substantial proportion of patients with extended CNI exposure (> 1 year) prior to SRL conversion.

A number of studies examined the late use of EVR with or without low-dose CNI (63–65,68). De Simone et al randomized patients (eGFR 20–60 mL/min) who underwent LT 1–5 years before to either EVR (trough 3–8 ng/mL with low-dose CNI; 6–12 ng/mL without CNI) versus standard CNI (no CNI trough specified) for 6 months (Table 4) (65). Despite identical rejection rates (1.4%), it failed to achieve the primary end point of 8 mL/min difference in eGFR. In a retrospective multicenter study of conversion from CNI to EVR after a median of 3 years post-LT, Saliba et al showed a statistically significant but clinically marginal improvement in eGFR (4 mL/min) after 12 months with an associated low (<2%) incidence of rejection and 13% EVR discontinuation rate (69). Another multicenter retrospective study examined the efficacy of EVR conversion with specific indications such as renal dysfunction (32.6%), hepatocellular carcinoma (30.2%), and *de novo* malignancy (29.7%) (63). Patients with renal dysfunction converted early after LT to EVR demonstrated an eGFR increase of 6.8 mL/min/1.73 m^2 ($p < 0.01$) at 12 months postconversion, while patients converted > 1 year post-LT had no GFR change. Also, a significant percentage of patients (30.2%) discontinued

Table 4: Randomized trials of calcineurin inhibitor (CNI) minimization after the first year post-liver transplantation

Author	N	Study design	Major findings
Abdelmalek (70)	607	CNI to SRL versus CNI Time from LT to enrollment: 6-144 months	• No improvement in GFR with SRL conversion • Higher AR rates with SRL conversion
De Simone (65)	145	EVR + low-dose CNI/CNI elimination versus standard-dose CNI × 6 months, GFR 20–60 at enrollment Time from LT to enrollment: 12–60 months	• No difference in eGFR or AR in both groups
Pageaux (67)	56	MMF + low-dose CNI versus standard CNI for chronic renal failure Time from LT to enrollment: 1 year post-LT	• Significant improvement in eGFR in MMF + low-dose CNI at 1 year • No AR in either group
Beckebaum (62)	90	MMF + low-dose CNI versus standard CNI for SCr > 1.2 mg/dL Time from LT to enrollment: 1 year post-LT	• Significant improvement in eGFR in MMF + low-dose CNI at 1 year • No AR in either group

CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EVR, everolimus; AR, acute rejection; MMF, mycophenolate mofetil; SCr, serum creatinine; SRL, sirolimus.

EVR due to intolerability. Finally, a small study demonstrated improvement in eGFR in late (mean 62 months) LT recipients undergoing CNI withdrawal in favor of EVR for renal dysfunction. However, 36% developed *de novo* proteinuria (64).

The efficacy of late conversion to MMF monotherapy or in conjunction with low-dose CNI has also been studied (Table 4). Pageaux et al randomized LT recipients with CKD after 1 year post-LT to either MMF (2–3 g/d) with 50% CNI reduction or CNI alone (up to 25% reduction allowable) (67). In the MMF group, there was a significant increase in GFR and no rejection occurred in either group. Beckebaum et al randomized 90 LT recipients ≥ 1 year post-LT with an SCr ≥ 1.2 mg/dL to either MMF (2 g/d) + low-dose CNI (target trough CsA 25–50 ng/mL, TAC 2–4 ng/mL) or standard CNI regimen without dose modifications (62). There was significant improvement in eGFR over a 1-year follow-up period in the MMF and low-dose CNI arm, without episodes of rejection. Furthermore, two other observational studies demonstrated significant GFR increases with conversion from standard CNI to reduced-dose CNI + MMF without adverse events (66,69). The main benefit of this CNI reduction strategy was seen in applying this regimen within 2 years of LT. Finally, a recent systematic review summarized the data on complete CNI withdrawal in favor of MMF in regard to renal dysfunction (71). Five trials reported significantly higher risks of AR (relative risk 4.96, 95% confidence interval 1.75–14), without graft loss or death, following full MMF conversion (67,69,71–73). However, GFR improved by a mean of 8.3 mL/min for those given MMF in combination with CNI reduction or elimination, even with GFR < 30 mL/min.

