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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.

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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 m^2 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 m^2 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 m^2 or ACR <30 mg/g of creatinine and <2.3 g/day if eGFR <45 ml/min/1.73 m^2 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 intraglomuerular 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 no 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 underwent 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
FSGS	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

References:

1. Suthanthiran M, Strom TB. Renal transplantation. N Engl J Med. 1994;331(6):365–76. [PubMed: 7832839]
2. Starzl TE, Klintmalm GB, Weil R 3rd, et al. Cyclosporin A and steroid therapy in sixty-six cadaver kidney recipients. Surg Gynecol Obstet. 1981;153(4):486–94. [PubMed: 6269238]
3. Terasaki PI, Cecka JM, Gjertson DW, et al. A ten-year prediction for kidney transplant survival. Clin Transpl. 1992:501–12. [PubMed: 1306721]
4. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant. 2004;4(3):378–83. [PubMed: 14961990]
5. Perl J Kidney transplant failure: failing kidneys, failing care? Clin J Am Soc Nephrol. 2014;9(7):1153–5. [PubMed: 24903388]
6. Fouque D, Aparicio M. Eleven reasons to control the protein intake of patients with chronic kidney disease. Nat Clin Pract Nephrol. 2007;3(7):383–92. [PubMed: 17592471]
7. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care. 2017;20(1):77–85. [PubMed: 27801685]
8. Kalantar-Zadeh K, Moore LW, Tortorici AR, et al. North American experience with Low protein diet for Non-dialysis-dependent chronic kidney disease. BMC Nephrol. 2016;17(1):90. [PubMed: 27435088]
9. Tantisattamo E, Dafoe DC, Reddy UG, et al. Current Management of Patients With Acquired Solitary Kidney. Kidney Int Rep. 2019;4(9):1205–18. [PubMed: 31517140] * This is a review pathophysiology of glomerular hyperfiltration as a cosequence of acquired solitary kidney in human mainly focusing on living kidney donation as well as care for these patients.
10. National Kidney F KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850–86. [PubMed: 23067652]
11. Bernardi A, Biasia F, Pati T, et al. Long-term protein intake control in kidney transplant recipients: effect in kidney graft function and in nutritional status. Am J Kidney Dis. 2003;41(3 Suppl 1):S146–52.
12. Kalantar-Zadeh K, Fouque D. Nutritional Management of Chronic Kidney Disease. N Engl J Med. 2017;377(18):1765–76. [PubMed: 29091561]
13. Soypacaci Z, Sengul S, Yildiz EA, et al. Effect of daily sodium intake on post-transplant hypertension in kidney allograft recipients. Transplant Proc. 2013;45(3):940–3. [PubMed: 23622593]
14. First MR, Vaidya PN, Maryniak RK, et al. Proteinuria following transplantation. Correlation with histopathology and outcome. Transplantation. 1984;38(6):607–12. [PubMed: 6390821]
15. Vathsala A, Verani R, Schoenberg L, et al. Proteinuria in cyclosporine-treated renal transplant recipients. Transplantation. 1990;49(1):35–41. [PubMed: 2301024]
16. Fernandez-Fresnedo G, Plaza JJ, Sanchez-Plumed J, et al. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. Nephrol Dial Transplant. 2004;19 Suppl 3:iii47–51.
17. Lin J, Valeri AM, Markowitz GS, et al. Angiotensin converting enzyme inhibition in chronic allograft nephropathy. Transplantation. 2002;73(5):783–8. [PubMed: 11907428]
18. Inigo P, Campistol JM, Saracho R, et al. Renoprotective effects of losartan in renal transplant recipients. Results of a retrospective study. Nephron Clin Pract. 2003;95(3):c84–90. [PubMed: 14646368]
19. Muirhead N, House A, Hollomby DJ, Jevnikar AM. Effect of valsartan on urinary protein excretion and renal function in patients with chronic renal allograft nephropathy. Transplant Proc. 2003;35(7):2412–4. [PubMed: 14611973]
20. Zaltzman JS, Nash M, Chiu R, Prasad R. The benefits of renin-angiotensin blockade in renal transplant recipients with biopsy-proven allograft nephropathy. Nephrol Dial Transplant. 2004;19(4):940–4. [PubMed: 15031353]

