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Editorial

Sustaining Success Through Innovation in Kidney Transplantation: From Early Achievement to Durable Patient and Graft Outcomes

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1. Introduction

Kidney transplantation is the preferred treatment for eligible patients with kidney failure, offering important advantages to survival and quality of life compared with maintenance dialysis. Progress in surgical techniques, immunosuppressive therapy, infection prevention, and perioperative care has transformed early outcomes. Nevertheless, durable allograft function remains threatened by chronic alloimmune injury, immunosuppressant toxicity, opportunistic infections, recurrent disease, and cardiovascular and metabolic complications. Furthermore, the persistent shortage of suitable kidneys continues to limit access to transplantation.

The aim of this Special Issue, "Sustaining Success Through Innovation in Kidney Transplantation", is to place emerging discoveries and clinical innovations within this broader challenge. The contributions considered here span pharmacological optimization, recipient health, organ preservation, and xenotransplantation. Collectively, they support a shift from viewing technical engraftment and short-term graft survival as sufficient endpoints toward individualized care that preserves allograft function and patient well-being over decades.

2. Individualizing Immunosuppression and Preventing Infection

Reducing rejection without causing excessive immunosuppression is a continuing clinical priority. Tacrolimus remains a cornerstone of kidney transplant immunosuppression, yet its narrow therapeutic index and variable exposure create challenges when treatment regimens change. Everolimus-based approaches may facilitate calcineurin inhibitor minimization in selected patients, but they introduce distinct tolerability considerations and potential pharmacokinetic interactions.

Cytomegalovirus (CMV) remains particularly consequential because of its direct infectious effects and its potential association with other complications after transplantation. In a randomized clinical trial involving high-risk donor-seropositive, recipient-seronegative kidney transplant recipients, letermovir was noninferior to valganciclovir for prevention of CMV disease through week 52 and caused less leukopenia or neutropenia [1]. These benefits must be considered together with interactions between antiviral and immunosuppressive agents.

In this Special Issue, Uchida et al. examined the initiation and discontinuation of letermovir in 20 living-donor kidney transplant recipients receiving everolimus and reduced-dose tacrolimus [2]. Tacrolimus and everolimus trough concentrations rose after letermovir initiation, necessitating dose reductions, and fell rapidly following withdrawal. No CMV

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DNAemia or CMV disease was observed during prophylaxis in this small cohort. The retrospective, single-center design limits generalizability, and the study was not designed to establish comparative antiviral effectiveness. Nevertheless, it offers a clinically actionable message: both starting and stopping letermovir require anticipatory therapeutic drug monitoring and prompt dose reassessment.

Personalization should therefore extend beyond the choice of immunosuppressive agents. Drug exposure, virological risk, treatment interactions, graft function, and immunological risk must be considered together. Prospective pharmacokinetic studies and validated dosing algorithms are needed to establish how such integrated approaches affect rejection, toxicity, infection, and long-term graft survival.

3. Recipient Health Beyond Graft Function

Long-term transplant success cannot be adequately assessed through serum creatinine, estimated glomerular filtration rate, or rejection episodes alone. Increasing numbers of older or medically complex recipients bring frailty, sarcopenia, impaired physical function, and metabolic complications into greater focus. These patient-centered outcomes may influence independence and quality of life even when graft function remains satisfactory.

Tomizawa et al. combined mouse experiments with a human observational study to examine associations among immunosuppressive medications, intestinal microbiota, and skeletal muscle [3]. In mice, tacrolimus and prednisolone were associated with changes in gut microbial composition and intestinal mucosal markers, including reduced Akkermansia abundance. In the clinical component, kidney transplant recipients and living donors differed in microbial diversity and postoperative psoas muscle volume changes. These observations raise the possibility of links between treatment-associated intestinal dysbiosis and muscle health; however, the human findings remain associative, and causality or a specific microbiome-mediated pathway cannot be inferred.

The implications extend beyond microbiome research. Future transplantation studies should incorporate objective measures of frailty, physical performance, nutritional status, and patient-reported outcomes. Whether microbiome-directed interventions, exercise, or nutritional strategies can improve these endpoints requires prospective investigation. Optimizing recipient health should be considered a central component of allograft stewardship, rather than an ancillary goal.

4. Preserving Donor Kidneys and Mitigating Ischemia–Reperfusion Injury

Expansion of deceased-donor transplantation increasingly entails the use of kidneys exposed to greater ischemic stress. Ischemia–reperfusion injury involves mitochondrial energetic failure, oxidative stress, endothelial dysfunction, and inflammatory activation; it can contribute to delayed graft function and potentially to subsequent graft injury. Preservation strategies must therefore be evaluated not only by how effectively they suppress metabolism during storage but also by their ability to maintain viability and support recovery.