Key Points and Recommendations

- There is no substantial evidence that reduction or elimination of CNI therapy in favor of mTOR-Is improves renal function when performed > 1 year post-LT (2C).
- There is evidence that MMF and concurrent reduction in CNI therapy result in modest improvement of renal function when performed > 1 year post-LT (2B).

General Prevention and Management of Renal Dysfunction in LT Recipients

Beyond studies that examine nephroprotective immunosuppressive strategies, little data specifically address the general prevention and treatment of CKD in the LT population. Clinicians therefore must extrapolate best nephrology practices from both nontransplant and kidney transplant CKD patients to LT recipients, recognizing that the validity of these principles is solely based on good evidence in these populations. Highlighted recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines pertinent to LT recipients are provided in Table 5 (74). To best understand and manage the trajectory of GFR decline, renal assessment should be performed at least annually by eGFR or mGFR and albuminuria (or proteinuria) measures, with guidelines for nephrology referral as outlined in Table 5.

Key elements to CKD management are control of diabetes and hypertension, prevalent in up to 30% and 70% of LT recipients, respectively, with attention to proteinuria. To date, there is insufficient evidence to

Table 5: Key recommendations from Kidney Disease Improving Global Outcomes (KDIGO) regarding management of chronic kidney disease (CKD), relevant to liver transplant recipients

Disease/ Complication	KDIGO Recommendation (Grade) - Native CKD
Hypertension	All adults with CKD and urine albumin excretion < 30 mg/24 h (or equivalent) whose office blood pressure (BP) is consistently > 140 mmHg systolic or > 90 mmHg diastolic be treated with BP-lowering drugs with the goal of ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic (1B) All adults with CKD and urine albumin excretion ≥ 30 mg/24 h (or equivalent) whose office BP is consistently > 130 mmHg systolic or > 80 mmHg diastolic be treated with BP-lowering drugs with the goal of ≤ 130 mmHg systolic and ≤ 80 mmHg diastolic (2D) Angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACE-I) therapy should be used in both diabetic and nondiabetic adults with CKD and urine albumin excretion > 300 mg/24 h (or equivalent) (1B) ARB or ACE-I therapy should be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 h (or equivalent) (2D)
Diet	Lower salt intake to < 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated (1C) Lower protein intake to 0.8 g/kg/d in adults with diabetes (2C) or without diabetes (2B) and glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 and suggest avoiding high protein intake (> 1.3 g/kg/d) in adults with CKD at risk of progression (2C). Avoid low protein intake in patients with malnutrition or at risk for malnutrition (1C)
Acidosis	In patients with CKD and serum bicarbonate concentrations < 22 mmol/L, oral bicarbonate supplementation can be given to maintain serum bicarbonate within the normal range, unless contraindicated (2B)
Diagnostic imaging	All patients with GFR < 60 mL/min/1.73 m^2 undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the KDIGO Clinical Practice Guideline for acute kidney injury (AKI) including: • Avoidance of high-osmolar agents (1B) • Use of lowest possible radiocontrast dose (Not Graded) • Withdrawal of potentially nephrotoxic agents before and after the procedure (1C) • Adequate hydration with saline before, during, and after the procedure (1A) • Measurement of GFR 48–96 h after the procedure (1C) Avoid gadolinium-containing contrast media in people with GFR < 15 mL/min/1.73 m^2 unless there is no alternative appropriate test (1B) People with GFR < 30 mL/min/1.73 m^2 who require gadolinium-containing contrast media should be preferentially offered a macrocyclic chelate preparation (2B)
Referral to nephrology	Referral to specialist kidney care services for people with CKD in the following (1B): • AKI or abrupt sustained fall in GFR • GFR <30 mL/min/1.73 m^2 • Consistent significant albuminuria (albumin:creatinine ratio ≥ 300 mg/g [≥30 mg/mmol] or albumin excretion rate ≥300 mg/24 h, equivalent to protein:creatinine ratio ≥ 500 mg/g [≥ 50 mg/mmol] or protein excretion rate ≥ 500 mg/24 h) • Progression of CKD (drop in eGFR from baseline by 25% or a sustained decline in eGFR of > 5 mL/min/1.73 m^2/year) • Urinary red cell casts or red blood cells > 20 per high-power field that is sustained and not readily explained • CKD and hypertension refractory to treatment with four or more antihypertensive agents • Persistent abnormalities of serum potassium • Recurrent or extensive nephrolithiasis • Hereditary kidney disease

