HHS Public Access

Author manuscript

*Am J Transplant*. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

*Am J Transplant*. 2016 September ; 16(9): 2532–2544. doi:10.1111/ajt.13765.

# Practice-Based Recommendations from the American Society of Transplantation Liver and Intestine Community of Practice

**J. Levitsky**[1,*], **J.G. O'Leary**[2,*], **S. Asrani**[2], **P. Sharma**[3], **J. Fung**[4], **A. Wiseman**[5], and **C.U. Niemann**[6]

[1]Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, IL

[2]Division of Hepatology, Baylor University Medical Center, Dallas, TX

[3]Department of Medicine, Division of Gastroenterology and Hepatology, University of Michigan Medical Center, Ann Arbor, MI

[4]Department of Surgery, Transplantation Center, The Cleveland Clinic, Cleveland, OH

[5]Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado School of Medicine, Denver, CO

[6]Department of Anesthesia and Surgery, University of California at San Francisco, San Francisco, CA

## 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

Corresponding Author: Josh Levitsky, MD, MS; j-levitsky@northwestern.edu.
*Co-First Authors

Disclosure: The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Honoraria (Speaker's Bureau, Consulting Fees): J.L. (Novartis, Gilead, Transplant Genomics, Inc.), J.G.O. (Astellas, Novartis), J.F. (Astellas), A.W. (Astellas, Veloxis, Merck). Research Funds: J.L. (Novartis), J.G.O. (Grifols, Fisher Scientific), J.F. (Novartis, Sanofi), A.W. (Bristol Meier Squibb, Alexion, Novartis, Oxford Immunotec, Chimerix).

SUPPORTING INFORMATION

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

population are provided to offer guidance for clinicians and identify gaps in knowledge for future investigations.

## 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)(<30mL/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 postoperative 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/1.73m$^2$ in the BELA groups and 71–75 mL/min/1.73m$^2$ 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%; 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 Cockroff-Gault CrCl formula revealed no significant difference between treatments, eGFR showed superiority for EVR using the MDRD-4 formula (+7.8 mL/min/1.73m$^2$; 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 $m^2$ ($p<0.01$) 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/1.73m$^2$. 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 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 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).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We acknowledge the support of the American Society for Transplantation Board of Directors and the Liver and Intestine Community of Practice. P.S. is supported by National Institutes of Health (NIH) grant KO8 DK-088946 and RO3 DK102480.

## 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 |
| **CNI** | Calcineurin Inhibitor |
| **CKD** | Chronic Kidney Disease |
| **CS** | Corticosteroids |
| **CsA** | Cyclosporine |
| **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 |

## 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(11):2372–2378. [PubMed: 21883908]
2. Ruebner R, Goldberg D, Abt PL, Bahirwani R, Levine M, Sawinski D, et al. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. Am J Transplant. 2012; 12(11):2958–2965. [PubMed: 22759237]
3. Hilmi IA, Damian D, Al-Khafaji A, Planinsic R, Boucek C, Sakai T, et al. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. Br J Anaesth. 2015; 114(6):919–926. [PubMed: 25673576]
4. Klaus F, Keitel da Silva C, Meinerz G, Carvalho LM, Goldani JC, Cantisani G, et al. Acute kidney injury after liver transplantation: incidence and mortality. Transplantation proceedings. 2014; 46(6): 1819–1821. [PubMed: 25131045]
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(6):1180–1186. [PubMed: 24631601]
6. Karapanagiotou A, Dimitriadis C, Papadopoulos S, Kydona C, Kefsenidis S, Papanikolaou V, et al. Comparison of RIFLE and AKIN criteria in the evaluation of the frequency of acute kidney injury in post-liver transplantation patients. Transplantation proceedings. 2014; 46(9):3222–3227. [PubMed: 25420865]
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(1):168–176. [PubMed: 17109735]
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(2):286–292. [PubMed: 24713190]
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(12):2045–2052. [PubMed: 24029423]

