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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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Abbreviations: ACE-I: Angiotensin Converting Enzyme-Inhibitor; AR: Acute Rejection; ARB: Angiotensin Receptor Blocker; AKI: Acute Kidney Injury; AKIN: Acute Kidney Injury Network; BAS: Basiliximab; BELA: Belatacept; BP: Blood Pressure; CNl: Calcineurin Inhibitor; CKD: Chronic Kidney Disease; CS: Corticosteroids; Cyclosporine (CsA); CrCL: Creatinine Clearance; 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; HLA: Human Leukocyte Antigen; IV: Intravenous; KDIGO: Kidney Disease Improving Global Outcomes; LI: Less Intensive; LT: Liver Transplantation; MDRD: Modification of Diet in Renal Disease; MELD: Model for End-Stage Liver Disease; mGFR: Measured Glomerular Filtration Rate; MI: More Intensive; MMF: Mycophenolate Mofetil; mTOR-I: Molecular Target of Rapamycin Inhibitor; NAC: N-Acetylcysteine; RAAS: Renin-Angiotensin-Aldosterone System; RIFLE: Risk, Injury, Failure, Loss of renal function, End-stage renal disease; Scr: Serum Creatinine; SCys: Serum Cystatin C; SLKT: Simultaneous Liver-Kidney Transplantation; SRL: Sirolimus; TAC: Tacrolimus

Abstract

Acute and chronic kidney disease after liver transplantation is common and results in significant morbidity and mortality. The introduction of MELD has directly correlated with an increased prevalence of perioperative renal dysfunction and the number of simultaneous liver-kidney transplants performed. Thus, kidney dysfunction in this population is typically multifactorial and related to pre-existing conditions, pre-transplant renal injury, peri-operative events, and post-transplant nephrotoxic immunosuppressive therapies. The management of kidney disease following liver transplantation is challenging, as by the time the serum creatinine is significantly elevated, few interventions impact the course of progression. Also, immunological factors such as antibody-mediated 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 Intestinal 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.

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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 pre-transplant renal injury, peri-transplant 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 ≥ 4 chronic kidney disease (CKD) ($< 30 \text{ mL/min}$) 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 five 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 pre-existing patient conditions, 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 data available 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 measured GFR (mGFR) in LT recipients (Table 1). However, the use of creatinine-based equations may lead to both over- and under-estimation 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 to measured GFR (20). Rather than an absolute value, an acute change in estimated GFR may provide the most prognostic value in AKI.

Cystatin-C is a non-glycosylated low molecular weight basic protein produced at a constant rate by nucleated body 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 cirrhotics (21, 22). Thus, given the limitations of creatinine-based eGFR measures, GFR may be better estimated 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 ($r^2=0.78-83$) in estimating measured GFR compared to creatinine-based estimations (MDRD-4, MDRD-6, CKD-EPI-Cr, $r^2=0.76-0.77$) (8). However, it still underestimated measured GFR by approximately 12%, particularly in low GFR groups.

Directly measurements of GFR represent the gold standard to assess renal function, although it is 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 transplant (SLKT) recipients to assess the relative contribution of native vs. transplanted kidneys to overall renal function (26, 27). However, these tests involve radiation exposure and also are expensive and impractical for serial monitoring.

Key Points and Recommendations:

- **Of the creatinine-based equations, CKD-EPI-creatinine and the MDRD-4 study equation provide the most accurate estimate of measured GFR 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 Transplant 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 requiring significant blood products 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 post-operative AKI (32, 33), in contrast to an earlier study (34). Of note, the United States 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 techniques impact 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 (will reference the biomarker table from the O'Leary paper being simultaneously submitted). The most commonly studied biomarker in LT-associated AKI is neutrophil gelatinase-associated lipocalin (NGAL) (36, 39-42). 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 which have been validated immediately prior to LT, during LT 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 hydroxethyl starch and chloride-liberal fluids should be avoided in liver transplant recipients. 1C**
- **There are currently promising biomarkers of renal injury available for study for detecting early AKI, which may ultimately lead to targeted strategies to avert significant post-operative renal injury and CKD. 2C**

