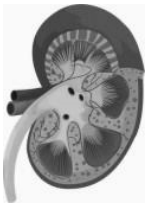
Kidney Transplantation in 2014: Good News for our Patients



SUCCESSFUL HOMOTRANSPLANTATION OF THE HUMAN KIDNEY BETWEEN IDENTICAL TWINS

"Tissue transplantation including that of a functioning kidney appears to be a feasible procedure in identical twins, but to date successful permanently function homografts appear to be limited to such individuals"

John P. Merrill, M.D., Joseph E. Murray, M.D., Hartwell Harrison, M.D.
and
Warren R. Guild, M.D., Boston

JAMA 160:277-282,1956

Miguel A. Vazquez, M.D.
Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
February 14, 2014

This is to acknowledge that Miguel A Vazquez, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Vazquez will be discussing off-label uses in his presentation.

Miguel A. Vazquez, M.D.
Professor of Internal Medicine
Clinical Director Nephrology Division
Medical Director Kidney Transplant Program, UT Southwestern St. Paul University Hospital
Nephrology Chief, Parkland Health and Hospital Systems

Dr. Miguel A. Vazquez is Professor of Medicine at UT Southwestern Medical Center. His clinical interests focus on the care of kidney transplant candidates and kidney transplant recipients, patients with end-stage renal disease on hemodialysis and patients with chronic kidney disease. Dr. Vazquez is actively involved in patient-oriented research in Nephrology in the areas of vascular access for dialysis, chronic kidney disease and kidney transplantation. He is principal investigator at UT Southwestern for the NIDDK-sponsored Hemodialysis Fistula Maturation Consortium. He is principal investigator in studies sponsored by NIDDK to improve chronic kidney disease care at Parkland Health and Hospital Systems.

Purpose & Overview:

The purpose of this presentation is to review recent advances in the field of kidney transplantation and active areas of research that are being translated into patient care. New practices and policies affecting the care of kidney transplant recipients will be presented in the context of current transplant outcomes and future treatment strategies for transplant recipients.

Objectives:

1. Understand the benefits of kidney transplantation as treatment for end-stage renal disease
2. Review recent advances in immunologic evaluation of transplant candidates
3. Understand principles of allograft rejection and treatment implications
4. Identify new policies and regulations affecting the field of kidney transplantation

Patients with end stage renal disease (ESRD) require life-sustaining dialysis treatments or a kidney transplant to survive. The total number of patients treated for ESRD in the United States now exceeds 600,000. The prevalent dialysis population continues to grow as more patients with Chronic Kidney Disease (CKD) progress to ESRD.[1, 2](see Figure 1)

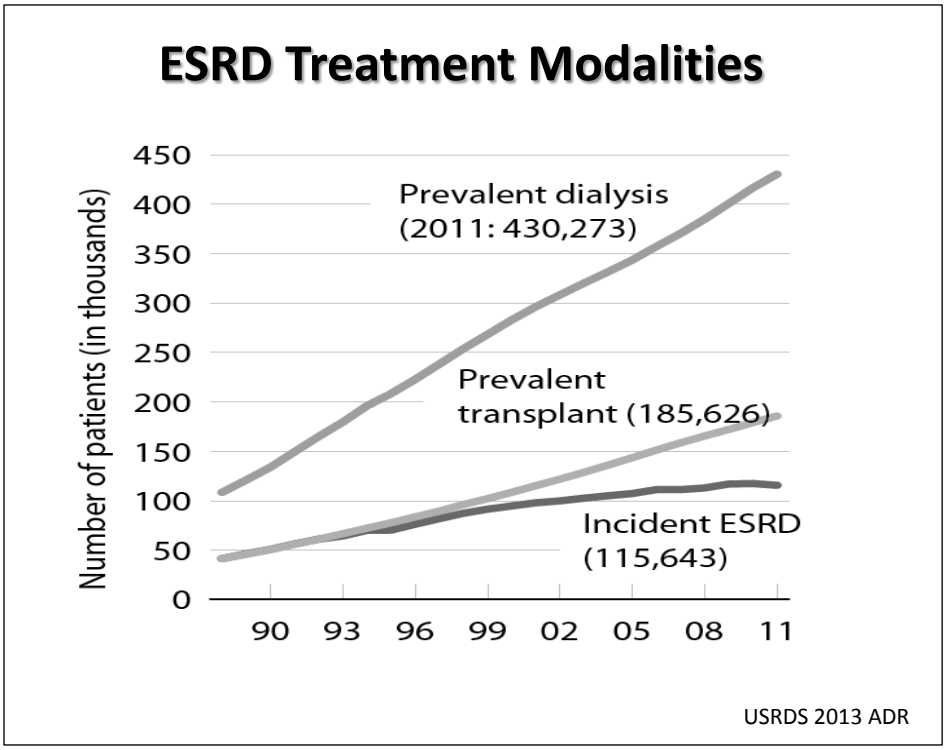


Figure1

A functioning kidney transplant is the best treatment for ESRD for patients who are able to undergo kidney transplant surgery and take immunosuppressive medications. Transplant recipients have a survival advantage over patients on dialysis. There are no randomized clinical trials of kidney transplantation versus dialysis, but analysis of registry data from large national data bases has consistently shown a benefit in survival for patients receiving a kidney transplant compared to patients treated with dialysis. In the United States, Wolfe and colleagues compared mortality and relative risks of death and survival for patients who underwent transplantation as compared to patients remaining on the kidney transplant waiting list on dialysis.[3] The relative risk of death was higher during the first few weeks after transplantation for those patients undergoing a kidney transplant than for those patients on dialysis with equal lengths of follow up since placement on the waiting list. By 18 months after transplant however, the risk of death was much lower (relative risk 0.32; 95% confidence intervals 0.30/0.35; $P<0.001$) for patients undergoing a kidney transplant. Similar findings with lower mortality risk for transplant patients compared to patients remaining on the waiting list treated with dialysis have been noted in studies from other countries.

Not only is a kidney transplant associated with better results in patients with ESRD but time on the transplant waiting list is one of the strongest independent risk factors for renal transplant

outcomes. The benefit of shorter waiting times prior to transplantation is observed both for living kidney donor recipients and deceased donor kidney transplant recipients.[1, 2] Patients who are able to undergo transplantation before starting dialysis (preemptive transplant) have very favorable outcomes.

Kidney transplant can prevent or reverse uremic complications. Regulation of blood pressure and extracellular volume is much better with a kidney transplant as compared to dialysis. Acidosis, hyperkalemia and hyperphosphatemia are corrected with a kidney transplant. Recipients of kidney transplants are hospitalized less often than patients treated with dialysis. The costs per year of caring for a kidney transplant recipient after the first year are about 1/3 of those costs of caring for a patient on hemodialysis and less than half of the costs of caring for a patient treated with peritoneal dialysis [1, 2]. Kidney transplant recipients also report better quality of life as compared to patients treated with dialysis.

