CKD in Recipients of Nonkidney Solid Organ Transplants: A Review

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Chronic kidney disease (CKD) after solid organ transplant is a common clinical presentation, affecting 10% to 20% of liver, heart, and lung transplant recipients and accounting for approximately 5% of the kidney transplant waiting list. The causes of CKD are different for different types of transplants and are not all, or even predominantly, due to calcineurin inhibitor toxicity, with significant heterogeneity particularly in liver transplant recipients. Many solid organ transplant recipients with advanced CKD benefit from kidney transplantation but have a higher rate of death while waitlisted and higher mortality after transplant than the general kidney failure population. Recent organ allocation policies and proposals have attempted to address the appropriate identification and prioritization of candidates in need of a kidney transplant, either simultaneous with or after nonkidney transplant. Future research should focus on predictive factors for individuals identified as being at high risk for progression to kidney failure and death and on strategies to preserve kidney function and minimize the CKD burden in this unique patient population.

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Liver, heart, and lung transplantation have expanded over recent decades, resulting in a substantial number of patients with multiple comorbidities surviving longer with a successful nonkidney solid organ transplant (NKSOT). Many of these comorbidities have a direct impact on kidney function, creating a growing cohort of patients with chronic kidney disease (CKD). There are important differences in the pathophysiology and pathology of CKD in the NKSOT population compared to the CKD general population that influence clinical management. Strategies to minimize CKD in this population begin before NKSOT by using allocation policy to provide kidney transplants in selected patients at high risk of CKD, and continue after transplant by addressing the traditional risk factors and immunosuppression. Increasingly, consideration is required of kidney replacement therapy, including later kidney transplant. This review highlights the evolving epidemiology of CKD in NKSOT, discusses the kidney-specific pathophysiological and histological processes prevalent in this population, and describes current management strategies, both preventative and therapeutic, for CKD in NKSOT recipients.

Epidemiology

As the survival of patients with lung, liver, and heart transplants improves and as baseline clinical characteristics evolve, so too does the increased risk of CKD. A landmark registry study demonstrated the prevalence of CKD (defined as a glomerular filtration rate [GFR] < 30 mL/min) in NKSOT recipients as approaching and exceeding 25% at 10 years.[1] The overall incidence of CKD was 16.5%, ranging from 6.9% in heart-lung transplants to as high as 21.3% in intestine transplants with a median follow-up of 36 months. Not surprisingly, CKD in this patient population was associated with increased mortality risk, with a relative risk of death of 4.55 (95% CI, 4.38-4.74; $P < 0.001$) compared to those without CKD.

Although there has not been another formal analysis performed that is as comprehensive as the registry study, it is likely that rates of CKD after NKSOT have increased due to increased prevalence of comorbidities such as obesity and diabetes in liver transplant candidates and risk profiles such as pretransplant acute kidney injury (AKI) in heart transplant candidates, given the expanded use of ventricular assist devices for cardiomyopathy as a bridge to transplant.[2,3]

After NKSOT, the incidence of kidney failure and subsequent kidney transplant eligibility is rising. In a registry analysis of liver transplant recipients in 1995-2010, the incidence of kidney failure with replacement therapy within 5 years of transplant increased more than 2.5-fold to >55 per 1,000 patient-years.[4] This trend has contributed to an increase in the number of prior NKSOT recipients who become candidates for kidney transplant. During 1995-2008, listing for subsequent kidney transplant increased by 330% among liver recipients, 307% among heart recipients, and 635% among lung recipients, accounting for 3.3% of the kidney transplant waiting list.[5]

Pathophysiology

A number of factors contribute to the high prevalence of CKD after NKSOT. Important risk factors include preexisting CKD, glomerulonephritis (particularly in liver transplant candidates), which in some cases is due to hepatitis B and C virus (HBV and HCV) infection, and comorbidities such as diabetes and hypertension. NKSOT transplant candidates with a high illness acuity may experience repeated AKI, which also drives the development of CKD. Importantly, the organ allocation schema for liver transplant heavily favors candidates with kidney dysfunction, which leads to a higher prevalence of NKSOT recipients with CKD after liver transplant. Finally while perhaps not the sole or primary contributor to CKD, calcineurin inhibitor (CNI) use is often implicated in progressive CKD in NKSOT recipients.

Peritransplant AKI

As reviewed by Rossi and Vella,[6] AKI is a frequent complication of NKSOT, with a reported incidence ranging from 16.9% to 46% (the incidence of AKI treated with dialysis ranges from 4.6% to 8%). Although pretransplant AKI may be expected to be reversible, its contribution to future CKD in NKSOT recipients is exacerbated due to peri/posttransplant insults that include but are not limited to CNI use.