21. Rigatto C, Foley R, Jeffery J, et al. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol. 2003;14(2):462–8. [PubMed: 12538748]
22. Mange KC, Feldman HI, Joffe MM, et al. Blood pressure and the survival of renal allografts from living donors. J Am Soc Nephrol. 2004;15(1):187–93. [PubMed: 14694172]
23. de Vries AP, Bakker SJ, van Son WJ, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. Am J Transplant. 2004;4(10):1675–83. [PubMed: 15367224]
24. Fernandez-Fresnedo G, Escallada R, Martin de Francisco AL, et al. Association between pulse pressure and cardiovascular disease in renal transplant patients. Am J Transplant. 2005;5(2):394–8. [PubMed: 15644000]
25. Merkus JW, Hilbrands LB, Hoitsma AJ, et al. Haemodynamic changes in human kidney allografts following administration of nifedipine: assessment with Doppler spectrum analysis. Transpl Int. 1992;5 Suppl 1:S17–20. [PubMed: 14621721]
26. McCulloch TA, Harper SJ, Donnelly PK, et al. Influence of nifedipine on interstitial fibrosis in renal transplant allografts treated with cyclosporin A. J Clin Pathol. 1994;47(9):839–42. [PubMed: 7962654]
27. Inigo P, Campistol JM, Lario S, et al. Effects of losartan and amlodipine on intrarenal hemodynamics and TGF-beta(1) plasma levels in a crossover trial in renal transplant recipients. J Am Soc Nephrol. 2001;12(4):822–7. [PubMed: 11274244]
28. Bakris GL, Weir MR, Secic M, et al. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int. 2004;65(6):1991–2002. [PubMed: 15149313]
29. van den Berg E, Geleijnse JM, Brink EJ, et al. Sodium intake and blood pressure in renal transplant recipients. Nephrol Dial Transplant. 2012;27(8):3352–9. [PubMed: 22499024]
30. Abou-Hassan N, Tantisattamo E, D'Orsi ET, O'Neill WC. The clinical significance of medial arterial calcification in end-stage renal disease in women. Kidney Int. 2015;87(1):195–9. [PubMed: 24869671]
31. Tantisattamo E, Han KH, O'Neill WC. Increased vascular calcification in patients receiving warfarin. Arterioscler Thromb Vasc Biol. 2015;35(1):237–42. [PubMed: 25324574]
32. O'Herrin JK, Hullett DA, Heisey DM, et al. A retrospective evaluation of 1,25-dihydroxyvitamin D(3) and its potential effects on renal allograft function. Am J Nephrol. 2002;22(5–6):515–20. [PubMed: 12381953]
33. Franch HA, Mitch WE. Catabolism in uremia: the impact of metabolic acidosis. J Am Soc Nephrol. 1998;9(12 Suppl):S78–81.
34. Coen G, Mazzaferro S, Ballanti P, et al. Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. Nephrol Dial Transplant. 1996;11(5):813–9. [PubMed: 8671900]
35. Yorgin PD, Scandling JD, Belson A, et al. Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant. 2002;2(5):429–35. [PubMed: 12123208]
36. Preisig P A cell cycle-dependent mechanism of renal tubule epithelial cell hypertrophy. Kidney Int. 1999;56(4):1193–8. [PubMed: 10610409]
37. van den Berg E, Engberink MF, Brink EJ, et al. Dietary acid load and metabolic acidosis in renal transplant recipients. Clin J Am Soc Nephrol. 2012;7(11):1811–8. [PubMed: 22935845]
38. Molnar MZ, Czira M, Ambrus C, et al. Anemia is associated with mortality in kidney-transplanted patients--a prospective cohort study. Am J Transplant. 2007;7(4):818–24. [PubMed: 17391125]
39. Schjelderup P, Dahle DO, Holdaas H, et al. Anemia is a predictor of graft loss but not cardiovascular events and all-cause mortality in renal transplant recipients: follow-up data from the ALERT study. Clin Transplant. 2013;27(6):E636–43.
40. Choukroun G, Kamar N, Dussol B, et al. Correction of postkidney transplant anemia reduces progression of allograft nephropathy. J Am Soc Nephrol. 2012;23(2):360–8. [PubMed: 22193388]
41. Tsujita M, Kosugi T, Goto N, et al. The effect of maintaining high hemoglobin levels on long-term kidney function in kidney transplant recipients: a randomized controlled trial. Nephrol Dial Transplant. 2018.** A open label multi-center randomized clinical trial that confirms the potential

renoprotective of targeting hemoglobin by using erythropoietin-stimulating agent to lowering progression of renal allograft dysfunction by in kidney transplant recipients with chronic allograft dysfunction.