Renal Protection Early (0-12 months) after Liver Transplantation

Deterioration in renal function following LT is multifactorial (43). Simple calculations of renal function at the time of transplant may provide a reasonable accurate assessment of the long term mortality and ESRD risk and may help guide such modifications of immunosuppression protocols, e.g. calcineurin-inhibitor (CNI) therapies (44-46). CNI-induced nephrotoxicity contributes to short and long term renal deterioration, presumably mediated by afferent arteriolar vasoconstriction (47). 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 Willebrand factor cleaving protease (ADAMTS13) (48, 49). Short and long term survival is clearly diminished in LT recipients with thrombotic microangiopathy and management includes conversion to alternate CNI therapy (cyclosporine, CsA) or even CNI withdrawal if severe and/or non-responsive.

In the immediate post-operative phase (<1 month), one approach to sparing renal function has been to administer short-term induction therapy (poly or monoclonal antibodies) with delayed CNI introduction (Table 3). This approach avoids the synergistic vasoconstrictive effects of CNI with known peri-operative risk factors associated with AKI (50). 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 DAC (Daclizumab) + MMF (mycophenolate mofetil) + CS (corticosteroids) + delayed low-dose TAC (target tacrolimus trough level 4-8 ng/mL, starting day 4-6) vs. MMF + CS + standard TAC dosing (target trough level 10-15 ng/mL for first month, thereafter 4-8 ng/mL) (51). 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% vs. 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 vs. MMF, reduced-dose TAC (target trough levels ≤8 ng/mL) + CS vs. DAC induction + MMF + reduced-dose TAC (delayed until day 5) + CS (52). The decrease in eGFR was significantly less in the DAC + delayed/reduced TAC + MMF + CS compared to standard TAC + CS. In addition, there was less AR in DAC + delayed/reduced TAC + MMF vs. reduced TAC + MMF vs. standard TAC (19.0% vs. 29.2% vs. 27.6%). By contrast, another study showed similar AR rates

(17.5% vs. 18.75%) but no renal benefit of DAC + delayed TAC vs. standard TAC (53), stressing the importance of both delaying TAC and aiming for lower target trough levels (52). The strategy of utilizing MMF to minimize CNI without induction therapy was employed in a multicenter prospective study that randomized *de novo* LT patients to standard TAC or reduced TAC + MMF (54). One year eGFR was higher in the reduced vs. standard TAC group, with a lower risk of AR (30% vs. 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 (55). This study enrolled 250 LT patients who were randomized into five groups: 3 BELA-containing groups (BAS (Basiliximab) + BELA more intensive [MI] + MMF; BELA MI + MMF; BELA less intensive [LI] + MMF); TAC + MMF and TAC (trough 6-12 ng/ml for both TAC groups). In the intent-to-treat analysis, the mean eGFR was 89–93 mL/min/1.73m² in the BELA groups and 71–75 mL/min/1.73m² 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%; 13%; 30%, 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-I) 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 post-operative phase (<1 month) in *de novo* LT was assessed in a phase II 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 5mg 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% vs. 26.4%) and the incidence of graft loss (26.4% vs. 12.5%), death (20% vs. 8%), hepatic artery/portal vein thrombosis (8% vs. 3%) and sepsis (20.4% vs. 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.

In spite of concerns for immediate post-LT use of mTOR-I, a number of studies have tested their use later (1-12 months) after LT when the safety profile may be more favorable. In the multicenter Spare the Nephron Liver trial, subjects maintained on CNI and MMF were prospectively randomized 4 to 12 weeks after LT to be converted from CNI to SRL (trough SRL 5-10 ng/ml) vs. 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/day) (57). The SRL + MMF group demonstrated better renal function improvement from baseline than CNI + MMF, although AR (12.2% vs. 4.1%) and rates of discontinuation for adverse events (36% vs. 27%) were significantly greater. The pivotal phase III H2304 Novartis trial evaluated everolimus (EVR) in combination with reduced TAC one month post-LT, with an arm of later TAC withdrawal,