Calcineurin Inhibitors

CNIs are implicated in chronic vascular injury to native kidneys when used for treatment of chronic glomerular diseases and in solid organ transplant (SOT) recipients.[7] Lesions associated with CNI use include focal hyalinosis of small renal arteries and arterioles, with progressive uniform vascular hyalinosis and obliteration, increasingly associated with global or segmental glomerulosclerosis, tubular atrophy, and striped interstitial fibrosis.[8,9] The mechanisms of this arteriolar disease suggest endothelial damage, perhaps related to promotion of transforming growth factor β (TGF-β) through a variety of mechanisms.[10] As I will describe shortly, these lesions are not uniformly identified in NKSOT recipients with reduced GFR.

Traditional Risk Factors

Traditional risk factors associated with CKD such as hypertension (seen in up to 70% of liver transplant recipients and 90% of heart transplant recipients) and diabetes (present in ∼30% of all NKSOT recipients) play an important role in progressive CKD after NKSOT.[3,11] Blood pressure at 1 year was recently described as an independent risk factor for GFR decline between 1 and 5 years after liver and heart transplant.[12] This analysis of 2,534 heart transplant recipients and 1,822 liver transplant recipients found an association between increasing systolic blood pressure at year 1 and higher odds of poor kidney function at year 5 after transplant (odd ratios per 20 mm Hg increment of 1.25 for heart transplant recipients [$P < 0.001$] and 1.35 for liver transplant recipients [$P < 0.001$]). Another large single-center study of 1,151 liver transplant recipients identified independent associations of CKD stage at 1 year, pretransplant diabetes, urinary tract infections in the first year, and hypercholesterolemia in the first year with CKD stage progression at 3, 5, and 10 years.[13] In heart transplant recipients, factors of age, female sex, pretransplant/early posttransplant reduced kidney function, diabetes, and hypertension were associated with the risk of CKD after transplantation.[14]

Unfortunately, modifiable risk factors are often ineffectively managed, as demonstrated by a recent analysis from a tertiary care center in which <30% of 602 liver transplant recipients were treated to a blood pressure < 140/90 mm Hg at 1 year. Blood pressure control was associated with a substantial reduction in risk of mortality (hazard ratio [HR], 0.48 [95% CI, 0.39-0.87]) and of cardiovascular events (HR, 0.65 [95% CI, 0.43-0.97]).[15]

Chronic Viral Infection

Viral infections such as with HBV and HCV have historically been significant contributors to the risk of CKD in liver transplant in particular. However, with the introduction of successful suppressive (for HBV) and curative (for HCV) antiviral therapies,[16-19] the contribution of viral infection to posttransplant kidney disease has diminished. This has been replaced by metabolic factors including obesity and diabetes inherent to the rapidly growing postliver transplant population with nonalcoholic fatty liver disease as the cause of liver failure. Although BK virus reactivation is common in kidney transplant recipients, this has not manifested as a significant risk in NKSOT recipients, with only case reports supporting any role and screening studies demonstrating a low rate of BK reactivation.[20]

Kidney Pathology in SOT CKD

In the largest kidney biopsy series to date, among a diverse population of NKSOT recipients, histologic assessment among lung (30 biopsies in 28 patients), heart (20 biopsies in 20 patients), and liver (41 biopsies and 39 patients) transplant recipients demonstrated differences in pathologies between SOT types (Table 1).[21] Arteriolar hyalinosis was much more prevalent in lung and heart transplant recipients than in liver transplant recipients

Table 1. Biopsy-Diagnosed Kidney Disease in Patients After Transplantation of Other Organs and Tissues

	Liver (n = 41)	Lung (n = 30)	Heart (n = 20)
Clinical characteristics			
Hypertension	62%	86%	90%
Diabetes	36%	39%	35%
Time after transplant, mo	35	19	66
eGFR at biopsy, mL/min	37.6	28.1	25.1
Cyclosporine-based	75%	33%	55%
Tacrolimus-based	23%	33%	10%
CNI plus mTOR inhibitor	5%	33%	35%
Histologic findings			
Acute tubular injury	49%	75%	70%
Interstitial fibrosis/tubular atrophy > 20%	51%	64%	35%
Arteriolar hyalinosis	13%	64%	35%
Benign nephrosclerosis	41%	54%	40%
Global glomerulosclerosis	18%	18%	30%
Nephrocalcinosis	13%	0	5%
Primary glomerular disease	26%[a]	0	15%[b]

Adapted from Schwarz et al,[21] with permission of the copyright holder (John Wiley and Sons). Abbreviations: CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin.
[a]IgA nephropathy: n = 6; minimal change disease: n = 1; membranoproliferative glomerulonephritis: n = 2.
[b]IgA nephropathy: n = 2; membranoproliferative glomerulonephritis: n = 1.

