Organ and Tissue Transplantation
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Carlo Gerardo B. Ramirez
Jerry McCauley *Editors*

Contemporary Kidney Transplantation

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Organ and Tissue Transplantation

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Jerry McCauley
Editors

Contemporary Kidney Transplantation

With 103 Figures and 63 Tables

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Foreword

The first successful kidney transplant was accomplished over six decades ago between identical twins at the Peter Bent Brigham Hospital in Boston. Kidney transplantation had more than a decade head start over other organ transplants because of its technical simplicity and availability of hemodialysis. Its early trials were dominated by immunologic failures and aggressive innovations to suppress allograft rejection. The early elegant solution of "cocktail" immunosuppression and the introduction of cyclosporine in the mid-1980s had led to improved outcomes after kidney transplantation, consequently surpassing dialysis as the preferred treatment option for end stage renal disease. This fostered a period of worldwide growth in transplant programs that had various developmental differences based on cultural views of the population being served. In the United States, brain death became a recognized entity and allowed infrastructure building to create the United Network of Organ Sharing (UNOS), which directed and regulated deceased donor organ allocation. In places where brain death was viewed as problematic, i.e., in many Asian countries, living donors became the main source of kidneys for transplantation. Successful outcomes following kidney transplantation has created a profound shortage of kidneys, consequently, less than a fifth of patients awaiting kidney transplantation are expected to receive a transplant in a given year. The changes from innovation and experimentation to close oversight and stringent regulations grew out of many things, but at least in part a component of stewardship of the use of a precious resource. From its inception, kidney transplantation like all other organ transplants had been dependent on multidisciplinary approach. This continues to be true today and in some respects many transplant programs are only as strong as the weakest areas of the program. Some areas of kidney transplantation have remained remarkably similar over long periods of time, and surgical techniques of donor and recipients being one of the aspects that has changed a little. On the other hand, many areas, such as immunologic monitoring and treatment protocols, have changed significantly and continue to change rapidly, requiring constant refinements in practice.

Jerry McCauley
Carlo B. Ramirez

Preface

This book will provide a comprehensive guide to a successful kidney transplant program in the highly regulated environment of today. The book starts with the history of kidney transplantation, which highlights innovations that have made kidney transplantation successful today. The book also includes specific nephrology concerns related to kidney transplantation, which include selection and evaluation of donors and recipients, and medical complications following kidney transplantation. Several chapters will focus on ethics, psychosocial and financial aspects of kidney transplantation, the role of transplant coordinators, and quality measures of a contemporary kidney transplant program. Components of an appropriate kidney transplant listing and important deceased donor kidney wait list maintenance procedures will be discussed in these chapters. They will also cover the required post-kidney transplant health maintenance and management, including major risk factors for graft loss as well as disease processes that kidney transplant patients are vulnerable to. A chapter will be dedicated to the new deceased donor kidney allocation strategy and the changes that have occurred with this new policy. A chapter on immunosuppression will discuss details of the various immunosuppressive medications used in kidney transplantation, including commonly used antirejection protocols. It will also cover certain unique kidney transplant circumstances, such as pregnancy after kidney transplantation, and combined kidney with liver, pancreas, or thoracic organ transplantation. Several chapters on relevant topics in kidney transplantation, i.e., anesthesia management, pathology, radiology, immunology, and epidemiology of end stage renal disease and kidney transplant, are included in the book. This book will describe details of the surgical techniques of deceased and living donor kidney transplantation. These include information on living kidney donor surgery, particularly minimally invasive nephrectomy techniques that have been popularized in the last 20 years. Comprehensive coverage of common surgical complications will also be part of this book, including management of urinary strictures, urinary leaks, lymphoceles, and vascular problems following kidney transplantation. Finally, this book is a unique source of information and guidance for the current generation of transplant professionals who have evolved from being pure clinicians into savvy administrators, knowledgeable in every regulatory aspect governing transplantation.

Jerry McCauley
Carlo B. Ramirez

Acknowledgment

We would like to thank the many patients and their families who have given us the high privilege of participating in their care. We also thank our families for their constant support. Our deep appreciation goes to Dr. Thomas Starzl for his tireless work in advancing organ transplantation and for his encouragement, mentoring, and unending optimism.

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Dr. McCauley is a past Chair of the OPTN/UNOS minority affairs committee and serves on the executive committee's committee governance working group and board governance subcommittee. He has also been a part of the OPTN/UNOS policy oversight committee, the simultaneous liver-kidney working group, and the membership and professional standards committee, where he participated in the performance analysis and improvement subcommittee. Dr. McCauley also served on the ad hoc communications committee. He was a trustee-at-large for the National Kidney Foundation of Western Pennsylvania as well as a member of the Quality Insights Renal Network 4 board of directors.

He helped start two new multiorgan transplant programs: one of the original four US kidney and liver transplant programs at the Veterans Administration in Pittsburgh, and the Mediterranean Institute for Transplantation and Advanced Specialized Therapies in Palermo (ISMETT), a joint effort by the Italian government and the University of Pittsburgh Medical Center. He was part of the team who developed Tacrolimus from inception and provided nephrology

support for the last two xenotransplants in humans (baboon to human liver transplants).

Dr. McCauley earned his medical and bachelor's degrees at Dartmouth College in Hanover, NH, and his master's in public health from the University of Pittsburgh.

Carlo B. Ramirez, MD, FACS, graduated from the University of the Philippines (UP) College of Medicine in 1985, where he also completed general surgery residency at the UP-Philippine General Hospital (UP-PGH) and Medical Center. He then finished clinical fellowship training in transplant surgery at the Thomas E. Starzl Transplant Institute at the University of Pittsburgh Medical Center. Dr. Ramirez is currently Associate Professor of Surgery at the Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, PA. He is also the Surgical Director of the Kidney Transplant Program at the Lankenau Medical Center in Wynnewood, PA. He is an abdominal transplant surgeon who has extensive experience in liver, kidney, and pancreas transplantation. Prior to Jefferson, Dr. Ramirez was at the National Kidney and Transplant Institute in Quezon City, Philippines, where he served as Chairman of the Department of Organ Transplantation. Concurrently, he served as Clinical Associate Professor and Chief of the Division of Transplantation at the UP-PGH and Medical Center. Prior to this, he worked as Consultant Transplant Surgeon and Deputy Director of the Department of Liver Transplantation and Hepatobiliary Surgery at the King Fahad National Guard Hospital in Riyadh, Saudi Arabia. His research interest focuses primarily on solid organ transplantation, immunosuppression, and organ donors. He authored over 100 scientific publications. Dr. Ramirez is also a member of numerous local and international professional and scientific transplant and surgical societies.

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A History of Kidney Transplantation

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Abstract

Kidney transplantation has a long rich history dating back to Indian plastic surgeon's refashioning of deformed noses until now when hundreds of thousands of grafts have been successfully transplanted. The advances were incremental with periods in which the gains were forgotten requiring duplication and delay. Skin grafts have provided invaluable information on the immunology of transplantation and remain a standard research method. Unfortunately, the erroneous claims of successful clinical skin grafting throughout history have only recently been corrected. It is difficult to assign primacy to any one pioneer for landmark advances since in most cases the "first" of any advance followed a substantial background of previous studies and in some cases the successful transplant was not a surprise to anyone. The credit should go to the many who worked tirelessly without reward to advance renal transplantation and all other forms of transplantation for the good of their patients. We live in an era when what was myth is now reality.

Keywords

Homo(allo)transplantation · Hetero(xeno) transplantation · Autograft · Freemartin cattle · Grafts · Acute renal failure · Immunosuppression · Carrel patch · Cyclosporine · Imuran · Tacrolimus · 6-Mercaptopurine · Total body irradiation (TBI) · Human histocompatibility antigen (HLA) · OPTN (Organ Procurement and Transplantation Network) · UNOS (United Network of Organ Sharing)

Introduction

Kidney transplantation is the most common and most successful of all forms of organ replacement. Its origin can be traced back into ancient times as myth or tradition, but it slowly became a reality after incremental developments in many areas of surgery, medicine, and immunology. We are fortunate in that many of the modern pioneers of transplantation have written about their experiences and roles in the history of transplantation in review articles and a volume titled "Transplantation: 35 Recollections" (Terasaki 1991a). This chapter will lean heavily upon the encyclopedic text of David Hamilton, "A history of Organ Transplantation" (Hamilton 2012) with its detailed discussion of early transplant history and the modern era in which he was a participant and contemporary of many of the giants of transplantation.

Ancient Myths and the Foundation for Early Transplantation

The concept of replacing human body parts can be found in some of the earliest records of humans (Bynum 1995). Indeed the first drawing depicted a figure with an animal head and human body. The ravages of disease, war, and punishment in the form of amputation of noses and other body parts generated a constant population of persons with less than full body integrity. Perhaps the best known example of myth/tradition is the report of Cosmos and Damian replacing the leg of a nobleman with the leg of a dead and buried Moor. Other accounts of such miraculous procedures can be found in most ancient cultures. Our current knowledge of transplantation makes these accounts medically impossible since the donor tissue was procured from subject in which blood flow had ceased days previously. Later in the more recent era, these principles would be explored with documented experiments using organs from donors with varying degrees of warm ischemia. In fact, Cosmos and Damian illustrated the first example of vascularized composite allograft (VCA) transplantation now being performed using arms, hands, faces, uterus, and other vascularized body parts. The period of myth and miracles later gave way to experimentation and refinement of surgical techniques.

Early surgeons sought to replace body parts using their hands. Perhaps the earliest account can be found in the Sanskrit text *Sushruta Samhita* published in about 600 BCE (Hamilton 2012). It detailed surgical reconstruction of damaged or amputated ears and noses using techniques that presaged modern plastic surgery. Sushruta was an Indian surgeon who created skin flaps and rotated them (preserving blood flow) to the defective areas and sutured them in place. After a period of healing and tissue growth, the flap was fashioned into a nose or ear, and the donor skin with its blood supply was resected. This was the first historical example of an *autograft* in which a patient's own tissues were moved to another location in their body. It illustrated many principles of modern transplantation including the importance of preserved blood flow and avoiding incompatible donors. The pivotal role of plastic surgery and surgeons in the history of transplantation was recently reviewed after the death of its most famous champion, Joseph Murray (Yaremchuk 2013). The techniques outlined by Sushruta apparently were not practiced in Greece or Egypt, but they are mentioned by the Romans Celsus (25 BCE) and Galen (129–216 AD) which may represent duplication of the texts of Sushruta (Hamilton 2012). Works by Arab surgeons such as Rhazes (924 AD) mention such techniques. As with many of the cultural and technical advances which reached their peak during the Roman period, plastic surgical advances were lost after the invasion and sacking of Rome which ushered in the Dark Ages or Middle Ages (fifth to fifteenth century AD).

Little to no progress was made during the Dark Ages in plastic surgery or other medical areas relevant to the development of transplantation. In fact much of the cultural, engineering, and medical knowledge was forever lost. The Renaissance (fourteenth to seventeenth centuries AD) was a period of intense rediscovery of ancient knowledge which in part took the form of a search for ancient texts from Greece and Rome. Sicily (due to trade routes) played a major role in the rediscovery of ancient texts, including those from India and the methods of plastic surgery. Gaspare Tagliacozzi (1545–1599) of Bologna was particularly influential with his text *De Curtorum Chirurgia per Insitionem* (On the Surgery of Mutilation by Skin Grafting) which provided detailed methods for skin grafting (Gnudi 1988; Hamilton 2012). During this period the idea of using skin from a different donor (homograft, later allograft) was considered to avoid the pain associated with the use of the patient's own skin as a flap. Tagliacozzi was against this practice, invoking the "singular character of the individual" as his major objection (Hamilton 2012). This idea of potential incompatibility between donor and recipient would become a hallmark of modern transplantation. Later Tagliacozzi's text was seriously misquoted leading to major errors in application. The major and most damaging error was

that he had used slaves or servants as donors to their masters, leaving the impression that skin grafting could be successfully accomplished between people. These claims of successful skin grafting between different persons would persist into the modern era of transplantation despite their almost universal failure.

Although the Renaissance period attempted to recover lost culture and medicine, it was steeped in the belief of magic and religious misconception. Tagliacozzi's objection to skin homografting was primarily based upon the "force and power" of each person's individuality which evoked religious or philosophical reasoning. He never asserted that the skin could be successfully grafted from one person to another. His text was, however, commonly misquoted to suggest that a slave skin donor had provided tissue in one of Tagliacozzi's procedures. The philosopher Tommaso Campanella (1568–1639) asserted that grafts from a deceased person would also die because the human soul residing in the graft was indivisible from its donor (Hamilton 2012). Although he accepted the misconception that successful skin grafting from the slave to master had occurred, using philosophical reasoning, he believed that the graft would die when the donor died. He also claimed that the donor and recipient could communicate with each other over long distances "by pricks inflicted upon themselves according to numbers" as quoted by the Jesuit priest Athanasius Kircher (1568–1639) who soundly rebuked such concepts (Hamilton 2012). Kircher suggested that such procedures would require the assistance of the devil. The idea that satanic or other supernatural forces were the major influences in successful homografts of skin slowly gave way to more scientific thinking, but the myth that Tagliacozzi had used human donors persisted. The major textbook of surgery from the 1600s (*Mellificium Chirurgiae* or *The Marrow of Surgery* by James Cook) described the Tagliacozzi procedure and included the inaccuracies that he used muscles, that the grafts were donated by someone else, and that the grafts would be lost if the donor died (Cook 1648) (Hamilton 2012). During the mid-1600s a surgical text described the repair of a skull injury in a Russian nobleman by use of a rabbit bone graft. The text claimed success, but the graft was removed when the recipient was threatened with excommunication by the church. This is probably another myth or fabrication, many of which were to plague transplantation for centuries to come, but these would increasingly be claimed by trained surgeons.