recommend a particular class of antihypertensives for LT recipients (75). In native CKD with proteinuria (> 1000 mg/d), agents that inhibit the renin-angiotensin-aldosterone system (RAAS) are considered first-line (76). There is general agreement that blood pressure goals for patients with CKD should be < 140/90 mmHg in the absence of proteinuria and < 130/80 mmHg in the presence of proteinuria, with a proteinuria goal < 1000 mg/d (77). While RAAS agents appear to be safe and effective after LT, calcium channel blockers have been proposed as first-line agents to treat hypertension due to the mechanistic advantage of blocking CNI-induced vasoconstriction (78–80).

Dietary interventions may assist in slowing the progression of CKD. Salt intake should be reduced to <2 g of sodium/day to improve blood pressure control, proteinuria, and GFR (81). Medications, such as RAAS agents, lose efficacy in patients on high-salt diets. Other less-substantiated interventions are the avoidance of high protein intake (> 1.3 g/kg/d) in patients at risk of CKD and lowering protein intake to 0.8 g/kg/d in patients

with GFR < 30 mL/min/1.73 m^2 (82,83). However, there is no clear evidence for low protein intake in LT recipients and this intervention may be contraindicated in malnourished patients or those at risk for malnutrition. Use of oral bicarbonate for acidosis (bicarbonate < 22 mmol/L) has been shown in small studies to slow CKD progression (84). However, these data must be balanced by the advantages of a low salt diet and the possible increase in fluid retention and hypertension with oral bicarbonate solutions with sodium components.

Patients with CKD who are receiving CNI therapy are particularly susceptible to hemodynamic insults and at higher AKI risk with exposure to nephrotoxins such as aminoglycosides, amphotericin B, nonsteroidal anti-inflammatory drugs, and radiocontrast. When possible, reducing or holding CNI therapy before and after contrast exposure should be considered with a temporary increase in other nonnephrotoxic immunosuppressive medications dictated by immunologic risk (74). Intravenous fluids, either isotonic saline or bicarbonate, should be considered at least 1 h before and up to 6 h after the study (85). The use of *N*-acetylcysteine is safe and may be of benefit, but its efficacy remains controversial (86). The use of gadolinium contrast for magnetic resonance imaging is associated with the rare, debilitating complication nephrogenic systemic fibrosis. Patients with advanced CKD (GFR < 30 mL/min) are at greatest risk for this complication, and alternative imaging should be considered (74).

Key Points and Recommendations: Refer to Table 5

Immunological aspects of SLKT and protecting the kidney graft

Given the rising numbers of SLKT performed, protecting the renal allograft in these patients has become increasingly important and involves immunological aspects distinct from native kidney protection. Ample data have demonstrated that the liver allograft can provide the renal allograft partial, but not complete, immunologic protection from rejection (87–98). It is known that the liver secretes class I HLA antigens, which can facilitate clearance of preformed HLA antibodies. Given the large volume of hepatocytes and 100-fold greater microvasculature in the liver versus renal allograft, there is greater dispersion of alloantibodies resulting in lower density and impact (97). As a result, the liver appears to generally protect the kidney graft from most preformed class I donor-specific antibodies (DSAs) (91,92,96). Unlike class I, class II antigen expression is minimal unless hepatic injury occurs in the perioperative period (99). Hence, the liver's ability to protect the renal allograft from preformed class II is more limited (91,92,96) and perhaps dependent on the amount of class II antibodies in the circulation and transplanted organs (99). In general, the rate of DSA formation between all solid organ transplant recipients is similar (100), highlighting a potential unifying mechanism of allosensitization.