Box 1. Relevant Recommendations From KDIGO in Solid Organ Transplant Recipients

For Hypertension and/or Albuminuria
- UAE <30 mg/d and BP >140/90: treat to ≤140/90 (grade 1B)
- UAE ≥30 mg/d and BP >130/80: treat to ≤130/80 (grade 2D)
- UAE ≥300 mg/d: use ACEI or ARB (grade 1B)
- DM and UAE 30-300 mg/d: use ACEI or ARB (grade 2D)

For CKD (eGFR < 60 mL/min)
- Dietary salt: Reduce intake to < 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride). (Grade 1C)
- Acidosis: Bicarbonate supplementation can be given for patients with bicarbonate concentrations < 22 mmol/L. (Sodium bicarbonate is typically given in a daily dose of 0.5 to 1 mEq/kg daily; 1 tablet of sodium bicarbonate has 7.7 mEq, so typical dose is 1-2 tablets 3 times per day.) (Grade 2B)

Nephrology Referral (Grade 1B)
- AKI or abrupt sustained fall in GFR
- GFR <30 mL/min/1.73 m^2
- Consistent significant albuminuria (UACR ≥ 300 mg/g [≥30 mg/mmol] or albumin excretion rate ≥300 mg/d, equivalent to UPCR ≥ 500 mg/g [≥50 mg/mmol] or protein excretion rate ≥ 500 mg/d)
- Progression of CKD (drop in eGFR from baseline by 25% or a sustained decline in eGFR of >5 mL/min/1.73 m^2 per year)
- Urinary red cell casts or >20 RBCs per high-power field that is 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

Based on KDIGO clinical practice guidelines.[36,38] Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; RBC, red blood cell; UACR, urinary albumin-creatinine ratio; UAE, urinary albumin excretion; UPCR, urinary protein-creatinine ratio.

whereas primary glomerular disease (in particular, IgA nephropathy) was more common in liver transplant patients. Further evidence of non–CNI-related renal toxicity in the liver transplant patient population was provided by a series of 81 biopsies performed a mean of 4.8 years after liver transplant in patients with a mean estimated GFR (calculated using the Modification of Diet in Renal Disease [MDRD] Study equation) of 38.7 mL/min and 24-hour urine protein of 1.37 g/d.[22] Primary glomerular diseases (focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis) were identified in 43% of the 81 biopsies, and glomerulosclerosis and arterionephrosclerosis were found universally. However, nodular hyalinosis (typically associated with CNI nephrotoxicity) was uncommon, only identified in 15% of biopsies. These findings (and a lack of isolated CNI nephrotoxicity) were similar in other biopsy series as well.[23,24] Overall, these biopsy series highlight the fact that diagnoses other than CNI nephrotoxicity are common and are different among the various types of organ transplant, with many features similar to native CKD. Caveats to these findings include selection bias, given the variability in inclusion criteria for biopsy from each single center; era effect, in that treatment for HBV and HCV in the direct-acting antiviral agent era may mitigate the preponderance of glomerular abnormalities; and evolving pathologic criteria for CNI nephrotoxicity, such that the sensitivity and sensitivity for identifying CNI toxicity as a cause of CKD in NKSOT are unknown.

Clinical Management

Assessment of GFR

GFR estimates, while potentially varying in accuracy across different populations, are likely acceptably applied for the NKSOT population with caveats. Assessment of GFR estimating equations in NKSOT patients was assessed by a systematic review in which the authors identified 26 equations used to estimate GFR in 3,622 individuals (53% kidney, 35% liver, and 12% other SOT recipients).[25] The performance of the CKD Epidemiology Collaboration (CKD-EPI) equation was superior to or comparable with alternative equations, and the CKD-EPI and MDRD Study equations were found to be as accurate in NKSOT populations as they are in other clinical populations, justifying their use in NKSOT recipients. The caveats that must be considered include the overestimation of GFR overall by these equations in the setting of reduced muscle mass, which is common in NKSOT recipients.[26-29] For example, in lung transplant recipients the CKD-EPI creatinine equation appears to be adequate but is inaccurate in the setting of cystic fibrosis, low arm muscle mass, and low body mass index, in which case cystatin C–based equations may be more accurate.[30]

From a practical standpoint, the CKD-EPI creatinine equation, followed by the MDRD Study equation, may be considered the most appropriate estimates of GFR in NKSOT. Clinicians should consider using the CKD-EPI cystatin C equation as a confirmatory test when clinically indicated, such as in cases where muscle mass is poorly represented by weight.