10. Kim WR, Stock PG, Smith JM, Heimbach JK, Skeans MA, Edwards EB, et al. OPTN/SRTR 2011 Annual Data Report: liver. Am J Transplant. 2013; 13(Suppl 1):73–102. [PubMed: 23237697]
11. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003; 349(10):931–940. [PubMed: 12954741]
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(12):1808–1813. [PubMed: 19938142]
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(11): 2243–2251. [PubMed: 18808402]
14. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant. 2012; 12(11):2901–2908. [PubMed: 22822723]
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(7):1431–1435. [PubMed: 25654627]
16. Asrani SK, Kim WR, Heimbach JH, Rosen CB, Berndt MM, Wiesner RH, et al. Acute Tubular Necrosis in present in the majority of patients undergoing liver transplantation. Hepatology. 2011; 54(S1):159A.
17. Wadei HM, Heckman MG, Rawal B, Taner CB, Mai ML, Cortese C, et al. Renal outcomes of liver transplant recipients who had pretransplant kidney biopsy. Transplantation. 2014; 98(12):1323–1330. [PubMed: 24914572]
18. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill 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(1):38. [PubMed: 15615589]
19. Cholongitas E, Marelli L, Kerry A, Senzolo M, Goodier DW, Nair D, et al. Different methods of creatinine measurement significantly affect MELD scores. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2007; 13(4):523–529.
20. Shaffi K, Uhlig K, Perrone RD, Ruthazer R, Rule A, Lieske JC, et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. Am J Kidney Dis. 2014; 63(6):1007–1018. [PubMed: 24703720]
21. De Souza V, Hadj-Aissa A, Dolomanova O, Rabilloud M, Rognant N, Lemoine S, et al. Creatinine-versus cystatine C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. Hepatology. 2014; 59(4):1522–1531. [PubMed: 24123197]
22. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013; 369(10):932–943. [PubMed: 24004120]
23. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367(1):20–29. [PubMed: 22762315]
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. [PubMed: 19414839]
25. Leithead JA, Ferguson JW. Chronic kidney disease after liver transplantation. J Hepatol. 2015; 62(1):243–244. [PubMed: 25263005]
26. Levitsky J, Baker T, Ahya SN, Levin ML, Friedewald J, Gallon L, et al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. Am J Transplant. 2012; 12(11): 2949–2957. [PubMed: 22759344]
27. Vagefi PA, Qian JJ, Carlson DM, Aparici CM, Hirose R, Vincenti F, 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(5):471–476. [PubMed: 23384317]