The overall number of kidney transplants performed in the United States has leveled at around 16,000 per year. The total number of patients who are alive and with a functioning kidney has continued to climb and is now over 181,000.[1, 2] Kidneys from deceased donors represent close to 2/3 of all kidneys transplanted. The short-term and long-term outcomes for both living and deceased donor kidney transplant recipients have continued to improve steadily.[1, 2] For deceased donor transplant recipients, the one year probability of a graft failure is 8.5% and the 10-year probability of failure is 54%. For living donor transplant recipients the probability of graft failure at one year is 3.2% and at 10 years 38%. Graft failures are classified according to whether patients return to dialysis or die with a functioning graft. Most of the improvements on outcomes for kidney transplants have been related to lower rates of return to dialysis. Rates of death with function have remained stable which is particularly encouraging as patients with more comorbidities are undergoing kidney transplants.

Successful transplantation of the human kidney is one of the most extraordinary accomplishments of modern medicine. Kidney transplantation was the first successful treatment for end-stage disease involving any major organ system. Advances in surgical techniques, progress in basic immunology and improvements in medical care of patients have all been fundamental to success of the field of kidney transplantation. Equally important, however, has been the development of multidisciplinary teams, initiatives to address scarcity of organs and implementation of quality assurance programs.

Surgical Advances

Successful kidney transplant was performed by Dr. Joseph Murray in 1954 between two identical twins.[4] Dr. Murray was awarded the Nobel Prize in Medicine in 1990 for his work in organ transplantation. The first kidney transplant in Texas was performed 50 years ago here at Parkland Hospital/UT Southwestern. Dr. Paul Peters, chairman of Urology, performed a successful transplant between two identical twin sisters.

In most kidney transplant surgeries, the kidney is placed in the right (or left) iliac fossa in an extra-peritoneal location.[4, 5] The external iliac artery is used commonly as the inflow vessel with an end-to-side anastomosis. The internal iliac artery can be also used as inflow vessel. The donor renal vein is anastomosed end-to-side to the external iliac vein. Urinary drainage is the

anastomosis of the donor ureter into the recipient bladder. In special cases, the donor ureter may drain via ureterostomy into immobilized native ureter of the recipient.

Advancements in surgical techniques have led to marked decreases in surgical complications after transplantation. Most surgical complications involve the transplant wound and one of the 3 anastomosis described above involving the renal artery, renal vein or ureter. Renal artery or renal vein thrombosis are rare complications that lead to graft failure unless immediately recognized and corrected. Urine leaks, wound infections and bleeding also require prompt attention. The incidence of surgical complications is now around 5-10% in most centers. Careful attention to surgical detail and prompt recognition with surgical intervention and interventional radiology procedures have been responsible for the marked decline in graft loses from surgical complications.[5]

Advances in Transplant Immunology

Rejection of the allograft has been the most formidable obstacle to transplantation in the past. Immune response to an allograft involves both the adaptive and innate immune system.[6, 7] The innate immune system responds to antigens in a nonspecific manner. The adaptive immune system recognizes alloantigens, usually polymorphic HLA molecules expressed, in all nucleated cells. The innate immune system is activated in the context of injury including ischemia-reperfusion of the allograft. The innate immune system in turn facilitates activation of the adaptive immune response via facilitation of antigen presentation. T-cell activation leads to activation of other cell types and production of cytokines. In T-cell mediated rejection, the allograft is infiltrated by effector T-cells, macrophages, B-cells and plasma cells. The diagnostic lesion in T-cell mediated rejection is mononuclear cell infiltration of the tubules (tubulitis) and in some cases infiltration of the intima of the small arteries (arteritis).[6-8](see Figure 2)

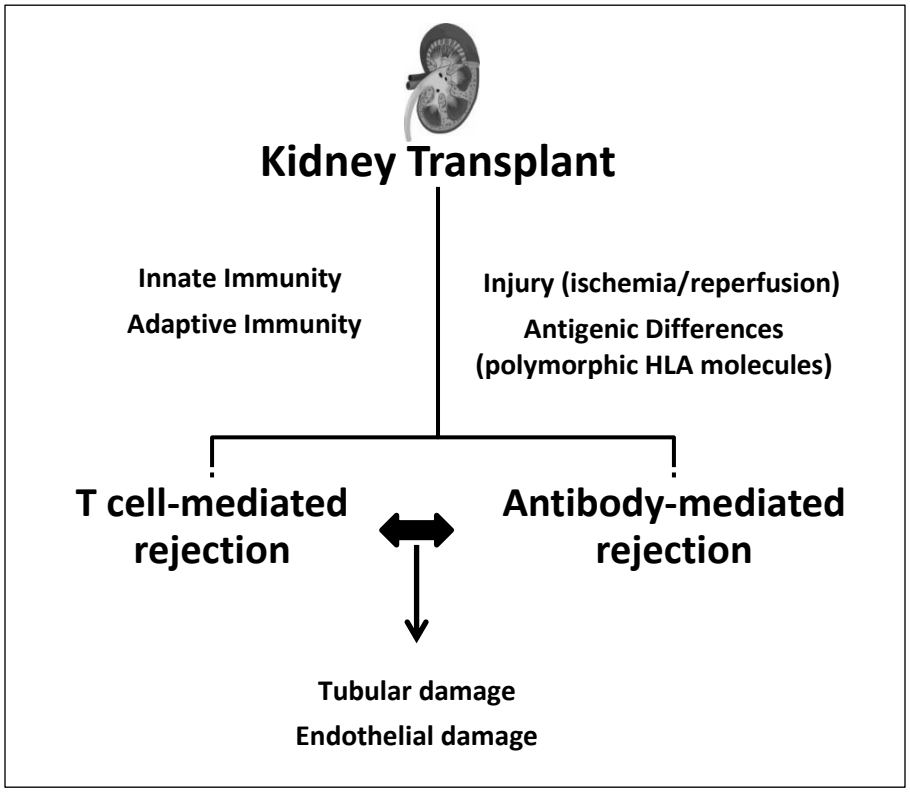


Figure 2

In antibody-mediated rejection, alloantibody is directed against donor antigens usually polymorphic HLA class I or class II molecules or other antigens expressed in the endothelium. Antibodies can lead to acute rejection or chronic deterioration of the allograft. Diagnosis of antibody-mediated rejection is based on clinical presentation, morphologic findings in the allograft, immunopathologic evidence of antibody action (such as demonstration of C4d on biopsies, and serologic evidence of circulating antibodies). The Banff classification of renal allograft pathology has provided the fundamental framework for descriptions of renal allograft rejection.[8, 9] Recent use of microarray assessments of gene expression provides additional information to support diagnostic assessments based on established criteria.