Although SLKT outcomes in patients with preformed DSA have been studied, it is unclear if *de novo* DSA formation is higher in SLKT versus LT alone (96,101,102). If DSA clearance is not achieved in renal allograft recipients, particularly that of class II, the risk for rejection and subsequent allograft loss may be significant (87,91,96). Studies have shown that SLKT patients with persistent posttransplantation DSA have higher rates of renal allograft rejection and loss (91,92). In the largest single-center SLKT experience without DSA data documented, 20% of patients had renal allograft rejection and those patients developed long-term impaired renal function (98). These data support the notion that it is no longer accepted that the kidney allograft is spared from rejection or dysfunction following SLKT. Future studies need to address optimal DSA and other immunologic monitoring as well as more focused immunosuppressive strategies in SLKT which have more immunologic challenges than LT alone.

Key Points and Recommendations

- The liver allograft provides partial immunologic protection of a simultaneous renal allograft from the same donor (1C).
- Renal allograft protection from preformed class I HLA DSA is greater than that from preformed class II HLA DSA (2C).
- Persistent DSA following SLKT may be associated with high rates of renal allograft rejection, injury, and loss (1C).

Looking to the Future

This review highlights current knowledge as well as knowledge gaps, including the need for efforts to more optimally evaluate and improve renal function in LT recipients. Perioperative and immediate postoperative nephroprotective strategies are not well developed and need to move beyond delaying CNI therapy for a few days post-LT. Preventing intraoperative AKI and eliminating CNI therapy with novel immunosuppressive agents would likely improve post-LT GFR the greatest; however, prospective randomized trials are needed to document safety and efficacy of proposed regimens, particularly those with costimulation blockade agents. Once CKD has set in > 1 year post-LT, there are no known immunosuppressive modifications that reliably improve GFR. Referral to nephrology specialist care aimed at limiting renal deterioration is most beneficial in this setting, but general nephrology approaches specific to the LT

recipient with renal dysfunction need to be tested and implemented. Recipients of SLKT may not be fully protected from renal dysfunction and can experience chronic immunologic injury (cellular or antibody mediated) and other renal injury events. Given the increasing SLKT population, novel immunosuppressive strategies and approaches more similar to those of kidney transplant–only recipients need to be evaluated. Finally, biomarkers that are not creatinine based and that detect early renal injury before the onset of diminished GFR are needed and should be rigorously studied, to identify and treat renal injury at its earliest stages (36,103–107).