28. Cabezuelo JB, Ramirez P, Rios A, Acosta F, Torres D, Sansano T, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int. 2006; 69(6):1073–1080. [PubMed: 16528257]
29. Hilmi IA, Peng Z, Planinsic RM, Damian D, Dai F, Tyurina YY, et al. N-acetylcysteine does not prevent hepatorenal ischaemia-reperfusion injury in patients undergoing orthotopic liver transplantation. Nephrol Dial Transplant. 2010; 25(7):2328–2333. [PubMed: 20179007]
30. Della Rocca G, Pompei L, Costa MG, Coccia C, Scudeller L, Di Marco P, et al. Fenoldopam mesylate and renal function in patients undergoing liver transplantation: a randomized, controlled pilot trial. Anesth Analg. 2004; 99(6):1604–1609. table of contents. [PubMed: 15562040]
31. Biancofiore G, Della Rocca G, Bindi L, Romanelli A, Esposito M, Meacci L, et al. Use of fenoldopam to control renal dysfunction early after liver transplantation. Liver Transpl. 2004; 10(8):986–992. [PubMed: 15390323]
32. Hand WR, Whiteley JR, Epperson TI, Tam L, Crego H, Wolf B, et al. Hydroxyethyl starch and acute kidney injury in orthotopic liver transplantation: a single-center retrospective review. Anesth Analg. 2015; 120(3):619–626. [PubMed: 25036375]
33. Nadeem A, Salahuddin N, El Hazmi A, Joseph M, Bohlega B, Sallam H, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. Crit Care. 2014; 18(6): 625. [PubMed: 25407504]
34. Mukhtar A, Aboulfetouh F, Obayah G, Salah M, Emam M, Khater Y, et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: a comparison with human albumin. Anesth Analg. 2009; 109(3):924–930. [PubMed: 19690268]
35. Pillebout E, Nochy D, Hill G, Conti F, Antoine C, Calmus Y, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant. 2005; 5(5):1120–1129. [PubMed: 15816895]
36. Niemann CU, Walia A, Waldman J, Davio M, Roberts JP, Hirose R, et al. Acute kidney injury during liver transplantation as determined by neutrophil gelatinase-associated lipocalin. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009; 15(12):1852–1860.
37. Grande L, Rimola A, Cugat E, Alvarez L, Garcia-Valdecasas JC, Taura P, et al. Effect of venovenous bypass on perioperative renal function in liver transplantation: results of a randomized, controlled trial. Hepatology. 1996; 23(6):1418–1428. [PubMed: 8675159]
38. Zacharias M, Mugawar M, Herbison GP, Walker RJ, Hovhannisyan K, Sivalingam P, et al. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev. 2013; 9:CD003590. [PubMed: 24027097]
39. Belcher JM, Garcia-Tsao G, Sanyal AJ, Thiessen-Philbrook H, Peixoto AJ, Perazella MA, et al. Urinary biomarkers and progression of AKI in patients with cirrhosis. Clin J Am Soc Nephrol. 2014; 9(11):1857–1867. [PubMed: 25183658]
40. Levitsky J, Baker TB, Jie C, Ahya S, Levin M, Friedewald J, et al. Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. Hepatology. 2014; 60(6):2017–2026. [PubMed: 25078558]
41. 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(5):1717–1723. [PubMed: 21257679]
42. Sirota JC, Walcher A, Faubel S, Jani A, McFann K, Devarajan P, 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. [PubMed: 23327592]
43. Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation. 2001; 72(12):1934–1939. [PubMed: 11773892]
44. Sharma, P.; Perlmutter, A. Renal Risk Index Calculator. 2013. [website]Available from: https://rri.med.umich.edu
45. Sharma P, Goodrich NP, Schaubel DE, Guidinger MK, Merion RM. Patient-Specific Prediction of ESRD after Liver Transplantation. J Am Soc Nephrol. 2013

46. 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(11):2651–2659. [PubMed: 16939515]
47. Remuzzi G, Bertani T. Renal vascular and thrombotic effects of cyclosporine. Am J Kidney Dis. 1989; 13(4):261–272. [PubMed: 2650537]
48. Shindoh J, Sugawara Y, Akamatsu N, Kaneko J, Tamura S, Yamashiki N, et al. Thrombotic microangiopathy after living-donor liver transplantation. Am J Transplant. 2012; 12(3):728–736. [PubMed: 22070669]
49. Verbiest A, Pirenne J, Dierickx D. De novo thrombotic microangiopathy after non-renal solid organ transplantation. Blood Rev. 2014; 28(6):269–279. [PubMed: 25266355]
50. Utsumi M, Umeda Y, Sadamori H, Nagasaka T, Takaki A, Matsuda H, et al. Risk factors for acute renal injury in living donor liver transplantation: evaluation of the RIFLE criteria. Transpl Int. 2013; 26(8):842–852. [PubMed: 23855657]
51. Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2005; 11(9):1064–1072.
52. Neuberger JM, Mamelok RD, Neuhaus P, Pirenne J, Samuel D, Isoniemi H, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. Am J Transplant. 2009; 9(2):327–336. [PubMed: 19120077]
53. Calmus Y, Kamar N, Gugenheim J, Duvoux C, Ducerf C, Wolf P, et al. Assessing renal function with daclizumab induction and delayed tacrolimus introduction in liver transplant recipients. Transplantation. 2010; 89(12):1504–1510. [PubMed: 20495510]
54. Boudjema K, Camus C, Saliba F, Calmus Y, Salame E, Pageaux G, et al. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. Am J Transplant. 2011; 11(5):965–976. [PubMed: 21466650]
55. Klintmalm GB, Feng S, Lake JR, Vargas HE, Wekerle T, Agnes S, 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(8):1817–1827. [PubMed: 25041339]
56. Asrani SK, Wiesner RH, Trotter JF, Klintmalm G, Katz E, Maller E, 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(2):356–366. [PubMed: 24456026]
57. Teperman L, Moonka D, Sebastian A, Sher L, Marotta P, Marsh C, et al. Calcineurin inhibitor-free mycophenolate mofetil/sirolimus maintenance in liver transplantation: the randomized spare-the-nephron trial. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2013; 19(7):675–689.
58. De Simone P, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, Saliba F, et al. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. Am J Transplant. 2012; 12(11):3008–3020. [PubMed: 22882750]
59. Saliba F, De Simone P, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, et al. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. Am J Transplant. 2013; 13(7):1734–1745. [PubMed: 23714399]
60. Fischer L, Saliba F, Kaiser GM, De Carlis L, Metselaar HJ, De Simone P, 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(7):1455–1462. [PubMed: 26151607]
61. Fischer L, Klempnauer J, Beckebaum S, Metselaar HJ, Neuhaus P, Schemmer P, et al. A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation--PROTECT. Am J Transplant. 2012; 12(7):1855–1865. [PubMed: 22494671]

