Chapter 22
Innovations in Kidney Transplantation

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22.1 Introduction

Since the 1960s, dialysis and kidney transplant (KT) have successfully treated patients with end-stage kidney disease (ESKD). Over the decades, both the renal replacement therapies (RRT) have evolved and incorporated new technologies, resulting in notable improvement in their results [1]. Compared to dialysis, KT provides better results for ESKD patients, including higher survival, reduced ratios of cardiac events, hospitalization and infections, and better quality of life [2].

The remarkable improvements in patient and allograft survivals after KT over the years was mainly a consequence of the advances in surgical techniques, a better understanding of transplant immunology, development of techniques for pre- and posttransplant immunological monitoring, the availability of new immunosuppressive drugs, and better management of infections [3, 4].

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Despite these advances, the improvements in long-term patient and graft survivals in the last three decades were incremental [3, 4], suggesting that sustaining and disruptive innovations are required to uptrend the good results.

22.2 Promising Innovations in Kidney Transplantation

The main current challenges in transplantation are the suboptimal access to this therapy [5], the burden of chronic immunosuppression, and subclinical immunological events impacting graft and patient survivals [6]. Some innovations have been evaluated to deal with these challenges, and results are encouraging. Table 22.1 summarizes these technologies and their application are following discussed.

Table 22.1 Main innovations in kidney transplantation

Unmet need	Innovative strategies
Access to KT: Access to the waiting list	Social media for improving education and outreach about transplantation for CKD patients and general nephrologists
	E-health and telehealth to "shorten the distance" to the transplant center and optimize pretransplant evaluation
Access to KT: Organ supply and allocation	Social media for providing information about transplantation for health professionals and overall society
	E-learning and telehealth for patients and potential donors' education
	Machine perfusion: Organ "resuscitation" and assessment of organ quality
	Telepathology and artificial intelligence for interpretation of donor biopsy slides
	Tools for optimizing donor risk assessment and support decisions on organ acceptance
	Tools for predicting CKD after living kidney donation
	Tools for optimizing organ allocation
	Tools for predicting the waiting list time
Access to KT: Faster organs´ shipping	Shipping organs by drones
Access to KT: Expanding organ source	Xenotransplantation
	Kidney bioengineering
	Artificial-implantable renal devices
Organ preservation	Techniques for deceased donor maintenance
	Hypothermic and normothermic pulsatile perfusion
	Ex-vivo kidney perfusion with oxygenation and delivery of drugs or cellular and genetic therapies
Immunological evaluation	Epitope evaluation
	Identification of non-HLA antibodies

Table 22.1 (continued)

Unmet need	Innovative strategies
Transplant surgery	Minimally invasive surgical techniques: Laparoscopic, robotic-assisted, minimally invasive video-assisted, minimal-access, and minimal skin incision techniques
Immunosuppression and other immunomodulatory treatments	Regenerative medicine—immune tolerance
	Development of new drugs
	Precision medicine to customize immunosuppressive regimen and long-term strategy
	Gene therapy to modulate genes involved in allograft damage processes
Posttransplant follow-up and monitoring	Biomarkers for early detection of allograft injury
	Tools for predicting outcomes
	Telemedicine and telemonitoring
	Tools and technologies to support patients with medication adherence

CKD chronic kidney disease, *KT* kidney transplant, *HLA* human leucocyte antigens

22.2.1 Access to Kidney Transplantation: Access to Waiting List

Despite robust evidence that KT is better than dialysis for most ESKD individuals [2, 7], a significant proportion of dialysis patients do not have access to this treatment. The main barriers in access to KT involve suboptimal referral and enlistment to KT and imbalance between supply and demand for organs [5]. The suboptimal referral to pretransplant evaluation and waiting list enrollment results from educational and socioeconomic barriers [8]. Therefore, technologies for providing accessible information are valuable.