42. Jindal RM, Hariharan S. Chronic rejection in kidney transplants. An in-depth review. Nephron. 1999;83(1):13–24. [PubMed: 10461031]
43. Denton MD, Davis SF, Baum MA, et al. The role of the graft endothelium in transplant rejection: evidence that endothelial activation may serve as a clinical marker for the development of chronic rejection. Pediatr Transplant. 2000;4(4):252–60. [PubMed: 11079263]
44. Labarrere CA, Lee JB, Nelson DR, et al. C-reactive protein, arterial endothelial activation, and development of transplant coronary artery disease: a prospective study. Lancet. 2002;360(9344):1462–7. [PubMed: 12433514]
45. Grotz W, Siebig S, Olschewski M, et al. Low-dose aspirin therapy is associated with improved allograft function and prolonged allograft survival after kidney transplantation. Transplantation. 2004;77(12):1848–53. [PubMed: 15223902]
46. Cottone S, Palermo A, Vaccaro F, et al. Inflammation and endothelial activation are linked to renal function in long-term kidney transplantation. Transpl Int. 2007;20(1):82–7. [PubMed: 17181657]
47. Bakri RS, Afzali B, Covic A, et al. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. Clin Transplant. 2004;18(2):201–4. [PubMed: 15016136]
48. Varagunam M, Finney H, Trevitt R, et al. Pretransplantation levels of C-reactive protein predict all-cause and cardiovascular mortality, but not graft outcome, in kidney transplant recipients. Am J Kidney Dis. 2004;43(3):502–7. [PubMed: 14981609]
49. Ducloux D, Kazory A, Chalopin JM. Predicting coronary heart disease in renal transplant recipients: a prospective study. Kidney Int. 2004;66(1):441–7. [PubMed: 15200454]
50. Winkelmayer WC, Lorenz M, Kramar R, et al. C-reactive protein and body mass index independently predict mortality in kidney transplant recipients. Am J Transplant. 2004;4(7):1148–54. [PubMed: 15196074]
51. Winkelmayer WC, Schaeffner ES, Chandraker A, et al. A J-shaped association between high-sensitivity C-reactive protein and mortality in kidney transplant recipients. Transpl Int. 2007;20(6):505–11. [PubMed: 17362474]
52. Abedini S, Holme I, Marz W, et al. Inflammation in renal transplantation. Clin J Am Soc Nephrol. 2009;4(7):1246–54. [PubMed: 19541816]
53. Lopez-Gomez JM, Perez-Flores I, Jofre R, et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol. 2004;15(9):2494–501. [PubMed: 15340000]
54. Vaziri ND. Roles of oxidative stress and antioxidant therapy in chronic kidney disease and hypertension. Curr Opin Nephrol Hypertens. 2004;13(1):93–9. [PubMed: 15090865]
55. Campise M, Bamonti F, Novembrino C, et al. Oxidative stress in kidney transplant patients. Transplantation. 2003;76(10):1474–8. [PubMed: 14657689]
56. Raj DS, Lim G, Levi M, et al. Advanced glycation end products and oxidative stress are increased in chronic allograft nephropathy. Am J Kidney Dis. 2004;43(1):154–60. [PubMed: 14712439]
57. Parra Cid T, Conejo Garcia JR, Carballo Alvarez F, de Arriba G. Antioxidant nutrients protect against cyclosporine A nephrotoxicity. Toxicology. 2003;189(1–2):99–111. [PubMed: 12821286]
58. Tariq M, Morais C, Sobki S, et al. N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant. 1999;14(4):923–9. [PubMed: 10328471]
59. Bostom AG, Lathrop L. Hyperhomocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. Kidney Int. 1997;52(1):10–20. [PubMed: 9211341]
60. Friedman AN, Rosenberg IH, Selhub J, et al. Hyperhomocysteinemia in renal transplant recipients. Am J Transplant. 2002;2(4):308–13. [PubMed: 12118851]
61. Shemin D, Bostom AG, Selhub J. Treatment of hyperhomocysteinemia in end-stage renal disease. Am J Kidney Dis. 2001;38(4 Suppl 1):S91–4. [PubMed: 11576930]
62. Rangaswami J, Mathew RO, Parasuraman R, et al. Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. Nephrol Dial Transplant.

2019;34(5):760–73. [PubMed: 30984976] * This articles demonstrates all common cardiovascular diseases in kidney transplant recipients with current available evidence especially management for each cardiovascular diseases.

63. Mathew AT, Obi Y, Rhee CM, et al. Incremental dialysis for preserving residual kidney function-Does one size fit all when initiating dialysis? Semin Dial. 2018;31(4):343–52. [PubMed: 29737013] * This article provides extensive review topics related to residual kidney function and incremental dialysis in non-kidney transplant patients.).
64. Marquez IO, Tambra S, Luo FY, et al. Contribution of residual function to removal of protein-bound solutes in hemodialysis. Clin J Am Soc Nephrol. 2011;6(2):290–6. [PubMed: 21030575]
65. Dorairajan S, Chockalingam A, Misra M. Myocardial stunning in hemodialysis: what is the overall message? Hemodial Int. 2010;14(4):447–50. [PubMed: 20955278]
66. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4(5):914–20. [PubMed: 19357245]
67. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4(12):1925–31. [PubMed: 19808220]
68. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis. 2010;56(2):348–58. [PubMed: 20605303]
69. Suda T, Hiroshige K, Ohta T, et al. The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. Nephrol Dial Transplant. 2000;15(3):396–401. [PubMed: 10692527]
70. Penne EL, van der Weerd NC, Grooteman MP, et al. Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. Clin J Am Soc Nephrol. 2011;6(2):281–9. [PubMed: 21030579]
71. Termorshuizen F, Korevaar JC, Dekker FW, et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. Am J Kidney Dis. 2003;41(6):1293–302. [PubMed: 12776283]
72. Jassal SV, Lok CE, Walele A, Bargman JM. Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis: results of a decision analysis. Am J Kidney Dis. 2002;40(1):178–83. [PubMed: 12087576]
73. Andrews PA, Standards Committee of the British Transplantation S. Summary of the British Transplantation Society Guidelines for Management of the Failing Kidney Transplant. Transplantation. 2014;98(11):1130–3. [PubMed: 25299519]
74. Kalantar-Zadeh K, Kovesdy CP, Streja E, et al. Transition of care from pre-dialysis prelude to renal replacement therapy: the blueprints of emerging research in advanced chronic kidney disease. Nephrol Dial Transplant. 2017;32(suppl_2):ii91-ii8.
75. Varas J, Perez-Saez MJ, Ramos R, et al. Returning to haemodialysis after kidney allograft failure: a survival study with propensity score matching. Nephrol Dial Transplant. 2019;34(4):667–72. [PubMed: 30053152]
76. Lin YF, Huang JW, Wu MS, et al. Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. Nephrology (Carlton). 2009;14(1):59–64. [PubMed: 19019171]
77. Fernandez-Lucas M, Teruel-Briones JL, Gomis-Couto A, et al. Maintaining residual renal function in patients on haemodialysis: 5-year experience using a progressively increasing dialysis regimen. Nefrologia. 2012;32(6):767–76. [PubMed: 23169359]
78. Zhang M, Wang M, Li H, et al. Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. Am J Nephrol. 2014;40(2):140–50. [PubMed: 25171342]