In 1663 the Royal Society of England (previously called the College for the Promoting of Physico-Mathematical-Experimental Learning) began to investigate skin grafting (Hamilton 2012). This was the earliest organized attempt at tissue transplantation experimentation. The studies by the Royal Society were stimulated by a proposal by John Wilkins (1614–1672) in September 1663. He proposed "the experiment of making a piece of skin of a dog to grow upon another." After great discussion the Society decided to start not by grafting the skin from one dog to another but to remove the skin and graft it back onto the same animal. They also proposed to attempt regrowing of hair and grafting a cock's spur to its own head. The latter experimentation was explored later by John Hunter in the 1700s. After several halfhearted attempts at skin grafting, the planned investigations ceased. The lack of success was primarily technical in that the skin shrunk after being removed preventing grafting, and in a later attempt the dog ran away ending the study. These efforts finally ended after an outbreak of the plague in London when the investigators left the city for safer environs.

The Beginning of Experimental Transplantation

After the ambitious plans of the Royal Society were not realized, little efforts were made to systematically study transplantation (Hamilton 2012). In the eighteenth century, however, the first scientific studies of transplantation began. During this period the belief that demonic possession was a prerequisite for transplantation and that the soul resided in each part of the body was almost dogma. The latter asserted that organs or body parts could not survive if the donor died.

Abraham Trembley (1710–1784) demonstrated that the freshwater coelenterate hydra (polyps) had the ability to regenerate if parts were resected. Importantly, he showed that two halves of different hydra could reunite. These studies raised the hope that human body parts could regenerate and that organ transplantation could be possible between different people. Over time it became clear that humans could not regenerate most organs or body parts, but it did hint at the later discovery of hepatic regeneration and pluripotent stem cells.

A more direct approach to questions of transplantation was first conducted by John Hunter (1728–1793) (Hamilton 2012). In fact many regard him as "the father of modern surgery." He was also perhaps the first to conduct well-designed studies in transplantation. Unlike his contemporaries, Hunter preferred not to make philosophical examinations but to perform actual experiments to answer important questions about the nature of life and transplantation in particular. When questioned by one of his later eminent students (Edward Jenner) about his theories, he was reported to have said "I think your solution is just but why think, why not try the experiment" (Hamilton 2012). At a time of superstition and clerical punishment, John Hunter conducted experiments into tissue vitality and what he called "the living principle" without resorting to religious explanations. He studied the contractility of umbilical cord muscle and determined that contraction (and therefore life) ended after about 48 h. He performed a series of experiments with animal glands in which he removed the testicle of a cock and placed it within the same animal's abdomen with excellent survival of the gland. Attempts at transplanting the cock's testicle into a hen were less successful, and he noted the lack of "virilization" suggesting no glandular function. His most famous experiments involved transplanting the spur of chickens from foot to comb similar to the proposed studies by the Royal Society. He was not the first to perform this operation since farmers produced them earlier to supply circus oddities.

Hunter also performed experiments and medical practice of tooth transplantation. Like skin grafting of the nose, teeth transplantation had an ancient origin so that Hunter was not the first to perform the operation (Hamilton 2012). The Royal Society in the 1600s had planned studies of tooth transplantation but did not complete them. Advertisements for tooth transplantation were common in the 1700s both in Europe and America. Even George Washington considered it for his famous dental problems. Hunter's standing as one of the most distinguished surgeons and his systematic investigation of a subject accounts for his lasting prominence. The donors of teeth were both of human and nonhuman origin. Typically servants were forced to donate their teeth with or without compensation. The impoverished citizens of London and other large cities gave their teeth for meager compensation. Animal teeth from dogs, sheep, or others were used in some cases. For Hunter and others, transplantation of teeth was a lucrative practice. He emphasized short times between extractions of the teeth, the use of the young and female as donors, and avoidance of animal teeth. Cadaver donors were avoided, and he preferred to use the teeth of servants to wealthy recipients (rather than random paid donors) to avoid venereal and other diseases common to this period. In fact none of the teeth were successfully transplanted since blood flow was never restored and all cellular elements died. They provided a short-term solution at great cost to the donor and recipient. Transmission of tuberculosis, syphilis, and bacterial infection was common particularly with animal donors. Growing concern over the ethics of preying on vulnerable servants and the poor ultimately helped to end this practice. The major reason for ending tooth transplantation however was failure of successful implantation.

Rediscovery of Plastic Surgery by the West

In October 1794 a report appeared in the *Gentleman's Magazine* (Hamilton 2012). It detailed the successful reconstruction of the nose. The patient was an Indian collaborator (Cowasjee) of the British who had been captured, and his nose and one hand had been cut off as an

example for traitors. After he escaped, the British referred him to a local Indian surgeon for reconstruction using what was known by the British and Indians to be an ancient but successful procedure. This report revived interest in nose reconstruction. It was the technique originally described by Sushruta and later Tagliacozzi. After reading of Tagliacozzi in the original text, John Ferriar (1761–1815) of Manchester and Edinburgh surgeons later dispelled the earlier myths attached to this procedure. Stories such as the failure of a nose graft from a distant slave after the death of the donor was debunked. In 1812 Joseph Carpue (1764–1846) performed rhinoplasty on two patients using the skin flap method and reported them in great detail in 1816. This report is said to be the beginning of modern plastic surgery in the West. Recurrent European wars and resulting deformities were responsible for the spread of skin grafting, and it was expanded beyond the nose, but again reports of successful homografts appeared. Erroneous reports of successful skin grafting between individuals would persist well into the twentieth century (Barker 2013a). Winston Churchill claimed that he had successfully donated skin to a fellow officer during the Boer War. He was fond of telling this story even as late as 1944 (Churchill 1944). Some also asserted that successful grafts of whole detached noses or ears were possible. Later Jacques-Louis Reverdin (1842–1929) showed that small thin (split thickness) autografts could heal (Hamilton 2012) (Reverdin 1869). Thick grafts did not revascularize due to the thick layer of fat and other tissues. Not only did some surgeons claim success for homografts but some actually used grafts from animals (xenografts). Skin from dogs, pigs, and frogs all were commonly used and said to be successful in the late 1880s. These claims of success were likely based upon poor follow-up, self-deception, and outright dishonesty by some surgeons.

Success of skin grafts stimulated the use of other tissues and glands (Reverdin 1869). The experiments of John Hunter with cock testicles were well known, and some placed glands including the thyroid, pancreas, testicles, and ovaries into the abdomen. Since the organs were intraabdominal and could not be observed, success was subjectively reported by the patient's improvement in symptoms (Hamilton 2012). Xenografts were used in these cases also with sheep being preferred by some practitioners. None of these grafts could have functioned. More encouraging results were found using bone, cornea, and blood. In the late nineteenth century, bone grafts were pioneered by Louis Ollier (1830–1900) in Paris (Hamilton 2012). The apparent success of these grafts was not a result of surviving donor cells but to the bone acting as a site for ingrowth of recipient cells. Likewise corneal transplants were attempted with some true success. We now know the cornea, due to its lack of blood supply, is a privileged immunological site. Random blood transfusions were also attempted with some success likely due to the limited number of blood types resulting in serendipitous matches. Other uncommonly grafted tissues included the spleen, eye, fallopian tube, and uvula (Hamilton 2012). Most forms of homotransplants or xenotransplants faded away by the early twentieth century from lack of true success. As with the earlier tooth transplants, transmission of diseases such as tuberculosis and venereal diseases plagued these procedures.

Early Organ Transplantation

Skin grafts and the myriad of tissues implanted were not vascularized, and until the late nineteenth and early twentieth century, there were few methods for repair or joining of vessels. Misadventures with bloodletting, gunshot, and knife wounds left life-threatening conditions which could only be repaired by cautery, ligation, or even amputation (Hamilton 2012). The first end-to-end arterial anastomosis was performed by Benjamin Murphy (1857–1916) in 1897. The patient had a gunshot wound of the femoral artery. Such a wound would require amputation since ligation would cause ischemia and gangrene of the entire leg. He apparently used overlapping sutures, and the patient recovered with full function of the limb. Many centers in Europe became interested in vascular surgery methods; Germany

and France were in the forefront. Experiments in suturing methods and improving material including finer needles and stents were developed during this period. Mathieu Jaboulay (1860–1913) in Lyon was the first to successfully perform suturing on small vessels using interrupted sutures with inverted edges and penetrating full layers of the vessel (Hamilton 2012).

Alexis Carrel (1873–1944) is commonly given credit for developing vascular surgery for which he received the Nobel Prize in 1912 (Hamilton 2012). He is also commonly credited with developing organ transplantation, but many others also played pivotal roles. His experiments with vascular surgery and resulting techniques are used frequently today. The 1902 report of his new stitching technique also included a statement that "this was simply a prelude to tomorrow's routine gland transplantation" (Carrel 1902). He had developed this work in the anatomy department of which Jaboulay was the chief surgeon. He was certainly aware of his work, but he did not use his technique initially preferring to use over and over continuous stitching with only partial-thickness stitches. He benefited from thinner suturing material and a new technique in which he would triangulate the vessel. His later development of the Carrel patch is well known to any modern vascular surgeon and is in routine use in vascular surgery and organ transplantation today.

With the ability to join vessels came the first experimental kidney transplants (Hamilton 2012). In 1902 Emerich Ullmann (1861–1937) removed a dog's kidney and reimplanted it into the neck vessels of the same dog. It produced urine and the animal was shown at the Vienna Medical Society in March 1902. He later performed a dog-to-goat kidney transplant, but it passed urine only a short time. That same year Alfred von Decastello (1872–1960) performed a dog-to-dog renal transplant using stents. This period marked many innovations in kidney transplantation. Floresco experimented with drainage of the ureter via a bladder anastomosis with the kidney placed in its normal anatomic site and placing the kidney in the pelvis (Hamilton 2012). He did not consider placing the kidney in the pelvic fossa to be a viable option (Toledo-Pereyra and Palma-Vargas 1999).

The first human kidney transplants were performed by Jaboulay in 1906 (Cooper 2012; Hamilton 2012). Renal failure was a fatal condition during this period, and he sought to save the lives of two patients (both women). In the first he used a pig's kidney (sacrificed 3 h earlier) which was connected to the vessels of her arm, and in the second he used a goat's kidney joined to the thigh. The pig kidney was connected end to end to the brachial artery using Payr's stents. Both kidneys produced urine immediately but stopped functioning on the third day; both patients died of renal failure. The first patient with nephrotic syndrome developed "albuminous urine" by the third day, and histologic examination revealed infarcted zones alternating with normal and both had vascular thromboses. Ernst Unger performed the second and third kidney transplants in 1909 in another woman with renal failure. The donor was a macaque monkey, and interestingly both kidneys were placed en bloc into a "gap created in the femoral artery." Similar to modern methods, donor and recipient operations were performed simultaneously, and the kidney was immediately implanted. Despite these precautions, the kidneys never functioned, and the patients died of renal failure. Specimens from these kidneys were taken and in one of the first histologic examinations of a transplanted kidney, "a lymphocytic infiltrate and mitotic figures were observed" (Hamilton 2012). Necrosis was also present but the pathologist felt it was "reparable." He also performed a little known transplant in which the donor was a human stillborn child and recipient a baboon with the expected graft failure (Kuss and Bourget 1992). Postmortem examination revealed patent vessels. In all early kidney transplant cases, the patients had advanced renal failure ("preterminal") and were said to have severe metabolic derangements associated with end-stage or advanced acute renal failure. Schonstadt performed the last documented xenotransplant using a Japanese monkey kidney into a girl with mercury poisoning. It functioned only 60 h, and she died after producing only a small amount of protein-laden urine (Kuss and Bourget 1992).

The failures of cross-species kidney transplants caused a halt in attempts in humans. Jaboulay's laboratory performed a series of autotransplants into the pelvis to determine if denervation and retransplantation alone mediated these poor results (Starzl 2011a; Hamilton 2012). They determined that autotransplanted kidneys functioned long-term with normal histology. Other early transplants suggested that cross-species transplants were not likely to be feasible, and there may be some other unknown factors precluding successful transplantation. There was much to be learned about warm ischemia, the role of immunology in general, and the formidable barrier posed by crossing species.

The First Glandular Transplants Between Humans

The utter failure of xenotransplants prompted the use of humans as donors. These homografts were not initially performed in kidney transplants but with glands (Cooper 2012; Hamilton 2012). The first human-to-human allografts were of the thyroid transplanted into three thyroid deficient "cretins" ages 8, 18, and 25 reported by Eugen Enderlen in 1909. The grafts were placed into the arm vessels using state-of-the-art techniques including the Carrel path, vessels from deceased donors, and near microvascular surgical techniques. Although the vessels remained patent, no evidence of glandular function was present by the crude measures of improved growth or increased intelligence. The second human allograft was of the testicle performed by Levi Hammond and H.A. Sutton in Philadelphia. The recipient's testicle had been removed due to cancer, but the contralateral testicle was present and presumably functioning. The donor testicle was removed from a patient who had died of a ruptured liver. The testicle was removed "shortly after death" but placed in warm storage (41 °F) for 19 h. After implantation it was left partially exposed in the scrotum for observation purposes. Although the authors claimed excellent perfusion of the gland, it atrophied after approximately 1 month. The failure of the testicular graft was attributed to what was known as "Halsted's law" (Hamilton 2012). This was a principle put forth by the famous and tragic surgeon William Halsted (1852–1922). He was perhaps the first American-born transplant surgeon among his many other accomplishments. He had performed gland grafting experiments in which he grafted slices of dog parathyroid to the dog's spleen. He determined that autografts survived but homografts died. From this and other works, he asserted that grafted glands would function only if the body needed the output from that gland and would fail if a second gland such as the testicle was providing function. This view was taken as sacrosanct when coming from the great Halsted and was applied later to renal transplantation erroneously.