62. Sterneck M, Kaiser GM, Heyne N, Richter N, Rauchfuss F, Pascher A, et al. Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomized trial in liver transplantation. Am J Transplant. 2014; 14(3):701–710. [PubMed: 24502384]

63. Beckebaum S, Klein CG, Sotiropoulos GC, Saner FH, Gerken G, Paul A, et al. Combined mycophenolate mofetil and minimal dose calcineurin inhibitor therapy in liver transplant patients: clinical results of a prospective randomized study. Transplantation proceedings. 2009; 41(6):2567–2569. [PubMed: 19715976]

64. Bilbao I, Salcedo M, Gomez MA, Jimenez C, Castroagudin J, Fabregat J, et al. Renal function improvement in liver transplant recipients after early everolimus conversion: A clinical practice cohort study in Spain. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2015; 21(8):1056–1065.

65. 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 transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009; 15(12): 1792–1797.

66. De Simone P, Metselaar HJ, Fischer L, Dumortier J, Boudjema K, Hardwigsen J, et al. Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: a prospective, randomized, multicenter trial. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009; 15(10):1262–1269.

67. Kornberg A, Kupper B, Thrum K, Krause B, Buchler P, Kornberg J, et al. Sustained renal response to mycophenolate mofetil and CNI taper promotes survival in liver transplant patients with CNI-related renal dysfunction. Digestive diseases and sciences. 2011; 56(1):244–251. [PubMed: 20824504]

68. Pageaux GP, Rostaing L, Calmus Y, Duvoux C, Vanlemmens C, Hardgwissen J, et al. Mycophenolate mofetil in combination with reduction of calcineurin inhibitors for chronic renal dysfunction after liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2006; 12(12):1755–1760.

69. Saliba F, Dharancy S, Lorho R, Conti F, Radenne S, Neau-Cransac M, et al. Conversion to everolimus in maintenance liver transplant patients: a multicenter, retrospective analysis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2011; 17(8):905–913.

70. Schlitt HJ, Jonas S, Ganten TM, Grannas G, Moench C, Rauchfuss F, et al. Effects of mycophenolate mofetil introduction in liver transplant patients: results from an observational, non-interventional, multicenter study (LOBSTER). Clinical transplantation. 2013; 27(3):368–378. [PubMed: 23405863]

71. Abdelmalek MF, Humar A, Stickel F, Andreone P, Pascher A, Barroso E, et al. Sirolimus conversion regimen versus continued calcineurin inhibitors in liver allograft recipients: a randomized trial. Am J Transplant. 2012; 12(3):694–705. [PubMed: 22233522]

72. Goralczyk AD, Bari N, Abu-Ajaj W, Lorf T, Ramadori G, Friede T, et al. Calcineurin inhibitor sparing with mycophenolate mofetil in liver transplantion: a systematic review of randomized controlled trials. Am J Transplant. 2012; 12(10):2601–2607. [PubMed: 22813081]

73. Schmeding M, Kiessling A, Neuhaus R, Heidenhain C, Bahra M, Neuhaus P, et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation. 2011; 92(8):923–929. [PubMed: 21832958]

74. Stewart SF, Hudson M, Talbot D, Manas D, Day CP. Mycophenolate mofetil monotherapy in liver transplantation. Lancet. 2001; 357(9256):609–610. [PubMed: 11558493]

75. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2013; (Suppl 3):1–150.