79. Caria S, Cupisti A, Sau G, Bolasco P. The incremental treatment of ESRD: a low-protein diet combined with weekly hemodialysis may be beneficial for selected patients. BMC Nephrol. 2014;15:172. [PubMed: 25352299]
80. Feldman L, Shani M, Efrati S, et al. N-acetylcysteine improves residual renal function in peritoneal dialysis patients: a pilot study. Perit Dial Int. 2011;31(5):545–50. [PubMed: 20705950]
81. McDonald SP, Marshall MR, Johnson DW, Polkinghorne KR. Relationship between dialysis modality and mortality. J Am Soc Nephrol. 2009;20(1):155–63. [PubMed: 19092128]
82. Perl J, Hasan O, Bargman JM, et al. Impact of dialysis modality on survival after kidney transplant failure. Clin J Am Soc Nephrol. 2011;6(3):582–90. [PubMed: 21233457]
83. Molnar MZ, Ichii H, Lineen J, et al. Timing of return to dialysis in patients with failing kidney transplants. Semin Dial. 2013;26(6):667–74. [PubMed: 24016076]
84. Molnar MZ, Ojo AO, Bunnapradist S, et al. Timing of dialysis initiation in transplant-naive and failed transplant patients. Nat Rev Nephrol. 2012;8(5):284–92. [PubMed: 22371250]
85. Douzdjian V, Rice JC, Carson RW, et al. Renal retransplants: effect of primary allograft nephrectomy on early function, acute rejection and outcome. Clin Transplant. 1996;10(2):203–8. [PubMed: 8664520]
86. Khakhar AK, Shahinian VB, House AA, et al. The impact of allograft nephrectomy on percent panel reactive antibody and clinical outcome. Transplant Proc. 2003;35(2):862–3. [PubMed: 12644168]
87. Ahmad N, Ahmed K, Mamode N. Does nephrectomy of failed allograft influence graft survival after re-transplantation? Nephrol Dial Transplant. 2009;24(2):639–42. [PubMed: 18852188]
88. Kassakian CT, Ajmal S, Gohh RY, et al. Immunosuppression in the failing and failed transplant kidney: optimizing outcomes. Nephrol Dial Transplant. 2016;31(8):1261–9. [PubMed: 26136481]
89. Ajmal S, Bayliss GP, Machan JT, et al. Impact of transplant nephrectomy on HLA-sensitization and re-transplantation. J Am Soc Nephrol 2013; 24: 598A.
90. Sibbel SP, Koro CE, Brunelli SM, Cobitz AR. Characterization of chronic and acute ESA hyporesponse: a retrospective cohort study of hemodialysis patients. BMC Nephrol. 2015;16:144. [PubMed: 26283069]
91. Scornik JC, Meier-Kriesche HU. Blood transfusions in organ transplant patients: mechanisms of sensitization and implications for prevention. Am J Transplant. 2011;11(9):1785–91. [PubMed: 21883910]
92. Scornik JC, Schold JD, Bucci M, Meier-Kriesche HU. Effects of blood transfusions given after renal transplantation. Transplantation. 2009;87(9):1381–6. [PubMed: 19424040]
93. Cheigh JS, Suthanthiran M, Fotino M, et al. Minimal sensitization and excellent renal allograft outcome following donor-specific blood transfusion with a short course of cyclosporine. Transplantation. 1991;51(2):378–81. [PubMed: 1825244]
94. Flye MW, Burton K, Mohanakumar T, et al. Donor-specific transfusions have long-term beneficial effects for human renal allografts. Transplantation. 1995;60(12):1395–401. [PubMed: 8545863]
95. Sawinski D, Trofe-Clark J, Leas B, et al. Calcineurin Inhibitor Minimization, Conversion, Withdrawal, and Avoidance Strategies in Renal Transplantation: A Systematic Review and Meta-Analysis. Am J Transplant. 2016;16(7):2117–38. [PubMed: 26990455]
96. Kumar J, Reccia I, Kusano T, et al. Systemic meta-analysis assessing the short term applicability of early conversion to mammalian target of rapamycin inhibitors in kidney transplant. World J Transplant. 2017;7(2):144–51. [PubMed: 28507917]
97. Traitanon O, Gallon L. Chimerism and tolerance induction in kidney transplantation. Nephron. 2015;129(1):34–8. [PubMed: 25531026]
98. Dafoe DC, Tantisattamo E, Reddy U. Precision Medicine and Personalized Approach to Renal Transplantation. Semin Nephrol. 2018;38(4):346–54. [PubMed: 30082055] * This article reviews a relevant and practicle point for caring kidney transplant recipient by emphasize an individualized and presice practice.