Alexis Carrel's Contribution to Transplantation

After failing his qualifying examinations for a faculty position in Lyon, Carrel moved to Chicago (Hamilton 2012). His position in Lyon was further compromised by the public assertion that he had witnessed a miracle cure at Lourdes. The anti-religious atmosphere among some French intellectuals and medical faculty marginalized his position there. After moving to Chicago, he developed a fruitful but troubled collaboration with Charles Guthrie (1880–1963). During the years 1905–1906, this team of young surgeons produced 21 joint publications with Carrel publishing 5 single-authored papers on vascular surgery and transplantation. Together they performed transplants of the spleen, small intestine, thyroid, and heart (Carrel 2001). It became clear that homografts functioned only for brief periods if at all. During this period they jointly developed what was to be known as the Carrel patch in which small blood vessels were connected using a cuff surrounding the smaller vessel. Carrel publicly, privately, and in print claimed almost sole credit for the development. The work leading to Carrel's Nobel Prize was started during this period, and Guthrie would later assert that the prize should have been awarded jointly for their collaboration. During this period, however, the Nobel Prize

could not be shared. This was changed later. Carrel and Guthrie worked separately after 1906, and Guthrie continued to pursue experiments in organ transplantation which included grafting of the heart, lung, and limbs, and unusual grafting of one dog's head to the neck of another resulting in a two-headed dog. He also showed that blood vessels could be stored and grafted into different animals with great success. These vessels lost their living cells and formed a scaffold without the risk of rejection or other immunological injury.

Carrel's contribution to transplantation is undeniable, and he is regarded as the first transplant surgeon by many. As is typically the case, the work of others served as the foundation or competition for his achievements. He cultivated the image of the lone brilliant surgeon and researcher in the media and in scientific publications. Drawings in magazines of the period showed him surrounded by a menagerie of animals with transplanted limbs, heads, and other body parts. He was commonly depicted as a scientific wizard. Despite this extreme self-promotion, he was responsible for important innovations in transplantation. He was one of the first to develop tissue culture and along with Charles Lindberg developed the first organ perfusion apparatus. His continued work after 1906 revealed the possibilities and limitations of transplantation at that time. It was possible to graft an array of organs or other body parts technically, but the immunologic barrier could not be overcome. The Nobel Prize given to Carrel in 1912 for vascular surgery, and transplantation was largely on the grounds of his work with vascular surgery. In his introduction to the Nobel Prize, Professor J. Akerman states "On the other hand, the experiments in which Carrel successfully transplanted whole organs or limbs from one animal to another have not found any application in man. For one thing, healthy kidneys, spleens and limbs are hardly ever available to the surgeon, and, for another, the experience we have gained with animals has taught us that organs transplanted from one animal to another usually degenerate in their new owners, often shriveling up after a variable length of time, and ceasing to function. As for preserving similar material – organs or limbs – from a healthy person, in order to use them when a sick or wounded person should have need of them, our knowledge does not yet extend as far as this" (Akerman 1912).

The Lost Era of Transplantation

Carrel and others had provided the ability to graft vascularized organs, but only very short-term graft survival was possible due to an unknown barrier (Carrel 2001). From approximately 1903 to the late 1920s, a group of distinguished investigators studied many areas of transplant immunology, but their work was forgotten and the principles had to be rediscovered decades later. David Hamilton calls this period the "lost era of transplantation immunology" (Hamilton 2012). The idea of immunity is ancient, and cultures from India, China, Africa, and Turkey recognized that those who recovered from smallpox were protected from future smallpox epidemics. They all practiced inoculation in which infected material was scratched into the skin to prevent disease in persons previously unexposed to smallpox. This technique conferred immunity on these patients. Paul Ehrlich (1854–1915) extended the belief that antibody was produced against infection and a second exposure resulted in a more robust response (secondary response or memory) to include this response to any form of material. It was dogma that rejection of the rat tumors were related to an antibody, but no antibody was detected. The idea that cellular mechanisms might generate such a response was resisted. Instead Ehrlich invoked a process called "atrepsia" popularized by Louis Pasteur which stated that bacteria (or grafts) ran out of nutrition which led to death of organisms (organs). George Schone performed mouse skin grafts while working in Ehrlich's laboratory which revealed that second skin grafts from the same donor died quicker than the first graft. This process was later termed the "second-set reaction." He also found that the rapidity of rejection correlated with the genetic distance of inbred strains. A Nobel Prize would be awarded to Medawar for "discovering" the second set among other phenomenon years later

without acknowledging the work of the "lost era." Additional studies during this "lost era" by James Murphy and others elucidated some of the roles of lymphocytes in rejection. Methods to suppress the immune system appeared during this period including the use of radiation, and chemical agents such as Benzol, and nitrogen mustard were first studied. Charles Todd (1869–1957) even studied methods of "matching" individuals. These and many other studies were mostly forgotten until decades later.

The exciting research into the mechanisms of graft rejection was to be overshadowed by the impending World War I. War is well known to stimulate innovation or stifle it; in this case it was stifled. Transplantation was given a prominent role in the 1914 International Society of Surgery located in New York, but war clouds suppressed attendance. A star-studded cast of speakers attended the meeting including Alexis Carrel, Emerich Ullmann, and many others. It was now well accepted that autografts regularly succeeded but homografts or xenografts invariably failed. Carrel gave what became known as his "road map" for successful transplantation in the future which included the need for methods of preventing rejection caused by lymphocytes with better chemical agents and suggested that there might be different phases in acceptance of the grafts which might be manipulated. We know now that during the first year, rejection risk is greatest but it decreases over time (accommodation). Shortly after this meeting, World War I began leading to a virtual cessation on research in transplantation and immunology.

Hamilton summarized the lost era, "both in Europe and in America, there had been excellent 'lost era' studies on the lymphocyte, lymphocyte movement, fetal unresponsiveness, privileged site, immunopotentiation, antilymphocyte sera, lymphocyte culture, cellular transfer, serological individuality, autoimmunity, and immunosuppression by radiotherapy and chemical treatment. Surgical skills gained in experimental organ grafting meant that a solid platform of reliable knowledge had been erected to allow progress in extending the survival of organ transplantation. These contributions came from established investigators in famous institutions and were published in the leading journals. . . .. The promising transplantation studies of Carrel's roadmap simply and mysteriously disappeared from the surgical agenda after World War I, and Carrel and Murphy moved on to study other matters. The many gains were abandoned and the insights of (the) 'lost era' were forgotten. Much later, when studies resumed, most of the lost and forgotten information was innocently rediscovered" (Hamilton 2012).

From Chaos to the Beginning of Clarity (1920s and 1930s)

World War I left most European nations in financial shatters, and the political atmosphere remained hostile to international scientific cooperation (Hamilton 2012). A defeated Germany became impoverished due to the war itself and the hefty reparations imposed by the victors. These left little resources for what had previously been the leading scientific institutions of Germany, and the mistrust mixed with hatred left prior scientific progress suspected and ultimately rejected. In the aftermath of the war, German scientists were barred from attending scientific meetings, and their scientific journals which had been in the forefront ceased to print or were downsized. The French and British had expended much of their national resources on the war and were similarly unable to support rigorous scientific inquiry. Added to financial limitations was a growing sense that applied scientific studies such as organ transplantation were of little benefit and that basic science should be the major focus of research with applied studies awaiting an understanding of basic mechanisms. This period was also punctuated by the opposite impulse of limited scientific rigor and erroneous claims of success in transplantation. The 1920s saw the return of homografting of skin and glands with even more strident declarations of success. Again there were assertions of successful grafting of whole organs such as ovaries and even restoration of sight in animals by bilateral transplantation of both eyes.

Most prominent of the gland transplanters during the 1920s was Serge Voronoff (1866–1951). As mentioned earlier, testicular transplantation had been performed during the nineteenth century, and extracts of testicles were said to possess restorative qualities in male virility during that period. Voronoff was a Parisian surgeon who had performed bone grafting during World War I and conducted experiments with testicle transplantation from young sheep to old rams claiming success in rejuvenating the rams (Hamilton 2012). From 1920 to 1924, he performed a series of monkey-to-human testicular transplants using thick slices of the gland placed in the scrotum. His results were published in well-respected journals, and like Carrel, he was an aggressive self-promoter who courted the media and became a rich celebrity for his claims. Other surgeons both in Europe and America developed lucrative practices in testicular transplantation. John Brinkley (1885–1942) of Kansas advanced testicular transplantation to the level of true quackery. Voronoff's procedure used thick slices of glands which were against later confirmed principles that grafts should be thin to allow vessel ingrowth. Brinkley took it a step further by transplanting the entire testicle of goats to humans with spectacular claims of rejuvenation in the typically older recipients. Although Voronoff was a well-trained surgeon, Brinkley had only briefly attended medical school and did not possess credentials to practice medicine. He marketed his procedure by mail and radio as a cure for many male ailments. A lucrative single operation clinic made him rich, and his income was supplemented by the sale of other "remedies." During this period many surgeons in academia and private practice in Europe, America, and other countries took up the practice of gland and skin transplantation without regard for the evidence from the "lost era" or the efficacy of their procedures. The medical journals published noncritical accounts of successful grafting of ovaries and skin among others which bolstered the reputations and earnings of these surgeons. As the claims and financial rewards grew, a reckoning was looming in the 1930s.

For Voronoff the end of his prominence and the beginning of disgrace began in 1930. He had been contracted by the French government to perform large-scale transplants of young sheep into scraggly older animals after previously suggesting that the procedure improved wool production. His claims advanced to the incredulous assertion that his procedure induced a permanent genetic change which could be transmitted to the offspring. The latter claims led to increased scrutiny by way of an inspection by an international group of veterinarians. Such was Voronoff's fame and standing in the scientific community that the group left without serious criticism of his results. Unfortunate for Voronoff was an almost simultaneous study by Henri Velu (1887–1973) which largely duplicated his work but with better scientific rigor. Velu found that the sheep glands were dead and suggested that they were destroyed by migrating cells. Carl Moore developed an assay for the testicular hormone and performed studies showing no hormone production from gland transplants which completely invalidated the work of the gland transplanters. Despite this irrefutable evidence, some practitioners continued their work but also used extracts of testicles and other useless preparations to delude patients. Some of these practices continue in various forms even today. Brinkley was ultimately discovered to be practicing medicine without a license and providing useless treatments for which he was totally discredited.

Despite the excesses of the 1920s, the 1930s saw the advent of increasing clarity in transplantation. The work of Leo Loeb (1865–1959) demonstrating that sufficiently inbred mice strains did not reject skin grafts was an important finding in that these animals were essentially identical twins. James Barrett Brown (1899–1971) performed skin grafts in identical twin humans and demonstrated that the grafts routinely survived (Brown 1937) (Hamilton 2012). Skin grafts from nonidentical twins routinely failed despite the persisting notion advanced by sloppy or deceptive science of the time. These relatively obscure finding during the time would lead to the first successful kidney transplant some 20 years later. Acceptance of skin grafts with inbred strains became the final test of strain inbreeding (Loeb's test), and successful skin grafting between humans proved they were identical twins predicting survival of organ transplants in the future.

Human Kidney Transplantation Begins

The first human-to-human kidney transplant was performed by Yu Yu Voronoy (1895–1961) a Russian surgeon in April 1933 (Voronoy 1937; Tilney 2003; Hamilton 2012). Unfortunately his detailed account of the operation and postoperative course was ignored until the 1950s although it was published in Russian, German, and Spanish in separate journals. World War I had devastated the economies of most western European countries, but Russia was less affected primarily due to its early exit caused by the Russian revolution. Its universities and research activities remained robust resulting in major innovations related to transplantation such as the development of the first blood bank. In most cases initially the blood came from deceased donors. Voronoy received his medical training and later began in practice and research in Kiev. Their interest in blood transfusion led to a natural interest in immunological methods and transplantation. As with many centers of the time, there was great interest in testicular transplantation. An important paper by Voronoy was titled "On the problems of the role and significance of specific complement-fixing antibodies in free transplantation of the testis" (Voronoy 1932). He later became interested in kidney transplantation performing many dog-to-dog kidney transplants. After moving to Kherson, he performed the first human-to-human kidney transplant (Starzl 2011a; Hamilton 2012). The recipient was a 26-year-old woman who had attempted suicide with "sublimate" (mercuric chloride). She developed acute renal failure and was anuric for approximately 5 days before the transplant was grafted into the thigh. The donor was a 60-year-old man who had died 6 h earlier with blood type B and the recipient was type 0. Obviously the extended warm ischemia time, blood group incompatibility, and mercury poisoning made a successful transplant impossible. Accordingly the patient never produced urine, and she died 48 h postoperatively. The detailed postmortem and histologic examination revealed the operation to be successful without evidence of thrombosis. Histologic examination of the native kidneys demonstrated acute tubular necrosis with mitosis and "acute changes of the glomeruli, tubules and endothelium." No cellular infiltrates were mentioned. Voronoy performed four other human-to-human kidney transplants from 1933 to 1949 which were unsuccessful (Barker 2013a). Other kidney transplants apparently occurred during the early 1930s but were not published and without the detail description of Voronoy. The results were the same: failure. Twenty years later transplant surgeons would again attempt kidney transplants to save patients with acute renal failure in the presence of the technical advance of dialysis.