Detection of Antibodies in Transplantation

Dr. Paul Terasaki was the first to describe the presence of pre-formed cytotoxic antibodies as an absolute contraindication for transplantation. HLA and non-HLA antibodies can lead to hyperacute rejection with immediate loss of the kidney or to acute or chronic antibody-mediated rejection and subsequent graft dysfunction and graft loss.[10, 11](see Figures 3a & 3b) Cell dependent cytotoxicity (CDC) and flow cytometry are traditional cell based assays used for HLA-specific antibody screening and for crossmatch testing of recipients against potential donors. The CDC assay has lower sensitivity but identifies antibodies that can mediate hyperacute rejection. The flow cytometry assay is more sensitive detecting antibodies binding to target lymphocytes and identifies a higher risk of rejection but is not necessarily a contraindication for transplantation. Recently solid-phase immunoassays (SPI) allow identification of antibody specificities with high precision and sensitivity.[11] Solid-phase immunoassays use solubilized HLA molecules in a microtiter plate (ELISA) or polystyrene beads performed on a flow cytometer or a small foot print fluoroanalyzer or Luminex.[11] Using single specificity HLA beads it is possible to know the antibody specificity in the serum of potential transplant recipients. This information combined with knowledge of the actual HLA antigen frequencies in a donor population allows for determination of a calculated PRA (cPRA). After introduction of cPRA into clinical practice in kidney transplantation it has been possible to offer more kidneys to highly sensitized transplant candidates. In addition, knowing the antibody specificities on a recipient allows to identify all unacceptable antigens to be avoided in a potential donor and to perform a “virtual crossmatch” without actually having to test serum directly from the recipient against cells from the donor. If necessary, crossmatch can be performed using a specific donor HLA molecule bound to beads to test a recipient serum in a direct recipient to donor crossmatch.[11] Most laboratories use a combination of the above tests depending on immunologic risk of a given transplant candidate to guide the evaluation before and after kidney transplantation.

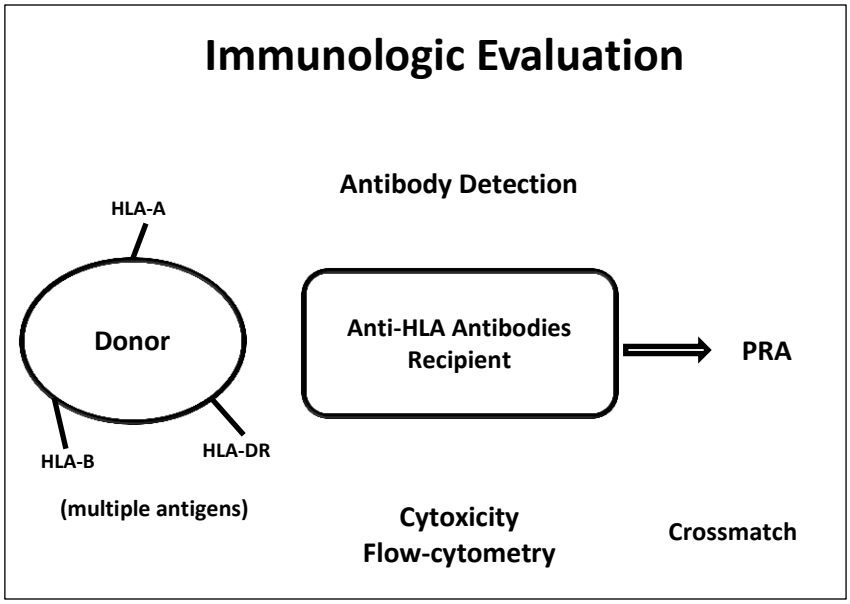


Figure 3a

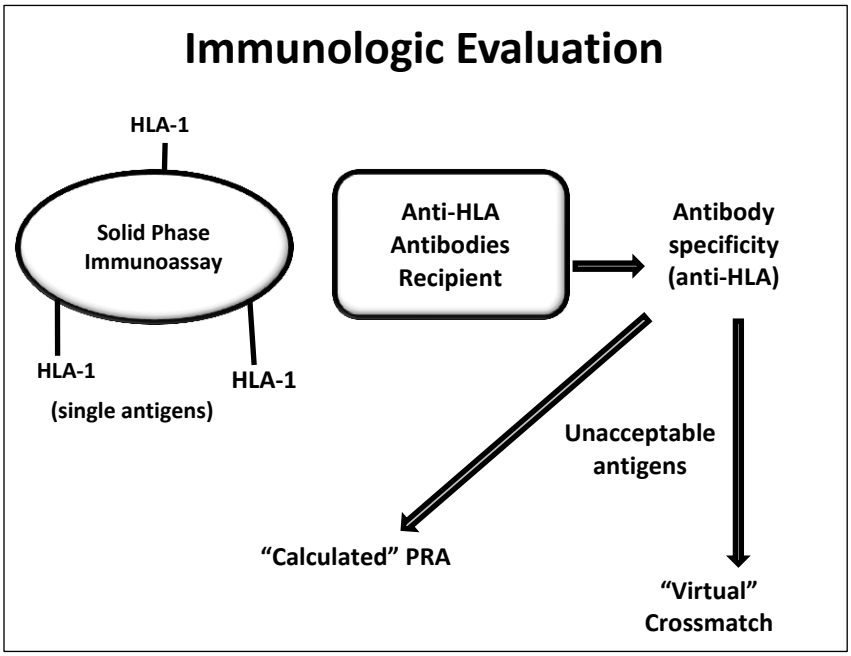


Figure 3b

Immunosuppression

Another major step in kidney transplantation has been the development of more effective immunosuppression. The rates of acute transplant rejection have declined steadily on the last few decades not only in relationship with the development of better methods to detect antibodies in patients at high immunologic risk but also with the availability of more effective immunosuppressive agents. Immunosuppressive drugs not only exert a therapeutic effect but may also have undesired consequences of immunosuppression and non-immune toxicity.[6, 7] Immunosuppressive drugs in kidney transplantation are used for induction (intense immunosuppression to prevent rejection early after transplant) maintenance (ongoing prevention of rejection), or to reverse rejection (augmented immunosuppression after development of

rejection).(see Figure 4) The major classes of immunosuppressive drugs used currently in kidney transplantation include antibodies, calcineurin inhibitors, corticosteroids, antimetabolites, and mTOR (target of rapamycin) inhibitors.[2, 6]

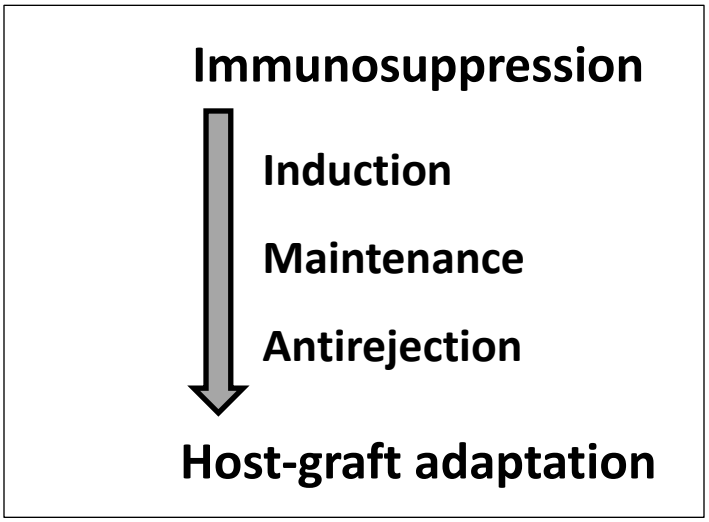


Figure 4

Most transplant recipients receive induction immunosuppression. T-cell depleting antibodies including thymoglobulin or IL-2 receptor antagonists are used in most patients at the time of transplant. Maintenance immunosuppression usually involves the use of 2 or 3 immunosuppressive agents.[2](see Table 1) In the United States most transplant recipients received a calcineurin inhibitor, an antimetabolite and in many cases corticosteroids. Some regimens may avoid steroids and other regimens may substitute an mTOR inhibitor for one of the other immunosuppressive drugs either the calcineurin inhibitor, steroid or antimetabolite. Recently, new antibodies including biologics such as belatacept, have been successfully used to prevent rejection. The number of rejection episodes has progressively declined over time.(see Figure 5)