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References

1. Sharma P, Schaubel DE, Guidinger MK, Goodrich NP, Ojo AO, Merion RM. Impact of MELD-based allocation on end-stage renal disease after liver transplantation. Am J Transplant 2011; 11: 2372–2378.
2. Ruebner R, Goldberg D, Abt PL, et al. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. Am J Transplant 2012; 12: 2958–2965.
3. Hilmi IA, Damian D, Al-Khafaji A, et al. Acute kidney injury following orthotopic liver transplantation: Incidence, risk factors, and effects on patient and graft outcomes. Br J Anaesth 2015; 114: 919–926.
4. Klaus F, Keitel da Silva C, Meinerz G, et al. Acute kidney injury after liver transplantation: Incidence and mortality. Transpl Proc 2014; 46: 1819–1821.
5. Leithead JA, Rajoriya N, Gunson BK, Muiesan P, Ferguson JW. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. J Hepatol 2014; 60: 1180–1186.
6. Karapanagiotou A, Dimitriadis C, Papadopoulos S, et al. Comparison of RIFLE and AKIN criteria in the evaluation of the frequency of acute kidney injury in post-liver transplantation patients. Transpl Proc 2014; 46: 3222–3227.
7. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant 2007; 7: 168–176.
8. Allen AM, Kim WR, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation - A time-dependent analysis using measured glomerular filtration rate. J Hepatol 2014; 61: 286–292.
9. Sharma P, Goodrich NP, Schaubel DE, Guidinger MK, Merion RM. Patient-specific prediction of ESRD after liver transplantation. J Am Soc Nephrol 2013; 24: 2045–2052.
10. Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: Liver. Am J Transplant 2013; 13(Suppl 1): 73–102.
11. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003; 349: 931–940.
12. Sharma P, Schaubel DE, Guidinger MK, Merion RM. Effect of pretransplant serum creatinine on the survival benefit of liver transplantation. Liver Transpl 2009; 15: 1808–1813.
13. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant 2008; 8: 2243–2251.
14. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: Current state and future directions. Am J Transplant 2012; 12: 2901–2908.
15. Allen AM, Kim WR, Larson JJ, Colby C, Therneau TM, Rule AD. Serum cystatin C as an indicator of renal function and mortality in liver transplant recipients. Transplantation 2015; 99: 1431–1435.
16. Asrani SK, Kim WR, Heimbach JH, et al. Acute tubular necrosis is present in the majority of patients undergoing liver transplantation. Hepatology 2011; 54(S1): 159A.
17. Wadei HM, Heckman MG, Rawal B, et al. Renal outcomes of liver transplant recipients who had pretransplant kidney biopsy. Transplantation 2014; 98: 1323–1330.
18. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004; 4: 38.
19. Cholongitas E, Marelli L, Kerry A, et al. Different methods of creatinine measurement significantly affect MELD scores. Liver Transpl 2007; 13: 523–529.
20. Shaffi K, Uhlig K, Perrone RD, et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. Am J Kidney Dis 2014; 63: 1007–1018.
21. De Souza V, Hadj-Aissa A, Dolomanova O, et al. Creatinine-versus cystatine C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. Hepatology 2014; 59: 1522–1531.
22. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013; 369: 932–943.
23. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20–29.
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612.
25. Leithead JA, Ferguson JW. Chronic kidney disease after liver transplantation. J Hepatol 2015; 62: 243–244.
26. Levitsky J, Baker T, Ahya SN, et al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. Am J Transplant 2012; 12: 2949–2957.
27. Vagefi PA, Qian JJ, Carlson DM, et al. Native renal function after combined liver-kidney transplant for type 1 hepatorenal