Medawar and the Beginning of Modern Transplant Immunology

Unlike World War I's stifling of transplant research, World War II would stimulate it leading to the rediscovery of previously elucidated mechanisms of immunology and propel transplantation into the modern era. World War II (the Battle of Britain in particular) produced a staggering number of burn victims and likewise death of people with perfect skin. A simple and practical measure could be to use the skin from dead people with intake skin for those with large devastating burns. With this modest idea, the British government enlisted Peter Medawar to investigate and make practical homografting of skin. The idea had the support at the highest levels of government in that Winston Churchill recounted as late as 1943 that he had donated skin to a fellow burned officer, and the skin graft was said to be successful to that very day. The realities of skin grafting between nonidentical twins were quite different. Studies were conducted on the casualties in the burn units of England which revealed that homografts did not survive and that a second graft from the same donor experienced accelerated loss. His famous paper "The behavior and fate of skin autografts and skin homografts in rabbits" confirmed the second set phenomenon which had been forgotten from previous work and ultimately in part led to a Nobel Prize for Medawar in 1960 in addition to other work confirming that rejection was an immunological phenomenon involving mobile lymphocytes (Medawar 1944). As with Carrel,

Medawar's body of work was expansive extending well beyond these studies. Grafting of skin during World War II was never successful and was ultimately abandoned. Medawar clung to the current dogma that antibody was the cause of graft failure but was apparently not aware of the previous work by James B. Murphy placing the mobile lymphocyte squarely in the middle of this immunological reaction. Medawar also finally brought clarity to the Freemartin cattle problem which stimulated further research into immunological tolerance. Freemartin cattle occurred when twins of different genders shared the same placenta. The female becomes masculinized due to intrauterine exposure to male hormones and becomes a sterile heifer with multiple gonadal anomalies. It was also found that the animals had mixture of two red cell blood types suggesting that more than just hormones had been exchanged with the animals becoming tolerant of discordant blood (Starzl 2011a; Barker 2013a; Hamilton 2012; Brent 1997). Medawar and Brent by injecting cells from adult animals into the fetuses of mice found that skin grafts from the adult donor were not rejected in these young animals after delivery. This was the first experimental demonstration of neonatal tolerance in transplantation. This search for tolerance would become the "holy grail" for transplantation until the present with no one demonstrating sustained tolerance in humans unlike in mice.

Successful Kidney Transplants

After World War II, groups in Europe and the United States rekindled serious research into organ transplantation. World War II had stimulated a renewed interest in organ transplantation at a time when the science was sufficient to support some early successes. In 1951–1952 Rene Kuss, Charles Dubost, and Marceau Servelle of France conducted a series of renal transplants with kidneys taken from prisoner donors shortly after death by guillotine (Barker 2013a; Hamilton 2012). The kidneys were transplanted hours after death resulting in limited to no therapeutic success in these recipients with acute renal failure. The most enduring result of this experience was the operation itself. Kuss had developed a procedure in which the kidney was placed in the pelvis with vascular anastomosis into the vessels of the groin and urinary drainage directly into the recipient bladder. This procedure had obvious advantages over placement in the thigh both cosmetically and in limiting complications. This procedure has become the standard operation until today with minimal alternations since its inception. Hundreds of thousands of procedures have been performed worldwide using this elegant operation.

In December 1953 the first living-related donor kidney transplant was performed by the collaboration of the nephrologist Jean Hamburger and surgeon Louis Michon of the Necker Hospital of Paris (Hamburger et al. 1962). This mother-to-son transplant functioned well for 3 weeks without immunosuppression before failure due to rejection. The patient was Marius Renard a 16-year-old carpenter who had damaged a kidney during a fall requiring nephrectomy. After the procedure was completed, he was found to have had only one kidney and was now anephric. As his uremic symptoms progressed, his mother proposed to Hamburger that she might donate her kidney. With the short warm ischemia time from a living donor, the graft functioned immediately with reversal of his uremia. The graft functioned until the 23rd postoperative day when he became anuric and died shortly thereafter. This limited success and sentimental story led to extensive international positive media coverage which elevated the standing of this fledgling treatment. The French experience stimulated interest from other groups worldwide resulting in visits there in the early 1950s to observe the operation and other methods. Among the visitors to Paris were John Merrill (1917–1984) a nephrologist and David Hume (1917–1973) a surgeon from the Peter Bent Brigham Hospital in Boston (Hume et al. 1955).

Kidney Transplantation in Boston: The First Successful Transplant

Within months of returning from Paris, the Boston group commenced renal transplantation in humans. Hume's report of the first nine cases

included a detailed summary of all renal transplantation to that point (Hume et al. 1955). It contained the series by Kuss including the many surgical complications encountered with the pelvic procedure including ureteral necrosis and extensive necrosis of the graft. Since none in the French series survived with function long-term, he stated in this paper that "In general, renal homotransplantation in the human has not been any more successful than in experimental animals." Perhaps for these reasons he did not place subsequent grafts in the pelvis using the Kuss method but in the thigh similar to Voronoy. The first patient in their series however did receive the graft in the pelvis, but this was placed by another surgeon in Springfield Massachusetts. Ethical concerns regarding the poor results of renal transplantation were growing, and Hume felt compelled to give a lengthy explanation of his reasoning for proceeding in his report. Primary among these was the futility of treating advanced renal failure (acute and chronic). Although none of the grafts in this series functioned long-term (five never produced urine, four had some function from 5 weeks to 5 months), his experience is notable for several reasons. First, he discussed the use of a new technology hemodialysis to support patients before and after transplantation. Prior to this series, he had provided support for Merrill's dialysis patients by placing tubing in the arteries and veins creating access to the circulation. At that time each dialysis treatment required a new operation at a different site. Second, he used adrenal corticosteroids (cortisone and ACTH) in some patients since it was known from animal studies that they could mitigate rejection of skin grafts even in presensitized animals. He concluded that steroids did not prolong graft survival from his experience. In addition, he noted the early recurrence of glomerulonephritis and suggested that "The rapid development of glomerulonephritis in a kidney transplanted to a patient with periarteritis, and the absence of this finding in transplants done in patients with chronic glomerulonephritis suggest that the titer of anti-glomerular antibodies in this latter disease must be at ineffective levels" (Hume et al. 1955). Finally, five of the nine received dialysis treatments prior to transplantation demonstrating the utility of dialysis as a bridge to transplantation.

In 1956 Hume moved to the Medical College of Virginia in Richmond, and a new surgeon Joseph Murray (a plastic surgeon by training) took the surgical lead at the Brigham. Hume continued his transplant work until his death in a plane crash in 1973. Coincidentally, Merrill drowned off a beach in a Caribbean island in 1984. In the 1950s Merrill and Murray developed a potent collaboration leading to the first long-term survival of a kidney transplant recipient: the twin transplants. In the 1950s the "Loeb's test" for twins was known, and it had been demonstrated in humans that skin grafts between twins enjoyed long-term survival. During World War II, Murray had worked in a military hospital in Valley Forge Pennsylvania on burn patients with his commanding officer James Barrett Brown a plastic surgeon who had reported the success of identical twin skin grafting in 1937 (Brown 1937). These two plastic surgeons illustrate the importance of plastic surgery in the early development of transplantation. Murray would later receive the Nobel Prize for transplantation but continued his private plastic surgery practice. After Hume's report and those of others suggesting the futility of human renal transplantation, experimentation with this procedure had almost ceased in many centers worldwide.

In December 1954 a ray of hope developed in Boston. Two days before Christmas, a renal transplant was performed between two identical twins resulting in the first long-term survivor (Hamilton 2012; Tilney 2003; Terasaki 1991a). The recipient was a 23-year-old man with progressive chronic renal failure who was initially maintained with periodic hemodialysis. Skin grafts confirmed that he and his twin brother were identical. After some temporary spontaneous improvement, he developed uremic symptoms. Merrill, Murray, and the patient's nephrologist had meticulously planned for the transplant, and the surgical team had practiced on deceased donors days before the operation. The graft was placed using the Kuss pelvic operation and produced urine immediately. Excellent graft function developed and the recipient retained the graft without rejection for 26 years

when he died of cardiovascular disease. Although this procedure generated great public interest and gave some hope to the medical transplant professionals, the results were predictable and did little to advance the science of the field. It was however the first practical demonstration of the transplant concept and for that reason must be considered perhaps the most pivotal event during those early dark days. Other centers developed their own twin kidney transplant programs, but this treatment would have limited application given the relatively rare clinical circumstances of finding identical twins. The practical experience gained by these transplant programs would prepare them for the next step which was to be transplantation of unrelated recipients with the use of medications designed to blunt the immune response.

Renal Transplantation Using Immunosuppression

The dismal experiences with renal transplantation except for the twins were in "unmodified" transplants. That is, transplantation without the use immunosuppression. By the late 1950s it became clear that some maneuver to alter the immune response to grafts would be necessary to prevent rejection and graft failure.

Irradiation and the Hope for Tolerance

Use of the atomic bomb in 1945 with subsequent radiation poisoning served as a stimulus to transplant research. Following the war there was ample funding to study the treatment of high-dose radiation. These studies led to the first experimental use of immunosuppression in transplantation. "Lost era" studies had revealed some of the immunosuppressive effects of total body irradiation but were abandoned when it failed to prolong grafts in dogs (Hamilton 2012). This information was forgotten as were much of the studies from this era. Following Medawar's demonstration of neonatal tolerance (Billingham et al. 1953) and his work demonstrating that rejection was an immunological event (Gibson and Medawar 1943), experiments in rabbits revealed that cortisone and total body irradiation could prolong skin grafts but only by a few days (Starzl 2011c). Joan Main and Richard Prehn demonstrated that mice treated with lethal doses of radiation could survive if infused with the bone marrow from the original recipient or others donors (Main and Prehn 1955). Skin grafts from the donor strain survived, while grafts from any new animals were quickly rejected. It became clear later that these animals possessed bone marrow-derived cells from both the recipient and donor. These "chimeras" generated great interest in the use of both radiation and bone marrow as a possible means of inducing tolerance in solid organ transplantation and formed the basis for developing bone marrow transplantation as a therapeutic strategy. Graft versus host (GVHD) was soon discovered in animal experiments and remains a risk in irradiated bone marrow transplant recipients. Mannick et al. used the chimeric strategy for renal transplantation in beagle dogs given sublethal doses of radiation and bone marrow infusion followed by renal transplantation (Mannick et al. 1959; Starzl 2011b). The animal developed chimerism, and the kidney function for 73 days before the animal died from pneumonia. In 1958 Murray used lethal total body irradiation (TBI) followed by bone marrow infusion in two kidney transplant patients, and the next ten patients received sublethal TBI without bone marrow (Murray et al. 1960). Only one patient in this series survived; the rest died from 0 to 28 days posttransplant. The surviving patient (a fraternal twin) was the first survivor of nonidentical twin renal transplantation, and he lived for an additional 20 years. During the same year, Hamburger transplanted a second fraternal twin using the latter approach by Murray (Hamburger et al. 1962). This patient also survived for more than 20 years. The French centers of Hamburger and Kuss performed four additional cases surviving longer than 1 year (Starzl 2011b). The two Hamburger cases were fraternal twins, but the two cases of Kuss were unrelated. According to Thomas Starzl (1926–2017), "During the critical period from January 1959 through the spring of 1962, the cumulative French experience was the principal

(and perhaps the only) justification to continue clinical trials in kidney transplantation." (Starzl 2011b). It was clear at this point that bone marrow was not required for successful transplantation and radiation alone helped but was insufficient for successful engraftment. Interestingly, Kuss and Hamburger had used adrenal cortical steroids as an adjunct to radiation. Kuss also used a new drug 6-mercaptopurine (6-MP) in one of his irradiated patients based upon previous work by Roy Calne (Starzl 2011b). This was perhaps the first use of multiple medications in transplantation which would later be called "cocktail therapy" and form the basis for successful transplantation.

Medication-Based Immunosuppression

The immunosuppressive effects of chemicals were known as early as the nineteenth century with benzoyl, but the toxic and potentially beneficial effects of mustard gas (nitrogen mustard) were the first to be studied in detail (Hamilton 2012). War casualties in World War I and accidents during World War II demonstrated that nitrogen mustard had a direct toxic effect on the bone marrow and decreased antibody production. Later it became evident that a derivative (tris-mustard) could be used to treat mouse lymphomas. This stimulated a search for nitrogen mustard derivatives which would be active against human cancers resulting in the first treatment for human leukemia. The antimetabolite 6-mercaptopurine (6-MP) was a result of these efforts, and its derivative (Imuran) would play a major role in transplantation in the future.

After radiation and 6-MP had been used with limited success in renal transplant patients, a search for more myelosuppressive agents were sought. Instead of using radiation, William Goodwin produced myelosuppression with methotrexate and cyclophosphamide in a renal transplant mother to daughter living donor transplant in 1960 (Goodwin et al. 1963). When rejection developed (presumably due to marrow recovery), he used prednisone several times to reverse rejection but did not report this case until 1963. This was the first demonstration of medication-induced immunosuppression and reversal of rejection of steroids.

In 1958 Robert Schwartz and William Dameshek of Tufts University and New England Medical Center of Boston found that 6-MP could reduce antibody responsiveness to antigen and that a short course plus timed doses of antigen could induce long lasting unresponsiveness to this antigen, i.e., induce tolerance (Schwartz and Dameshek 1959a). They studied other agents and found that methotrexate and azathioprine in addition to others were less effective. The next year they demonstrated that given continuously 6-MP could prolong the survival of rabbit skin grafts (Schwartz and Dameshek 1959b). Shortly thereafter Calne in London (Calne 1960) and Hume in Richmond Virginia (Zukoski et al. 1960) demonstrated that 6-MP could prolong kidney graft survival in the dog model. Calne soon moved to the Peter Brent Brigham hospital to continue his studies with 6-MP and its analogue azathioprine (Starzl 2011a). His results with these drugs in dogs revealed that most animals died within 100 days but some survived beyond 6 months. This was a sufficient success to proceed to human trials (Calne 1961; Calne et al. 1962; Calne and Murray 1961). Their experience in dogs and later three human renal transplant cases exposed the limitations of using these drugs as single agents (Hopewell et al. 1964).

