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Novel options for failing allograft in kidney transplanted patients to avoid or defer dialysis therapy

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Abstract

Purpose of review—Despite improvement in short-term renal allograft survival in recent years, renal transplant recipients (RTR) have poorer long-term allograft outcomes. Allograft function slowly declines with periods of stable function similar to natural progression of chronic kidney disease (CKD) in non-transplant population. Nearly all RTR transitions to failing renal allograft (FRG) period and require transition to dialysis. Conservative CKD management before transition to end-stage renal disease (ESRD) is an increasingly important topic; however, there is limited data in RTR regarding how to delay dialysis initiation with conservative management.

Recent findings—Since immunological and non-immunological factors unique to RTR contribute to decline in allograft function, therapies to slow progression of FRG should take both sets of factors into account. Renal replacement therapy (RRT) either incremental dialysis or re-kidney transplantation should be explored. This required taking benefits and risks of continuing immunosuppressive medications into account when allograft nephrectomy may be necessary.

Summary—FRG may benefit from various interventions to slow progression of worsening allograft function. Until there are stronger evidence to guide interventions to preserve renal function, extrapolating evidence from non-transplant patients and clinical judgement are necessary. The goal is to provide individualized care for conservative management of RTR with FRG.

Keywords

dialysis after allograft loss; failing renal allograft; immunosuppression; kidney transplantation; residual renal allograft function

1. Introduction

Kidney transplantation (KT) is a treatment of choice for an appropriate advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. After the introduction of cyclosporine (CsA) in the early 1980s, short-term renal allograft outcomes were improved [2, 3], but long-term outcomes remains poor [4]. Renal transplant recipients (RTR) will ultimately develop allograft failure with time, requiring dialysis initiation or re-initiation [5].

Allograft survival varies according to multiple factors, as such the pattern and time course deterioration of allograft function can be unpredictable. We define failing renal allograft (FRG) as “*a process of progressive decline in renal allograft function after a successful kidney transplantation with a previously established baseline renal allograft function*”.

Common causes of CKD and ESRD occur in kidney recipients with allograft failure (KRAF); but immunological factors are the specific causes of worsening allograft function. Table 1 summarizes common etiologies of FRG.

Given the RTR undergo “*for cause*” allograft biopsy rather than protocol biopsy, prevalence of each cause of FRG is unclear. Moreover, transplant providers may forego renal biopsy since a biopsy of a FRG may not change management or the outcome.

In addition to complications from worsening allograft function, the level of immunosuppression causes pathogenesis and clinical manifestations FRG, which are different from non-transplant advanced CKD patients (Figure 1).

Over immunosuppression causes chronic calcineurin inhibitor (CNI) nephrotoxicity, opportunistic infections, and malignancies; whereas, under immunosuppression increases risks of acute rejection, and sensitization which decreases possibility of receiving compatible donors for subsequent KT (Figure 2). The expected clinical course after imbalance of immunosuppression in RTR will ultimately lead to FRG (Figure 3).

In this articles, we review therapies which delay allograft function decline, and propose an approach for transiting from FRG to subsequent renal replacement therapy (RRT). Given the recent focus of delaying or preventing renal function decline, therapies that delay need for RRT, and utilizing an incremental approach to RRT are recommended in the review.

2. Therapy to slow progression of failing renal allograft

Available evidence and controversies of non-pharmacological and pharmacological approaches to slow progression of FRG are reviewed (Table 2).

2.1 Non-pharmacological management

2.1.1 Low dietary protein intake—High protein intake increases renal blood flow (RBF), intraglomerular pressure, and ultimately causes increased glomerular filtration rate (GFR). This appears to be the physiologic mechanism to allow the kidneys to increase excretion of nitrogen waste products from high dietary protein [6]. This renal hemodynamic change, also known as glomerular hyperfiltration [7], may lead to glomerular injury and nephrosclerosis. These occur as a long-term consequence of higher protein intake in both non-dialysis CKD patients or person with a solitary kidney including living kidney donors [8, 9*].

The RTR with FRG are in the later stages of non-dialysis-dependent CKD (CKD-T) [10]. Decreased functioning nephron mass leads to pathophysiological processes of glomerular hyperfiltration and glomerulomegaly, and ultimately secondary focal segmental glomerulosclerosis (FSGS) manifesting as proteinuria. One prospective observational study demonstrated effect of high protein intake and progression of allograft function. Patients with moderate protein (0.8 g/kg/day) and sodium (3 g/day) intake had no change in allograft function during a 12-year follow-up; whereas, allograft function declined >40% of excretion efficiency in patients with higher protein (1.4 g/kg/day) and sodium intake (5 g/day) [11].

Although there is not much evidence to confirm the advantage of low-protein diet (LPD) in RTR, from evidence of reno-protective effect of LPD in CKD patients, protein intake of 1 g/kg/day if estimated glomerular filtration rate (eGFR) >45 ml/min/1.73 m² or albumin-to-creatinine ratio (ACR) <30 mg/g of creatinine, and 0.6–0.8 g/kg/day if eGFR <45 ml/min/1.73 m² or ACR >30 mg/g of creatinine is suggested [12].

2.1.2 Low dietary sodium intake—High sodium intake causes renal damage directly from vascular injury and indirectly from elevated blood pressure (BP) and proteinuria. The same mechanism of renal injury is via glomerular hyperfiltration that is seen with a high protein diet.

The above-mentioned study revealed that moderate sodium intake slows progression of allograft function compared to high sodium intake. However, this effect may be attributable to lower protein intake in the former group [11].

Another study including 38 RTR participating in low sodium intake of <80 mmol/day demonstrated that systolic blood pressure (SBP), diastolic blood pressure (DBP), average and night time SBP and DBP from a 24-hour ambulatory blood pressure measurements decreased after 14 days of low dietary sodium intake; however, urinary protein excretion was unchanged [13].

