

Immunosuppressive Practices in Failed Kidney Grafts in South Asia- An Investigative Survey



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INTRODUCTION

Short-term kidney allograft survival has improved consistently, but improvements in long-term graft survival remain less impressive.^{1,2} As the pool of kidney transplant recipients grows, so does the number with failing grafts. The United States Renal Data System data suggest that graft failure constitutes 4.6% of the incident dialysis population.³

A failed allograft often represents the end of the road for patients in resource-limited countries, with a minority returning to dialysis or relisting for kidney transplantation.⁴ Immunosuppression withdrawal reduces infection risk at the cost of increased chances of alloimmune injury, loss of residual kidney function, and allosensitization. There is no consensus on achieving the right balance between these competing risks. The structure of the health care system also influences these decisions.

Although there are data from Western countries examining immunosuppression practices in the failing allograft,⁵ little information is available from resource-limited countries. Understanding local preferences allows us to identify possible solutions and improve the uptake of evidence-based treatment. We surveyed transplant nephrologists from Asian countries to understand their practices in managing immunosuppression in failing grafts.

RESULTS

The survey had participants from 7 countries. The respondent characteristics, transplant program characteristics, and kidney transplant statistics are

depicted in [Supplementary Tables S1, S2, and S3](#), respectively.

The most common immunosuppressive regimen ([Supplementary Figure S1](#)) used was tacrolimus + mycophenolate mofetil + steroid. Approximately 74% used tacrolimus, and 69% used mycophenolate mofetil in more than 90% of their patients ([Supplementary Figure S2](#)).

The Weaning Protocol

Most respondents (88%) individualized weaning, whereas the rest followed a standardized protocol. Most programs withdrew antimetabolite (64%) first, whereas 36% preferred withdrawing calcineurin inhibitor or mammalian target of rapamycin inhibitor first ([Table 1](#)). Most (90%) continued steroids indefinitely, whereas 6.8% continued calcineurin inhibitor. Only 3.7% stopped all immunosuppression once the patient reached dialysis.

The important factors considered in deciding immunosuppression were ongoing features of rejection (76%), history of infections (73%), and plans to retransplant (71%) ([Figure 1](#)). Most (61%) considered an estimated glomerular filtration rate <15 ml/min for weaning. The trough tacrolimus levels maintained in failing grafts was ≥ 4 ng/ml in 55% of centers, and 29% did not measure drug levels. A calcineurin inhibitor to mammalian target of rapamycin inhibitor switch was considered by 26% of the respondents. In 58% of the programs, <10% of patients were off all immunosuppression 1 year after starting dialysis. Approximately 70% each considered prior sensitization and cumulative immunosuppression data, and 40% performed a graft biopsy before weaning immunosuppression

Table 1. Immunosuppression weaning practice

Immunosuppression in the failing grafts	Percentage
Managing failed grafts	
Individualized decision	88.4
Standardized protocol	11.60
Leave to the dialysis team	0
General policy of the unit	
Continue steroids	53.7
Continue low-dose combination drugs	22.6
Gradually stop all immunosuppression	20
Stop all drugs while on dialysis	3.7
The weaning protocol	
First drug to be withdrawn	
Antimetabolite	63.80
CNI	33.00
mTOR inhibitors	3.0
Drug withdrawn next	
CNI	58.90
Antimetabolite	30.30
mTOR inhibitors	10.80
Drugs continued indefinitely	
Steroid	90.0
CNI	6.80
Antimetabolites	1.60
mTOR Inhibitor	1.10

CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin.

(Supplementary Figure S3). Approximately 45% considered graft nephrectomy when persistent signs of rejection or graft intolerance were present.

Whereas 51% offered hemodialysis to those with failing allografts, 30% left the choice to the patients, and 18% decided the modality based on patient characteristics. Most respondents (94%) note that $\leq 10\%$ of patients with a failed graft were on peritoneal dialysis. Most (73%) noted that $< 20\%$ patients were relisted for a second transplant.

DISCUSSION

This study reports on the practice of managing patients with failing kidney allografts in resource-limited

countries of South Asia. Whereas Western practices are governed by medical characteristics and the prospects of getting a repeat transplant, Asian practices focus on prolonging the function of the failing graft. Our survey noted similarities to Western practice in the choice of immunosuppression regimen, an individualized weaning decision, and the weaning sequence.⁵ The differences included the indefinite continuation of low-dose steroids, a heightened concern for infections, low preference for peritoneal dialysis, and a lower chance of a retransplant.

Whereas less than 5% of our respondents had stopped all immunosuppression at the end of 1 year, more than 70% did so in a survey from the United States.⁵ Weaning differed based on the availability of a living donor in another US survey, where 41% continued immunosuppression in the absence of a living donor.⁶ Most countries in the current survey have a weak deceased donor transplant program (14% of total kidney transplants in India,⁷ compared with 77% in the United States).⁸ Therefore, there is a temptation to squeeze the most life out of the current, albeit failing graft, by delaying immunosuppression weaning.