syndrome: Initial report on the use of postoperative Technetium-99 m-mercaptoacetyltriglycine scans. Transpl Int 2013; 26: 471–476.
28. Cabezuelo JB, Ramirez P, Rios A, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int 2006; 69: 1073–1080.
29. Hilmi IA, Peng Z, Planinsic RM, et al. N-acetylcysteine does not prevent hepatorenal ischaemia-reperfusion injury in patients undergoing orthotopic liver transplantation. Nephrol Dial Transplant 2010; 25: 2328–2333.
30. Della Rocca G, Pompei L, Costa MG, et al. Fenoldopam mesylate and renal function in patients undergoing liver transplantation: A randomized, controlled pilot trial. Anesth Analg 2004; 99: 1604–1609, table of contents.
31. Biancofiore G, Della Rocca G, Bindi L, et al. Use of fenoldopam to control renal dysfunction early after liver transplantation. Liver Transpl 2004; 10: 986–992.
32. Hand WR, Whiteley JR, Epperson TI, et al. Hydroxyethyl starch and acute kidney injury in orthotopic liver transplantation: A single-center retrospective review. Anesth Analg 2015; 120: 619–626.
33. Nadeem A, Salahuddin N, El Hazmi A, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. Crit Care 2014; 18: 625.
34. Mukhtar A, Aboulfetouh F, Obayah G, et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: A comparison with human albumin. Anesth Analg 2009; 109: 924–930.
35. Pillebout E, Nochy D, Hill G, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant 2005; 5: 1120–1129.
36. Niemann CU, Walia A, Waldman J, et al. Acute kidney injury during liver transplantation as determined by neutrophil gelatinase-associated lipocalin. Liver Transpl 2009; 15: 1852–1860.
37. Grande L, Rimola A, Cugat E, et al. Effect of venovenous bypass on perioperative renal function in liver transplantation: Results of a randomized, controlled trial. Hepatology 1996; 23: 1418–1428.
38. Zacharias M, Mugawar M, Herbison GP, et al. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev 2013; 9: CD003590.
39. O'Leary JG, Levitsky J, Wong F, Nadim MK, Charlton M, Kim WR. Protecting the kidney in liver transplant candidates: Practice-based recommendations from the American Society of Transplantation Liver and Intestine Community of Practice. Am J Transplant 2016; doi: 10.1111/ajt.13790.
40. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Urinary biomarkers and progression of AKI in patients with cirrhosis. Clin J Am Soc Nephrol 2014; 9: 1857–1867.
41. Levitsky J, Baker TB, Jie C, et al. Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. Hepatology 2014; 60: 2017–2026.
42. Wagener G, Minhaz M, Mattis FA, Kim M, Emond JC, Lee HT. Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. Nephrol Dial Transplant 2011; 26: 1717–1723.
43. Sirota JC, Walcher A, Faubel S, et al. Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation. BMC Nephrol 2013; 14: 17.
44. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: Risk of development and treatment. Transplantation 2001; 72: 1934–1939.
45. Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: Where will MELD lead us? Am J Transplant 2006; 6: 2651–2659.
46. Remuzzi G, Bertani T. Renal vascular and thrombotic effects of cyclosporine. Am J Kidney Dis 1989; 13: 261–272.
47. Shindoh J, Sugawara Y, Akamatsu N, et al. Thrombotic microangiopathy after living-donor liver transplantation. Am J Transplant 2012; 12: 728–736.
48. Verbiest A, Pirenne J, Dierickx D. *De novo* thrombotic microangiopathy after non-renal solid organ transplantation. Blood Rev 2014; 28: 269–279.
49. Utsumi M, Umeda Y, Sadamori H, et al. Risk factors for acute renal injury in living donor liver transplantation: Evaluation of the RIFLE criteria. Transpl Int 2013; 26: 842–852.
50. Yoshida EM, Marotta PJ, Greig PD, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen versus a standard-dose tacrolimus and mycophenolate mofetil regimen: A multicenter randomized clinical trial. Liver Transpl 2005; 11: 1064–1072.
51. Neuberger JM, Mamelok RD, Neuhaus P, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: The 'ReSpECT' study. Am J Transplant 2009; 9: 327–336.
52. Calmus Y, Kamar N, Gugenheim J, et al. Assessing renal function with daclizumab induction and delayed tacrolimus introduction in liver transplant recipients. Transplantation 2010; 89: 1504–1510.
53. Boudjema K, Camus C, Saliba F, et al. Reduced-dose tacrolimus with mycophenolate mofetil versus standard-dose tacrolimus in liver transplantation: A randomized study. Am J Transplant 2011; 11: 965–976.
54. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-based immunosuppression in *de novo* liver transplant recipients: 1-year experience from a phase II randomized study. Am J Transplant 2014; 14: 1817–1827.
55. Asrani SK, Wiesner RH, Trotter JF, et al. *De novo* sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: The 2000-2003 phase II prospective randomized trial. Am J Transplant 2014; 14: 356–366.
56. Teperman L, Moonka D, Sebastian A, et al. Calcineurin inhibitor-free mycophenolate mofetil/sirolimus maintenance in liver transplantation: The randomized spare-the-nephron trial. Liver Transpl 2013; 19: 675–689.
57. De Simone P, Nevens F, De Carlis L, et al. Everolimus with reduced tacrolimus improves renal function in *de novo* liver transplant recipients: A randomized controlled trial. Am J Transplant 2012; 12: 3008–3020.
58. Saliba F, De Simone P, Nevens F, et al. Renal function at two years in liver transplant patients receiving everolimus: Results of a randomized, multicenter study. Am J Transplant 2013; 13: 1734–1745.
59. Fischer L, Saliba F, Kaiser GM, et al. Three-year outcomes in *de novo* liver transplant patients receiving everolimus with reduced tacrolimus: Follow-up results from a randomized, Multicenter Study. Transplantation 2015; 99: 1455–1462.
60. Fischer L, Klempnauer J, Beckebaum S, et al. A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation–PROTECT. Am J Transplant 2012; 12: 1855–1865.
61. Sterneck M, Kaiser GM, Heyne N, et al. Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a