compared to standard-exposure TAC (58-60). Everolimus (trough EVR 3-8 ng/ml) plus reduced-exposure TAC (trough TAC 3-5 ng/ml) resulted in less AR episodes (4.1% vs. 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%) vs. TAC controls (14.1%). The PROTECT study was a multicenter, prospective, open-label trial in which LT patients 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) (61). Although the Cockcroft-Gault CrCl formula revealed no significant difference between treatments, eGFR showed superiority for EVR using the MDRD-4 formula (+7.8 mL/min/1.73m²; p = 0.02). Rates of mortality, rejection (17.7% vs. 15.3%) and efficacy failure were similar between the two study groups. Importantly, a 24-month extension showed continued renal benefit of EVR vs. CNI therapy (62).

Key Points and Recommendations:

- **Delay and reduction of CNI exposure may reduce or protect against perioperative AKI but typically requires antibody induction. 2C**
- **CNI therapy can be reduced to improve renal function but it is typically required to prevent rejection within the first post-operative year. 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-I and MMF early after LT to minimize CNI nephrotoxicity, this strategy does not seem to equally apply later after LT (63-70). The trials examining these proposed 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 (Table 3 & 4) (71). 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) vs. 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% vs. 1.9%) and discontinuations mainly for adverse events or side effects

(49.9% vs. 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 (64-66, 69). De Simone *et al* randomized patients (eGFR 20-60 mL/min) who underwent LT 1 to 5 years prior to either EVR (trough 3-8 ng/ml with low dose CNI; 6-12 ng/ml without CNI) vs. standard CNI (no CNI trough specified) for 6 months (Table 4) (66). Despite identical rejection rates (1.4%), it failed to achieve the primary endpoint 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%) (64). Patients with renal dysfunction converted early after LT to EVR demonstrated an eGFR increase of 6.8 mL/min/1.73 m² (p<0.01) at 12 months post-conversion, while patients converted >1 year post-LT had no GFR change. Also, a significant percentage of patients (30.2%) discontinued 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 (65).

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 one year post-LT to either MMF (2-3 g/day) with 50% CNI reduction or CNI alone (up to 25% reduction allowable) (68). 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 a 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 (63). 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 (67, 70). The main benefit of this CNI reduction strategy was seen in applying this regimen within 1-2 years of LT. Finally, a recent systematic review summarized the data on complete CNI withdrawal in favor of MMF in regard to renal dysfunction (72). Five trials reported significantly higher risks of AR (RR=4.96 CI: 1.75-14), without graft loss or death, with full MMF conversion (68, 70, 72-74). 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-I improves renal function when performed >1 year post-LT. 2C**
- **There is evidence that MMF and concurrent reduction in CNI therapy results in 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 strategies using alternative immunosuppressive strategies, little data specifically address the general prevention and management of CKD in the LT population. Clinicians therefore must extrapolate best practices from both non-transplant CKD and kidney transplant recipients 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 (75, 76). To best manage and understand the trajectory of GFR decline, renal assessment should be at least annually by estimated or measured GFR and albuminuria (or proteinuria) measurement, with guidelines for referral to a nephrologist.

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 recommend a particular class of anti-hypertensives for LT recipients (77). In native CKD with proteinuria (>1000 mg/d), agents that inhibit the renin-angiotensin-aldosterone system (RAAS) are considered first-line agents (78). 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 (79). While RAAS agents appear to be safe and effective following LT, calcium channel blockers have been proposed as first-line agents to treat hypertension due to the mechanistic advantage of blocking CNI-induced vasoconstriction (80-82).