Social media has shown to be a powerful tool to reach patients with chronic diseases, fostering health literacy. These platforms enable the transmission of scientifically relevant content in an easy-to-understand language to an unlimited number of patients [9, 10]. Beyond patient health literacy, general nephrologists and other healthcare providers assisting chronic kidney disease (CKD) patients on predialysis and dialysis must recognize that KT is the best treatment option for ESKD [11, 12]. Social media is also an interesting web-based tool for health professionals' education, providing access to updated information, connection with experts, experience exchange, and engagement in scientific debates [13]. Importantly, misleading and erroneous information are usual in social media. Therefore, both patients and healthcare professionals should be warned about avoiding platforms whose content is not validated by an expert professional or an academic institution [14, 15].

In addition to social media, e-health and telehealth are potentially valuable tools to help CKD patients access the waiting list, "shorten the distance" to the transplant center, thus supporting and streamlining the pretransplant evaluation process [16–18].

22.2.2 Access to Kidney Transplantation: Organ Supply and Allocation

The main barrier to KT is probably the organ shortage. ESKD prevalence is growing worldwide, and the number of kidney donors has not risen to match the demand [19]. A multifaceted approach is required to break down these barriers to reduce the organ-supply imbalance.

New technologies are promising in supporting this fundamental step. Trustworthy social media are valuable tools to provide education for the general population and health professionals, impacting potential donor notification, improving donor maintenance, encouraging living organ donation, and reducing family refusal of deceased organ donation [20, 21]. E-learning and telehealth are also potentially effective tools for educating potential donors [22].

Another critical step to increase organ supply is to reduce organ discard. Machine pulsatile perfusion is routinely used to reduce delayed graft function (DGF) [23]. Beyond this classic use, evidence suggests that machine perfusion favors organ acceptance by providing the assessment of organ quality and allowing organ "resuscitation" [24, 25].

Telepathology and digital pathology using artificial intelligence are new strategies to ensure faster scanning times and more reproducible biopsy reports, potentially impacting on organ acceptance rates [26].

Using traditional statistical models or machine learning techniques, risk-prediction equations have been developed to optimize donor and recipient risk assessment and support the decision-making process. Currently, the most widely used predictor is the ***Kidney Donor Profile Index (KDPI)*** calculator, which combines ten donor-related variables and summarizes the likelihood of graft failure after a deceased donor kidney transplant. The formula is available on: https://optn.transplant.hrsa.gov/data/allocation-calculators/kdpi-calculator/

In the website http://www.transplantmodels.com/ (Copyright Johns Hopkins University, 2020), other predictive formulas are currently available:

- ***ESRD Risk Tool for Kidney Donor Candidates***: predicts the estimated risk of ESKD after living kidney donation.
- **Kidney Donor Risk of ESRD**: predicts the risk of ESRD in individuals who have already donated a kidney.
- **Live Donor KDPI Calculator**: calculates the risk score for a recipient of a potential live donor kidney.
- **KT Candidacy Calculator for Patients 65+:** estimates the probability of 3-year survival after KT in patients aged ≥65.
- **Johns Hopkins IRD Kidney Transplant Calculator**: estimates recipient mortality after receiving an Infectious Risk Donor (IRD) kidney.
- **Order of Deceased Donor and Living Donor Kidney Transplantation in Pediatric Recipients**: compares long-term patient survival after living and deceased KT in pediatric recipients.

- **KDPI-EPTS Survival Benefit Estimator**: predicts the 5-year survival benefit for receiving a kidney, based on candidate's Estimated Post-Transplant Survival (EPTS) and the kidney's Kidney Donor Profile Index (KDPI).
- **Kidney Transplant in the Context of the COVID-19 Pandemic**: estimates 5-year survival after KT and on the waiting list during COVID-19 pandemics.

Recently, using machine learning techniques, Brazilian authors developed a calculator to predict the waiting list time in São Paulo State: https://gustavomodelli.shinyapps.io/time_list_in_tx/ [27]. In addition to predictions, new technologies can be used to perform donor-recipient matches, whether for a living or deceased donor transplant.