Maintenance Immunosuppression

Corticosteroids	66%
Calcineurin inhibitors	
Tacrolimus	91%
Cyclosporine	4%
Antimetabolites	
Mycophenolate	93%
Azathioprine	0.3%
mTOR inhibitors (Sirolimus)	3%

Data from OPTN/SRTR 2013 ADR

Table 1

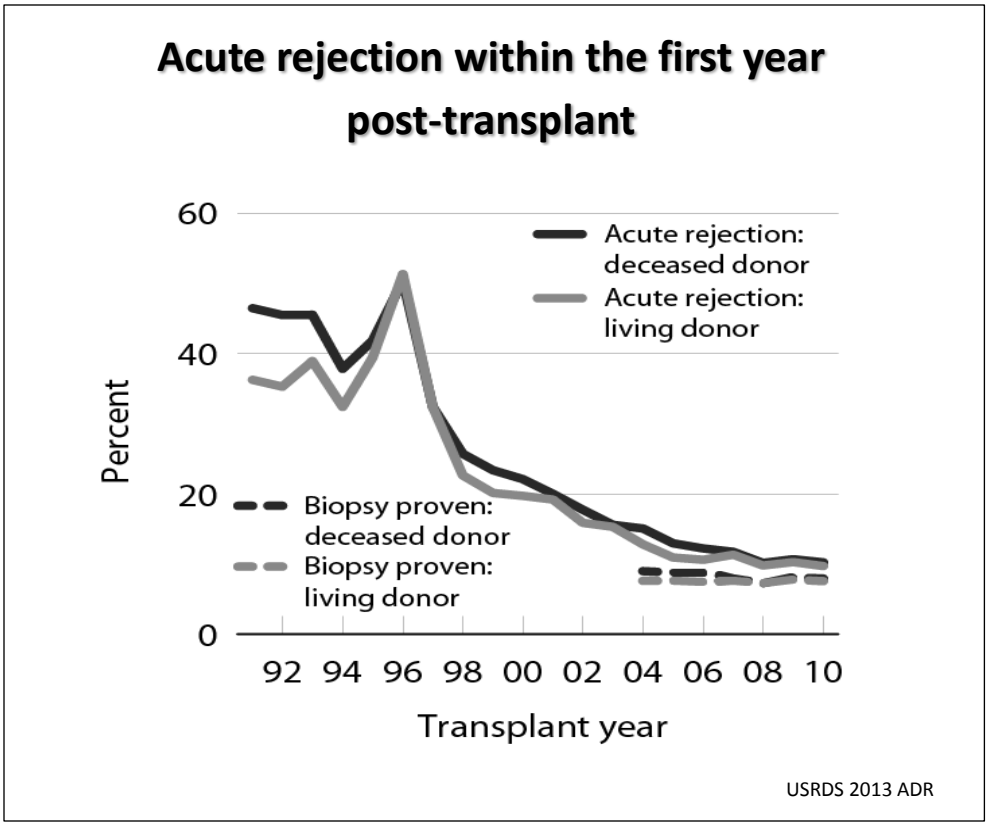


Figure 5

Treatment of rejection depends on clearly establishing the type of rejection. The Banff classification of renal allograft pathology is used in most transplant centers to describe histologic changes observed in the presence of antibody-mediated rejection or T-cell mediated rejection and differentiate acute rejection from chronic changes including transplant glomerlopathy or interstitial fibrosis and tubular atrophy.[8, 9] Microarray assessment of gene expression from biopsy samples can further expand on the clinical, serologic and histologic information available. Recently, specific gene signatures in the urine have been shown to be of diagnostic and prognostic importance for acute cellular rejection in kidney allograft recipients.[12]

Ischemia-Reperfusion Injury

Injury is present in all kidney transplants. The severity and impact of injury in transplantation is determined by donor factors related to the donor, factors related to organ procurement, preservation, implantation and reperfusion, and factors related to the recipient.(see Figure 6) In brain dead donors there is an intense inflammatory response that further increases injury. In the case of donors after circulatory death the longer warm ischemia time also contributes to allograft injury. Ischemic and non-ischemic injuries interact with innate and adaptive immune responses leading to additional damage from ischemia-reperfusion injury.[13] Some studies have shown that ischemia-reperfusion injury can lead to slow graft function of the allograft, delayed function of the allograft defined as a requirement for dialysis in the first seven days after transplantation or in extreme cases to primary non-function on failure of the allograft. Delayed graft function is usually a consequence of ischemia-reperfusion injury.