Evidence of renoprotective effect of low sodium diet in RTR remains scant. We suggest sodium intake <3 g/day if eGFR >45 ml/min/1.73 m² or ACR <30 mg/g of creatinine and <2.3 g/day if eGFR <45 ml/min/1.73 m² or ACR >30 mg/g of creatinine [12].

2.2 Pharmacological management

2.2.1 Antiproteinuria—Proteinuria in RTR is associated with poor allograft outcomes [14–16]. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) lower proteinuria and slow progression of allograft function in patients with chronic allograft nephropathy (CAN) [17–19]. One retrospective observational study followed 56 patients with biopsy-proven CAN for 5 years. Compared to rate of rising serum creatinine before ACEI or ARB initiation, the rate was decreased after initiation of these medications [20]. Although there is inadequate evidence that this would prolong allograft survival in advanced allograft dysfunction in the long-term follow-ups, ACEI or ARB may be considered as antiproteinuric agents in patients with FRG unless there is side effects such as hypotension, hyperkalemia, anemia, or rising serum creatinine.

2.2.2 Blood pressure control—Hypertension is associated with poor allograft and patient outcomes [21–24]. Calcium channel blockers (CCB) appears to mitigate nephrotoxic effect of CNI from its vasodilatory property [25] and delays chronic histological changes including interstitial fibrosis in RTR taking CsA [26]; however, this protective effect of CCB in RTR with chronic renal allograft dysfunction (CGD) is unclear. Moreover, dihydropyridine CCB (DCCB) cause afferent arteriolar vasodilatation, increased intraglomerular pressure, filtration fraction, and ultimately proteinuria [27].

A systematic review with meta-analysis including 28 randomized clinical trials (RCT) showed that non-dihydropyridine CCB (NDCCB) had antiproteinuric effect in non-kidney transplant adult regardless presence or absence of diabetes [28]. Although there is no strong evidence of antiproteinuric effect of NDCCB in RTR, NDCCB allows lowering CNI dose without interfering CNI hepatic metabolism, this results in lower CNI exposure. The combination of NDCCB, low-dose CNIs, and ACEI/ARB in RTR may be considered in the setting of proteinuria.

Low sodium intake is required to maximize the effect of antihypertensive medications [13, 29]. Since high sodium intake causes increased intraglomerular pressure and proteinuria and salt-sensitive hypertension is common in patients with a declined renal function, ACEI/ARB and NDCCB should be used with low sodium diet.

2.2.3 Chronic Kidney Disease-Mineral Bone Disorder management—Medial arterial calcification (MAC), which is a risk for cardiovascular disease (CVD), is common in CKD and ESRD [30]. After successful KT, bone-mineral metabolism derangement may return to lower values or persist depending on pre-transplant levels. Though MAC appear to be irreversible [31]. One single-center case-control study was conducted in RTR with biopsy-proven CAN or elevated serum Cr 0.3 mg/dL from baseline serum creatinine at transplant discharge. Patient in these groups treated with calcitriol for secondary hyperparathyroidism after KT had a significant improvement in allograft function compared to age- and gender-matched control RTR [32]. Although RTR with FRG likely require

therapy to control mineral and bone metabolism abnormalities, additional evidence are required to confirm the benefit of chronic kidney disease-mineral bone disorder (CKD-MBD) therapy in the RTR population.

2.2.4 Post-transplant metabolic acidosis—In RTR with FRG, CNI both CsA and tacrolimus cause metabolic acidosis (MA) via non-CNI pathway. High protein intake may cause MA. MA alters muscle protein catabolism [33] leading to muscle protein loss, renal osteodystrophy in CKD [34], and post-transplant anemia (PTA) [35]. However, MA induces renal hypertrophy which increases GFR as a compensatory mechanism of low nephron mass [36]. It is unclear that treating MA improves allograft function. Correcting MA is a benign intervention that improves muscle and bone health, PTA, and frailty. Therefore, sodium bicarbonate may be used in RTR with FRG. Additionally, low animal protein and high plant-based diet can improve MA [37].

2.2.5 Post-transplant anemia—PTA is associated with allograft loss [38, 39]. Correction of anemia with erythropoiesis-stimulating agent (ESA) in RTR with FRG may protect renal ischemia and avoid complications of PTA. Two recent RCT showed a renoprotective effect of correcting anemia by ESA in RTR with CAN. RTR in high hemoglobin group treated with ESA to target hemoglobin of 12.5–15 g/dL had a lower rate of eGFR decline compared to patients with a low hemoglobin of 10.5–11.5 g/dL [40, 41**].

2.2.6 Aspirin—CGD includes several histological features including vascular damage, narrowing of small and glomerular vessels, interstitial fibrosis and tubular atrophy, and glomerulosclerosis [42]. These histological changes resulted from factors causing endothelial cell activation, adhesion and activation of platelets and leukocytes [43–45], which are similar in CVD. Therefore, aspirin may slow progression of CGD. A retrospective cohort study revealed that RTR receiving low-dose aspirin (100 mg/day) had a lower rate of rising serum creatinine, proteinuria, and microscopic hematuria both short- and long-term aspirin therapy (aspirin use <50% and >50% of overall graft survival time, respectively) [45]. Although, additional evidence is required, aspirin may be considered in RTR with FRG who have CVD or CV co-morbidity if there is no contraindications.

2.2.7 Anti-oxidants—Inflammation begins at the time of KT through allograft loss and continues until allograft nephrectomy [46–53]. Increased oxidative stress in CKD causes increased proinflammatory cytokines which lead to interstitial inflammation and CKD progression [54]. Oxidative stress also occurs in RTR with CAN especially from CNI use [55, 56].

Vitamin C and E, nutritional antioxidants, neutralize some effects of CsA. Additionally, antioxidants improve histological injury from CsA and renal function [57]. N-acetyl-cysteine (NAC) improves markers of oxidative stress and histologic changes from CsA in rat [58]. Although there is not enough evidence in RTR with FRG and clinical studies are required, antioxidants may be considered in these patients.

Hyperhomocystenemia is highly prevalent in ESRD patients and RTR [59, 60].