General Principles

Because there are few formal data pertaining to CKD management that are specific to NKSOT recipients, their management must rely upon extrapolations from best nephrology practices in the native and kidney transplant CKD patient populations. As described previously, given the variable and unpredictable kidney histology in NKSOT recipients with kidney dysfunction, kidney biopsy is likely underused in the NKSOT population. As in the general population,[31] a kidney biopsy should be considered under circumstances of rapid or unexplained decline in kidney function, active urine sediment, and/or increasing or nephrotic-range proteinuria.

Table 2. Key Clinical Trials Evaluating Immunosuppression Modifications to Preserve Kidney Function in Recipients of Nonkidney Solid Organ Transplants

Study	Organ	Timing After Transplant	N	Key Finding
Fischer et al[40] (randomized prospective)	Liver	1 mo	719	CNI minimization with mTORi was associated with improved GFR and reduced risk of rejection vs standard CNI; CNI elimination with mTORi was associated with excessively high rejection rate.
Teperman et al[41] (randomized prospective)	Liver	1-3 mo	293	SRL converson from CNI was associated with higher GFR but higher rejection rates and medication discontinuation rates.
Abdelmalek et al[42] (randomized prospective)	Liver	6-144 mo	607	Conversion from CNI to SRL did not improve GFR and was associated with higher rejection rates.
De Simone et al[43] (randomized prospective)	Liver	12-60 mo	145	CNI minimization or elimination with mTORi was not associated with improvement in GFR.
Beckebaum et al[44] (randomized prospective)	Liver	12 mo	90	CNI minimization with addition of MMF was associated with higher GFR and no increase in acute rejection.
Gustafsson et al[45] (randomized prospective)	Heart	7-11 wk	115	CNI conversion to SRL was associated with increased acute rejection but reduced chronic allograft vasculopathy and higher GFR; findings persisted with 5-7 year follow-up.
Asleh et al[46] (single-center retrospective)	Heart	>3 mo	402[a]	CNI conversion to SRL was associated with reduced chronic allograft vasculopathy and mortality in overall cohort, and less CAV attenuation and higher all-cause mortality in those with proteinuria.
Zuckerman et al[47] (randomized prospective)	Heart	1-8 y	116	CNI conversion to SRL was associated with modest improvement in GFR, higher rejection rates, and high (33%) SRL discontinuation rate.
Gullestad et al[48] (randomized prospective)	Heart/Lung	>12 mo	282	Addition of mTORi to 3-drug regimen with CNI minimization was associated with stabilization of GFR over 5 years, higher infection incidence.
Glanville et al[49] (randomized prospective)	Lung	<3 mo	165	CNI minimization combined with mTORi did not improve GFR and was associated with higher incidence of acute rejection.

Search used for compilation of studies included all articles from 2005-2021 with the following terms: sirolimus and/or mTOR inhibitor and/or mycophenolate and/or belatacept; and liver transplant and/or lung transplant and/or heart transplant; and/or GFR and/or glomerular filtration rate and/or chronic kidney disease and/or kidney disease; and/or conversion. Priority was given for randomized trials and multicenter trials for final selection. Abbreviations: CAV, cardiac allograft vasculopathy; CNI, calcineurin inhibitor; (e)GFR, (estimated) glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor; SRL, sirolimus.
[a]137 with proteinuria assessment at time 0 and 1 year after conversion.

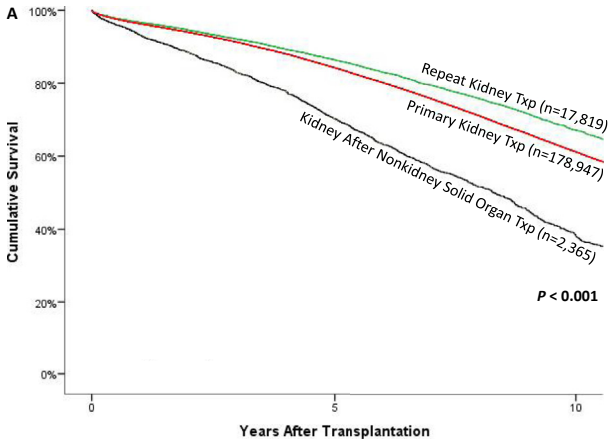
KDIGO clinical practice guideline recommendations that pertain most specifically to the solid organ transplant patient population are summarized in Box 1.[32-33] Blood pressure goals should be less than or equal to 140/90 mm Hg in general; if CKD (eGFR < 60 mL/min), proteinuria, or diabetes is present, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are considered first-line therapies with an adjusted blood pressure target of less than or equal to 130/80 mm Hg. Despite recent data in the native CKD population that intensive blood pressure lowering to goal <120/80 mm Hg (when measured in a standardized manner in the office setting) prevents the decline of GFR,[34] no studies to date have demonstrated a protective effect with more aggressive blood pressure goals or specific agents in the NKSOT population.