22.2.3 Access to KT: Faster Organ Shipping

Prolonged cold ischemia time is a risk factor for DGF and graft loss. Thus, strategies to reduce this time are desirable. Depending on the territorial extension of the region and the country allocation model, a complex transportation network is necessary, and a long time is required for the organ to reach its destination.

Dramatic advances in unmanned aircraft systems (drones) allow for high races and long distances covering autonomous, monitored, and pilotless travel. As well as in other areas, drones have been presented as a cheaper and safer alternative for organ shipping [28]. The first successful kidney travel for transplantation was recently reported. The kidney was effectively transplanted and showed promptly reperfusion and function [29]. Barriers and concerns related to this technology should be individualized and further discussed.

22.2.4 Access to KT: Expanding Organ Source

Even in a hypothetical scenario of optimizing the supply of organs from living and deceased donors, it is likely that this supply of organs will not meet the growing demand. Therefore, it is necessary to evolve in developing alternatives for renal replacement.

Xenotransplantation and kidney bioengineering are promising strategies to expand organ offer, potentially providing an unlimited and ready-to-use supply of transplantable organs. The main barriers to kidney xenotransplantation are immunological events and organ-derived infections. Genetic engineering techniques have overcome these barriers with good preclinical data [30]. Recently, a kidney grown in a genetically altered pig was successfully implanted in a brain-dead human patient at the N.Y.U. Langone Transplant Institute. The allograft was not immediately rejected and produced urine for at least 54 h, encouraging scientists [31, 32].

Another potential source of organs is bioengineering and regeneration technologies, manufacturing kidneys. Techniques to obtain acellular extracellular matrix scaffolds (decellularization) and 3D printing using biomaterial (polymers) have been studied and improved over the last decades. However, the production of regeneration-competent cells is still challenging. Probably closer to becoming a reality is using stem cells to repair and regenerate poorly functioning organs and reduce the need for immunosuppressants after transplantation [33, 34].

Also encouraging, but with no forecast of becoming viable in the coming years, is replacing kidney function using artificial-implantable renal assist devices. Pioneered by UC San Francisco researchers, the equipment is based on microelectromechanical systems technology, with two chambers containing silicon-nanopore membranes: a hemofilter to remove toxins, water, and salts; and a bioreactor seeded with renal proximal tubule cells to reabsorb water and salts [35].

22.2.5 Organ Preservation

Significant advances have occurred in organ preservation since the 1960s, including a better understanding of the impact of optimizing organ preservation before harvest, the development of increasingly better preservation solutions, and the use of pulsatile perfusion [36, 37]. Despite these advances, innovations on organ preservation are still required to ensure organ quality, supporting the decision-making process on the acceptance or refusal of kidneys, reducing DGF rates, and improving kidney function and survival.

In this regard, promising attempts to improve preservation have been carried out. As an example, researchers at the University of California have demonstrated that the use of mild hypothermia (34 to 35 °C) in brain-dead deceased kidney donors reduced DGF among recipients. Notably, the study was prematurely stopped after the interim analysis of 370 of 500 planned donors on the recommendation of an independent data monitoring committee [38].

As for pulsatile perfusion, incremental innovations have been progressively described since the 1970s. In addition to traditional hypothermic pulsatile preservation techniques [23], promising results have been described with ex vivo normothermic kidney perfusion, gas delivery, such as oxygen, and delivery of drugs, polymeric nanoparticles, stem cells, and genetic therapies [39, 40].