Supraphysiologic dose of folate, vitamin B6, and B12 normalizes homocysteine in chronic

stable RTR and mild to moderate CKD patients; however, this treatment do not lower homocysteine in >90% of ESRD patients [61].

Since homocysteine lowering therapy is not associated with CV outcomes and all-cause mortality in CKD, ESRD, and kidney transplant patients or rate of commencement in dialysis initiation, we do not recommended for RTR with FRG [62*].

3. Preparation for subsequent kidney transplantation

Once allograft begins the FRG period, the plan should be to slow the rate of decline in allograft function, while the next RRT with dialysis or subsequent KT is being prepared. The feasibility of receiving a subsequent KT is one of the main factors that dictates the choice of RRT and immunosuppressive medication management. At this phase, immunosuppressive medication and dialysis management can be therapeutic strategies to slow progression of the FRG.

3.1 Immunosuppressive medication management during failing renal allograft

General considerations—Once allograft function begins to progressively declines, three main factors that should be taken into the consideration for immunosuppressive medication management are candidacy for the next KT, potential unacceptable complications from maintaining immunosuppressive medications, and residual renal allograft function (RGF) (Figure 4).

Clinical significance of residual renal allograft function—There are several benefits of preserving residual kidney function (RKF) in non-kidney transplant populations including solute clearance, volume control, reduced inflammation, and survival benefits [63*]. Table 3 summarizes possible mechanism leading to the benefits from preserving RKF including solute control [64], volume control [65–67], inflammatory reduction [68], improvement in anemia [68], nutrition [69, 70], and QoL [71].

For RTR returning to dialysis after allograft loss (DAGL), preservation of RGF is also crucial. A study using a decision analytic model (Markov model) among a theoretical cohort of patients with chronic allograft failure demonstrated survival benefit of higher RGF from maintaining immunosuppressive medications in RTR returning to peritoneal dialysis (PD) compared to those who were in FRG and withdrew immunosuppressive medications [72].

The following is a proposed immunosuppressive medication management in RTR with FRG (Figure 5).

3.1.1 Candidacy for the next kidney transplantation—RTR with FRG, who are potential candidates for the subsequent KT, should maintain immunosuppressive medications at the lowest dose. The balance should aim to suppress alloreactivation and preserve RGF, while avoiding complications from immunosuppression. The anticipated time to receive the next KT and RGF can guide the appropriate level of immunosuppression.

3.1.1.1 Patients with an anticipated short waiting time: RTR with FRG who are anticipated to receive the subsequent KT soon such as those having potential living kidney donors or listed in transplant centers with a short waiting time e.g. <2 years, should continue immunosuppressive medications that adequately suppress alloreactivation regardless their RGF. However, complications from immunosuppression need to be monitored to avoid unnecessarily over immunosuppression.

3.1.1.2 Patients with an anticipated long waiting time: For RTR with FRG and low likelihood to receive subsequent KT in a short period of time, RGF can guide immunosuppressive medication management. Patients who still have RGF, immunosuppressive medications should be tapered to the lowest levels possible but can maintain RGF and avoid acute rejection in a failed allograft. This strategy avoids escalation of immunosuppression or transplant renal allograft nephrectomy. Generally, mycophenolate is first tapered off followed by steroids. CNI is then tapered to the lowest dose possible.

In patients who lose their RGF, all immunosuppressive medications should be tapered until completely off generally after 6 months of allograft loss to avoid acute rejection in a failed allograft.

The degree of sensitization at the time of FRG can also guide the strategy to taper immunosuppressive medications. Highly sensitized RTR have lower risks of further sensitization compared to non-sensitized patients because immunosuppressive medication tapering or withdrawal likely increases the possibility to broaden reactive antibodies and make non-sensitized patients become highly sensitized [73].

3.1.2 Non-candidate for the next kidney transplantation—In patients who are not a candidate for re-transplantation, further tapering of immunosuppressive medications may be a better approach.

Immunosuppressive medication management in patients who are not candidates for re-transplantation is similar to RTR with FRG and acceptable transplant candidacy, except for non-transplant candidate patients who lose their RGF, all immunosuppressive medications should be tapered until completely off after 6 months of allograft loss regardless availability of potential living kidney donors.

3.2 Dialysis care during failing renal allograft

Patients with FRG may ultimately require dialysis initiation either temporary dialysis while waiting for subsequent KT or permanent dialysis in patients who are not a candidate for the next KT. Transition care for advanced CKD patients to ESRD involves in factors contributing to outcomes such as time of dialysis initiation, type of RRT, prelude conditions and comorbidities [74]. For RTR who return to DAGL, conditions during functioning allograft and FRG periods and immunological factors contribute to outcomes post-transition to dialysis. Compared to transplant naïve HD patients, RTR who re-initiated HD after allograft loss had similar survival [75].

There are benefits of RGF, and a potential risk of a rapidly decline in RGF once dialysis is initiated. Utilizing incremental HD strategy with 1–2 times-per-week HD is one strategy to preserve RGF.

Several observational cohort studies demonstrated a slower decline in RKF in non-transplant dialysis patients having twice-weekly HD compared to those having thrice-weekly HD [76–79].

A pilot study examined the effect of oral NAC, as an antioxidant, on RKF in non-transplant incidental PD patients. After 1 months of oral NAC 1,200 mg twice daily, urine output, residual Kt/V, and residual urea and creatinine clearance were significantly increased [80]. Hence, NAC may be also considered in RTR returning to PD.

Although there is no evidence showing survival benefit of incremental dialysis in RTR returning to DAGL, preservation of RGF by incremental HD remains beneficial and should be utilized in these patients.

Dialysis modality—In transplant naïve ESRD patients, PD provides better survival during the early post-dialysis transition compared to HD, but the survival benefit does not persist in the long-term [81, 82]. For RTR returning to DAGL, both PD and HD lead to similar short- and long-term survivals. A study including 2,111 RTR who underwent DAGL demonstrated no difference in survival between patients who underwent PD and HD at early (2 years) and late (>2 years) after dialysis initiation [82].