Dietary interventions may assist in slowing the progression of CKD. Salt intake should be reduced to <2 grams of sodium per day to improve blood pressure control, proteinuria, and GFR (83). 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/day) in patients at risk of CKD and lowering protein intake to 0.8 g/kg/day in patients with GFR <30 mL/min/1.73m². 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 (84, 85). Use of oral bicarbonate for acidosis (bicarbonate <22 mmol/l) has been shown in small studies to slow CKD progression (86). 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 on CNI therapy are particularly susceptible to hemodynamic insults and at higher AKI risk with exposure to nephrotoxins such as aminoglycosides, amphotericin B, non-steroidal anti-inflammatory agents, and radiocontrast. When possible, reducing or holding CNI therapy pre- and post-contrast exposure should be considered with a temporary increase in other non-nephrotoxic immunosuppressive medications dictated by immunologic risk (75). Intravenous fluids, either isotonic saline or bicarbonate, should be considered at least 1 hour prior and up to 6 hours after the study (87). Use of N-acetylcysteine is safe and may be of benefit, but its efficacy still remains controversial (88). 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 (75).

To best manage and understand the trajectory of GFR decline, renal assessment should be at least annually evaluated by estimated or measured GFR and albuminuria (or proteinuria) measurements, with guidelines for referral to a nephrologist outlined in Table 5 (75).

Key Points and Recommendations: See 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 has demonstrated that the liver allograft can provide renal allografts partial, but not complete, immunologic protection from rejection (89-100). 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 vs. renal allograft, there is greater dispersion of alloantibodies resulting in lower density and impact (99). As a result, the liver appears to generally protect the kidney graft from most preformed class I donor specific antibodies (DSA) (93, 94, 98). Unlike class I, class II antigen expression is minimal unless hepatic injury occurs in the perioperative period (101). Hence, the liver's ability to protect the renal allograft from preformed class II is more limited (93, 94, 98) and perhaps dependent on the amount of class II antibodies in the circulation and transplanted organs (102). In general, the rate of DSA formation between all solid organ transplant recipients is similar (103), highlighting a potential unifying mechanism of allo-sensitization.

Although SLKT outcomes in patients with preformed DSA have been studied, it is unclear if *de novo* DSA formation is higher in SLKT vs. LT alone (98, 104, 105). 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 (89, 93, 98). Studies have shown that SLKT patients with persistent post-transplant

DSA have higher rates of renal allograft rejection and loss (93, 94). 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 (100). These data support the notion that it is no longer accepted that the kidney allograft is spared from rejection or dysfunction in the setting of an SLKT. Future studies need to address optimal DSA and other immunologic monitoring as well as more focused immunosuppressive strategies in SLKT recipients to afford the best outcomes in combined organ transplants 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 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 and knowledge gaps, including the need for efforts to more optimally evaluate and improve renal function in LT recipients. Perioperative and immediate post-operative 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 more than one year post-LT, there are no known immunosuppressive modifications that reliably improve GFR. Referral to nephrology specialist care in this setting aimed at limiting renal deterioration is most beneficial but general nephrology approaches specific to the LT recipient with renal dysfunction need to be tested, analyzed and implemented. Recipients of SLKT may not be fully protected from renal dysfunction and can suffer 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 alone recipients need to be evaluated and tested. 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, in order to identify and treat renal injury at its earliest stages (36, 106-110).

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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).

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TABLE 1: COMMON METHODS FOR MEASURING GLOMERULAR FILTRATION RATES

MEASURE	FORMULA	CALCULATION
Estimated		
Creatinine		
	MDRD4	$175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$
	MDRD6	$198 \times [S_{cr} \text{ (mg/dL)}]^{-0.858} \times [\text{age}]^{-0.1678} \times [0.822 \text{ if patient is female}] \times [1.178 \text{ if patient is black}] \times [\text{serum urea nitrogen concentration (mg/dL)}]^{-0.293} \times [\text{urine urea nitrogen excretion (g/d)}]^{0.249}$
	2009 CKD-EPI Creatinine equation	$141 \times \min(S_{cr}/\kappa, 1)^\alpha \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$ where: S_{cr} 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 S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.
Cystatin C		
	2012 CKD-EPI cystatin C equation	$133 \times \min(\text{SCysC}/0.8, 1)^{-0.499} \times \max(\text{SCysC}/0.8, 1)^{-1.328} \times 0.996^{\text{Age}} [x0.932 \text{ if female}]$ 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	$135 \times \min(\text{SCr}/\kappa, 1)^\alpha \times \max(\text{SCr}/\kappa, 1)^{-0.601} \times \min(\text{SCysC}/0.8, 1)^{-0.375} \times \max(\text{SCysC}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} [x0.969 \text{ if female}] [x1.08 \text{ if black}]$ 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, $\min(\text{SCr}/\kappa, 1)$ indicates the minimum of SCr/ κ or 1, and $\max(\text{SCr}/\kappa, 1)$ indicates the maximum of SCr/ κ or 1; $\min(\text{SCysC}/0.8, 1)$ 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