76. Niu W, Yang Z, Shang XY, Fu XL, Tang Y, Jiang M, et al. The relationship between CD4+ CD25+ regulatory T cell in the peripheral blood and poor or nonresponsiveness to hepatitis B vaccine. Zhonghua Yu Fang Yi Xue Za Zhi. 2009; 43(1):28–31. [PubMed: 19534876]
77. 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.
78. Kent DM, Jafar TH, Hayward RA, Tighiouart H, Landa M, de Jong P, 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(6):1959–1965. [PubMed: 17475813]
79. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, 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(5): 507–520. [PubMed: 24352797]
80. Najeed SA, Saghir S, Hein B, Neff G, Shaheen M, Ijaz H, et al. Management of hypertension in liver transplant patients. Int J Cardiol. 2011; 152(1):4–6. [PubMed: 21215474]
81. Midtvedt K, Hartmann A, Foss A, Fauchald P, Nordal KP, Rootwelt K, et al. Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared to lisinopril. Transplantation. 2001; 72(11):1787–1792. [PubMed: 11740389]
82. Mourad G, Ribstein J, Mimran A. Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants. Kidney Int. 1993; 43(2):419–425. [PubMed: 8382753]
83. Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GL, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. Am J Nephrol. 2006; 26(3):268–275. [PubMed: 16763384]
84. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev. 2009; (3):CD001892. [PubMed: 19588328]
85. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev. 2007; (4):CD002181. [PubMed: 17943769]
86. Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. Kidney Int. 2014; 85(3):529–535. [PubMed: 24107852]
87. Zoungas S, Ninomiya T, Huxley R, Cass A, Jardine M, Gallagher M, et al. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med. 2009; 151(9):631–638. [PubMed: 19884624]
88. Vaitkus PT, Brar C. N-acetylcysteine in the prevention of contrast-induced nephropathy: publication bias perpetuated by meta-analyses. Am Heart J. 2007; 153(2):275–280. [PubMed: 17239689]
89. Saidman SL, Duquesnoy RJ, Demetris AJ, McCauley J, Ramos H, Mazariegos G, et al. Combined liver-kidney transplantation and the effect of preformed lymphocytotoxic antibodies. Transpl Immunol. 1994; 2(1):61–67. [PubMed: 8081794]
90. Neumann UP, Lang M, Moldenhauer A, Langrehr JM, Glanemann M, Kahl A, et al. Significance of a T-lymphocytotoxic crossmatch in liver and combined liver-kidney transplantation. Transplantation. 2001; 71(8):1163–1168. [PubMed: 11374419]
91. Askar M, Schold JD, Eghtesad B, Flechner SM, Kaplan B, Klingman L, et al. Combined liver-kidney transplants: allosensitization and recipient outcomes. Transplantation. 2011; 91(11):1286–1292. [PubMed: 21478816]
92. Fung J, Makowka L, Tzakis A, Klintmalm G, Duquesnoy R, Gordon R, et al. Combined liver-kidney transplantation: analysis of patients with preformed lymphocytotoxic antibodies. Transplantation proceedings. 1988; 20(1 Suppl 1):88–91. [PubMed: 3279673]
93. Olausson M, Mjornstedt L, Norden G, Rydberg L, Molne J, Backman L, et al. Successful combined partial auxiliary liver and kidney transplantation in highly sensitized cross-match positive recipients. Am J Transplant. 2007; 7(1):130–136. [PubMed: 17227562]
94. Dar W, Agarwal A, Watkins C, Gebel HM, Bray RA, Kokko KE, et al. Donor-directed MHC class I antibody is preferentially cleared from sensitized recipients of combined liver/kidney transplants. Am J Transplant. 2011; 11(4):841–847. [PubMed: 21446981]

95. 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(9):1403–1405. [PubMed: 8629305]

96. 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(2):331–334. [PubMed: 2382298]