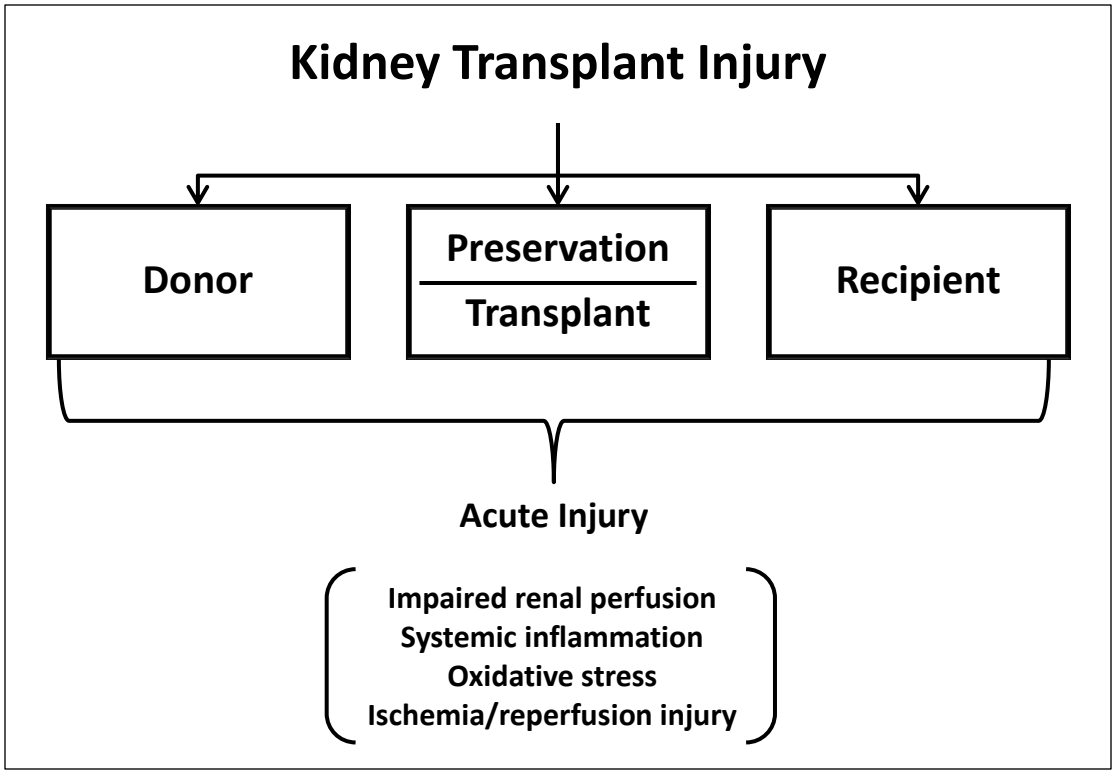


Figure 6

Several predictive models incorporating donor factors, recipient factors as well storage, preservation, and recipient factors can help determine the likelihood of delayed function after transplant. Histopathological findings and recently transcriptome analysis may provide additional information to predict the likelihood of delayed function. The rates of delayed graft function range from close to 40% for recipients of kidneys from donors after circulatory death to less than 5% for recipients of kidneys from living donors. Consequences of delayed graft function include need for dialysis, higher costs and longer hospitalizations. Acute rejections is more frequent in patients with delayed function some studies suggest lower allograft and patient survival in transplant recipients who experience delayed graft function.[13] Several interventions are potentially effective in decreasing delayed graft function. Donor management and optimization of perfusion prior to organ retrieval is effective. Some studies have also shown that cold pulsatile machine perfusion during kidney storage is beneficial and reduces delayed graft function. Meticulous management of the donor including maintaining optimal effective arterial blood volume is also effective in decreasing the likelihood of delayed graft function.

In addition to acute immune-mediated responses and ischemia-reperfusion injury, renal allografts are also at risk for chronic immune-mediated damage. Transplant glomerlopathy is the most important cause of reduced graft survival in some reports. Alloantibodies play a pathogenic role in the development of transplant glomerlopathy. Most patients will show characteristic histopathologic findings including basement membrane multilamination, deposition of C4d and duplication (double contours) of the glomerular basement membrane. Many patients will also have alloantibodies circulating in blood.

The renal allograft can also be affected by any of the same conditions that involve native kidneys.(see Figure 7) Recurrent and *de novo* glomerular diseases are important contributors to allograft loss. Post-transplant glomerular disease is diagnosed more frequently in allografts that are followed long term. Infections can lead to allograft failure. BK virus allograft nephropathy is an important cause of graft failure. Other infections such as allograft pyelonephritis can also lead to declines in renal function. Transplant immunosuppression drugs, especially calcineurin inhibitors, are known to have nephrotoxicity and can lead to kidney failure. Histologic finding suggestive of chronic calcineurin inhibitor nephrotoxicity, including progressive arteriolar hyalinosis, ischemic glomerulosclerosis, and interstitial fibrosis are almost universally present in patients treated long term with calcineurin inhibitors. Anatomic problems including obstruction of the ureter and/or bladder as well as renal artery stenosis can lead to progressive allograft dysfunction if unrecognized and not corrected. Medical conditions can affect the allograft even to a larger extent than seen in native kidneys. Common diseases such as diabetes and hypertension can lead to renal deterioration and eventually graft failure. Non-adherence is another very important and often unrecognized and preventable cause of graft dysfunction and subsequent failure. Finally, many transplant recipients are found to have findings of interstitial fibrosis and tubular atrophy in kidney transplant biopsies. Although detailed information including clinical history allows identification of a specific cause for graft malfunction in most patients, there are some cases where these nonspecific findings in biopsy cannot be directly associated with any specific cause for graft failure. For those patients with chronic kidney disease after transplantation (CKD-T) it is important to implement those strategies which are effective in treating CKD and its associated complications.

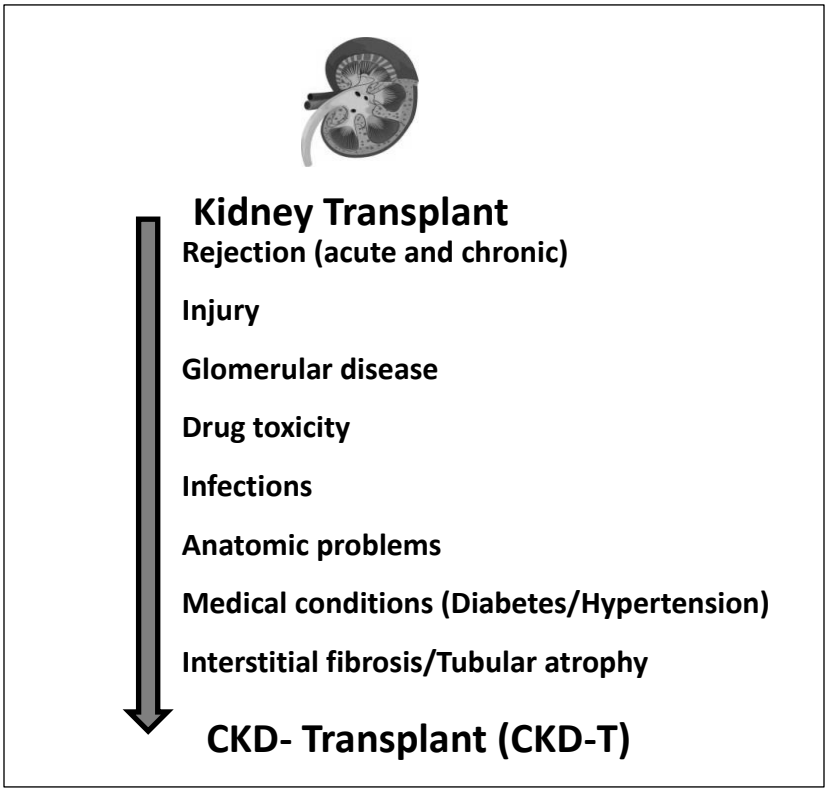


Figure 7

The overall rate of decline of renal function in long term kidney transplant recipients has improved in recent years. All cause graft failure has declined mainly as a result of lower rates of patients returning to dialysis or requiring re-transplantation. Rates of death with function have remained relatively stable over the last decade.[1, 2](see Figure 8) Kidney transplant recipients enjoy a survival advantage compared to patients on dialysis but still suffer from excessive and premature mortality. Cardiovascular disease is the most important cause of death at all times after kidney transplantation followed by infections and malignancies.[1, 2](see Figure 9) Multiple comorbidities including prior duration of chronic kidney disease, diabetes, hypertension, dyslipidemia and nontraditional risk factors contribute to the progression of cardiovascular disease in transplant recipients. Transplant recipients are also at much higher risk of infection than immunocompetent individuals. Infection risks and patterns of infection change at different times after transplantation and are influenced by the net state of immunosuppression and by exposures of transplant recipients to infections agents. Kidney transplantation is also associated with an increase in the risk of cancers at most sites. Cautious reduction of immunosuppression and vigilance to institute prompt diagnostic interventions in treatment of malignancies is essential. Liver disease and other chronic medical problems also contribute to patient death, especially many years after kidney transplantation.