The Brigham group concentrated on combinations of the available agents including adrenal cortical steroids, actinomycin C, and azaserine in combination with 6-MP or azathioprine. Interestingly, they did not find the combination of azathioprine and steroids to be effective (Calne 1961; Calne et al. 1962). In this series of ten patients, two were treated with 6-MP and eight with azathioprine-based treatment. Only one patient survived longer than 6 months.

During the same period Thomas Starzl had started a series of human kidney transplants in Denver Colorado during the fall of 1962 to April 1963 using combined azathioprine and steroids

but also using high-dose prednisone (200 mg/day) to treat rejections (Starzl et al. 1963). Nine of the ten patients in his series acquired long-term graft survival including two patients with graft survival greater than 35 years. In September 1963 the National Research Council in Washington DC invited 25 physicians involved in transplantation to discuss the state of the art of transplantation to that point (Hamilton 2012; Starzl 2011b; Barker 2013a). Starzl was one of the last to be invited. At that point 244 living-related and 68 deceased donor transplants comprised the world's experience, and only 10% survived greater than 6 months. With such results the mood of the meeting was gloomy and pessimistic about the near-term future of transplantation. Starzl's 90% long-term success stood in stark contrast to others' experience. His report followed the Brigham's series of 68 cases which was the largest single-center series, but they also had the prevailing 90% failure rate beyond 6 months. Although the tapes from this meeting have been lost, it was clear that the response to Starzl's report was disbelief. The dramatic shift in patient and graft survival from Starzl was minimized in the final proceedings of the meeting, but it had singlehandedly changed the fortunes of renal transplantation. Many of those attending the meeting later visited Starzl's program and subsequently adopted his protocol. Nicholas Tilney described the impact of Starzl's protocol as "letting the genie out of the bottle" (Tilney 2003). Starzl's recollection of the impact was summarized, "Elsewhere, the kidney gold rush began. At the beginning of 1963, the only active kidney transplant programs in the United States were at the Brigham, in Richmond, and at the University of Colorado. More than 25 new ones sprang up in the United States alone within the next year. We were inundated with fellowship applications, providing a talented pool from which came many of the leading figures in transplantation of the next generation. Kidney transplantation seemed to have become a clinical service overnight" (Terasaki 1991b). As with many new treatments, the routine graft survival of 90% was more optimistic than would be seen in renal transplantation for decades. The euphoria in the transplant community would need to be tempered by the reality of routine clinical application. About the euphoria Starzl stated "This was partly an illusion. It would not be possible for many more years to safely transplant cadaveric organs of any kind, including the kidney. Well into the late 1970s, Terasaki reported a compilation from 105 American programs of nearly 5,000 cadaveric kidney cases in which the 1 year graft survival was only 45% with an average patient mortality of nearly 20%. Individual centers tended not to report their own poor results, erroneously believing that everyone else must be doing better" (Terasaki 1991b). During this period in which renal transplantation had become a routine clinical service, chronic hemodialysis was also becoming available providing a growing number of potential recipients for kidney transplants.

Growth of Dialysis

In parallel and in support of renal transplantation was the development of the artificial kidney. The beginning of modern dialysis can be traced to Willem Kolff and his pioneering work in the Netherlands under Nazi occupation (Kolff 1998). In 1946 he sent his four machines to England, Canada, and the United States. The fourth was said to have been lost behind the Iron Curtain. Modifications to his original machine were made in several centers including the Brigham in Boston where Merrill used his modification to treat acute renal failure in some of the early transplant recipients. Refinements continued until patients could be maintained indefinitely on hemodialysis. Improved vascular access using arteriovenous fistulas and grafts eliminated the need for surgical placement of access for each treatment which had been required in the early period. In 1972 an amendment to the Social Security Act created dialysis support as an entitlement for all Americans. The costs of providing this coverage were vastly underestimated leading to one of the most costly government programs in the United States. It also created an enormous demand for renal transplantation. In 2013 more than 468,000 patients

were on regular dialysis and 193,000 were living with a renal transplant with annual costs of about $31 billion dollars/year (Saran et al. 2016). Hemodialysis is most costly (~$85,000/patient/year) compared to ~$30,000/patient/year for renal transplant recipients.

Period of Consolidation (1964–1980)

After the Starzl "cocktail" approach to immunosuppression was accepted, the number of active clinical transplant programs grew in the United States and globally. Imuran and prednisone were given daily as maintenance with large doses of steroids being used to reverse rejection. The limitations of rejection treatment soon became evident since rejections were often refractory, and recurrent treatment often resulted in serious life-threatening infection.

Antilymphocyte Globulins

By 1966 heterologous antilymphocyte globulin (ALG) was developed to treat rejection (Starzl et al. 1967; Starzl 2011a). The use of ALG was an extension of thoracic duct drainage studies in rats by McGregor (McGregor and Gowans 1964) which led to lymphocyte depletion and extended skin graft survival. Once in clinical practice, concerns emerged about the batch-to-batch variation in potency of ALG. Najarian and Simmons standardized their immunization protocol, but the consistency of the product remained suboptimal (Najarian et al. 1969). Monoclonal antibodies were soon developed using hybridoma technology resulting in the first commercially produced product (OKT3) directed at T cells with consistent potency (Cosimi et al. 1981). These agents were used to treat rejection with greater success. The new approach of giving them perioperatively in high-risk patients early to avoid rejection (induction therapy) soon became popular. Such refinements improved graft survival, but approximately 50% 1 year graft survival remained common in many programs.

Refinement of Other Measures Supporting Transplantation

Despite the marginal results during the consolidation period, advances in other areas supporting transplantation occurred. Sharing of donor kidneys and attempts to develop transplantation of the heart, lung, pancreas, and intestine dictated a coordinated approach to organ procurement and preservation. The importance of cooling the organs was confirmed. Early transplant success had been jeopardized by long periods of warm ischemia. Initially the whole donor was exposed to hypothermia, but later the value of intravascular infusions into the graft itself was discovered (Marchioro et al. 1963). Soon approaches developed beyond simply infusing the grafts with saline. Special solutions were developed which could improve the time of safe preservation. The first of these was "Collins solution" (Collins et al. 1969) which was used for about 20 years followed by "UW solution" which is the current standard (Kalayoglu et al. 1988).

Histocompatibility Screening Comes of Age

The discovery of the first human leukocyte antigen (HLA) in 1958 by Dausset and of anti-leukocyte antibodies from pregnant women set the stage for screening patients prior to transplantation (Starzl 2011a). The microcytotoxicity test developed by Paul Terasaki in 1964 was the worldwide standard for over 30 years. The importance of ABO compatibility in avoiding hyperacute rejection was also determined during this period. Later hyperacute rejection was seen in an ABO compatible living-related renal transplant, and the recipient was found to have preformed antibodies to the donor. This could now be detected by the microcytotoxicity test of Terasaki, and the immunologic disaster could be avoided. The value and limitations of the HLA matching effect were also explored during this period by Terasaki revealing that imperfect HLA matches resulted in better-than-expected outcomes.

Medical Complications of Treatment

Longer survival of transplanted kidneys uncovered a number of medical complications related to immunosuppression or side effects of medications. This period was plagued by serious infections due to the high doses of steroids used. For the first time opportunistic infections became prevalent. Since Imuran is a relatively week immunosuppressant, repeated doses of prednisone were required to treat rejection, and the maintenance doses were very high compared to modern standards. Transplant physicians became skilled in the management of unusual and common infections. In many centers the number of treatments for rejection within a short period was limited to avoid life-threatening infection. Cryptococcal meningitis was a particularly common complication of overzealous attempts to salvage rejecting grafts. Noninfectious complications were also common. Imuran increased the risk of skin cancers, liver disease, and bone marrow suppression particularly when used with allopurinol. High-dose steroids caused hyperglycemia or diabetes long-term, growth retardation in children, avascular necrosis, exacerbation of hypertension, and other problems.

Cyclosporine Era

The consolidation period allowed transplant surgeons and physicians to hone the surgical and medical management of renal transplant recipients, but the limitations of the available immunosuppressants were painfully evident. Not only were the outcomes in renal transplant recipients poor, but extrarenal transplantation was essentially impossible and there were calls for a moratorium on heart, liver, and other extrarenal transplantation until adequate immunosuppressive agents could be developed. Cyclosporine was this agent and it had a profound effect on transplantation. It was developed as part of routine screening by the Sandoz Pharmaceutical Company in Basel Switzerland in 1973. Preclinical studies disclosed that it was a potent immunosuppressant agent which could prevent rejection of the kidney, heart, and liver transplants in dogs (Starzl 2011a). In 1978 it was first used in human renal transplant recipients as monotherapy or with Imuran by Calne (Calne et al. 1978). He later used it for human recipients of kidney, pancreas, and liver transplants which demonstrated its ability to prevent rejection, but it had a different side effect profile than Imuran (Calne et al. 1979). Myelosuppression was not evident but nephrotoxicity, neurotoxicity, diabetes and a 10% rate of B cell lymphoma was discovered. Starzl duplicated his "cocktail" approach by adding prednisone to cyclosporine as baseline immunosuppression in renal and liver transplant recipients which minimized the side effects including posttransplant lymphoma (Starzl 2011d; Barker 2013b; Hamilton 2012). This protocol proved to be effective in other extrarenal transplants including the heart, lung, and pancreas which stimulated a second global explosion of transplant programs but this time for extrarenal grafts.

Tacrolimus

The cyclosporine/prednisone protocol became the standard of treatment beginning in about 1980 with some programs adding Imuran as an "adjuvant" agent. For the first time deceased donor transplants of all types could be performed with 1 year graft survival approaching 90% in low-risk patients. In 1989 a second agent (tacrolimus or FK506 as it was initially termed) was introduced which would further improve outcomes with a somewhat different side effect profile (Starzl et al. 1990). In the 1990s there was a great competition between the manufacturers of cyclosporine and tacrolimus, but once tacrolimus became generic, the "drug wars" ceased and now both companies produce the drug. Tacrolimus is now the predominant calcineurin inhibitor used in the United States with approximately 95% of new renal transplant recipients being discharged on it. It was initially found to reverse refractory rejections when given intravenously achieving high drug levels. The nephrotoxicity was felt to be equivalent, but tacrolimus was said to be more

Table 1 Milestones in renal transplantation

Year (s)	Name	Achievement
600 BCE	Sushruta	Wrote *Sushruta Samhita* Sanskrit text describing restorative surgery of ears and noses
1597	Gaspare Tagliacozzi	Wrote *De Curtorum Chirurgia per Insitionem* (On the Surgery of Mutilation by Skin Grafting)
1700s	John Hunter	"Father of experimental surgery," performed experiments on bone, glands, and teeth grafting. Used cock's comb as graft bed for it spurs. Did tooth transplants as "clinical" service
1902	Alexis Carrel	Developed vascular surgery allowing transplantation of vascularized organs
1902	Emerich Ullman	Performed an autotransplant of a dog's kidney into the neck vessels
1902	Alfred von Decastello	Performed dog-to-dog kidney transplant
1906	Mathieu Jaboulay	Attempted the first human kidney transplant (donors pig and goat, transplanted to arm)
1909	Ernst Unger	Performed two monkey-to-human kidney transplants
1937	Yu Yu Voronoy	First human-to-human transplant
1930s	Leo Loeb	Skin grafts survival only in identical twins (mice)
1937	James Barrett Brown	Skin grafts survive only in identical twins (humans)
1943	Peter Medawar	Neonatal tolerance, rejection of an immune process
1940s	Willem Kolff	First successful hemodialysis machines
1953	Jean Hamburger	First living-related renal transplant
1954	Joseph Murray	First successful renal transplant (twins)
1955	Main and Prehn	Radiation and bone marrow immunosuppression
1958	Jean Dausset	Discovered the human leukocyte antigen (HLA) system
1958	Robert Schwartz and William Dameshek	6-Mercaptopurine and Imuran as immunosuppressants
1963	Thomas Starzl	Combination of Imuran and prednisone introduced
1966	Thomas Starzl	Antilymphocyte globulin (ALG) used clinically
1972	US Congress	Amendment to Social Security Act established dialysis support as entitlement
1978	Roy Calne	Cyclosporine used clinically in renal transplants
1980	Thomas Starzl	Combined prednisone with cyclosporine improved efficacy and decreased toxicity
1984	US Congress	National Transplant Act
1989	Thomas Starzl	FK506 (tacrolimus) used in humans

neurotoxic and caused more posttransplant diabetes. Its increased potency has allowed successful intestinal and VCA grafts which were not possible under cyclosporine (Table 1).