Sodium/glucose cotransporter 2 (SGLT2) inhibitors have been shown to slow CKD progression in both the diabetic and nondiabetic CKD populations[33] but have not been studied extensively in the NKSOT population (or those with a kidney transplant); their effectiveness among NKSOT recipients might be reduced due to differences in infection risk and metabolic/hemodynamic concerns due to attendant CNI use. Additional recommendations with reasonable supporting evidence include a low-salt diet (less than 2 g/d of sodium) and treatment of metabolic acidosis[35-39] for patients with bicarbonate concentrations less than 22 mmol/L.

Immunosuppression Modifications

For transplant clinicians, it is tempting to try to modify immunosuppression (eg, reduce or eliminate CNIs) in the setting of CKD in NKSOT recipients to attempt to slow progression. Potential strategies include introduction of mTOR inhibitors (sirolimus, everolimus), introduction of mycophenolate mofetil (MMF) with CNI minimization or

A



B

Comparison Groups	Graft Failure: HR (95% CI)	P	Mortality: HR (95% CI)	P
Repeat kidney vs primary kidney Txp	1.055 (0.998-1.145)	.057	1.054 (0.982-1.131)	.148
Kidney-after-liver vs primary kidney Txp	1.304 (1.124-1.513)	<.001	1.445 (1.183-1.767)	<.001
Kidney-after-heart vs primary kidney Txp	1.747 (1.456-2.097)	<.001	1.497 (1.286-1.742)	<.001
Kidney-after-lung vs primary kidney Txp	2.123 (1.516-2.974)	<.001	3.309 (2.395-4.572)	<.001

Figure 1. (A) Patient survival (Kaplan-Meier curves) after primary kidney transplant (n = 178,947), repeat kidney transplant (n = 17,819), and kidney-after-SOT (n = 2,365) from 2000-2014. (B) Hazard ratio of kidney graft loss and mortality after kidney transplant, comparing primary kidney, repeat kidney, and kidney-after-SOT recipient outcomes. Those with previous SOT, particularly those with prior lung transplant had inferior patient and kidney allograft survival when compared to primary or repeat kidney transplant due to posttransplant mortality rather than death-censored kidney graft loss (Fig 1B). Panel A ©2017 John Wiley and Sons, reproduced from El-Husseini et al[62] with permission of the copyright holder.

withdrawal, or CNI conversion to belatacept-based therapy. Unfortunately, there is no strong evidence that reduction or elimination of CNI therapy improves kidney function when performed greater than 1 year after NKSOT, with modest evidence supporting modifications within the first posttransplant year. Table 2 summarizes the key clinical trials that form current perspectives on immunosuppression modifications to preserve kidney function, and further detailed discussion follows.

CNI Withdrawal

The impact of CNI conversion to sirolimus is highlighted by a large multicenter trial of 607 liver transplant recipients randomized to sirolimus conversion or continuation of CNI maintenance therapy (mean of 4.0 ± 2.9 years from transplant).[42] An on-therapy analysis demonstrated a decline in creatinine clearance (estimated by the Cockcroft-Gault formula) that was greater in the sirolimus arm (−4.45 mL/min over 12 months) versus CNI maintenance (−3.07 mL/min), and transition was associated with higher acute rejection rates and with a high rate of sirolimus discontinuation compared with CNI continuation (36% vs 11%, P < 0.001). Further evidence of a lack of improvement with CNI conversion to mTOR inhibitors is summarized in a meta-analysis of randomized controlled trials in liver transplantation (10 trials with a total of 1,927 patients).[50] Overall, a higher eGFR 1 year after randomization to mTOR inhibitor was reported (by 7.5 [95% CI, 3.2-11.8] mL/min/1.73 m^2), but this improvement was demonstrated only in studies with early conversion within 1 year after transplant. Conversion was also associated with a higher acute rejection rate (relative risk, 1.8 [95% CI, 1.3-2.3]) and a higher mTOR inhibitor discontinuation rate compared with CNI continuation (relative risk of discontinuation, 2.2 [95% CI, 1.4-3.4]). Although data are less robust in heart transplantation, conversion from CNI to mTOR inhibitor (sirolimus) in a prospective trial of 116 patients showed similar findings of modest improvements in GFR (+3.0 vs −1.4 mL/min/1.73 m^2; P = 0.004), coupled with higher rejection rates and a high rate of mTOR inhibitor discontinuation specifically due to adverse events (33.3% vs 0; P < 0001).[51,52]