22.2.6 Immunological Evaluation

The compatibility between donor and recipient Human Leukocyte Antigens (HLA) is a major determinant of acute rejection and graft survival and remains the core of kidney allocation. Many advances have occurred in past decades since their identification, mainly in HLA typing techniques, but also in clinical interpretation of anti-HLA antibodies before and after (de novo) transplantation. Recently, much effort

has been made to identify better allocation by advancing from HLA to epitope matching [41]. An epitope is defined as the polymorphic amino acid configurations recognized by activated B cells, so previous antibodies against an epitope can actively initiate the rejection. A computer algorithm program HLAMatchmaker (http://www.epitopes.net/index.html) made available an extensive panel of HLA alleles and their respective antibody reactive patterns (eplets) to identify epitopes that can react to specific antibodies. Applications, such as EpVix (https://www.epvix.com.br/), uses HLAMatchmaker to provide a useful and fast automated epitope virtual crossmatching at the beginning of organ allocation [42]. For highly sensitized patients, this free platform could be helpful in the allocation of suitable organs applying the virtual crossmatch by finding the acceptable HLA mismatches. An acceptable mismatch is a mismatch at antigen level but involves structural and functional compatible eplets, which, in turn, are of low risk to initiate rejection. Although this technique is part of allocation policy in some transplant programs, we need further larger studies to recommend its widespread use in clinical practice [43].

Although not common, there have been reported acute antibody-mediated rejection associated with non-HLA antibodies. The surveillance of these antibodies should be suspected in cases of absence of anti-HLA antibodies since they are not routinely tested. The reports cite antibodies against Major Histocompatibility Complex class I related chain A antigen (MICA); angiotensin type 1 receptor (AT1R); endothelin-1 type A receptor (Anti-ETAR); FMS-like tyrosine kinase 3 (FLT3); epidermal growth factor-like repeats and discoidin I-like domain 3 (EDIL3); intercellular adhesion molecule 4 (ICAM4) [44].

22.2.7 Transplant Surgery

In high-risk patients, minimally invasive surgical techniques have been attempted to reduce post-operative complications, resulting in shorter hospitalization and lower costs and morbidity. The most undesirable perioperative outcomes are wound dehiscence and infection, incisional hernias, longer analgesic need, and worse cosmesis. Minimally invasive techniques described in kidney transplantation include laparoscopic, robotic-assisted, minimally invasive video-assisted, minimal-access kidney transplantation, and minimal skin incision techniques [45].

One of the most promising options is the robotic-assisted kidney transplant (RAKT), first performed in the early 2000s [46]. Since then, robotic urological platforms and specific technical modifications were progressively developed, accumulating much experience. First aimed for obese patients (body mass index higher than 35–40 kg/m^2) planned to living donor transplants [47], this technique evolved for deceased donor transplants [48], and initial experiences were limited to patients without surgical challenges, that is, without severe atherosclerotic disease in iliac vessels, highly complex graft anatomy, or multiple abdominal surgery. Prolonged cold ischemia, re-warm, and total surgery time are potential disadvantages. Currently limited to high-volume and academic transplant centers, initial RAKT reports are promising, potentially providing favorable surgical and functional results [45, 46].

22.2.8 Immunosuppression

One of the most desired goals of transplantation researchers is to induce operational tolerance. Given its immunomodulatory properties, stem cells have been tested for decades, but the good preclinical results are yet to be reproduced in clinical studies [49]. While we await advances in clinical studies on operational immunotolerance, the use of long-term immunosuppressive medications remains mandatory.

The development of cyclosporine was probably the most disruptive innovation in kidney transplant immunosuppression. Since then, new drugs incorporated into the therapeutic arsenal have brought incremental improvements in the safety and efficacy profile, ensuring the current low rates of early acute rejection and a good safety profile. Since 2010, with the approval of everolimus and belatacept, no new drug was approved for use in the maintenance immunosuppressive regimen. Currently, clinical studies at more advanced stages are with iscalimab, an anti-CD40 monoclonal antibody that blocks the costimulatory pathway. For the prevention and treatment of antibody-mediated rejection in sensitized patients, studies have been carried out with drug repositioning, such as eculizumab and C1 esterase inhibitors, complement pathway inhibitors; imlifidase, an IgG-degrading enzyme of *Streptococcus pyogenes*; tocilizumab, an interleukin-6 inhibitor; daratumumab, a humanized monoclonal anti-CD38 antibody; and belimumab, a humanized antibody that inhibits the activity of B-lymphocyte stimulator [50].