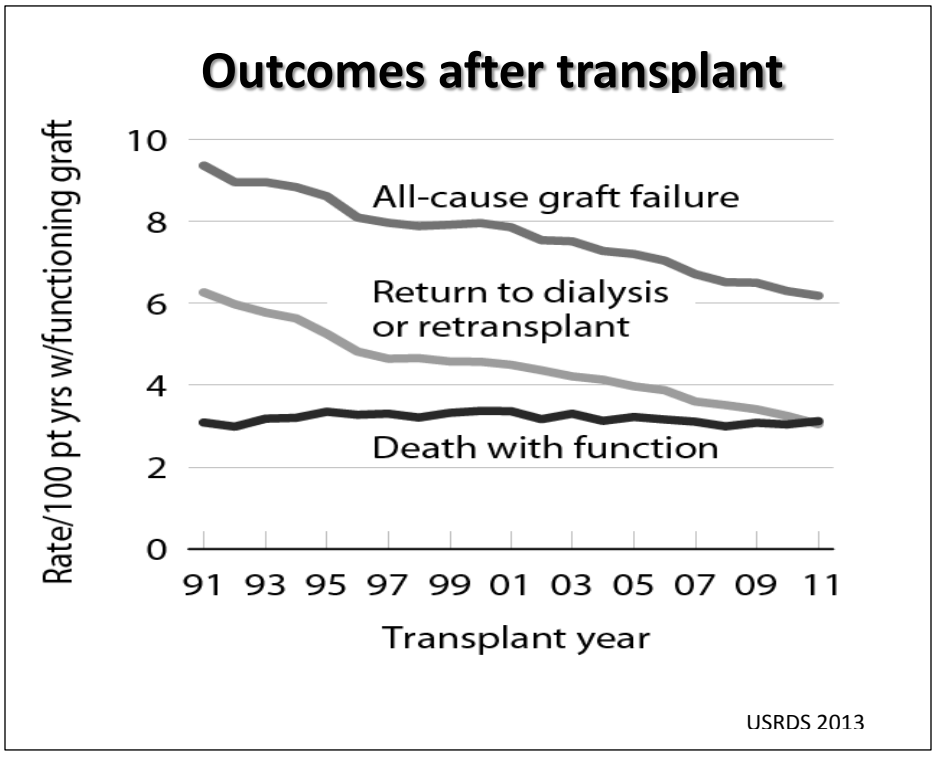


Figure 8

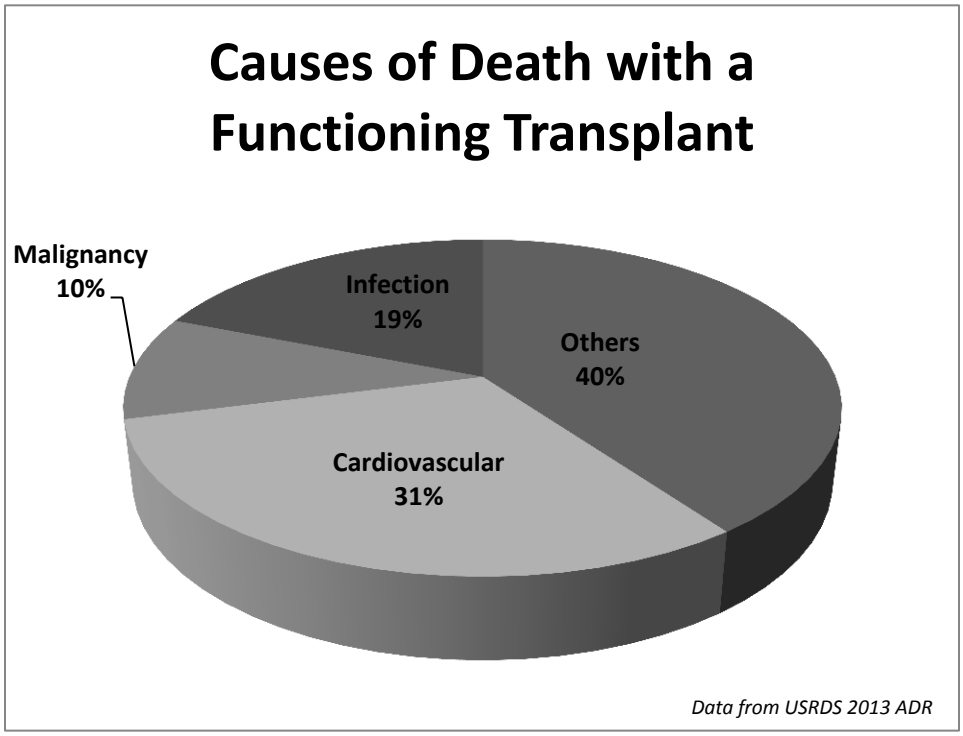


Figure 9

Kidney transplant recipients suffer from multiple chronic medical conditions and comorbidities. Improvements in overall medical care, however, have allowed for better control of multiple conditions and patients to enjoy a functioning transplant for many years.

Improving Access to Transplantation

Patients with kidney failure can undergo a kidney transplant from a living donor or from a deceased donor. Recipients of living kidney donors have the best graft in patient survival. The other major advantage of living kidney donation is avoiding the need to wait a long time for a kidney transplant to become available. The total number of candidates on the waiting list has increased annually. The median time to transplant for wait-listed adult patients is now over 4 years in the United States.[2] The number of living kidney donor transplantations increased markedly in the 1990's when waiting times for deceased donor kidney transplant became progressively higher. In addition, the introduction of laparoscopic donor nephrectomy also contributed to the increase in living kidney donation. In recent years, however, the annual number of living kidney donor transplants has slowly declined.[1, 2] It is not clear if change in demographics in the population with ESRD may have contributed to this change in trends of living kidney donation.

Living kidney donation is an accepted surgical and medical intervention. Several long term studies have examined the long term consequences of kidney donation. A report of the long term consequences of kidney donation in 3,698 donors who donated kidneys between 1963-2007 found that survival and risk of ESRD in carefully screened kidney donors appeared to be similar to those in the general population.[14] Most donors have preserved GFR and reported excellent quality of life. Donors from some minority populations may show increased risks for some medical conditions in comparison to donors from nonminority populations.[15]

Given the benefits of living kidney donation there have been several initiatives to increase access to transplantation for recipients who have potential living donors who are ABO incompatible or have a positive crossmatch with their donors.[16, 17] *Paired Kidney Donation* transplantation is performed when two or more candidates within compatible donors exchange donor grafts so that two or more compatible transplants can occur. As more pairs of potential donors/recipients are included, the quantity of transplants and the quality of the matches improves. In an open chain, kidney paired donation continues to be extended by donating to a recipient who offers an additional donor. A non-directed donor is an individual who donates a kidney to a recipient with whom they have no emotional or genetic relationship. Non-directed donor chains can initiate a domino set of paired donations. A bridge donor is a donor whose intended recipient has already received a kidney from another incompatible pair donor and then waits to donate to a suitable recipient at a later time, therefore extending the donor chain. In the United Stated there are several kidney paired donation registries and national initiative for kidney paired donation has been recently initiated by the United Network for Organ Sharing. Some highly sensitized transplant candidates are not able to receive a transplant from an intended living donor (relative or emotionally related donor). Even with current desensitization techniques these transplant candidates remain unable to undergo transplantation from their intended donors. Kidney paired donation has the potential to facilitate access to transplantation to these patients.