CNI Minimization

Minimizing CNI (rather than eliminating) may be safer and better tolerated but also has a more modest effect on kidney protection. In liver transplant, a systematic review of randomized trials identified 4 trials in which MMF was introduced and CNI minimized more than 5 years from transplant, with stable or improved GFR and no increase in risk of rejection.[52]

In heart and lung transplants, a randomized trial of 282 recipients more than 1 year from transplant minimized CNI (cyclosporine <75 ng/mL or tacrolimus <4 ng/mL) while adding the mTOR inhibitor everolimus to a 3-drug regimen (CNI, azathioprine or mycophenolate, and prednisone).[48] The 5-year follow-up demonstrated that measured GFR remained stable in the CNI minimization group (changing from 51.3 to 51.4 mL/min) but decreased in the controls (from 50.5 to 45.3 mL/min) (P = 0.004) with similar rates of rejection, death, and major cardiac events but higher pneumonia rates in the 4-drug/CNI minimization arm. In a 3-year multicenter randomized trial of 165 lung transplant recipients, conversion from MMF to everolimus with CNI dose reduction demonstrated no differences in kidney function with higher rates of side effects and biopsy-proven acute cellular rejection in the mTOR inhibitor arm.[49] In a minority of patients mTOR inhibitors have been associated with progressive proteinuria and may synergize with CNI to exacerbate CNI nephrotoxic effects.[53,54] A recent study in heart

Box 2. Future Research Needs in the Prevention and Management of CKD in NKSOT

Pre/Peritransplant
- Role of kidney biopsy in determining etiology/severity of pretransplant kidney injury and relationship to posttransplant kidney function
- Biomarkers to predict kidney recovery in AKI immediately after transplant
- Interventions to preserve kidney function intra/postoperatively
- Perioperative immunosuppression strategies to promote renal recovery

Posttransplant
- Role of SGLT2 inhibition in NKSOT recipients with CKD
- Appropriate blood pressure goal in NKSOT recipients
- Role of kidney biopsy in the management of CKD after NKSOT
- Immunosuppression strategies to slow progression of CKD
- Noninvasive biomarkers in predicting CKD progression in NKSOT

Risk-benefit analyses of nephrotoxic immunosuppressive medication use (eg, calcineurin inhibitors, mTOR inhibitors), comparing their proposed benefits upon NKSOT graft outcomes and patient complications versus kidney complications.
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; mTOR, mammalian target of rapamycin; NKSOT, nonkidney solid organ transplant; SGLT2, sodium/glucose cotransporter 2.

Box 3. Eligibility Criteria for Simultaneous Liver-Kidney Transplantation

Per OPTN/UNOS criteria for eligibility for simultaneous liver-kidney transplant, candidates must meet at least 1 of the following conditions:
1. CKD with GFR <60 mL/min for >90 days with:
   a. Kidney failure treated by maintenance KRT, or
   b. GFR <30 mL/min at time of listing for kidney
2. Sustained AKI with:
   a. 6 Consecutive weeks of KRT, or
   b. GFR <25 mL/min for 6 consecutive weeks, or
   c. Combination of 2a and 2b for 6 consecutive weeks
3. Metabolic disease (hyperoxaluria, aHUS, familial non-neuropathic systemic amyloidosis, or methylmalonic aciduria)[a]

"Safety net" provision for kidney after liver transplant: Liver transplant recipients who continue to receive dialysis or who have GFR ≤20 mL/min in the period 2-12 months after liver transplant will receive priority for kidney allocation for kidneys with KDPI >20%.

These criteria were adopted in August 2017[68] (pp 147-148 and 215-217) in response to annual increases in SLK transplants since 2012 and a lack of consistency in selection of candidates; there was a subsequent decrease in SLK transplants and an increase in kidney after liver transplants.[69] Abbreviations: aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDPI, kidney donor profile index; KRT, kidney replacement therapy; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; SLK, simultaneous liver-kidney transplant.
[a]Candidates with these primary diseases are eligible for SLK transplant regardless of GFR or CKD status.

transplantation found that the presence of proteinuria in patients converted to mTOR inhibitors was associated with higher all-cause mortality.[46] For this reason mTOR inhibitors are discouraged from use for those patients with an estimated or measured GFR <40 mL/min/1.73 m^2 or proteinuria.