Beyond the persistent quest for more effective and safe drugs, less nephrotoxic, and for providing a better quality of life, a fundamental challenge is to match the ideal immunosuppressive regimen for each patient, that is, individualization. In this regard, personalized precision medicine emerged as an up-and-coming innovation. By combining clinical data, omics (genomics, proteomics, metabolomics, and transcriptomic), and big data analytics, this strategy promises to support better decisions about the initial immunosuppressive regimen, drug exposures (ideal doses, and concentrations), and long-term strategy [51].

In addition to drugs and cell therapy, the clinical application of gene therapy is also promising in kidney transplantation. By using vectors (plasmids, nanostructured, or viruses) for delivery of extrachromosomal material to target cells, this therapy has the potential to modulate genes involved in kidney damage processes. Currently, most studies are focused on identifying the mechanisms and target genes involved in allograft damage, such as ischemia-reperfusion injury, immune response resulting in acute and chronic rejection, and fibrosis [52].

22.2.9 Posttransplant Follow-Up and Monitoring

Knowing what inflammation process is dominating the allograft was always a challenge. Graft invasive biopsy is the gold standard and fully available method to get the best answer. However, the possibility of accessing the signature of DGF, acute and chronic rejection by examining the blood or urine is now and ever in the

pipeline. Many biomarkers were raised and failed, but the aim of identifying biomarkers that early detect allograft injury remains pursued. Since graft damage is often multifactorial and multigenic, an isolated biomarker probably cannot predict or detect deleterious events. However, each biomarker might add information to understand the injury [53].

Recently, personalized precision medicine has emerged as a potential tool to individualize posttransplant immunosuppressive strategies. Genomic (DNA analysis) and transcriptomic (RNA analysis) biomarkers have been increasingly explored to contribute to this strategy [51].

As an example, a urinary panel of six cell-free microRNAs (miRNAs) (miR-9; miR-10a; miR-21; miR-29a; miR-221; miR-42) showed promising results in predicting DGF when analyzed in the first urine and within 5 days after kidney transplantation [54]. mRNA transcripts, called gene signature, in blood, urine, or graft biopsy has been investigated for predicting acute rejection or long-term outcomes. The findings reinforce the hypothesis that a gene expression profile can reflect the renal tissue immune pathways and act as an adjuvant tool for diagnosing and monitoring graft rejection. The number of genes included in this diagnostic "packages" varies from 3 to 19, and englobe genes involved in T-cell response (e.g., IFN-γ), chemokines (e.g., CXCL-10), and transcriptional factors (e.g., TIMP1) [53].

Other recently proposed biomarkers are small fragments of cell-free DNA (cf-DNA), derived from donor (dd-cf-DNA) graft cells, identified in the recipient blood due to cell death or injury. Despite some controversy about the method standardization, a dd-cf-DNA level greater than 0.34% of total cf-DNA is found in acute rejection episodes and DGF. A recent metanalysis showed that higher titles of dd-cf-DNA were found in patients with antibody-mediated rejection (ABMR) but not in T-cell-mediated rejection. These findings highlight that it should be of preferential utility in highly sensitized patients [55].

Also used by personalized precision medicine are big data and tools for predicting posttransplant outcomes. The validated risk-prognostication system (integrative Box/iBox) (http://www.paristransplantgroup.org) is another valuable attempt to define early surrogate endpoints to help identify patients at high risk of future graft loss and then design potential therapeutical interventions. The risk is evaluated at the time of a graft biopsy. Measurements included in the model are estimated glomerular filtration rate (eGFR), proteinuria, patterns of histopathology, and circulating anti-HLA Donor Specific Antibodies (DSA). The resulting score provides an estimated graft survival in the next 3, 5, and 7 years, which has shown accurate performance in validation cohort in Europe, at different times post-transplant, at different clinical settings such as immunosuppressive regimens, and randomized controlled trials [56]. In addition to the iBox, several predictors have been developed in recent years to predict other post-transplant outcomes, such as DGF, CMV infection, COVID-19-related death, among others [57–59].