Deceased Donor Kidney Transplantation

Most kidney transplant candidates receive a kidney from a deceased kidney donor. *Standard criteria donor (SCD)* kidneys are obtained from young donors who are not known to have any preexisting conditions that may affect allograft survival. *Expanded criteria donor (ECD)* kidneys are from deceased donors older than 60 years or from ages 50-59 with at least two of the following characteristics; history of hypertension, serum creatinine level greater than 1.5mg/dl or cerebrovascular accident as cause of death. The risk of graft failure at 3 years after transplantation for a recipient of an expanded criteria donor kidney is 70% higher than for a standard donor kidney transplant recipient. Patients who benefit the most from the availability of ECD kidneys are those with the highest mortality rates while on the waiting list or with long waiting times in their organ procurement organization. Older patients with more comorbidities may benefit from accepting ECD kidneys early after the onset of end-stage renal disease while younger and healthier patients may benefit from waiting to receive organs that may last longer.

Most deceased organ donors have suffered from brain death or irreversible loss of all functions of the entire brain including the brain stem. *Donors after cardiac or circulatory death* (DCD) are those in which death is declared on the basis of cardiopulmonary criteria (irreversible cessation of circulatory and respiratory function) rather than neurological criteria to declare brain death. Another group of donors that has recently come to attention are those considered at higher risk for transmission of infections. Donors in this category may have behavioral risk factors or potential exposures to infections that may increase the risks for transplant recipients. Application of new techniques for testing of high risk donors as well as open and careful discussion of potential benefits: risks of accepting high risk donors should guide individualized decision making for potential transplant candidates.

Allocation is the process the Organ Procurement and Transplantation Network (OPTN)/UNOS (United Network for Organ Sharing) uses to determine which transplant candidates are offered which organs.[18, 19] The allocation system distributing scarce resources such as deceased

donor organs is based on the principles of utility and equity. In kidney transplantation the principle of utility attempts to maximize outcomes such as patient and graft survival. The principle of equity aims to achieve fairness in which access to a transplant may occur at times at the expense of outcomes. The current kidney allocation system incorporates waiting time status as a primary determinant in kidney allocation (equity) as well as biological matching/tissue typing (equity). Kidneys are currently allocated preferentially based on the absence of HLA mismatches. Kidneys from donors younger than 35 years of age are allocated preferentially to pediatric candidates. Kidneys from ECD donors are allocated to candidates who consent receiving these organs. Kidneys from standard criteria donors are allocated to all candidates on the waiting list. Kidneys from donation after cardiac death are allocated according to sequences that speed placement by focusing on local distribution. Limitations on the current allocation system include higher than necessary discard rates of kidneys, variability in access to transplantation by candidate blood type and geographic location and the reality that many kidneys with long potential for longevity are allocated to candidates with significantly shorter potential longevity and vice versa.

After a long period of discussions and public hearings the OPTN/UNOS has approved a new national kidney allocation system to improve post-transplant survival benefit, increase utilization of donated kidneys and increase transplant access for biologically disadvantaged candidates. Although the new allocation policy is expected to improve patient survival and broaden access to transplant, it will not address a shortage of donor kidneys.[2] Without availability of additional donor kidneys, changes in the allocation system shift kidneys between different patient groups. The changes in the allocation system will include trade-offs between equity and utility.[19] The principle foundation of the new proposed system will be longevity matching to reduce mismatches between possible donor kidney longevity and life expectancy of recipients.

The longevity of a potential donor kidney is estimated using the kidney donor profile index (KDPI). Variables in the KDPI include donor age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C virus status and donation after cardiac death status. The KDPI is calculated using the kidney donor risk index (KDRI) which in addition to the above variables also includes HLA-B and DR mismatches with the recipient, cold ischemic time of the organ and transplant procedure type (en bloc, single or double). The KPDI is a percentile of donors with each KDRI.[2, 18] The estimated post-transplant survival (EPTS) is determined by the recipient age, diabetic status, time on dialysis, and number of prior solid organ transplants.[18, 19]

There are four distinct pathways for kidney allocation in the new system. In sequence A the kidneys on the top 20% KPDI (predicted to have the greatest longevity) will be allocated to patients with the top 20% EPTS (predicted to have the longest survival after transplantation). In sequence B kidneys with KDPI greater than 20% but less than 35% will be preferentially allocated to pediatric recipients. In sequence C kidneys with KDPI greater than 35% but less than 85% will be allocated based on points determined by cPRA, HLA matching and waiting time. In sequence D kidneys with KDPI greater than 85% will be allocated both locally and regionally with the aim of offering shorter waiting times to offset risks of decreased graft longevity in older candidates.

Other components of this new allocation system include an increase in priority for sensitized candidates with a cPRA sliding scale. There will be pre-registration dialysis time incorporated in

the model. Candidates with blood type B will be eligible to accept candidates from donors with blood type A_2 or A_2B. Payback for organs to other organ procurement organizations and regional variances have been eliminated.

The new allocation system for kidney transplants is estimated to result in an additional 8,000 additional life years gained annually and improved access to transplantation for moderately and highly sensitized candidates. There should be improved access for ethnic minority candidates while preserving comparable levels of kidney transplants at the regional and national levels. It is believed that the discard rate of organs will be lower with this new allocation system.

Quality Improvement and Regulation in Kidney Transplantation

Kidney transplantation in the United States is closely regulated and performance improvement initiatives have been at the cornerstone of efforts of most transplant centers for decades. The Health Resources in Services Administration (HRSA) established the Organ Procurement and Transplantation Network (OPTN) which regulates kidney transplants via the United Network for Organ Sharing (UNOS) and in collaboration with the Scientific Registry of Transplant Recipients (SRTR) provide detailed reports on kidney transplant recipient outcomes. UNOS oversees regulation of kidney transplantation in the United States. The SRTR releases program-specific reports that include center-specific outcomes for internal and external reviews. Centers identified as underperforming are referred for further review, investigation and possible exclusion from transplantation.[20, 21] In addition to program-specific reports, OPTN/UNOS also makes available cumulative sum charts (CUSUM) that provide continuous, real-time, risk adjusted assessment of clinical outcomes for any transplant center. A benefit of implementation of this real-time clinically relevant system of monitoring outcomes is that it may facilitate efforts to improve transplant outcomes in a timely manner.