Time to initiate dialysis after allograft loss—Mortality is not different between early and late dialysis initiations in transplant naïve patients, but more evidence showed that late dialysis initiation is associated with better outcomes. There is little evidence showing benefit of early dialysis initiation in RTR with allograft loss, but survival outcome may be worsened in some populations such as women and healthy young patients [83]. eGFR is not the best marker to determine the time of dialysis initiation since some factors such as predialysis care, late referral, dialysis dose, timing of immunosuppression reduction and RGF may contribute to outcomes after re-initiation of dialysis [84].

3.3 Transplant renal allograft nephrectomy and blood transfusion

Failed allograft is thought to be “antibody sink” that prevents a higher level of broadly reactive antibodies [73]. In CsA era, transplant nephrectomy increased panel reactive antibodies (PRA) [85, 86] especially when patients were unsensitized or nephrectomy was performed within 6 months after allograft failure [86]. One study showed that PRA levels significantly effect subsequent allograft survival regardless transplant nephrectomy of the prior failed renal allograft [87]. Although transplant nephrectomy is associated with the development of antigenicity, it did not affect rate of re-transplantation, allograft or patient survivals [85, 88].

Generally, transplant nephrectomy is indicated in case of acute complications such as allograft rejection or infection. One single study demonstrated that patients with vascular

thrombosis or non-compliance were more likely to undergo nephrectomy; whereas, those with chronic rejection were less likely to require nephrectomy [88, 89].

Given its role of persistent inflammation, failed allograft may contribute to anemia and ESA resistant [90]. Apart from prior transplantation and pregnancy, blood transfusion is among the most common cause of sensitization [91]. A leukocyte-reduced blood cannot prevent sensitization [91]. Donor specific transfusion (DST) by using human leukocyte antigen (HLA)-matched blood lowers risk of sensitization. In patients with functioning allograft and maintaining immunosuppressive medications, blood transfusion was not related to increased HLA antibodies [92]. Using CsA (1 day prior through 1 week post-transfusion) [93] or azathioprine (concomitant with transfusion) [94] in failed allograft patients who are not on immunosuppressive medication was effective in lowering levels of sensitization. Graft-versus host disease can be prevented by using irradiated blood [91].

Special consideration to prevent and mitigate failing renal allograft

Apart from death with a functioning graft, chronic CNI nephrotoxicity is one of the most common causes of CGD. Minimizing CNI exposure at the early or even later stage post-transplantation is one of the strategies that have been utilized for several decades. These strategies include CNI minimization, conversion, avoidance, and withdrawal by using mammalian target of rapamycin (mTOR) inhibitor or belatacept. Systematic reviews and meta-analyses consistently demonstrated that mTOR inhibitors and belatacept are associated with favorable renal allograft function but associated higher risk of rejection [95, 96].

Tolerance induction is another elegant strategic approach to withdraw CNI and essentially all immunosuppressive medications. There are several protocols used in different research transplant centers with various populations and outcomes [97]. Although tolerance induction remains a research technique, cumulative evidences of promising outcomes provides hope in improving allograft outcomes. One must weight the potential infectious and hematological risks from possible over immunosuppression from the tolerance induction protocols, however.

Conclusion

Care for RTR with FRG is complex and both immunological and non-immunological factors are required. Several therapeutic strategies are not from strong evidence and some are extrapolated from non-transplant CKD or ESRD patients. Preparation for the next RRT either dialysis or subsequent KT should be planned by adjusting immunosuppressive medications as per individual conditions. The goal is to maximize the possibility of receiving subsequent KT and avoid complications from unnecessarily over immunosuppression [98*]. Lastly, despite strategies to slow progression of FRG may delay worsening allograft function, the ultimate outcome is allograft loss. Patients should be counseled and those who are candidates for a subsequent KT, should be referred to transplant center early. Apart from medical consideration, psychological management is also required since successful therapy for FRG depends heavily on the patients' cooperation.

Transplant teams, primary nephrologists, and primary care physicians need to collaborate in the care for such these complex patients.

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin-to-creatinine ratio
ARB	angiotensin receptor blocker
BP	blood pressure
CAN	chronic allograft nephropathy
CCB	calcium channel blocker
CGD	chronic renal allograft dysfunction
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral and bone disorder
CKD-T	non-dialysis-dependent CKD
CNI	calcineurin inhibitor
CsA	cyclosporine A
CVD	cardiovascular disease
DAGL	dialysis after allograft loss
DBP	diastolic blood pressure
DCCB	dihydropyridine calcium channel blocker
DST	donor specific transfusion

GFR	glomerular filtration rate
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FRG	failing renal allograft
FGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
HLA	human leukocyte antigen
KRAF	kidney recipients with allograft failure
KT	kidney transplantation
LPD	low-protein diet
MA	metabolic acidosis
MAC	medial arterial calcification
mTOR	mammalian target of rapamycin
NAC	N-acetyl-cysteine
NDCCB	nondihydropyridine calcium channel blocker
PD	peritoneal dialysis
PRA	panel reactive antibody
PTA	post-transplant anemia
QoL	quality of life
RBF	renal blood flow
RCT	randomized clinical trial
RGF	residual renal allograft function
RKF	residual kidney function
RRT	renal replacement therapy
RTR	renal transplant recipient
SBP	systolic blood pressure

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Key points

- Long-term allograft outcomes remains poor from CGD secondary to various pathogenesis and risk factors.
- FRG is a continuous process and involves in both immunological and non-immunological factors.
- Several therapeutic interventions to slow FRG should be an integration of both non-pharmacological and pharmacological approaches.
- Preparation for the next RRT either dialysis or re-KT for RTR with FRG should be planned and individualized to provide appropriate immunosuppressive medication management, maximize possibility of the subsequent KT, and avoid complications from unnecessarily over immunosuppression.
- CNI minimization or withdrawal either by using mTOR inhibitor or belatacept and tolerance induction can avoid effect of CNI nephrotoxicity, but increased risk for rejection or complications from tolerance induction protocols should be considered.