United Network of Organ Sharing (UNOS): National Distribution of Organs for Transplantation

After innovations in organ preservation allowed grafts to be stored successfully for hours, sharing organs between transplant centers became possible. Paul Terasaki developed the first sharing organization in 1967, and the Boston Interhospital Organ Bank was established in 1968 (Terasaki 1991a). Other organizations sprang up throughout the country with organ sharing locally or regionally at best. During this period entrepreneurial programs could travel long distances to procure organs and transplant them back at their home center without consideration to the needs of those waiting in that local area. Other ethical concerns developed as this "local shop" approach did not foster fair or efficient distribution of organs. In addition there was a growing concern that foreign recipients may be receiving a disproportionate share of organs because programs

could charge them more. These and other concerns led the Congress to establish the National Organ Transplant Act (NOTA; P.L. 98–507) in 1984. This act established the Organ Procurement and Transplantation Network (OPTN) and required that it be operated by a private, nonprofit organization under federal contract. The Southeast Organ Procurement Foundation (SEOPF) had been established in 1968 and eventually served 12 cities which formed the structure for a new nonprofit organization (United Network of Organ Transplantation (UNOS)) which won the contract to administer organ transplantation in the entire United States in 1986 (McDiarmid et al. 2008). No longer would the organs belong to the center procuring them but they became a national resource distributed under clear rules. UNOS continues to hold the contract nationally and administered the transplantation of 411,600 kidney transplants, from January 1988 to April 2017 (Table 2) (UNOS Data). This feat has not been accomplished without controversy and adjustments to its policies. Fortunately, these adjustments to allocation policy are overseen by transplant professionals, UNOS staff, donors, and recipients as part of their committees which are charged with constant oversight. A major function of UNOS is to assure that programs perform transplants safely. This has resulted in measures of quality such as patient and graft survival estimates which are annually updated. Programs with worse than expected outcomes must improve or ultimately can become "member not in good standing" which usually causes them to close since they are not allowed to bill Medicare. National allocation policy for transplantation will never be a finished product, and some may believe that UNOS has not been as responsive to needed policy changes as quickly as they should.

The massive success of renal transplantation and transplantation in general is a testament to the pioneers and patients in this field. It is considered by many to be one of the modern medical miracles. As illustrated in Table 2, many other organs are currently successfully being transplanted including the liver, heart, lung, intestine, and pancreas. The success of some vascularized composite grafts such as arms, legs, uterus, and penis harkens back to the mythical beginnings of transplantation but are now a reality. All of these extrarenal organ transplants have benefitted from the experiences in renal transplantation. In fact any new immunosuppressive agents or protocols are always studied first in the kidney because of the availability of a proven artificial organ replacement (dialysis). Renal transplantation is likely in a second consolidation phase with no significant milestones occurring since the introduction of tacrolimus. Clinical efforts to induce tolerance have been ongoing as have the increasing recognition that antibody-mediated mechanisms are important in long-term graft survival. No recent attempts at renal xenotransplantation have been attempted although unsuccessful attempts have been made with liver transplants during the 1990s (Starzl et al. 1993). Perhaps the most exciting work in transplantation now occurs in VCA grafts including arms, leg, face, and others. We have essentially come full circle from Cosmos and Damian's miracle to our modern miracle.

Table 2 Total transplants performed in the United States from January 1988 to April 2017 (Saran et al. 2016)

Organ	Transplants
Total	**697,791**
Kidney	411,600
Liver	150,469
Pancreas	**8,427**
Kidney/pancreas	22,365
Heart	66,737
Lung	34,130
Heart/lung	1,206
Intestine	2,835
Abdominal wall	1
Head and neck: craniofacial	4
Head and neck: scalp	1
GU: penile	1
GU: uterus	6
Upper limb: bilateral	5
Upper limb: unilateral	4

Conclusion

Renal transplantation has had a long and storied development which now has improved the lives of millions globally. Continued improvements will

be made from incremental work at the bench and the bedside. Although improvements in primary prevention are beginning to reduce the need for transplantation, there will likely always be recipients who will need renal replacement therapies. The field has come a long way but has much more distance to cover.

Cross-References

- Immunology of Kidney Transplantation
- Medical Complications After Kidney Transplantation: Early
- Medical Complications After Kidney Transplantation: Late
- Organ Preservation, Preparation, and Procurement Surgery in Kidney Transplantation
- Recipient Selection for Kidney Transplantation
- The Regulatory and Legal Environment of a Contemporary Kidney Transplant Program
- Transplant Immunosuppression

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Recipient Selection for Kidney Transplantation

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Contents

Abstract

Individuals who suffer from chronic kidney disease potentially have three broad options for treatment: hemodialysis, peritoneal dialysis, or transplantation. Many patients wish to receive a kidney transplant. Transplant professionals must determine whether transplantation is a wise option for these patients. This chapter discusses commonly used selection criteria to evaluate individual candidacy for kidney transplantation while explaining the rationale and justification for these criteria.

Keywords

Cancer screening · Cardiovascular screening · Contraindications for kidney transplantation · Ethics of recipient selection · Expected posttransplant survival (EPTS) score · Infection screening · Justice versus utility · Life expectancy · Obesity · Psychosocial screening · Quality of life · Risks of kidney transplantation · Selection criteria

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Introduction

Unlike other solid organ transplants, kidney transplantation is an elective surgery, as the option of either peritoneal dialysis or hemodialysis exists for the vast majority of patients suffering from end-stage renal disease. In fact, the Centers for Medicare and Medicaid Services (CMS) guidelines mandate that during pretransplantation counseling, patients (as well as their potential donors) are informed of their alternative treatment options. The decision as to whether to place a potential patient on the active waiting list is a complex decision that takes into account the expected benefit (or, in some cases, detriment) of kidney transplantation over that of dialysis, issues of treating all patients equitably, and societal responsibilities of transplant professionals in wisely allocating a limited supply of donor organs.

This chapter will attempt to outline the relative benefits and risks of adult kidney transplantation in effort to explain why it may be appropriate to deny some patients for consideration for transplantation. The authors will delineate common potential recipient screening and selection criteria to help make these decisions regarding each individual patient. Finally, the ethics of recipient selection with regards to justice versus utility, how the current UNOS allocation policies impact the issues surrounding justice versus utility, and certain controversial recipient selection issues will be briefly addressed.

Benefits of Kidney Transplantation

Quality of Life

Quality of life is less than optimal for most patients with advanced chronic kidney disease or end-stage renal disease. Patients managed with hemodialysis experience the discomfort of two large bore needles placed three times weekly. The time commitment of travel to and from a dialysis center as well as treatment duration of around 4 h consumes approximately 15 h of time per week with typical in-center hemodialysis. Dietary restrictions of phosphorus, potassium, and fluid provide an additional burden for most patients. In one study that looked at the hospital utilization among chronic stable dialysis patients, dialysis patients spent on average approximately 14.8 hospital days per year in the hospital (Arora et al. 2000). Although peritoneal dialysis can provide some lifestyle flexibility and less dietary restrictions, the commitment to perform multiple exchanges daily or use of a cycler nightly can be taxing and lead to technique burnout. Of the 7% of end-stage renal disease patients who choose peritoneal dialysis as their modality of renal replacement therapy, 39% of these patients had experienced at least one 30-day conversion to hemodialysis by 3 years (Shen et al. 2013).

Given these issues, many patients opt for kidney transplantation in the hopes of improving their quality of life. Literature supporting quality of life improvement with transplantation shows improvement in parameters such as cognitive function, quality of social interactions, sexual function, sleep, social support, patient satisfaction, physical functioning, pain, emotional well-being, and emotional role in transplant recipients as compared with either hemodialysis patients or peritoneal dialysis patients (Kostro et al. 2016).

Life Expectancy

To date, there has not been a prospective randomized controlled study comparing survival benefits with transplantation as compared to dialysis. The data that suggests that kidney transplantation improves life expectancy is imperfect at best. The 2015 United States Renal Data System (USRDS) comments on the most recent available year of patient data from 2013 reporting an adjusted mortality rate of 138 per 1000 patient-years for all patients with end-stage renal disease. Patients maintained on dialysis had an adjusted mortality rate of 169 per 1000 patient-years as compared to patients who had received transplants who had an adjusted mortality rate of only 35 per 1000 patient-years (United States Renal Data System 2015). This would strongly imply

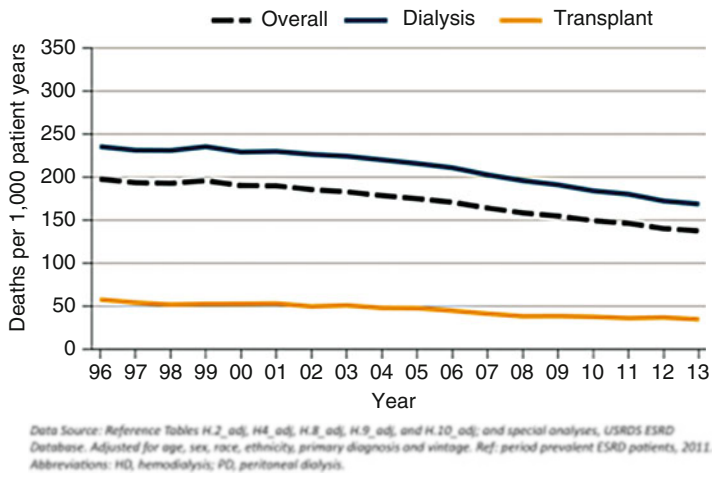

Fig. 1 All-cause mortality rates in patients with end-stage renal disease are significantly lower in transplant recipients than in patients treated with other modalities (Reference Tables H.2_adj, H.8_adj, H.9_adj, and H.20_adj); and special analysis, USRDS ESRD Database. Adjusted for age, sex, race, ethnicity, primary diagnosis and vintage. Ref: period prevalent ESRD patients, 2011. Abbreviations: HD hemodialysis, PD peritoneal dialysis)

that transplantation has a dramatic favorable impact on patient survival (Fig. 1).

Transplant recipients deemed eligible to undergo renal transplant, however, have characteristics that would favor overall survival with or without transplantation. To compare these, "healthier" patients suffering from end-stage renal disease with all patients forced to remain on dialysis will inevitably skew data in favor of transplantation. This was evident in an analysis of the United States Renal Data System (USRDS) database that revealed an improvement in standardized mortality ratios in waitlisted dialysis patients as compared to nonwaitlisted dialysis patients across all subgroups (Wolfe et al. 1999) (Fig. 2).

In an effort to get around this source of bias, further analysis of the USRDS database has been performed comparing the survival rates between patients accepted for renal transplantation who have undergone surgery with those who have been deemed eligible for transplantation, but have not yet received a renal allograft (waiting list patients). In one of the largest most comprehensive studies to date, survival analysis using data from the United States Renal Data System (USRDS) analyzed nearly 230,000 patients on dialysis and compared outcomes with 46,000 patients on the transplant waiting list of whom 23,000 had received a deceased donor kidney transplant (Wolfe et al. 1999). This study assessed the relative risk of death and survival with an adjustment for age, race, sex, cause of end stage renal disease, geographic region, time from first treatment for end-stage renal disease to placement on the waiting list, and years since initial placement on the list. The results of this study revealed that the relative risk of death during the first 2 weeks after transplantation was 2.8 times as high as that for patients on the waiting list and remained elevated until 106 days after transplantation. After this time, the risk was lower among the transplant recipients, but the likelihood of survival did not become equal in the two groups until day 244 because of initial higher risk among the transplant recipients (Fig. 3).

In addition, the long-term mortality rate was 48–82% lower among transplant recipients (annual death rate 3.8 per 100 patient-years) than patients on the waiting list, with larger benefits among patients who were 20–39 years old, white patients, and younger patients with diabetes.

Even this data is imperfect, as many waitlisted patients will remain on the waiting list by medical necessity since they must decline organ offers because of interval comorbidities prohibiting

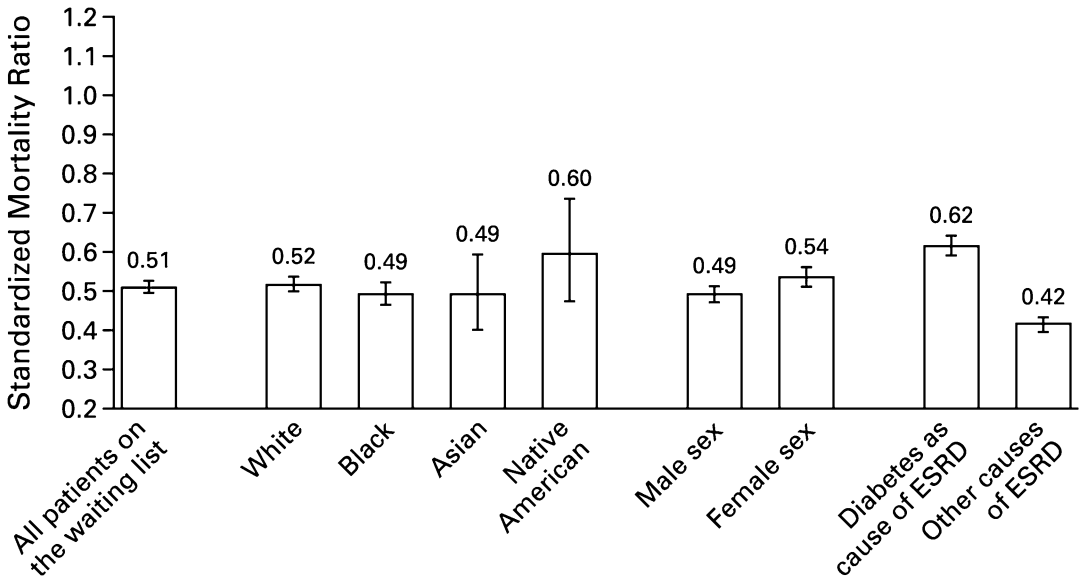

Fig. 2 Waitlisted end-stage renal disease patients standardized mortality ratios are lower than the general end-stage renal disease population

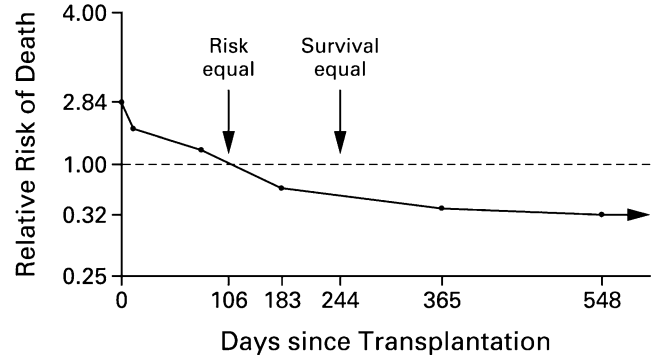

Fig. 3 Relative risk of death for deceased donor kidney transplant recipients versus waitlisted controls versus time posttransplant

safe transplantation. As such, nontransplanted patients on the waiting list are still not likely to be a perfect comparator group compared to transplant recipients. Since the time of this article, published in 1999, technological advances in both dialysis and transplantation have had an impact on survival rates of both groups of patients casting some doubt on the validity of its conclusions for today's transplant decision making.