Belatacept Conversion

The costimulation inhibitor belatacept is approved in kidney transplantation as a result of landmark trials demonstrating improved GFR and better patient and graft survival, despite higher acute rejection rates compared with cyclosporine.[55,56] It is currently not approved for use as a de novo immunosuppressive agent in liver, lung, or heart transplant recipients. It carries a black box warning in liver transplant as a result of a multicenter study demonstrating an increase in graft loss and death compared with standard immunosuppression.[57] A number of small case series have been published describing conversion to belatacept in liver, lung, and heart transplant recipients (summarized in Perez et al[58] and Chandrashekaran et al[59]). Although the outcomes in these reports were generally favorable, including stabilization of kidney function when conversion was used for renoprotection, safety is not well understood in these populations, and these findings are best considered exploratory at this point.

In summary, there are mixed data supporting CNI minimization or withdrawal with mTOR inhibitors during the first year after transplant to preserve GFR. After the first year after transplant, CNI minimization with MMF adjunctive therapy may improve GFR in the setting of mild CKD in liver transplant, with little evidence to support mTOR inhibitor use to preserve kidney function after the first year in liver, heart, or lung transplant recipients and only modest experience with belatacept in these settings.

Outcomes of Subsequent Kidney Transplant in the NKSOT Population

The NKSOT population forms a rapidly growing cohort of patients on the kidney transplant waiting list, raising concerns regarding equity and access to kidney transplant for the native CKD population. A 2010 registry analysis compared outcomes of patients with prior NKSOT (lung, heart, or liver) to primary kidney transplant candidates and to repeat kidney transplant candidates.[60] Pertinent findings include (1) waiting list mortality was 2- to 4-fold higher for patients with prior heart, liver, lung transplant; (2) kidney transplant provided a significant survival advantage for NKSOT recipients compared to their waitlisted NKSOT counterparts, comparable to the survival benefit in kidney retransplant recipients yet still inferior to primary kidney transplant recipients; and (3) the kidney after lung transplant population had a significantly higher mortality risk than other cohorts, both in the waitlist and posttransplant phase of care. These findings have been corroborated by more recent analyses (Fig 1).[61,62]

Table 3. Management Considerations of Kidney Disease in the Nonkidney Organ Transplant Candidate/Recipient, With Proposed Clinical Provider Roles and Responsibilities

Clinical Presentation	Assessment	Nephrology-specific Interventions	Transplant Center	Transplant Nephrology	General Nephrology
Pretransplant					
Progressive CKD and progressive end-stage organ disease	Kidney function assessment (eg, renal ultrasound, urinalysis, urine protein, eGFR/mGFR)	HTN and volume status management, CKD education and management (Box 1)	✓		✓
Acute exacerbation of organ disease and kidney function	Evaluation for intercurrent kidney injuries; renal preservation strategies	Avoidance of nephrotoxic insults, medication review, imaging modality review, management of hemodynamic status	✓		✓
Imminent transplant	Determination of eligibility for simultaneous organ/kidney transplant	Formal consultation, review of criteria for kidney transplant	✓	✓	
	Management of AKI	Assessment for transplant eligibility, management of short-term dialysis	✓	★	★
Posttransplant: 0-2 Months					
Reduced kidney function/recovery	Management of AKI	Assessment for nephrotoxic insults, management of short-term dialysis	✓	★	
	Immunosuppression	Assessment for/implementation of kidney-protective strategies	✓	✓	
Posttransplant: 2-12 Months					
CKD	CKD management; assessment of GFR	HTN and volume status management, CKD education and management (Box 1)	✓		✓
	Immunosuppression	Assessment for/implementation of kidney-protective strategies	✓	✓	
	Eligibility for kidney transplant	Living kidney donor education, "safety net" eligibility assessment	✓	✓	
Posttransplant: > 12 Months					
CKD	CKD management; assessment of GFR	HTN and volume status management, CKD education and management (Box 1), consideration of kidney biopsy, dialysis modality planning			✓
	Immunosuppression	Assessment for/implementation of kidney-protective strategies	✓		✓
	Determination of eligibility for kidney transplant	Transplant referral and assessment, living kidney donor education	✓	✓	✓

This template will vary according to the individual transplant center's resources and personnel but forms a basis for collaborative care across the transplant continuum. Checkmark indicates roles and responsibilities are established; focus should be on strategies to increase collaboration and encourage ongoing management of CKD. Star denotes roles and responsibilities are less established; focus should be on appropriate transitions of care and follow-up after treatment interventions. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; (e)GFR, (estimated) glomerular filtration rate; HTN, hypertension; mGFR, measured glomerular filtration rate.