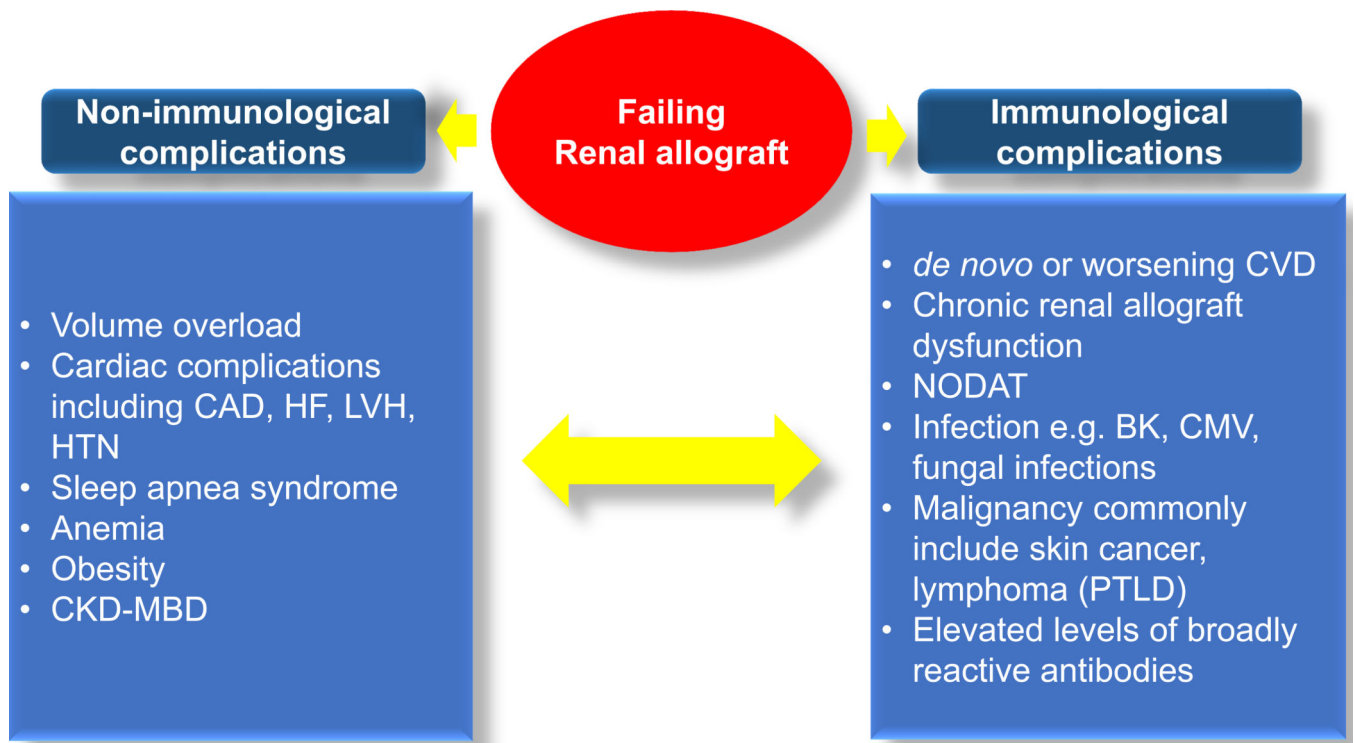


Figure 1:

Consequences of failing renal allograft both non-immunological and immunological complications and their interconnection.