The long-term follow-up of a KT recipient precludes close and prolonged clinical and laboratory monitoring. Access to conventional care should be limited for persons who live in rural areas, with multiple comorbidities, and difficult to travel or live in developing countries [60].

Telemedicine and telemonitoring are hopeful strategies to overcome the physical barriers and have been progressively and widely accepted worldwide [61]. Because of some translational, legal, and operational issues, telenephrology was not widely used in clinical practice before the coronavirus disease 2019 (COVID-19) pandemic. Inaccuracy of symptoms report, limited physical examination (video-dependent inspection only), ethical questions, reimbursement policies, lack of specific healthcare laws are some issues that require attention and improvement [62].

The recommended social distancing to avoid COVID-19 infection challenged the pretransplant evaluation and the post-transplant follow-up. The transplant community rapidly adapted to clinical practice toward adopting telenephrology strategies through the available technology, such as a mobile phone. The number of KT drastically fell after the COVID-19 pandemic in some countries. However, satisfactory experiences have been related to promoting access to pretransplant evaluation and in chronic follow-up care (clinical consultation, professional training, reminders, and self-monitoring) [60, 62]. Patients reported telehealth was convenient and minimized time, financial, and overall treatment burden [63]. Despite the limitations to broadly implement in all services, telehealth would be part of the COVID-19's legacy [62, 63].

Finally, tools and technologies to support patients with medication adherence are necessary, and they have been tested. Nonadherence to immunosuppressives is a major risk factor for worse kidney allograft outcomes. Non-adherent patients have a seven-fold increased risk of graft failure and acute rejection episodes and consequently higher costs to health systems [64]. Nonadherence is a multilevel behavior, which involves factors associated with the patient (sociodemographic profile, details of previous CKD treatment, psychosocial aspects, type of donor, immunosuppressive regimen), healthcare professionals (trust, satisfaction, communication quality), transplant center (composition of the team, patterns of care), and finally, with healthcare system (financial burden of immunosuppressives) [65]. Nonadherence is a potentially modifiable factor for poor outcomes [66]. However, strong evidence indicating the best strategies to reduce it are still lacking [67]. Recently reports supported measures directed to the patient to enhance the self-care and self-monitoring. Electronic devices and applications (eHealth) are being further employed to help patients adhere to post-transplant care. A recent metanalysis of randomized controlled trials of eHealth interventions showed a 34% increase in medication adherence. The type of intervention with the best results is multifunctional, defined by a strategy including two or more functions such as reminder, self-monitoring, educational, behavioral counseling, and clinical decision support system. Most interventions involved professional clinical support and a pre-defined delivery dose regimen [68].

Another perspective is to move the intervention focus from the patient to higher levels of care toward provider-related and system-related factors. It is mainly because the effect of published reports is small and collected from low-quality evidence [66, 67]. Toward this direction, a Brazilian multicenter study showed, for the first time, that a characteristic of post-transplant care, a more convenient treatment, assessed by the patient's satisfaction with the frequency of consultations, was associated with better adherence to immunosuppressives [69].

22.3 Conclusion and Future Perspectives

Notwithstanding the significant disruptive and incremental innovations developed in the last decades, some barriers and unmet needs remain relevant, affecting transplant access and allograft survival. Innovations and new technologies are mandatory to overcome these barriers and meet these unmet needs. Noteworthy, for these technologies to become a global reality, it is essential that pharmacoeconomic studies are carried out, especially in low-income countries, where resources are scarce.

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