randomized trial in liver transplantation. Am J Transplant 2014; 14: 701–710.
62. Beckebaum S, Klein CG, Sotiropoulos GC, et al. Combined mycophenolate mofetil and minimal dose calcineurin inhibitor therapy in liver transplant patients: Clinical results of a prospective randomized study. Transpl Proc 2009; 41: 2567–2569.
63. Bilbao I, Salcedo M, Gomez MA, et al. Renal function improvement in liver transplant recipients after early everolimus conversion: a clinical practice cohort study in Spain. Liver Transpl 2015; 21: 1056–1065.
64. Castroagudin JF, Molina E, Romero R, Otero E, Tome S, Varo E. Improvement of renal function after the switch from a calcineurin inhibitor to everolimus in liver transplant recipients with chronic renal dysfunction. Liver Transpl 2009; 15: 1792–1797.
65. De Simone P, Metselaar HJ, Fischer L, et al. Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: A prospective, randomized, multicenter trial. Liver Transpl 2009; 15: 1262–1269.
66. Kornberg A, Kupper B, Thrum K, et al. Sustained renal response to mycophenolate mofetil and CNI taper promotes survival in liver transplant patients with CNI-related renal dysfunction. Dig Dis Sci 2011; 56: 244–251.
67. Pageaux GP, Rostaing L, Calmus Y, et al. Mycophenolate mofetil in combination with reduction of calcineurin inhibitors for chronic renal dysfunction after liver transplantation. Liver Transpl 2006; 12: 1755–1760.
68. Saliba F, Dharancy S, Lorho R, et al. Conversion to everolimus in maintenance liver transplant patients: A multicenter, retrospective analysis. Liver Transpl 2011; 17: 905–913.
69. Schlitt HJ, Jonas S, Ganten TM, et al. Effects of mycophenolate mofetil introduction in liver transplant patients: Results from an observational, non-interventional, multicenter study (LOBSTER). Clin Transplant 2013; 27: 368–378.
70. Abdelmalek MF, Humar A, Stickel F, et al. Sirolimus conversion regimen versus continued calcineurin inhibitors in liver allograft recipients: A randomized trial. Am J Transplant 2012; 12: 694–705.
71. Goralczyk AD, Bari N, Abu-Ajaj W, et al. Calcineurin inhibitor sparing with mycophenolate mofetil in liver transplantion: A systematic review of randomized controlled trials. Am J Transplant 2012; 12: 2601–2607.
72. Schmeding M, Kiessling A, Neuhaus R, et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation 2011; 92: 923–929.
73. Stewart SF, Hudson M, Talbot D, Manas D, Day CP. Mycophenolate mofetil monotherapy in liver transplantation. Lancet 2001; 357: 609–610.
74. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2012; 2013(Suppl 3): 1–150.
75. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int 2012; Suppl 2: 337–414.
76. Kent DM, Jafar TH, Hayward RA, et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. J Am Soc Nephrol 2007; 18: 1959–1965.
77. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311: 507–520.
78. Najeed SA, Saghir S, Hein B, et al. Management of hypertension in liver transplant patients. Int J Cardiol 2011; 152: 4–6.
79. Midtvedt K, Hartmann A, Foss A, et al. Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared with lisinopril. Transplantation 2001; 72: 1787–1792.
80. Mourad G, Ribstein J, Mimran A. Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants. Kidney Int 1993; 43: 419–425.
81. Jones-Burton C, Mishra SI, Fink JC, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. Am J Nephrol 2006; 26: 268–275.
82. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev 2009; CD001892.
83. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev 2007; CD002181.
84. Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. Kidney Int 2014; 85: 529–535.
85. Zoungas S, Ninomiya T, Huxley R, et al. Systematic review: Sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med 2009; 151: 631–638.
86. Vaitkus PT, Brar C. N-acetylcysteine in the prevention of contrast-induced nephropathy: Publication bias perpetuated by meta-analyses. Am Heart J 2007; 153: 275–280.
87. Saidman SL, Duquesnoy RJ, Demetris AJ, et al. Combined liver-kidney transplantation and the effect of preformed lymphocytotoxic antibodies. Transpl Immunol 1994; 2: 61–67.
88. Neumann UP, Lang M, Moldenhauer A, et al. Significance of a T-lymphocytotoxic crossmatch in liver and combined liver-kidney transplantation. Transplantation 2001; 71: 1163–1168.
89. Askar M, Schold JD, Eghtesad B, et al. Combined liver-kidney transplants: Allosensitization and recipient outcomes. Transplantation 2011; 91: 1286–1292.
90. Fung J, Makowka L, Tzakis A, et al. Combined liver-kidney transplantation: Analysis of patients with preformed lymphocytotoxic antibodies. Transpl Proc 1988; 20(1 Suppl 1): 88–91.
91. Olausson M, Mjornstedt L, Norden G, et al. Successful combined partial auxiliary liver and kidney transplantation in highly sensitized cross-match positive recipients. Am J Transplant 2007; 7: 130–136.
92. Dar W, Agarwal A, Watkins C, et al. Donor-directed MHC class I antibody is preferentially cleared from sensitized recipients of combined liver/kidney transplants. Am J Transplant 2011; 11: 841–847.
93. Katznelson S, Cecka JM. The liver neither protects the kidney from rejection nor improves kidney graft survival after combined liver and kidney transplantation from the same donor. Transplantation 1996; 61: 1403–1405.
94. Eid A, Moore SB, Wiesner RH, DeGoey SR, Nielson A, Krom RA. Evidence that the liver does not always protect the kidney from hyperacute rejection in combined liver-kidney transplantation across a positive lymphocyte crossmatch. Transplantation 1990; 50: 331–334.
95. Starzl TE, Demetris AJ, Todo S, et al. Evidence for hyperacute rejection of human liver grafts: The case of the canary kidneys. Clin Transplant 1989; 3: 37–45.
96. O'Leary JG, Gebel HM, Ruiz R, et al. Class II alloantibody and mortality in simultaneous liver-kidney transplantation. Am J Transplant 2013; 13: 954–960.