The Centers for Medicare and Medicaid services (CMS) has also implemented conditions of participation for transplant programs in order to be eligible for reimbursement for organ transplantation. CMS uses SRTR report cards with center-specific outcomes to evaluate individual transplant center.[20, 21] If the observed number of adverse outcomes at a given transplant center exceeds the expected number then the center may lose certification for Medicare/Medicaid eligibility.

Most transplant centers also have very active internal quality assessment and improvement initiatives. In transplantation external reports are readily available for review not only by regulators but by payers and patients to guide their selection of transplant programs.

Summary

The treatment of end-stage renal disease has been a success story for hundreds of thousands of patients.[22](see Table 2) Kidney transplantation was the first successful treatment of end organ damage when performed 60 years ago and still remains one of the most novel and dynamic fields in modern medicine. Advances in kidney transplantation have been possible due to the combination of pioneering surgical techniques, fundamental progress in basic science and the immunology of transplantation as well as advances in the medical care of patients with multiple comorbidities. Kidney transplantation has benefited tremendously from a multidisciplinary approach to the care of patients. Challenges in availability of organs for transplant will require

innovative solutions involving both living kidney donation and deceased donor kidney transplantation. Future research directions should lead to better immunosuppressive regimens with lower toxicity and closer to more effective strategies that may ultimately lead to tolerance to allografts. Kidney transplant recipients continue to teach us how science and medicine can help to make lives better for millions of individuals each day.

Table 2

Advances Kidney Transplantation
➢ Patients
➢ Pioneering surgical techniques
➢ Solid scientific foundation
➢ Comprehensive multidisciplinary medical care
➢ Innovative solutions to new challenges
➢ Ethical foundation
➢ Patients

References

1. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2013, Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases
2. Organ Procurement and Transplanatation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). 2012: OTPN/SRTR.
3. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, and Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *The New England journal of medicine*. 341(23): p. 1725-30 1999.
4. Merrill JP, Murray JE, Harrison JH, and Guild WR. Successful homotransplantation of the human kidney between identical twins. *Journal of the American Medical Association*. 160(4): p. 277-82 1956.
5. Humar A and Matas AJ. Surgical complications after kidney transplantation. *Seminars in dialysis*. 18(6): p. 505-10 2005.
6. Halloran PF. Immunosuppressive drugs for kidney transplantation. *The New England journal of medicine*. 351(26): p. 2715-29 2004.
7. Gaber LW, Knight RJ, and Patel SJ. A surgeons' guide to renal transplant immunopathology, immunology, and immunosuppression. *The Surgical clinics of North America*. 93(6): p. 1293-307 2013.
8. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, Cosio F, David DS, Drachenberg C, Einecke G, Fogo AB, Gibson IW, Glotz D, Iskandar SS, Kraus E, Lerut E, Mannon RB, Mihatsch M, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Roberts I, Seron D, Smith RN, and Valente M. Banff 07 classification of renal allograft pathology: updates and future directions. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 8(4): p. 753-60 2008.
9. Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. *Journal of the American Society of Nephrology : JASN*. 18(4): p. 1046-56 2007.
10. Patel R and Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. *The New England journal of medicine*. 280(14): p. 735-9 1969.
11. Tait BD, Susal C, Gebel HM, Nickerson PW, Zachary AA, Claas FH, Reed EF, Bray RA, Campbell P, Chapman JR, Coates PT, Colvin RB, Cozzi E, Doxiadis, II, Fuggle SV, Gill J, Glotz D, Lachmann N, Mohanakumar T, Suciu-Foca N, Sumitran-Holgersson S, Tanabe K, Taylor CJ, Tyan DB, Webster A, Zeevi A, and Opelz G. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation*. 95(1): p. 19-47 2013.
12. Suthanthiran M, Schwartz JE, Ding R, Abecassis M, Dadhania D, Samstein B, Knechtle SJ, Friedewald J, Becker YT, Sharma VK, Williams NM, Chang CS, Hoang C, Muthukumar T, August P, Keslar KS, Fairchild RL, Hricik DE, Heeger PS, Han L, Liu J, Riggs M, Ikle DN, Bridges ND, Shaked A, and Clinical Trials in Organ Transplantation 04 Study I. Urinary-cell mRNA profile and acute cellular rejection in kidney allografts. *The New England journal of medicine*. 369(1): p. 20-31 2013 PMCID 3786188.

13. Cavaille-Coll M, Bala S, Velidedeoglu E, Hernandez A, Archdeacon P, Gonzalez G, Neuland C, Meyer J, and Albrecht R. Summary of FDA workshop on ischemia reperfusion injury in kidney transplantation. *American journal of transplantation :* 13(5): p. 1134-48 2013.
14. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR, and Matas AJ. Long-term consequences of kidney donation. *The New England journal of medicine*. 360(5): p. 459-69 2009 PMCID 3559132.
15. Lentine KL, Schnitzler MA, Xiao H, Saab G, Salvalaggio PR, Axelrod D, Davis CL, Abbott KC, and Brennan DC. Racial variation in medical outcomes among living kidney donors. *The New England journal of medicine*. 363(8): p. 724-32 2010 PMCID 3041966.
16. Montgomery RA, Zachary AA, Ratner LE, Segev DL, Hiller JM, Houp J, Cooper M, Kavoussi L, Jarrett T, Burdick J, Maley WR, Melancon JK, Kozlowski T, Simpkins CE, Phillips M, Desai A, Collins V, Reeb B, Kraus E, Rabb H, Leffell MS, and Warren DS. Clinical results from transplanting incompatible live kidney donor/recipient pairs using kidney paired donation. *JAMA : the journal of the American Medical Association*. 294(13): p. 1655-63 2005.
17. Melcher ML, Blosser CD, Baxter-Lowe LA, Delmonico FL, Gentry SE, Leishman R, Knoll GA, Leffell MS, Leichtman AB, Mast DA, Nickerson PW, Reed EF, Rees MA, Rodrigue JR, Segev DL, Serur D, Tullius SG, Zavala EY, and Feng S. Dynamic challenges inhibiting optimal adoption of kidney paired donation: findings of a consensus conference. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 13(4): p. 851-60 2013.
18. UNOS: Proposal to Substantially Revise the National Kidney Allocation System. Online, www.hhs.gov. 2014.
19. Friedewald JJ, Samana CJ, Kasiske BL, Israni AK, Stewart D, Cherikh W, and Formica RN. The kidney allocation system. *The Surgical clinics of North America*. 93(6): p. 1395-406 2013.
20. Axelrod DA, Kalbfleisch JD, Sun RJ, Guidinger MK, Biswas P, Levine GN, Arrington CJ, and Merion RM. Innovations in the assessment of transplant center performance: implications for quality improvement. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 9(4 Pt 2): p. 959-69 2009.
21. Schold JD, Buccini LD, Heaphy EL, Goldfarb DA, Sehgal AR, Fung J, Poggio ED, and Kattan MW. The prognostic value of kidney transplant center report cards. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 13(7): p. 1703-12 2013 PMCID 3696034.
22. Friedman EA. End-stage renal disease therapy: an American success story. *JAMA : the journal of the American Medical Association*. 275(14): p. 1118-22 1996.