Similar results have been confirmed in other studies (Rabbat et al. 2000; Meier-Kriesche et al. 2001) including favorable benefits of transplantation with kidneys previously referred to as marginal kidneys and kidneys recovered after donor cardiac death (Ojo et al. 2001; Merion et al. 2005; Snoeijs et al. 2010) as well as with repeat deceased donor kidney transplantation (Ojo et al. 1998).

Risks of Kidney Transplantation

The relative risk of death among recipients of a transplant is initially higher than that of remaining on dialysis as demonstrated in the studies from the preceding section. This is to be expected related to risks associated with surgery and to the use of high-dose immunosuppressive

therapy. The subsequent decrease in the risk of death counterbalanced the initially high rates of death and resulted in a cumulative survival benefit. As such, recipient selection criteria should take into account this increased mortality risk posttransplant for the first several months and exclude patients who are likely not able to withstand the physiologic stressors of kidney transplantation.

Based on 2012 American College of Cardiology/American Heart Association guidelines, kidney transplantation was considered an intermediate to high-risk procedure in light of it being, in part, a vascular surgery and a potentially intraperitoneal surgery (Lentine et al. 2012). However, the most recent 2014 American College of Cardiology/American Heart Association guidelines criteria now consider renal transplantation a high-risk procedure (Fleisher et al. 2014). The following chapter ▶ "Kidney Transplantation: Surgical Complications" discusses potential surgical complications of kidney transplantation. As such, this chapter will not address these complications.

In addition to these surgical complications, kidney transplantation involves placing patients at risk from suppression of their immune system with the use of agents that may increase their risk of infections, increase their risk of cancer, and enhance cardiovascular risk factors. These issues are well addressed in two preceding chapters in this book entitled ▶ "Medical Complications After Kidney Transplantation: Early" and ▶ "Medical Complications After Kidney Transplantation: Late" and will not be further addressed in this chapter.

Selection Criteria

Criteria used prior to wait-listing chronic kidney disease or end-stage renal disease patients for kidney transplantation must take into account the unique risks that kidney transplantation imparts to patients related to major surgery and immunosuppressive therapy. These criteria when properly applied should help to limit patient mortality in the early posttransplant period and screen for diseases potentially exacerbated by immunosuppression. One should not consider patients for transplantation until renal function has irreversibly deteriorated beyond a threshold level of clearance, because transplantation at higher levels of renal function does not confer superior outcomes compared to transplantation at lower levels (Ishani et al. 2013).

There are multiple factors that may render a patient with advanced chronic kidney disease or end-stage renal disease ineligible for transplantation. Several societies and organizations have previously published clinical practice guidelines for the evaluation of the renal transplant recipient aiming to articulate a consensus viewpoint for listing criteria. Fifteen such guidelines published between 2001 and 2011 comparing the quality, scope, and consistency of these international guidelines on wait-listing for kidney transplantation were analyzed in a study done by Batabyal et al. (2012). Whereas some recommendations were consistent among the 15 published guidelines, there were differences in age cutoffs, estimated life expectancy (2–5 years), and glomerular filtration rate at listing (15–20 mL/min/1.73 m^2). Recommendations specified only broad cardiovascular contraindications. Recommended cancer-free periods also varied substantially, and whereas uncontrolled infections universally contraindicated kidney transplantation, human immunodeficiency virus thresholds and adherence to highly active antiretroviral therapy were inconsistent. Most guidelines recommended psychological screening, but did not provide specific clinical assessment tools. The authors concluded that four major criteria were consistent across guidelines: (1) recipient age, (2) life expectancy, (3) medical criteria, and (4) social and lifestyle circumstances and psychosocial considerations.

The United Network of Organ Sharing Scientific Registry of Transplant Recipients committee has analyzed the role that four specific factors play in predicting outcomes in deceased donor recipients referred to as the expected posttransplant survival (EPTS) score. This score takes into account (a) candidate time on dialysis, (b) current diagnosis of diabetes, (c) prior solid organ transplants, and (d) candidate age, and is in

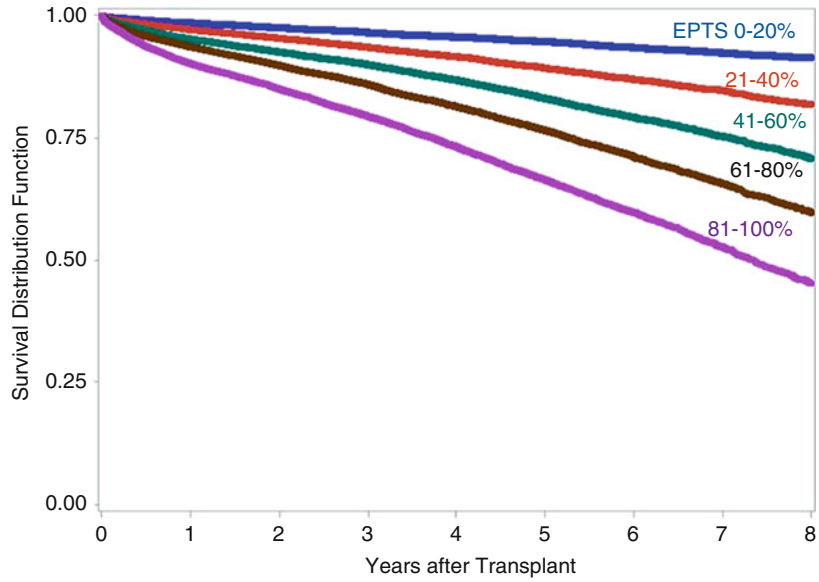

Fig. 4 UNOS predicted deceased donor kidney transplant recipient survival based on EPTS score (based on OPTN data as of February 7, 2014)

current UNOS allocation policies to match kidneys with higher expected longevity to recipients with higher longevity in an effort to maximize the utility of transplantation of higher quality kidneys (Fig. 4).

Although there is much variation in opinion regarding suitability for kidney transplantation in the literature, most would agree that there are absolute contraindications for kidney transplantation. These would include active infections, active malignancy, active substance abuse, reversible renal failure, uncontrolled psychiatric disease, documented active and ongoing treatment nonadherence, and a significantly shortened life expectancy. As such, the initial evaluation of the potential recipient should include a thorough medical and surgical history, psychosocial history, and a detailed physical examination targeted toward identifying such comorbidities.

Infection Screening

Immunosuppression may exacerbate latent infections. As such, it is advisable to screen all potential recipients for hepatitis B, hepatitis C, syphilis, human immunodeficiency virus, and tuberculosis. Evidence of active infection warrants treatment prior to transplantation with concomitant immunosuppression in most cases. Discussion regarding unique issues surrounding hepatitis C and hepatitis B follows below. The cytomegalovirus serostatus of potential recipients guides posttransplant prophylactic antiviral therapy and should be determined for all potential recipients. Because of the severity of potential disease in patients who are exposed to varicella zoster while immunosuppressed, all patients who are seronegative for varicella zoster virus should receive immunization prior to transplantation. Finally, it is advisable to screen all potential transplant recipients for Epstein Barr virus as seronegative recipients are at a higher risk of posttransplant lymphoproliferative disease and are not safely able to receive belatacept immunosuppression posttransplant.

In patients with viral hepatitis, immunosuppression with kidney transplantation upregulates viral replication and enhances ongoing liver damage (Carbone et al. 2011). Transjugular liver biopsy can assess the severity of underlying liver damage prior to kidney transplantation. This information can help gauge both the risk of immunosuppression in precipitating end-stage liver disease or liver-related mortality and to identify patients who would benefit from dual organ transplantation. Although chronic hepatitis B infection may not be considered an

absolute contraindication to transplantation in all centers, those patients who are seropositve for hepatitis B should at least be tested for hepatitis B e-antigen and hepatitis B virus DNA titers prior to transplant as an additional assessment to predict risk of reactivation. Likewise, most centers would consider cirrhosis to be an absolute contraindication to kidney transplantation alone, but limited literature regarding kidney transplantation in the setting of hepatitis B-related cirrhosis has been reported (Nho et al. 2015).

The issue of hepatitis C therapy prior to transplantation remains controversial in light of newer highly effective antiviral agents now approved for use in patients on dialysis. Patients who suffer from active hepatitis C in the absence of advanced liver disease may opt to accept kidneys from hepatitis C positive donors. Accepting hepatitis C positive organs may result in earlier transplantation and lower dialysis "vintage" at the time of transplant improving expected posttransplant outcomes. Hepatitis C may then be treated post transplantation. The treatment of hepatitis now is so successful that the Ethics Committee of the United Network for Organ Sharing (UNOS) has suggested that it is even justifiable to transplant hepatitis C positive kidneys into hepatitis C negative recipients (Reese et al. 2015). The authors' center opts to defer treatment of hepatitis C in end-stage renal disease patients with stage 0–2 fibrosis with proper patient consent until after kidney transplantation, to treat hepatitis C prior to kidney transplantation with stage 3 fibrosis to protect against cirrhosis, and to refer patients with stage 4 cirrhosis for combined liver kidney transplantation.

Patients suffering from recurrent bacterial infections such as diverticulitis or pyelonephritis may benefit from surgical intervention prior to transplantation and immunosuppression.

Cardiovascular Screening

Although renal transplantation confers a decreased risk of long-term mortality for kidney transplant recipients, an increased short-term posttransplant mortality risk exists as discussed above. Cardiovascular disease is extremely common in this patient population. Studies have shown that patients with chronic kidney disease often have significant asymptomatic coronary artery disease (CAD) with prevalence estimates of 37–53% for at least one coronary artery with 50% or greater stenosis (Ohtake et al. 2005). For renal transplant recipients, cardiovascular disease (CVD) is a significant source of mortality and morbidity as well and is the most common cause of death in the first 30 days post transplantation (Ojo et al. 2000). In fact, cardiovascular complications account for over 30% of deaths from a reported cause in patients with a functioning renal allograft (United States Renal Data System 2015). Justifiably, clinicians are highly encouraged to screen for CVD before transplant.

The objective of screening these patients should be to predict which recipients would have a cardiac event post transplantation preventable with pretransplant intervention. The goal of transplantation is not only the survival of the graft but also the survival of the transplant recipient. This provides a compelling argument to screen all these at-risk transplant patients to both improve outcomes and maximally utilize a scarce resource.

Presently, the appropriate cardiac risk assessment strategy for chronic kidney disease and end-stage kidney disease patients awaiting kidney transplantation is still in contention. The American Society of Nephrology (ASN) and the American Society of Transplantation (AST) recommend chemical stress echocardiography or scintography as part of the screening process. Depending on test results, a patient may require an angiogram and revascularization (Kasiske et al. 2001). In comparison, the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend no preoperative cardiac evaluation given that kidney transplantation poses an intermediate risk if the patient has good functional status (Fleischer et al. 2007). The lack of consensus leads to difficulty in determining which patients require no testing, noninvasive cardiac testing, or invasive interventions prior to kidney transplantation. For the patients and the provider, screening all patients listed for transplant is expensive, time consuming, and impractical.

Many transplant programs support the guidelines of ASN and AST. Therefore, there is great emphasis on focused screening for those who are at a higher risk of coronary artery disease of the general end-stage renal population. The ASN and AST advocate noninvasive cardiac stress imaging, including stress echo or nuclear myocardial perfusion testing for patients with diabetes, prior ischemic heart disease, or two of the following – men >45 years, women >55 years, ischemic disease in a first-degree relative, smoking, hypertension, cholesterol >200 mg/dl, HDL <35 mg/dl, or left ventricular hypertrophy (Kasiske et al. 2001).

The most commonly used noninvasive screening tests for ischemic heart disease include exercise electrocardiogram testing and myocardial perfusion studies (MPS) such as thallium/sestamibi scintigraphy or echocardiography with exercise or dobutamine (Rabbat et al. 2003). Because of the markedly reduced exercise capacity of patients on dialysis, exercise testing is often not feasible, so MPS is commonly used. As to what is the preferred MPS, there is no consensus. Each individual transplant center can best choose the appropriate study with an interdisciplinary team including the cardiologist. Patients with critical lesions should then be referred for intervention with coronary angioplasty, bypass surgery, or stent placement.

In addition to coronary artery disease, potential transplant candidates often suffer from nonischemic cardiac conditions of prognostic importance for success after renal transplantation. These factors include systolic and diastolic cardiac dysfunction, pulmonary hypertension, and valvular heart disease.

Structural and functional impairment of the cardiac muscle is very common in patients with chronic kidney disease. The term "uremic cardiomyopathy" describes the structural abnormalities that go hand in hand with diastolic dysfunction and chronic kidney disease progression. Abnormalities on echocardiogram, particularly left atrial volume, have emerged as a risk marker for death in ESRD patients post kidney transplantation (Patel et al. 2014; Kainz et al. 2013). Diastolic dysfunction is also associated with an increased incidence of perioperative cardiovascular events (Fayad et al. 2016). Several studies, however, have demonstrated improvement in structural cardiac parameters after renal transplantation (Souza et al. 2012; Zolty et al. 2008). It is important in pretransplant cardiovascular screening to assess myocardial dysfunction and to determine if there is likely to be any reversibility post transplant. Patients with advanced irreversible cardiomyopathy warrant consideration for combined kidney-heart transplantation.