Scr: Serum Creatinine; SCys: Serum Cystatin C

TABLE 2: RANDOMIZED TRIALS OF PERI-OPERATIVE RENAL PROTECTION STUDIES 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	<ul style="list-style-type: none"> 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 poor quality
Mukhtar (34)	40	Prospective randomized (living donor transplantation): 6% HES 130/0.4 vs. albumin 5% intraoperatively and first 4 post-LT days	<ul style="list-style-type: none"> 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 q4 h x 12 doses vs. 0.9% IV saline given similarly	<ul style="list-style-type: none"> No difference in AKI between NAC and placebo at day 14
Grande (37)	77	Prospective randomized non-blinded: Intraoperative venous-venous bypass vs. no bypass	<ul style="list-style-type: none"> No statistical difference was found in renal function or need for hemodialysis between groups
Della Rocca (30)	43	Prospective randomized non-blinded: Fenoldopam $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ vs. dopamine $2 \mu\text{g} \cdot \text{kg}^{-1}$ during	<ul style="list-style-type: none"> Significantly less AKI and requirement for diuretics at day 3 post-LT in fenoldopam group

		and until 48 h post-LT	
Biancofiore (31)	140	Prospective randomized non-blinded: Fenoldopam patients $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ vs. dopamine $3 \mu\text{g} \cdot \text{kg}^{-1}$ vs. placebo during and until 96 h post-LT	<ul style="list-style-type: none"> No change in CrCl with fenoldopam but significantly less drop in CrCl with dopamine vs. placebo

AUTHOR	N	STUDY DESIGN	MAJOR FINDINGS
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AKI: Acute Kidney Injury; CrCL: Creatinine Clearance; HES: Hydroxyethyl Starch; NAC: N-Acetylcysteine.

TABLE 3: RANDOMIZED TRIALS OF CALCINEURIN-INHIBITOR MINIMIZATION IN THE FIRST YEAR POST-LIVER TRANSPLANTATION

Early (<1 month) CNI minimization studies			
Yoshida (51)	148	Immediate post-LT: DAC + reduced TAC delayed 6 days vs. standard TAC	<ul style="list-style-type: none"> Improved GFR in reduced, delayed TAC No difference in AR rates
Neuberger (52)	525	Immediate post-LT: standard TAC vs. reduced-dose TAC+MMF vs. DAC + reduced TAC delayed 5 days + MMF	<ul style="list-style-type: none"> Significantly less drop in GFR in reduced, delayed TAC Less AR in reduced, delayed TAC
Calmus (53)	199	Immediate post-LT: DAC + standard TAC delayed 5 days vs. standard TAC	<ul style="list-style-type: none"> No difference in month 12 SCr > 1.43 mg/dL No difference in AR rates
Boudjema (54)	195	Immediate post-LT: reduced TAC + MMF vs. standard TAC	<ul style="list-style-type: none"> Significantly better GFR at month 12 in reduced TAC + MMF Significantly less AR in reduced TAC+MMF
Klintmalm (55)	250	Immediate post-LT: BAS + BELA MI + MMF vs. BELA MI + MMF vs. BELA LI + MMF vs. TAC + MMF vs. TAC	<ul style="list-style-type: none"> Significantly better month 12 GFR in all BELA groups Significantly higher AR rates in all BELA groups Significantly diminished month 12 survival in BELA LI + MMF
Asrani (56)	222	Immediate post-LT: standard TAC vs. reduced TAC + SRL	<ul style="list-style-type: none"> No difference in GFR Graft loss, death, vascular thrombosis and sepsis higher in reduced TAC + SRL
Delayed (1-12 month) CNI minimization studies			
Teperman (57)	293	Week 4-12 post-LT: CNI + MMF vs. CNI to SRL+ MMF	<ul style="list-style-type: none"> Significant month 12 eGFR increase in SRL + MMF High side effects and discontinuation in SRL + MMF Higher rejection rate in SRL + MMF
De Simone (58) Saliba (59) Fischer (60)	719	Week 4 post-LT: TAC elimination plus EVR vs. reduced TAC + EVR vs. standard TAC	<ul style="list-style-type: none"> 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 (61)	203	Week 4 post-LT: BAS induction for all; CNI to EVR vs. CNI continuation	<ul style="list-style-type: none"> Significant improvement in GFR with EVR conversion No difference in AR rates
Abdelmalek (71)	607	Month 6-144: CNI to SRL vs. CNI continuation	<ul style="list-style-type: none"> 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.