97. Starzl TE, Demetris AJ, Todo S, Kang Y, Tzakis A, Duquesnoy R, et al. Evidence for hyperacute rejection of human liver grafts: The case of the canary kidneys. Clinical transplantation. 1989; 3:37–45. [PubMed: 21151799]

98. O'Leary JG, Gebel HM, Ruiz R, Bray RA, Marr JD, Zhou XJ, et al. Class II alloantibody and mortality in simultaneous liver-kidney transplantation. Am J Transplant. 2013; 13(4):954–960. [PubMed: 23433356]

99. O'Leary JG, Demetris AJ, Friedman LS, Gebel HM, Halloran PF, Kirk AD, et al. The role of donor-specific HLA alloantibodies in liver transplantation. Am J Transplant. 2014; 14(4):779–787. [PubMed: 24580828]

100. 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(2):340–345. [PubMed: 25195555]

101. O'Leary JG, Cai J, Freeman R, Banuelos N, Hart B, Johnson M, et al. Proposed Diagnostic Criteria for Chronic Antibody-Mediated Rejection in Liver Allografts. Am J Transplant. 2015

102. JG OL, JCR, FNB, BHMJ, et al. Proposed diagnostic criteria for chronic antibdody-mediated jrecetion in liver allografts. Am J Transplant. 2015 In Press.

103. JG OL, MS, MC CL, PAZAD, et al. The influence of immunosuppressive agents on the risk of de novo donor-specific HLA antibbody production in solid organ transplant recipients. Transplantation. 2015 ePub.

104. Taner T, Gandhi MJ, Sanderson SO, Poterucha CR, De Goey SR, Stegall MD, et al. Prevalence, course and impact of HLA donor-specific antibodies in liver transplantation in the first year. Am J Transplant. 2012; 12(6):1504–1510. [PubMed: 22420671]

105. Kaneku H, O'Leary JG, Banuelos N, Jennings LW, Susskind BM, Klintmalm GB, et al. De novo donor-specific HLA antibodies decrease patient and graft survival in liver transplant recipients. Am J Transplant. 2013; 13(6):1541–1548. [PubMed: 23721554]

106. Biancofiore G, Pucci L, Cerutti E, Penno G, Pardini E, Esposito M, et al. Cystatin C as a marker of renal function immediately after liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2006; 12(2):285–291.

107. 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. Transplantation proceedings. 2007; 39(10):3257–3260. [PubMed: 18089366]

108. Ling Q, Xu X, Li J, Wu J, Chen J, Xie H, et al. A new serum cystatin C-based equation for assessing glomerular filtration rate in liver transplantation. Clin Chem Lab Med. 2008; 46(3): 405–410. [PubMed: 18254705]

109. Gerhardt T, Poge U, Stoffel-Wagner B, Ahrendt M, Wolff M, Spengler U, et al. Estimation of glomerular filtration rates after orthotopic liver transplantation: Evaluation of cystatin C-based equations. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2006; 12(11):1667–1672.

110. Levitsky J, Salomon DR, Abecassis M, Langfelder P, Horvath S, Friedewald J, et al. Clinical and plasma proteomic markers correlating with chronic kidney disease after liver transplantation. Am J Transplant. 2011; 11(9):1972–1978. [PubMed: 21794091]

**TABLE 1**

COMMON METHODS FOR MEASURING GLOMERULAR FILTRATION RATES

| MEASURE | FORMULA | CALCULATION |
|---|---|---|
| **Estimated** | | |
| Creatinine | | |
| | MDRD4 | $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$ |
| | 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 | $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] where: $S_{cr}$ is serum creatinine in mg/dL, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is −0.329 for females and −0.411 for males, min indicates the minimum of $S_{cr}/\kappa$ or 1, and max indicates the maximum of $S_{cr}/\kappa$ or 1. |
| Cystatin C | | |
| | 2012 CKD-EPI cystatin C equation | $133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [×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 | $135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age}$ [×0.969 if female] [×1.08 if black] where: SCr is serum creatinine (in mg/dl), SCysC is serum cystatin C (in mg/l), $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ 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 |