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.

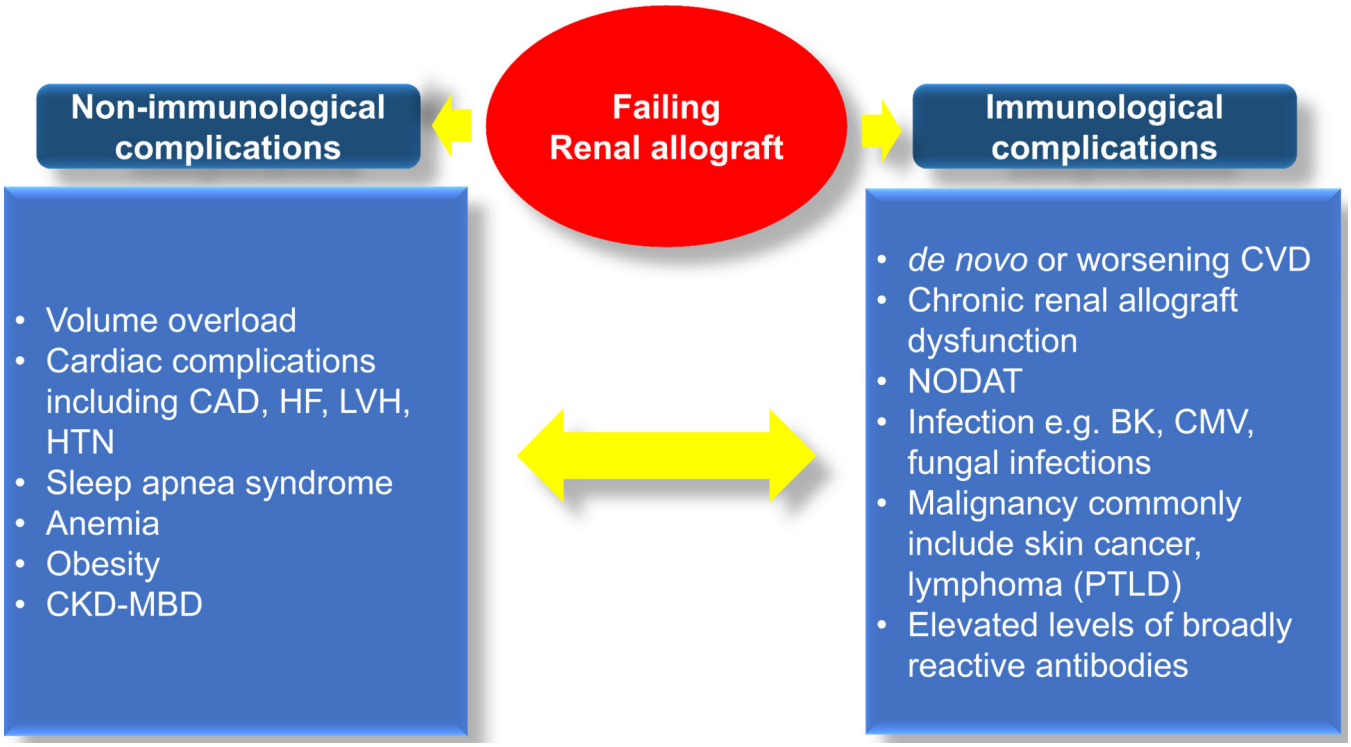

Figure 1:

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

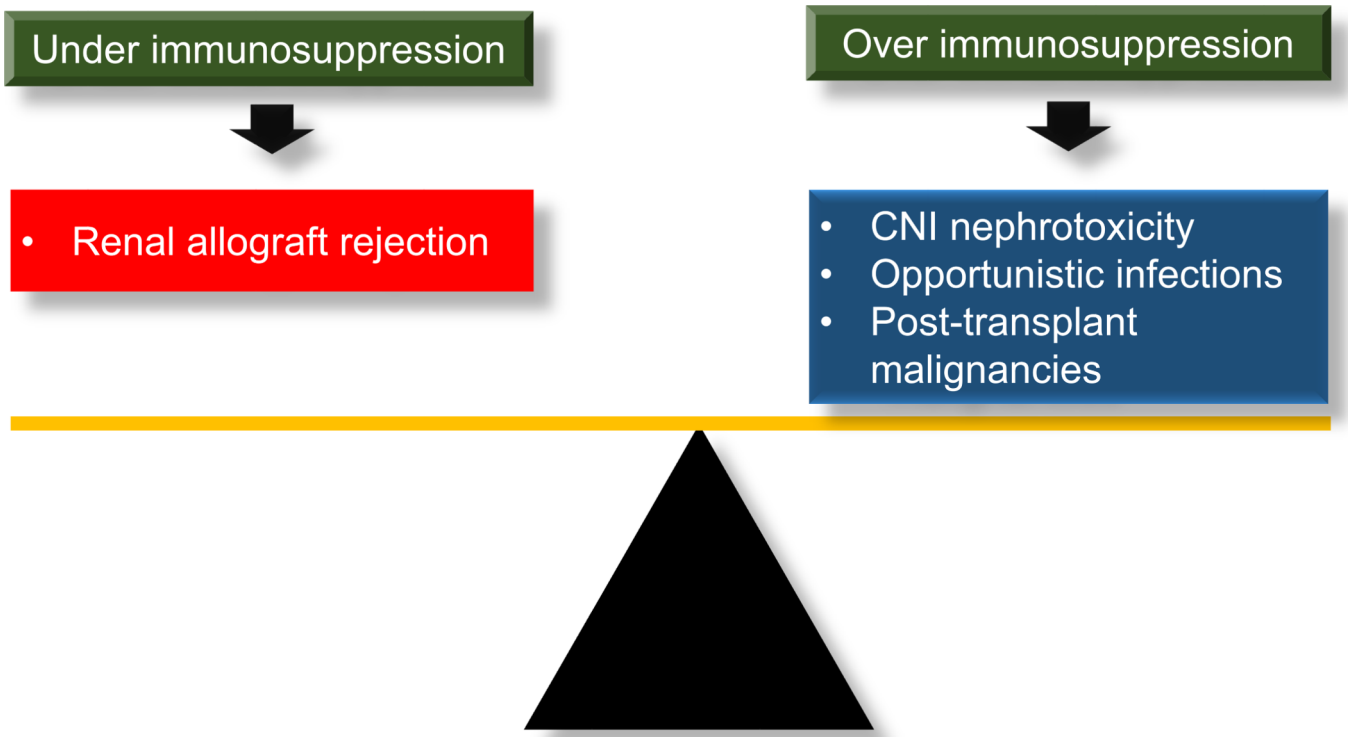

Figure 2:

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

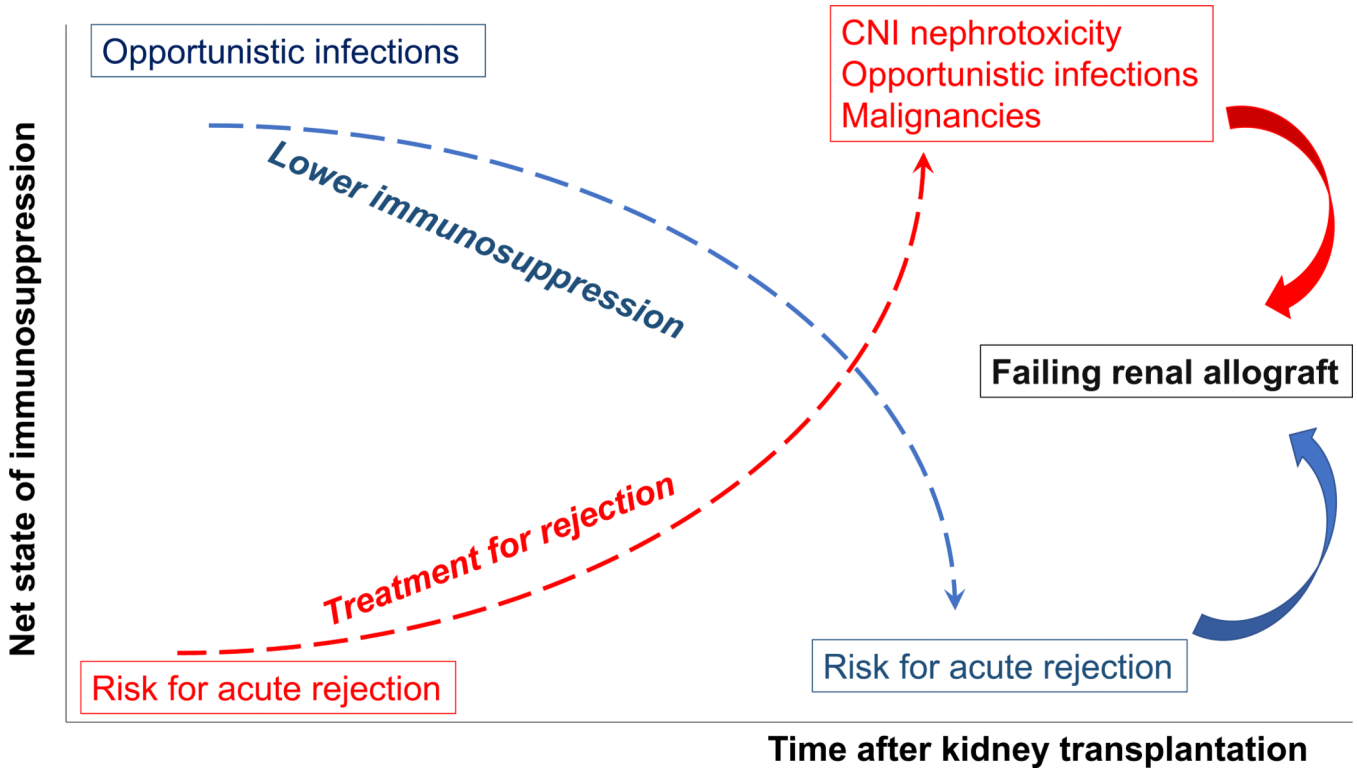

Figure 3:
Common clinical course from imbalance of immunosuppression in kidney transplant recipients. Both over and under immunosuppression will ultimately lead to failing renal allograft.