TABLE 4: RANDOMIZED TRIALS OF CALCINEURIN-INHIBITOR MINIMIZATION STUDIES AFTER THE FIRST YEAR POST- LIVER TRANSPLANTATION

AUTHOR	N	STUDY DESIGN	MAJOR FINDINGS
Abdelmalek (71)	607	Month 6-144: CNI to SRL vs. CNI continuation	<ul style="list-style-type: none"> No improvement in GFR with SRL conversion Higher AR rates with SRL conversion
De Simone (66)	145	Prospective randomized controlled: EVR + low dose CNI/CNI elimination vs. standard dose CNI x 6 months, GFR 20-60 at enrollment Time from LT to enrollment: 12-60 months	<ul style="list-style-type: none"> No difference in eGFR or AR in both groups
Pageaux (68)	56	Prospective randomized controlled: MMF + low dose CNI vs. standard CNI for chronic renal failure Time from LT to enrollment: 1 year post-LT	<ul style="list-style-type: none"> Significant improvement in eGFR in MMF+ low dose CNI at 1 year No AR in either group
Beckebaum (63)	90	Prospective randomized controlled (2:1): MMF + low dose CNI vs. standard CNI for SCr>1.2 mg/dl Time from LT to enrollment: 1 year post-LT	<ul style="list-style-type: none"> 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; SCr, serum creatinine; SRL, sirolimus.

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 hours (or equivalent*) whose office BP is consistently >140mm Hg systolic or >90mm Hg diastolic be treated with BP-lowering drugs with the goal of ≤140mm Hg systolic and ≤90mm Hg diastolic (1B)
	All adults with CKD and urine albumin excretion ≥30 mg/24 hours (or equivalent*) whose office BP is consistently >130mm Hg systolic or >80mm Hg diastolic be treated with BP-lowering drugs with the goal of <130mm Hg systolic and <80mm Hg diastolic (2D)
	ARB or ACE-I therapy should be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent*) (1B)
	ARB or ACE-I therapy should be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (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/day in adults with diabetes (2C) or without diabetes (2B) and GFR <30 ml/min/1.73 m ² , and suggest avoiding high protein intake (>1.3 g/kg/day) 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 AKI including: <ul style="list-style-type: none"> • 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 hours 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): <ul style="list-style-type: none"> • AKI or abrupt sustained fall in GFR; • GFR <30 ml/min/1.73 m² • Consistent significant albuminuria (albumin/creatinine ratio ≥300 mg/g [≥30 mg/mmol] or albumin excretion rate ≥300 mg/24 hours, equivalent to protein/creatinine ratio ≥500 mg/g [≥50 mg/mmol] or protein excretion rate ≥500 mg/24 hours) • Progression of CKD (a drop in in eGFR from baseline by 25% or a sustained decline in eGFR of more

than 5 ml/min/1.73 m²/yr).

- urinary red cell casts, RBC >20 per high power field sustained and not readily explained
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
- persistent abnormalities of serum potassium
- recurrent or extensive nephrolithiasis
- hereditary kidney disease

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