A prior history of infection ranked high (73%) in deciding the fate of immunosuppression in our study. In a survey of US transplant programs (KRAFT Study), infection risk was rated important by $> 90\%$ of respondents.⁶ By contrast, in another US-based survey,⁵ fewer (38%) respondents considered infection to be of importance.⁵ Asian transplant recipients are exposed to a higher risk of infections owing to geoclimatic and demographic conditions.⁹ Gregoor *et al.*,^{S1} showed an increased risk of mortality and infection with continued immunosuppression. However, their patients were routinely offered nephrectomy at graft failure, and sicker patients continued immunosuppression. Knoll *et al.*^{S2} showed survival benefit with

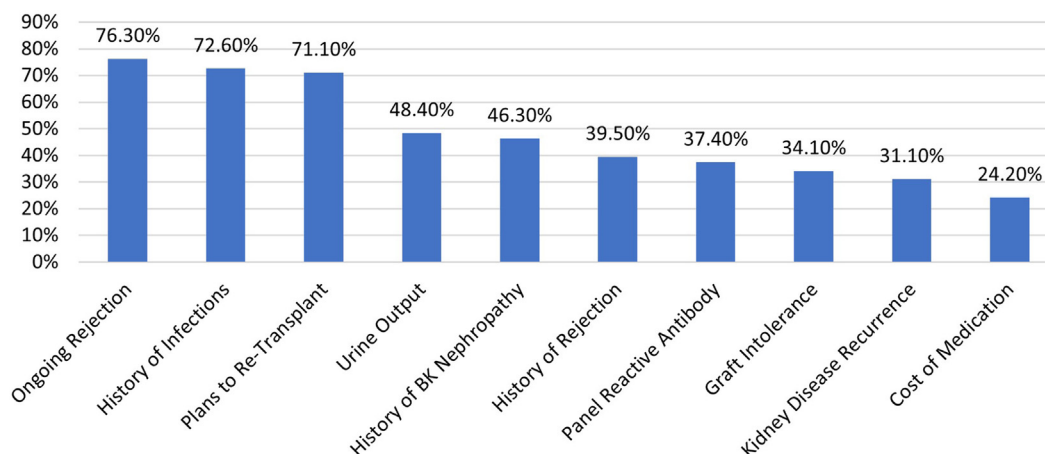


Figure 1. Factors considered in deciding the fate of immunosuppression.

continuing immunosuppression without increased risk of infection-related hospitalizations.

Urine output was considered an important factor in nearly half the respondents in our survey, compared with 33% in the KRAFT study. Patients who have a higher urine output may have better survival on peritoneal dialysis.^{S3}

Most Asian nephrologists favored continuing steroids indefinitely, likely due to the perceived low risk of adverse effects,^{S4} low cost and absence of a need for drug monitoring. A late conversion to belatacept may prolong graft life^{S5} but needs to be confirmed by prospective studies. Our study noted few takers for belatacept, presumably because of poor availability and cost.

We found a heterogeneity in estimated glomerular filtration rate thresholds of weaning immunosuppression, and the tacrolimus levels targeted in failed grafts. Over two-thirds of respondents considered cumulative immunosuppression and prior sensitization data in management, whereas the KRAFT study notes sensitization risk as important (90%).

The risk-benefit calculus behind graft nephrectomy is unclear; 45% in our survey considered it only if there were persistent signs of rejection, whereas KRAFT study responders preferred it in 79% of cases with steroid-resistant rejection. Continuing calcineurin inhibitors may prevent graft nephrectomy.^{S6}

Hemodialysis was the preferred dialysis modality for most respondents. Peritoneal dialysis use was low despite the evidence for better preservation of residual kidney function.^{S7} This likely reflects the general practice in the region where the peritoneal dialysis use is low. The proportion of patients re-enlisted for transplant was also lower, likely due to prevalent financial and resource limitations.

The worse survival of patients after graft failure compared with those with a functioning graft and transplant-naïve patients on dialysis is attributed to higher infectious and cardiovascular risks.^{S8} Data on the impact of continuing immunosuppression on patient survival are conflicting,^{S1,S2,S9} suggesting a need for randomized trials.

As with other surveys, our study has limitations. There may be recall bias, and the numbers are approximate. The responses might not reflect the status of those centers that did not participate.

In conclusion, our survey provides a snapshot of current immunosuppression practices in patients with failing renal allografts in our region, influenced largely by the limitations imposed by the health care system. Systematic data collection in this population is required to study the impact of different practices of

immunosuppression management on outcomes to help develop tailored recommendations.

DISCLOSURE

VJ has research grants from Baxter and GSK and reports consultancy and Advisory Board honoraria from Baxter Healthcare and AstraZeneca, with the policy of all payments to the organization. SB declared no competing interests.

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SUPPLEMENTARY MATERIALS

[Supplementary File \(PDF\).](#)

[Supplementary Methods.](#)

[Supplementary References.](#)

[Survey Questionnaire.](#)

Figure S1. Immunosuppression regimens in the study.

Figure S2. Individual drug use in the study.

Figure S3. Practice of graft nephrectomy.

Table S1. Respondent characteristics.

Table S2. Transplant program characteristics in the study.

Table S3. Kidney transplants per year.

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