CAD, coronary artery disease

CKD-MBD, Chronic Kidney Disease-Mineral Bone Disorder

CVD, cardiovascular disease

HF, heart failure

HTN, hypertension

LVH, left ventricular hypertrophy

NODAT, new-onset diabetes after transplantation

PTLD, post-transplant lymphoproliferative disorder

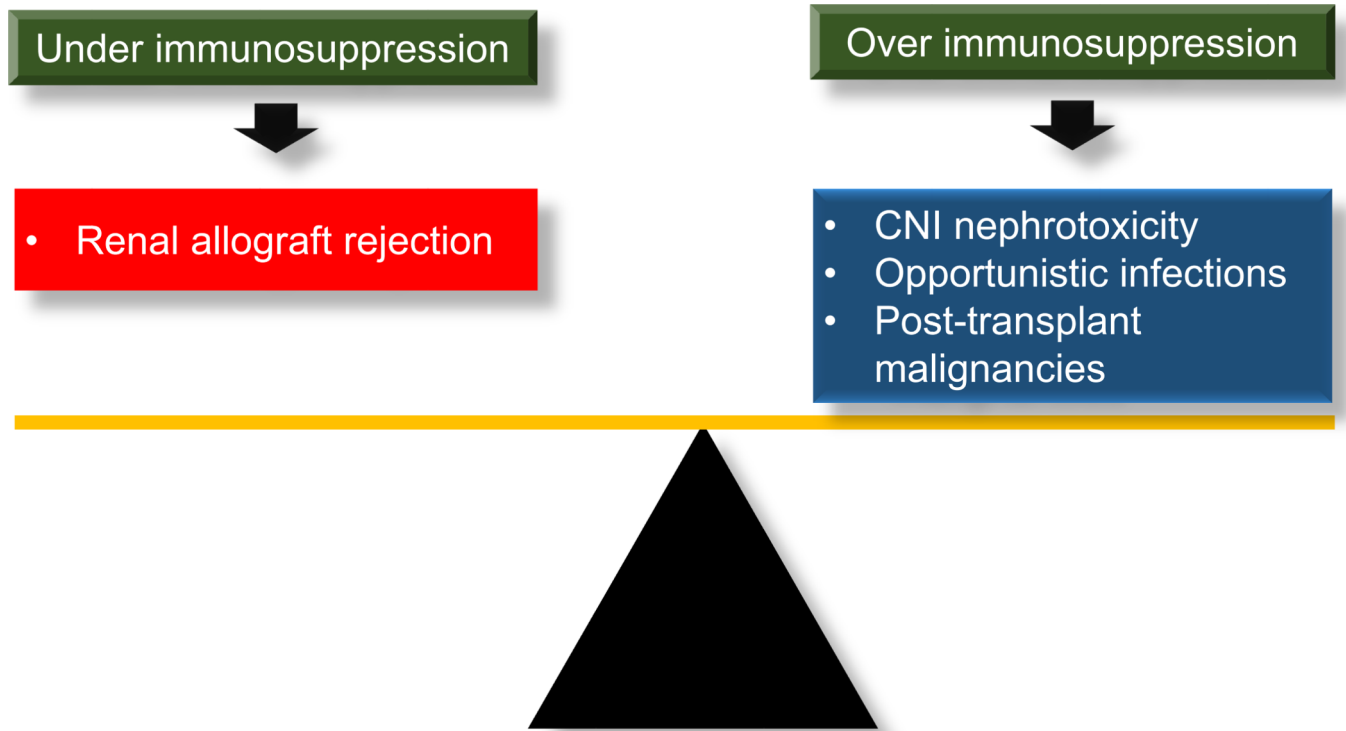


Figure 2:
Balance between continuing immunosuppressive medications to prevent renal allograft rejection and being at risk for complications from net stage of over immunosuppression in kidney transplant recipients with failing renal allograft
CNI, calcineurin inhibitor

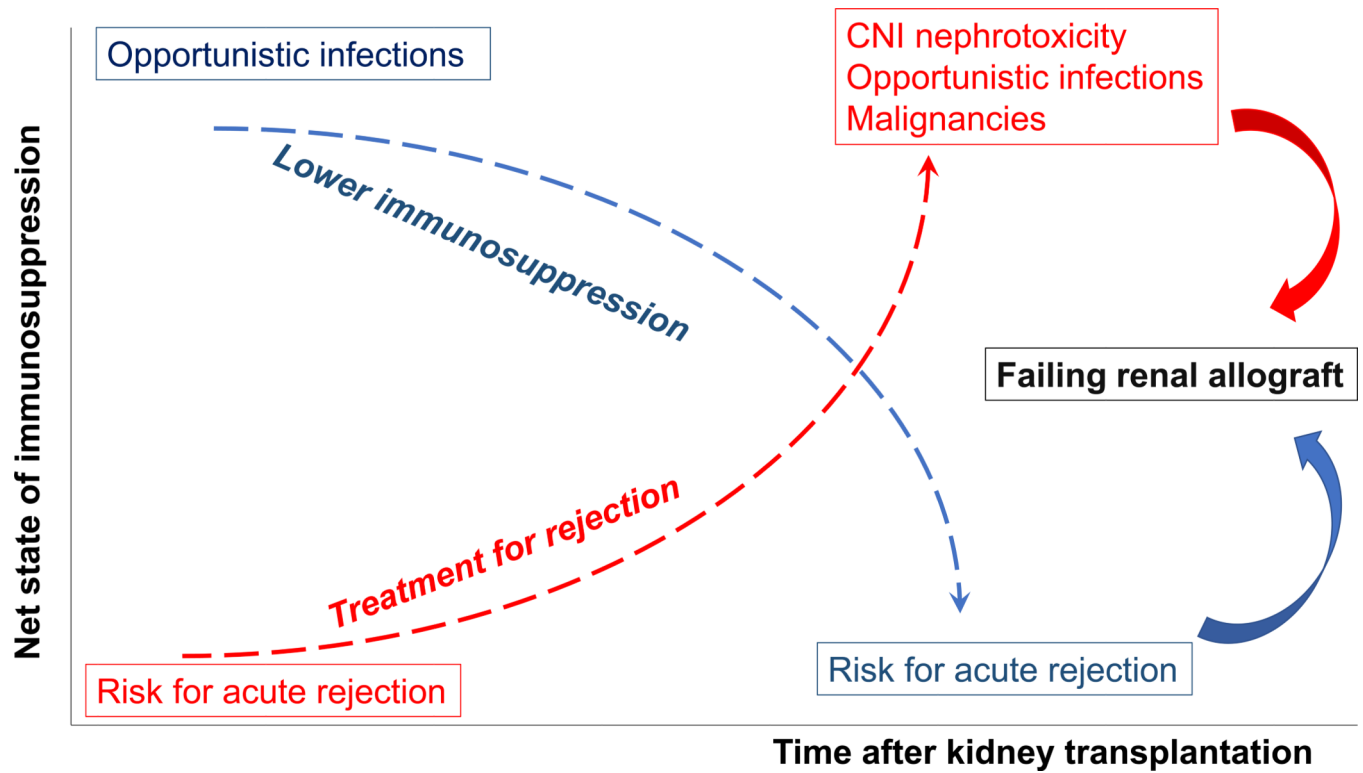


Figure 3:
Common clinical course from imbalance of immunosuppression in kidney transplant recipients. Both over and under immunosuppression will ultimately lead to failing renal allograft.