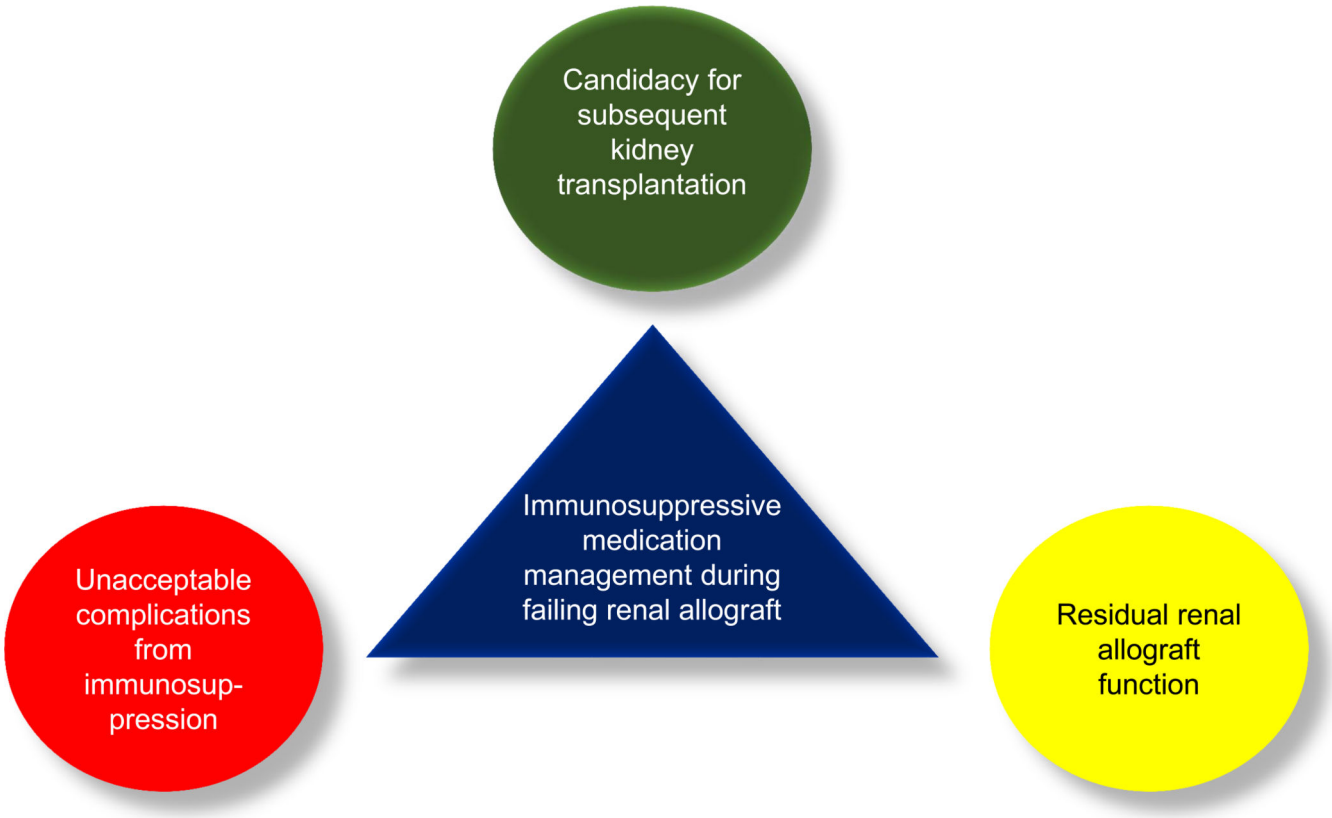

Figure 4:
Three main factors to consider for immunosuppressive medication management during failing renal allograft