97. O'Leary JG, Demetris AJ, Friedman LS, et al. The role of donor-specific HLA alloantibodies in liver transplantation. Am J Transplant 2014; 14: 779–787.
98. Nilles KM, Krupp J, Lapin B, Sustento-Reodica N, Gallon L, Levitsky J. Incidence and impact of rejection following simultaneous liver-kidney transplantation. J Hepatol 2015; 62: 340–345.
99. O'Leary JG, Cai J, Freeman R, et al. Proposed diagnostic criteria for chronic antibody-mediated rejection in liver allografts. Am J Transplant 2016; 16: 603–614.
100. O'Leary JG, Samaniego M, Barrio MC, et al. The influence of immunosuppressive agents on the risk of *de novo* donor-specific HLA antibody production in solid organ transplant recipients. Transplantation 2016; 100: 39–53.
101. Taner T, Gandhi MJ, Sanderson SO, et al. Prevalence, course and impact of HLA donor-specific antibodies in liver transplantation in the first year. Am J Transplant 2012; 12: 1504–1510.
102. Kaneku H, O'Leary JG, Banuelos N, et al. *De novo* donor-specific HLA antibodies decrease patient and graft survival in liver transplant recipients. Am J Transplant 2013; 13: 1541–1548.
103. Biancofiore G, Pucci L, Cerutti E, et al. Cystatin C as a marker of renal function immediately after liver transplantation. Liver Transpl 2006; 12: 285–291.
104. Ling Q, Xu X, Li JJ, Chen J, Shen JW, Zheng SS. Alternative definition of acute kidney injury following liver transplantation: Based on serum creatinine and cystatin C levels. Transpl Proc 2007; 39: 3257–3260.
105. Ling Q, Xu X, Li J, et al. A new serum cystatin C-based equation for assessing glomerular filtration rate in liver transplantation. Clin Chem Lab Med 2008; 46: 405–410.
106. Gerhardt T, Poge U, Stoffel-Wagner B, et al. Estimation of glomerular filtration rates after orthotopic liver transplantation: Evaluation of cystatin C-based equations. Liver Transpl 2006; 12: 1667–1672.
107. Levitsky J, Salomon DR, Abecassis M, et al. Clinical and plasma proteomic markers correlating with chronic kidney disease after liver transplantation. Am J Transplant 2011; 11: 1972–1978.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: The GRADE system: rating quality of evidence and strength of recommendations (18).