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 | • No reliable evidence that interventions during surgery can provide protection from renal injury<br>• 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 | • No difference in CrCl in both groups<br>• 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 × 12 doses vs. 0.9% IV saline given similarly | • 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 | • 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 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 non-blinded: Fenoldopam patients 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. dopamine 3 $\mu g \cdot kg^{-1}$ vs. placebo during and until 96 h post-LT | • No change in CrCl with fenoldopam but significantly less drop in CrCl with dopamine vs. placebo |

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

| AUTHOR | N | STUDY DESIGN | MAJOR FINDINGS |
|---|---|---|---|
| **Early (<1 month) CNI minimization studies** | | | |
| Yoshida (51) | 148 | Immediate post-LT: DAC + reduced TAC delayed 6 days vs. standard TAC | • Improved GFR in reduced, delayed TAC<br>• 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 | • Significantly less drop in GFR in reduced, delayed TAC<br>• Less AR in reduced, delayed TAC |
| Calmus (53) | 199 | Immediate post-LT: DAC + standard TAC delayed 5 days vs. standard TAC | • No difference in month 12 SCr > 1.43 mg/dL<br>• No difference in AR rates |
| Boudjema (54) | 195 | Immediate post-LT: reduced TAC + MMF vs. standard TAC | • Significantly better GFR at month 12 in reduced TAC + MMF<br>• 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 | • Significantly better month 12 GFR in all BELA groups<br>• Significantly higher AR rates in all BELA groups<br>• Significantly diminished month 12 survival in BELA LI + MMF |
| Asrani (56) | 222 | Immediate post-LT: standard TAC vs. reduced TAC + SRL | • No difference in GFR<br>• 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 | • Significant month 12 eGFR increase in SRL + MMF<br>• High side effects and discontinuation in SRL + MMF<br>• Higher rejection rate in SRL + MMF |
| De Simone (58)<br>Saliba (59)<br>Fischer (60) | 719 | Week 4 post-LT: TAC elimination plus EVR vs. reduced TAC + EVR vs. standard TAC | • Month 12/24/36 eGFR superior for reduced TAC + EVR<br>• Reduced incidence and severity of AR in reduced TAC + EVR<br>• 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 | • Significant improvement in GFR with EVR conversion<br>• No difference in AR rates |
| Abdelmalek (71) | 607 | Month 6–144: CNI to SRL vs. CNI continuation | • No improvement in GFR with SRL conversion<br>• 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 | • No improvement in GFR with SRL conversion<br>• Higher AR rates with SRL conversion |
| De Simone (66) | 145 | Prospective randomized controlled:<br>EVR + low dose CNI/CNI elimination vs. standard dose CNI × 6 months, GFR 20–60 at enrollment<br>Time from LT to enrollment: 12–60 months | • No difference in eGFR or AR in both groups |
| Pageaux (68) | 56 | Prospective randomized controlled:<br>MMF + low dose CNI vs. standard CNI for chronic renal failure<br>Time from LT to enrollment: 1 year post-LT | • Significant improvement in eGFR in MMF+ low dose CNI at 1 year<br>• No AR in either group |
| Beckebaum (63) | 90 | Prospective randomized controlled (2:1):<br>MMF + low dose CNI vs. standard CNI for SCr>1.2 mg/dl<br>Time from LT to enrollment: 1 year post-LT | • Significant improvement in eGFR in MMF+ low dose CNI at 1 year<br>• 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:<br>• Avoidance of high osmolar agents (1B);<br>• Use of lowest possible radiocontrast dose (Not Graded);<br>• Withdrawal of potentially nephrotoxic agents before and after the procedure (1C);<br>• Adequate hydration with saline before, during, and after the procedure (1A);<br>• 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)<br>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):<br>• AKI or abrupt sustained fall in GFR;<br>• GFR <30 ml/min/1.73 $m^2$<br>• 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)<br>• 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 $m^2$/yr).<br>• urinary red cell casts, RBC >20 per high power field sustained and not readily explained<br>• CKD and hypertension refractory to treatment with 4 or more antihypertensive agents<br>• persistent abnormalities of serum potassium<br>• recurrent or extensive nephrolithiasis<br>• hereditary kidney disease |