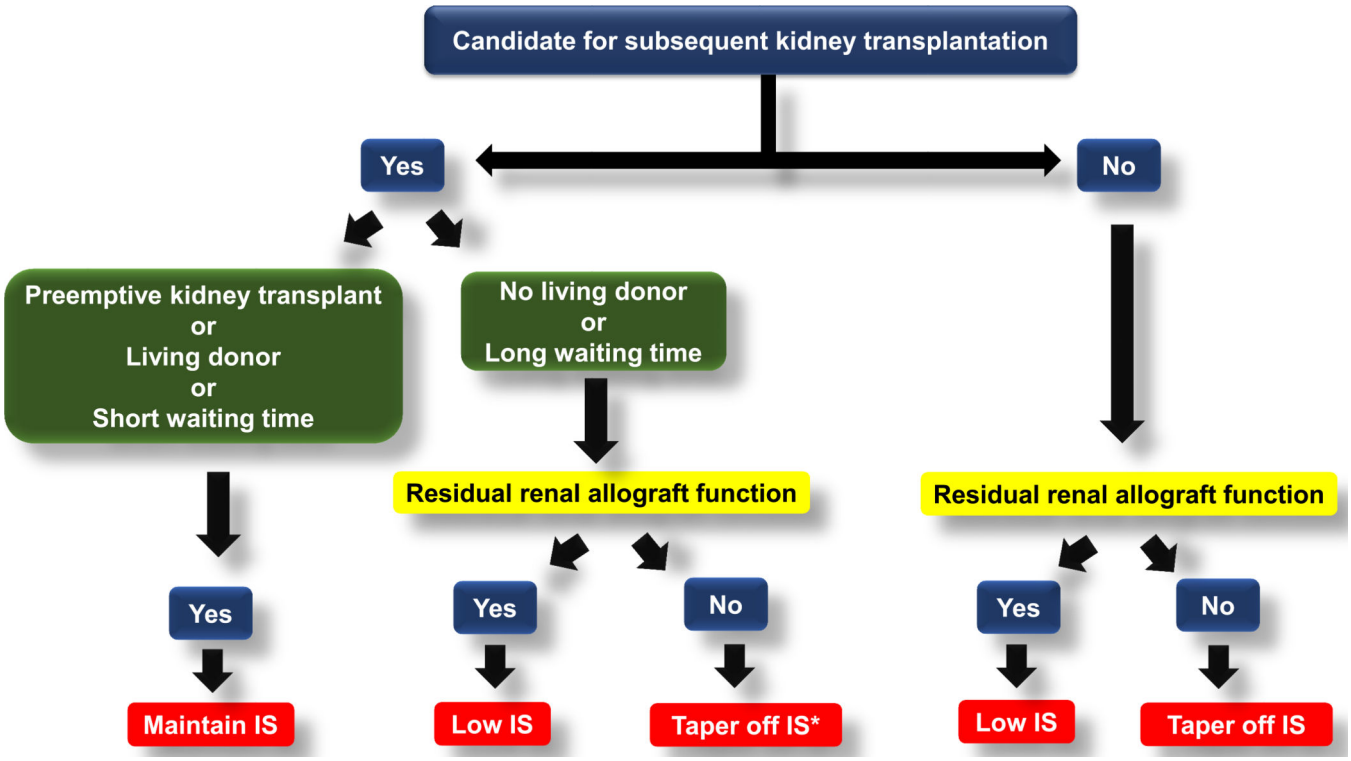

Figure 5:

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		
Prerenal causes	• Systemic diseases • Reno-vascular disease	• Orthostatic hypotension commonly in long-standing diabetes mellitus, cardio-renal syndrome
Intrinsic renal causes	• Recurrent native renal disease in a transplant renal allograft • Interstitial disease	• E.g. FSGS, MGN, IgAN, LN • E.g. recurrent transplant pyelonephritis
Post-renal causes	• Transplant nephrolithiasis	
Immunological-related causes		
Acute renal allograft rejection	• Unintended lowering immunosuppression • Intended lowering immunosuppression	• Non-medication adherence • E.g. Lowering immunosuppression during over immunosuppressed stage when the following complications occur: CMV, BK, GI side effects, malignancy
Chronic renal allograft dysfunction or the old term “transplant glomerulopathy”	• ChronicABMR	• Untreated, inadequately treated, or even unsuccessfully treated acute renal allograft rejections leading to ongoing inflammatory process and ultimately chronic scarring
Immunosuppressive medications	• Chronic CNI nephrotoxicity	• Long-standing exposure to high level of immunosuppressive medications
Opportunistic infection	• BKVAN	• 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

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Table 2:

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

Non-pharmacological interventions		
	Low dietary protein intake Plant-based protein diet	• Avoid glomerular hyperfiltration
	Low dietary sodium intake	• Avoid direct vascular injury or indirect injury from elevated blood pressure • Avoid glomerular hyperfiltration • Maximize effect of antihypertensive medications especially in salt-sensitive hypertension
	Weight control and nutrition management	• Malnutrition-inflammation complex syndrome (MICS) • Protein energy wasting (PEW) • Reversal of the reverse epidemiology
	Smoking cessation	• Acute hemodynamic e.g. elevated blood pressure and intraglomerular pressure • Chronic effects e.g. endothelial cell dysfunction
Pharmacological interventions		
	Antiproteinuria	• Angiotensin-converting enzyme inhibitor • Angiotensin receptor blocker • Non-dihydropyridine calcium channel blocker
	Blood pressure control[*]	• Dihydropyridine calcium channel blocker counteracts with vasoconstrictive effect of CNI by causing renal artery vasodilation • Decrease interstitial volume by calcium channel blocker (nifedipine)
	Glycemic control	• Lower severe arteriolar hyalinosis lesions
	Cholesterol control	• Inconclusive for renoprotective effect • Cardiovascular morbidity and mortality
	Volume control	• Salt-sensitive hypertension • Decreased residual renal allograft function
	Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) management	• Calcitriol ?
	Post-transplant metabolic acidosis	• 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
	Post-transplant anemia	• Possible protection from renal ischemia
	Aspirin	• Possible prevention of endothelial damage which can lead to chronic renal allograft dysfunction
	Anti-oxidants	• 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.

Table 3

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

Benefits	Mechanism
Solute clearance	• B2-microglobulin • protein bound solutes
Volume control	• Lower ultrafiltration volumes in each hemodialysis session • Less intradialytic hypotension • Less myocardial stunning • reduction in cardiovascular mortality
Inflammatory reduction	• C-reactive protein and interleukin-6
Anemia management	• Less anemia with less use of epoetin alpha
Nutritional improvement	• Better overall nutritional status • Better control of serum phosphorus.
Quality of life and survival	• Better quality of life

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