Given the increase in the last decade in the age and comorbidities of the NKSOT population, a pertinent question is how the elderly NKSOT recipient with advanced CKD fares after kidney transplant.[63] Of 5,023 prior NKSOT recipients over the age of 65 on the kidney transplant waiting list in 1995-2016, there were 863 candidates who ultimately received a kidney transplant. Kidney transplant conferred a survival benefit, with a greater than 50% reduction in mortality for prior lung, liver, and heart transplant recipients (overall adjusted HR,

0.47 [95% CI, 0.42-0.54]; P < 0.001). Death-censored graft loss was similar to older kidney transplant recipients but mortality was higher (5-year patient survival of 36% vs 28%; adjusted HR, 1.40 [95% CI, 1.28-1.54]; P <0.001). These findings underscore the importance of timely referral of SOT recipients, including elderly patients, for kidney transplant.[60,64]

Early Identification and Management of NKSOT Candidates and Recipients at Risk of CKD

Ultimately, improved predictors and proactive interventions to optimize kidney function and prevent progressive CKD after NKSOT are needed (Box 2). In the pretransplant period, improvements in the management of AKI (eg, hepatorenal syndrome[65]) are necessary, as are better tools to determine the degree of chronic kidney injury before transplant, beyond creatinine-based determinations.[66,67] In an effort to mitigate the risks of prior/ongoing kidney injury on posttransplant outcomes, careful assessments of NKSOT candidates' kidney function and appropriate allocation of simultaneous kidney-SOT have been prioritized. In August 2017, a new allocation system for simultaneous liver-kidney (SLK) transplantation was implemented (Box 3).[68-71] This policy provides clear definitions of eligibility for combined organ transplant, either on the basis of the degree of CKD (GFR <30 mL/min with a history of GFR <60 mL/min for more than 3 months) or the duration of AKI (GFR <25 mL/min and/or receipt of dialysis for more than 6 weeks). For circumstances in which liver transplant recipients did not receive a simultaneous kidney transplant but had persistent kidney failure, a safety net plan was implemented in which liver transplant recipients with GFR <20 mL/min beginning 2 to 12 months after liver transplant become eligible for subsequent kidney transplant, with substantial allocation priority. Efforts to implement a similar policy for simultaneous heart-kidney transplant are underway, with consensus recommendations modeled after the United Network for Organ Sharing (UNOS) SLK policy.[72,73]

Beyond allocation policy, a number of emerging approaches to the prevention and treatment of CKD after SOT deserve further study. Clinical risk tools are available to predict those liver transplant candidates at most risk of kidney failure 5 years after transplant, which could be used for further risk stratification.[4,74] Patient education programs and clinical pathways can better streamline care for individuals at risk and those with established disease.[75,76] Involvement of the general nephrologist earlier in posttransplant management may be valuable because even mild CKD in the first year after liver transplant has been associated with increase in mortality (Table 3).[77]

Biomarkers of injury also should be further explored. For example, urinary neutrophil gelatinase-associated lipocalin (NGAL) when measured at 24 hours after reperfusion has been shown to be independently associated with CKD at 5 years after liver transplant.[78] Kidney injury–sparing immunosuppressive strategies should be further developed and may include delayed CNI introduction to promote renal recovery for those with postoperative reduced kidney function[79,80] and later CNI conversion with novel immunosuppressive agents such as belatacept. Ideally, future studies may test interventions based upon these preliminary findings (Box 2).

Conclusion

In NKSOT recipients, the etiology of CKD is often multifactorial. Judicious use of simultaneous kidney-SOT and management of perioperative AKI are important interventions for NKSOT patients at risk for advanced CKD. Subsequently, blood pressure control and diabetes control are primary considerations, while immunosuppression manipulation should be considered a secondary intervention with unproven benefit particularly after the first year of transplant. Once NKSOT recipients have progressed to late-stage CKD and kidney failure, consideration of kidney transplant is important as the SOT population enjoys survival benefits compared with remaining on the waiting list. However, survival of SOT recipients after kidney transplant (particularly the lung transplant population) remains inferior to the primary kidney transplant population. Collaborative care between transplant clinicians and nephrology practitioners is likely to be valuable in the SOT patient population to attenuate kidney function decline, appropriately manage late-stage CKD, and reduce the increasing burden upon the kidney transplant waiting list.

Article Information

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