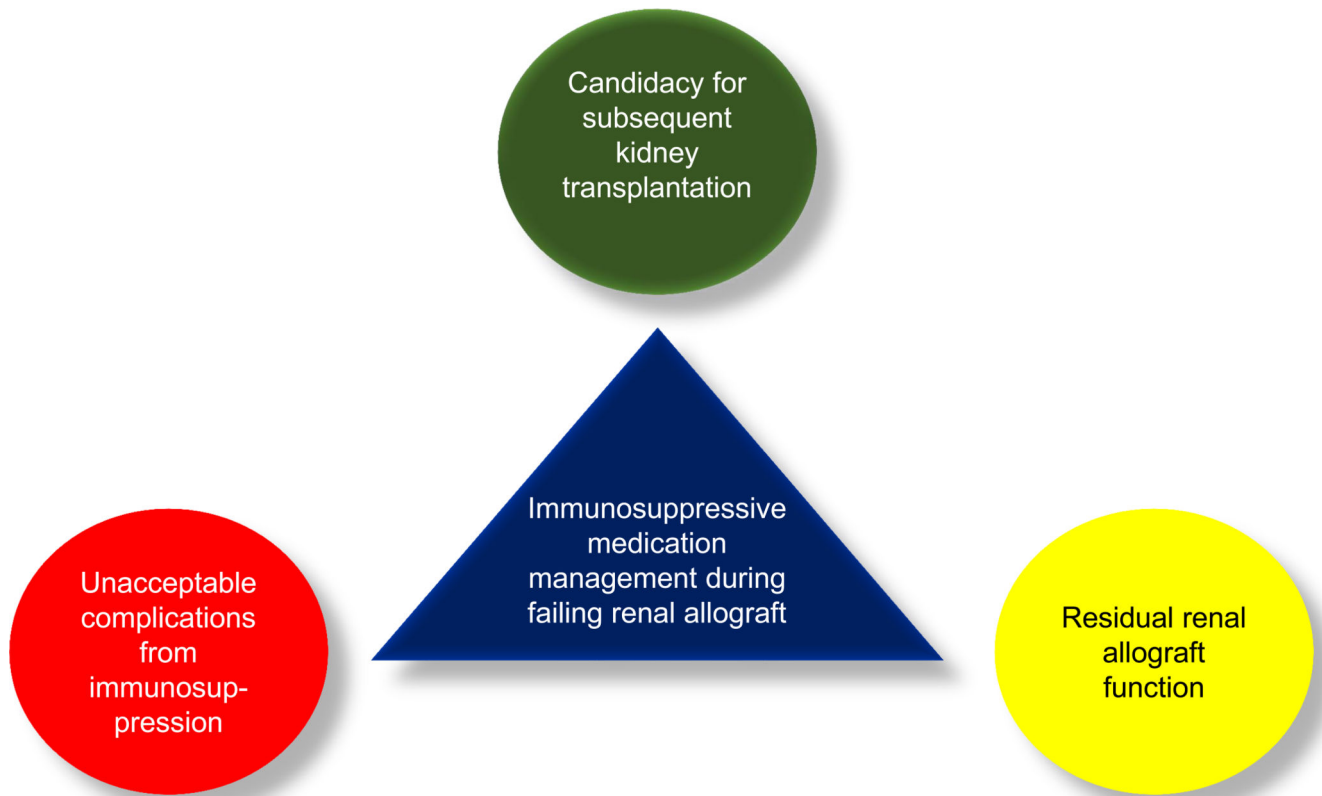


Figure 4:
Three main factors to consider for immunosuppressive medication management during failing renal allograft

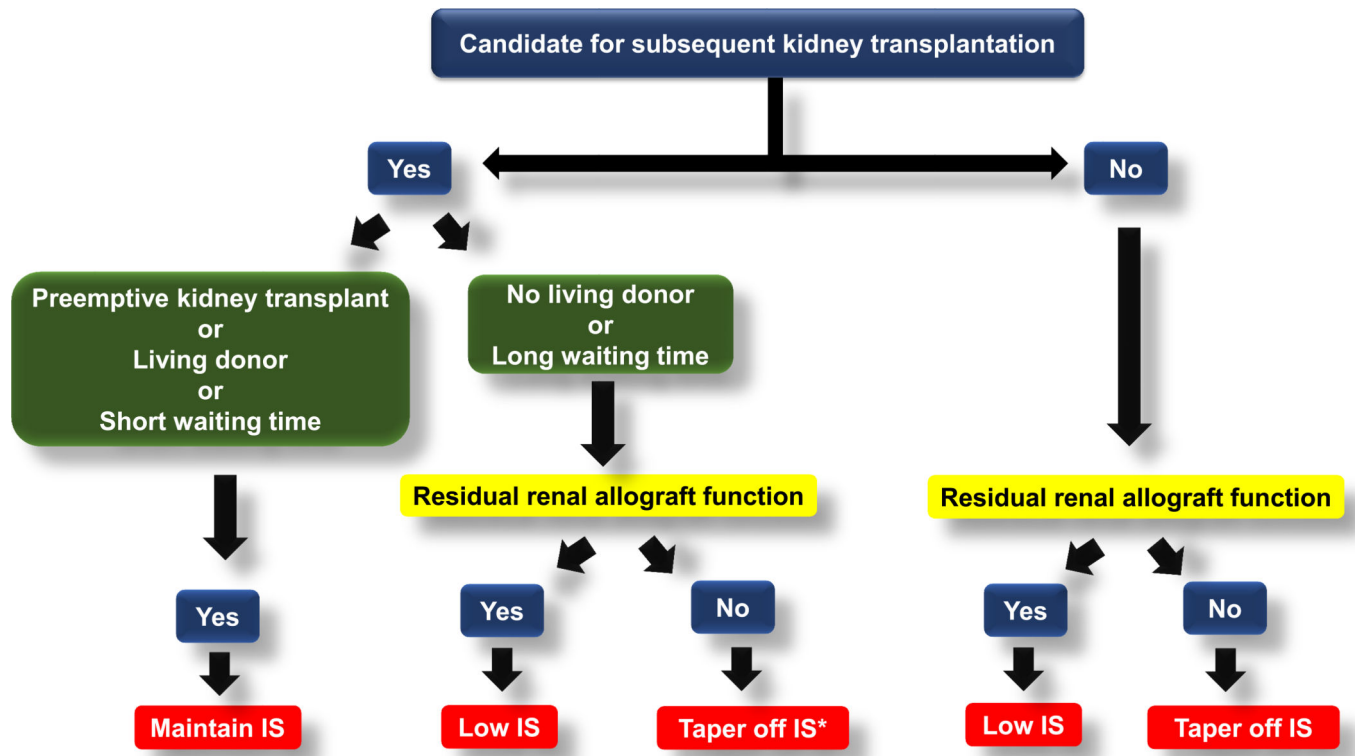


Figure 5:

Proposed algorithm for immunosuppressive medication management in kidney transplant recipients with failing renal allograft

IS, immunosuppressive medications

- if the patients can receive KT sooner such in the case of available potential living kidney donors or being also listed in other transplant programs with a short waiting time, maintaining low does, single agent immunosuppressive medication should be considered unless their immunosuppressive medications are already tapered off

Table 1:

Common etiologies of failing renal allograft.