In a landmark randomized study, Moers et al. demonstrated improved early transplantation outcomes with hypothermic machine perfusion compared with static cold storage in deceased-donor kidney transplantation [4]. This established a foundation for approaches that combine controlled temperature and oxygen delivery with functional assessment.

Kondo et al.'s contribution to this Special Issue, evaluated extracellular-type solution at 22 °C for porcine kidneys exposed to two hours of warm ischemia [5]. Under the tested experimental conditions, subnormothermic storage produced more favorable functional and metabolic measures during subsequent ex vivo normothermic perfusion and better early post-transplant findings than 4 °C storage. The small sample sizes, short follow-

up, and experimental model preclude direct application of this protocol to clinical donor kidneys. Nonetheless, the study emphasizes that preservation temperature cannot be assessed independently of solution composition, ischemic history, and metabolic conditions.

The next phase of organ preservation research should integrate hypothermic oxygenated perfusion, normothermic machine perfusion, and selected metabolic or injury biomarkers to assess repair potential and organ suitability. Robust clinical studies are needed to establish whether these approaches improve long-term outcomes and enable safe utilization of kidneys otherwise judged unsuitable for transplantation.

5. Expanding Access: Exchange Programs and Xenotransplantation

The shortage of donor kidneys remains an overriding limitation of transplantation worldwide. More effective use of existing donor opportunities and exploration of new organ sources are complementary, rather than competing, priorities. Kidney paired donation can overcome donor–recipient incompatibility and provide access to transplantation through coordinated matching. The feasibility of nonsimultaneous extended donor chains was demonstrated by Rees et al. [6], illustrating the benefits of collaboration, logistical innovation, and transparent allocation systems.

Xenotransplantation may offer a more fundamental change in organ availability. Yamanaka et al. review the immunological, genetic, infectious, ethical, and translational challenges of kidney xenotransplantation in this Special Issue [7]. Gene editing has reduced important barriers involving carbohydrate antigens and species incompatibility, but immune responses, coagulation abnormalities, pathogen surveillance, and durability of function remain unresolved.

The clinical significance of this progress was illustrated by Kawai et al., who reported transplantation of a genetically modified porcine kidney into a living recipient with kidney failure [8]. Initial xenograft function was achieved, and dialysis was not required after transplantation. The patient experienced a treated rejection episode and died on postoperative day 52 from cardiac causes, while the graft remained functioning. This case provides an important proof of clinical feasibility but cannot establish long-term efficacy or safety. Translation of xenotransplantation into standard care will demand sustained graft function, reproducible outcomes, rigorous infection surveillance, ethical oversight, and equitable access.

6. Precision Surveillance and Remaining Unmet Needs

The mechanisms responsible for late graft loss are heterogeneous. Chronic antibody-mediated injury, recurrent kidney disease, cumulative drug toxicity, cardiovascular risk, and infection may coexist, making reliance on conventional biochemical monitoring insufficient. Molecular biomarkers offer opportunities for earlier recognition of injury and more individualized decisions.

In a multicenter investigation, Aubert et al. reported that donor-derived cell-free DNA provided useful information for detecting kidney allograft rejection [9]. However, diagnostic discrimination alone is not proof that routine biomarker-guided management improves graft longevity. Pragmatic trials should test whether biomarker-triggered interventions reduce irreversible injury without increasing the burden of biopsies or unnecessary intensification of immunosuppression.

The expanding use of organs from donors with complex infectious histories also requires careful, evidence-based risk stratification. Contemporary hepatitis B guidance addresses vaccination, surveillance, prophylaxis, and management in transplant-associated contexts [10]. The broader lesson is that transplantation success depends on the coordinated

management of donor characteristics, infectious risk, immunosuppression, and recipient comorbidities throughout follow-up.

Priority questions include how to select patients for reduced-exposure immunosuppression, which preservation biomarkers reliably predict recoverable function, how to use emerging immune and molecular surveillance tools, and how to expand access without compromising safety. Meaningful endpoints should include long-term graft and patient survival, cardiovascular health, functional status, treatment burden, and quality of life. Well-designed multicenter prospective studies are essential to distinguish promising mechanisms from interventions that genuinely improve patient outcomes.

7. Conclusions

The future of kidney transplantation will be defined not simply by preventing early graft failure but by sustaining the benefits of transplantation over the recipient's lifetime. The investigations highlighted in this Special Issue demonstrate how rational pharmacotherapy, microbiome and functional-health research, improved organ preservation, and xenotransplantation can contribute to this objective. Their findings also illustrate the importance of critical evaluation: mechanistic insights and favorable early results require validation against durable clinical outcomes.

By integrating immunology, infectious diseases, pharmacology, molecular diagnostics, preservation science, and patient-centered care, transplantation medicine can move toward a more individualized and sustainable paradigm. Innovation will ultimately be judged by its capacity to deliver safe, equitable, and lasting improvements in graft function, patient survival, and quality of life.

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