	Groups of diseases or conditions	Common diseases or conditions
Non-immunological-related causes		
<i>Prerenal causes</i>	<ul style="list-style-type: none"> • Systemic diseases • Reno-vascular disease 	<ul style="list-style-type: none"> • Orthostatic hypotension commonly in long-standing diabetes mellitus, cardio-renal syndrome
<i>Intrinsic renal causes</i>	<ul style="list-style-type: none"> • Recurrent native renal disease in a transplant renal allograft • Interstitial disease 	<ul style="list-style-type: none"> • E.g. FSGS, MGN, IgAN, LN • E.g. recurrent transplant pyelonephritis
<i>Post-renal causes</i>	<ul style="list-style-type: none"> • Transplant nephrolithiasis 	
Immunological-related causes		
<i>Acute renal allograft rejection</i>	<ul style="list-style-type: none"> • Unintended lowering immunosuppression • Intended lowering immunosuppression 	<ul style="list-style-type: none"> • Non-medication adherence • E.g. Lowering immunosuppression during over immunosuppressed stage when the following complications occur: CMV, BK, GI side effects, malignancy
<i>Chronic renal allograft dysfunction or the old term “transplant glomerulopathy”</i>	<ul style="list-style-type: none"> • Chronic ABMR 	<ul style="list-style-type: none"> • Untreated, inadequately treated, or even unsuccessfully treated acute renal allograft rejections leading to ongoing inflammatory process and ultimately chronic scarring
<i>Immunosuppressive medications</i>	<ul style="list-style-type: none"> • Chronic CNI nephrotoxicity 	<ul style="list-style-type: none"> • Long-standing exposure to high level of immunosuppressive medications
<i>Opportunistic infection</i>	<ul style="list-style-type: none"> • BKVAN 	<ul style="list-style-type: none"> • Leading to interstitial disease or post-renal obstruction
ABMR, antibody-mediated rejection		
BKVAN, BK virus-associated nephropathy		
CMV, cytomegalovirus		
CNI, calcineurin inhibitor		
FSGS, focal segmental glomerulosclerosis		
GI, gastrointestinal		
IgAN, immunoglobulin A nephropathy		
LN, lupus nephritis		

General therapeutic interventions to slow progression of failing renal allograft by divided into non-pharmacological and pharmacological approaches

Table 2:

Non-pharmacological interventions	<p><i>Low dietary protein intake Plant-based protein diet</i></p> <ul style="list-style-type: none"> • Avoid glomerular hyperfiltration <p><i>Low dietary sodium intake</i></p> <ul style="list-style-type: none"> • Avoid direct vascular injury or indirect injury from elevated blood pressure • Avoid glomerular hyperfiltration • Maximize effect of antihypertensive medications especially in salt-sensitive hypertension <p><i>Weight control and nutrition management</i></p> <ul style="list-style-type: none"> • Malnutrition-inflammation complex syndrome (MICS) • Protein energy wasting (PEW) • Reversal of the reverse epidemiology <p><i>Smoking cessation</i></p> <ul style="list-style-type: none"> • Acute hemodynamic e.g. elevated blood pressure and intraglomerular pressure • Chronic effects e.g. endothelial cell dysfunction
Pharmacological interventions	<p><i>Antiproteinuria</i></p> <ul style="list-style-type: none"> • Angiotensin-converting enzyme inhibitor • Angiotensin receptor blocker • Non-dihydropyridine calcium channel blocker <p><i>Blood pressure control*</i></p> <ul style="list-style-type: none"> • Dihydropyridine calcium channel blocker counteracts with vasoconstrictive effect of CNI by causing renal artery vasodilation • Decrease interstitial volume by calcium channel blocker (nifedipine) <p><i>Glycemic control</i></p> <ul style="list-style-type: none"> • Lower severe arteriolar hyalinosis lesions <p><i>Cholesterol control</i></p> <ul style="list-style-type: none"> • Inconclusive for renoprotective effect • Cardiovascular morbidity and mortality <p><i>Volume control</i></p> <ul style="list-style-type: none"> • Salt-sensitive hypertension • Decreased residual renal allograft function • Calcitriol ? <p><i>Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) management</i></p> <ul style="list-style-type: none"> • Correcting metabolic acidosis may not improve renal allograft function but there may improve muscle and bone health and anemia • Sodium bicarbonate • Low animal protein diet and high plant-based diet <p><i>Post-transplant metabolic acidosis</i></p> <ul style="list-style-type: none"> • Possible protection from renal ischemia • Possible prevention of endothelial damage which can lead to chronic renal allograft dysfunction <p><i>Post-transplant anemia</i></p> <ul style="list-style-type: none"> • Vitamin C • Vitamin E • Nutritional antioxidants • N-acetyl-cysteine • ? Supraphysiologic dose of folate, vitamin B6, and vitamin B12

* Antihypertensive medications should be used with low sodium diet for maximize antihypertensive effect of medications.

Possible mechanism leading to the benefits from residual renal function in dialysis-dependent patients

Table 3

Benefits	Mechanism
Solute clearance	<ul style="list-style-type: none"> • B2-microglobulin • protein bound solutes
Volume control	<ul style="list-style-type: none"> • Lower ultrafiltration volumes in each hemodialysis session • Less intradialytic hypotension • Less myocardial stunning • reduction in cardiovascular mortality
Inflammatory reduction	<ul style="list-style-type: none"> • C-reactive protein and interleukin-6
Anemia management	<ul style="list-style-type: none"> • Less anemia with less use of epoetin alpha
Nutritional improvement	<ul style="list-style-type: none"> • Better overall nutritional status • Better control of serum phosphorus.
Quality of life and survival	<ul style="list-style-type: none"> • Better quality of life