Pulmonary hypertension occurs in as many as 40–50% of patients with end-stage renal disease on hemodialysis (Ramasubbu et al. 2010). In a retrospective study, pulmonary hypertension was an independent risk factor for early graft dysfunction post deceased donor kidney transplantation (Zlotnick et al. 2010). As is the case with myocardial dysfunction, pulmonary hypertension may improve post kidney transplantation (Casas-Aparicio et al. 2010). Prior to transplant, aggressive diuresis or ultrafiltration on dialysis may improve pulmonary artery pressures. If improvements in pulmonary artery pressures are unsuccessful, right heart catheterization may be necessary to better define perioperative risk and reversibility post transplantation. Patients with uncorrectable severe pulmonary hypertension are poor candidates for kidney transplant.

Like coronary artery disease, myocardial dysfunction, and pulmonary hypertension, valvular heart disease is common in end-stage renal disease patients (Abbott et al. 2003). There are no particular guidelines regarding valvular disease management for renal transplantation candidates. However, patients with moderate to severe AS may benefit from valve replacement prior to kidney transplant to maximize posttransplant outcomes.

Cancer Screening

Increased risk for malignancy in the renal transplant population is a major source of morbidity and mortality. Aside from cardiovascular disease and infection, death from malignancy is one of the three major causes of death post transplantation (Adami et al. 2003). Furthermore, renal transplant

recipients are two to three times more likely to develop cancers than the general population (Maisonneuve et al. 1999).

Active malignancy is a contraindication for kidney transplantation for several reasons. First, the shortage of organs available for transplant is such that their use cannot be justified in patients with limited life expectancy. Second, the immunosuppression needed to ensure an acceptable graft survival might accelerate the progression of an underlying malignancy.

Upon eradication of a malignancy, however, cancer survivors with renal disease would likely benefit from transplantation. The necessary length of cancer-free interval to have reasonable certainty that the cancer is fully cured and not likely to recur with intensive immunosuppression post transplantation varies between different transplant centers and types of cancers. In situ or superficial cancers of the cervix, skin, bladder, etc. may not require any interval until safe transplantation with immunosuppression, but extensive cancers may require longer disease free intervals until transplantation. The American and Canadian Transplant Societies advise at least 2 years of disease-free intervals for most cancers and up to 5 years for certain cancers such as stage II breast cancer, extensive cervical cancer, stage C colorectal cancer, melanoma (other than in situ), and invasive renal cell carcinoma (Kasiske et al. 2001; Knoll et al. 2005). The Israel Penn International Transplant Tumor Registry is a useful resource to provide consultative guidelines regarding recommended disease-free intervals prior to transplantation in ambiguous cases.

In patients who have never had a cancer, the authors' center uses the American Cancer Society routine cancer screening recommendations for the general population for patients prior to transplantation (http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer). More intense screening for renal cell carcinoma is advisable in patients with analgesic nephropathy, Balkan nephropathy, or Chinese herb nephropathy. Likewise, patients with prior exposure to cyclophosphamide may warrant more intense screening for bladder carcinoma; however, no convincing evidence exists to support these recommendations.

Psychosocial Screening

The psychosocial evaluation is to identify behavioral, financial, and social barriers that can influence adherence to a complex medical regimen and thereby adversely affect posttransplant graft and patient survival. Most programs rely on a multidisciplinary team including social workers or other mental health professionals who have the experience and expertise in evaluating transplant patients for potential barriers (DePasquale et al. 2014).

Defining absolute psychiatric contraindications to transplant is difficult at best. Psychiatric disorders are common among transplant patients (House et al. 1990). Preoperatively, adjustment disorders with depression and anxiety are highly prevalent. Incidence of depression is between 2% and 16% and the incidence of anxiety is as high as 39% (Trzepacz et al. 1991). Studies reveal mixed outcomes in this subset of transplant patients. Some studies cite a strong influence of psychiatric illness on posttransplant mortality and morbidity (Dew 1994), but Woodman et al. (1999) investigated lung transplant patients and found that premorbid psychiatric history did not correlate with a worse outcome post transplant. Referral to a mental health professional prior to transplantation may be appropriate as these disorders are readily treated.

Patients with chemical dependence in the way of alcohol abuse and/or drug abuse pose a particular challenge for transplant teams. Given that these behaviors can undermine the immediate and long-term success of a kidney transplant, most transplant centers have policies and procedures in place to address these issues. Selection practices among centers are variable. All efforts to treat substance abuse prior to transplant is advisable. It is reasonable to insist that these candidates undergo counseling, and that caregivers and drug abuse centers can document a set drug-free period. Furthermore, given the

relatively high recidivism rates associated with addiction, ongoing involvement with counseling and support groups is well advised post transplant.

Financial feasibility of good outcomes post transplantation is also a topic of discussion in the pretransplant psychosocial evaluation. All potential recipients should undergo a review of personal financial resources and insurance coverage. The high cost of medications and the need for frequent postoperative follow-up care make transplantation a long-term financial and time commitment and may pose a hardship for many families, especially if the recipient is the primary source of income. These situations may create pressures for patients to discontinue their medications, miss follow-up appointments, and risk losing their renal allograft to rejection.

Finally, the psychosocial (and medical) evaluation should include an assessment of a potential transplant recipient's pre-existing pattern of adherence to medical recommendations. Evidence exists to show that pretransplant medication nonadherence predicts posttransplant medication nonadherence (Dobbels et al. 2009). Moreover, lack of adherence to immunosuppressive medication is one of the leading causes of graft failure post transplant (Brickman and Yount 1996). Certainly, intense scrutiny is justified with patients who have lost a prior allograft to documented immunosuppressive nonadherence. In patients who are already on dialysis, adherence can be evaluated by assessing patients dietary, medication, and treatment compliance by assessing potassium and phosphorus levels, interdialytic weight gains, blood pressure and diabetes control, and frequency of missed dialysis sessions. Observation of patient willingness and ability to follow through with pretransplant screening recommendations in a timely fashion provides a means to assess patient adherence as well. Identifying and addressing obstacles to adherence, such as substance abuse or financial limitations, prior to transplantation as discussed above is advisable. As part of the screening and transplant evaluation, transplant personnel should emphasize the importance of adherence to medication and regular posttransplant follow-up.

Obesity

There is a worldwide epidemic of obesity and the prevalence of patients with a pretransplantation body mass index (BMI) of greater than 30 kg/m^2 is only increasing (Obesity – Preventing and Managing the Global Epidemic 1997). There is a distinct trend toward increased mortality in obese transplanted patients in comparison to nonobese transplanted patients (Orofino et al. 1997; Meier-Kriesche et al. 2002). Obesity is also a strong risk factor in the screening for transplantation because of correlation with delayed graft function, longer hospital stay, poor wound healing, infection, diabetes, hypertension, and worsening renal function post transplantation (Pischon and Sharma 2001; Kasiske et al. 2003). Although BMI is an imperfect measure of obesity or of distribution of body fat, many centers will have defined maximal acceptable BMI for consideration for transplantation.

Close cooperation between the transplant center dietitian and dialysis unit dietitian is advisable to achieve healthy pretransplant weight loss to maximize chances of successful transplant outcome without jeopardizing protein calorie nutrition while remaining on dialysis. The role of bariatric surgery to help patients achieve successful weight loss prior to transplantation awaits further study.

Ethics of Recipient Selection

Ethical dilemmas surrounding organ transplantation stem from a disproportionately high demand for a markedly limited supply. In order to navigate this dilemma, the United States Department of Health and Human Services lays down the framework for ethics regarding transplantation in the United States. Three established principles of ethics guide policy. These principles are utility, justice, and respect for persons (United States Department of Health and Human Services. Organ Procurement and Transplantation Network: Ethics – Ethical Principles in the Allocation of Human Organs).

With organ transplantation, utility is the concept that clinicians should aim to perform the maximum amount of good with the limited resources that we have. Utility is further broken down to the principles of beneficence and nonmaleficence, which are doing good and avoiding harm, respectively. Beneficence can be practically measured as graft survival, patient survival, and, more subjectively, quality of life. Nonmaleficence is manifest as minimizing the mortality and morbidity associated with transplant to the recipient as well as the donor in cases of living donation.

Justice, as applied to organ transplantation, states that the system that allocates organs are fair to all parties involved. No bias in the allocation system regarding the recipient's socioeconomic status, race, sex, or any other factors is appropriate. Thus, from a perspective of justice, the goal is not to do the maximum amount of good, but to do that good in an equitable fashion.

The principle of respect for persons states that human beings are autonomous entities. Patient autonomy requires that patients have a right to receive full information regarding their condition and all options available and that they should be free to make decisions without coercion from their healthcare provider. A patient who is incapable of understanding their condition, such as a minor, mentally handicapped, or a patient incapacitated by illness, is considered to be of diminished autonomy and warrants extra protection. A patient, who is at risk of being coerced or potentially coerced, such as prisoners, should also receive extra protection appropriate to the circumstances. A fully autonomous individual has the right to decline to donate a kidney, decline to accept a kidney, and deserves the right to a transparent allocation system.

There is much potential for conflict among these three principles. Studies have shown that there are worse outcomes in terms of graft survival for patients with more comorbid illness, patients in lower socioeconomic positions, less educated, and Black patients (Kasiske et al. 1991). A purely utilitarian system for organ allocation with a goal toward maximizing allograft survival would favor healthier, more educated, financially well off, and non-Black patients. Such a system would be unethical as it would be in direct violation of the principle of justice in that those factors should not influence organ distribution, in spite of potentially improved patient and graft survival in patients who would ultimately receive the transplants. Both utility and justice are equal considerations in a system that is both equitable and beneficent.

The UNOS allocation system put into effect in December of 2104 attempts to match the highest quality deceased donor kidneys with patients with the highest expected posttransplant survival (EPTS) scores as discussed above. This allocation scheme represents an attempt to enhance the principle of utility in organ allocation on a national level while having a limited detrimental effect on the principle of justice.

Clinical scenarios involving potential recipients who are incarcerated, institutionalized, or mentally handicapped provide challenging ethical dilemmas for transplant centers. The United Network of Organ Sharing specifically makes note in their policy that it is not acceptable to exclude a potential recipient for kidney transplantation solely due to incarceration (United States Department of Health and Human Services. Organ Procurement and Transplantation Network: Ethics – Convicted Criminals and Transplant Evaluation). Efforts prior to transplant to insure that these individuals will be able to reasonably be expected to gain quality of life benefit from kidney transplantation, reliably receive their required posttransplant medications, and reliably return to the transplant office post transplant for follow-up care is essential. In difficult cases, transplant centers may need to turn to their hospital ethics committees or legal counsel for guidance.

Conclusion

The intent of this chapter has been to discuss the rationale and ethics behind common recipient selection criteria used to determine candidacy for kidney transplantation. The space allocated to discuss recipient selection criteria does not permit an exhaustive discussion of issues faced in

assessing all potential patients for kidney transplantation. Some unaddressed issues include age, frailty, cause of primary renal disease, peripheral arterial disease, hypercoagulable states, and bladder dysfunction. Selection criteria involving chronic pulmonary, hepatic, or cerebrovascular diseases may require special attention in individual potential recipients. Likewise, the authors have not discussed systemic illnesses that affect allograft and patient survival such as sickle cell disease, oxaluria, cystinosis, or amyloidosis. Ultimately, no two patients desirous of receiving a kidney transplant are identical. In all cases, transplant professionals must make decisions most beneficial to individual patients while acting as wise stewards of a limited supply of deceased organs available.

Cross-References

- Ethical Issues in Organ Transplantation
- Infection in Kidney Transplantation
- Medical Complications After Kidney Transplantation: Early
- Medical Complications After Kidney Transplantation: Late
- Psychosocial and Personal Financial Aspects of Transplantation
- Kidney Transplantation: Surgical Complications

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Living Donor Evaluation and Selection

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Abstract

Living donors are frequently used for kidney transplantation in the United States. This option offers a superior patient and graft survival over deceased donor transplantation. It is also an excellent solution to close the widening gap between patients awaiting renal transplantation and number of transplants done. Organ Procurement and Transplantation Network (OPTN) has specified the minimum general and kidney-specific requirements for suitability as a living kidney donor. Transplant programs across the United States have specific medical criteria for living donation which may be beyond the minimum specified by OPTN. Although living kidney donation is deemed safe, a thorough evaluation to assess medical suitability, infectious and malignancy transmission risk, and assessment of residual organ reserve in the donor is required. This chapter covers all aspects of medical evaluation of the living kidney donor in detail. In general, most programs are now more willing to accept donors with treated hypertension, obesity, or a history of kidney stones provided that certain conditions are met. Such aspects of medically complex living kidney donors are also presented here. Certain recipient conditions that should prompt genetic testing in related living donor candidates are also discussed. Other OPTN requirements such as psychosocial evaluation of living donors and their follow-up by the donor center are also highlighted.

Keywords

Living kidney donor · Infection transmission · Malignancy transmission · Psychosocial evaluation · Independent living donor advocate

Abbreviations

AER	Albumin excretion rate
AUA	American Urologic Association
BMI	Body mass index
CMS	Centers for Medicare and Medicaid Services
DTAC	Disease Transmission and Advisory Committee
ESRD	End-stage renal disease
KDIGO	Kidney Disease Improving Global Outcomes
NAT	Nucleic acid test
OPTN	Organ procurement and transplantation network
PHS	Public Health Service
SRTR	Scientific Registry of Transplant Recipients
TBMN	Thin basement membrane nephropathy
UNOS	United Network for Organ Sharing
WHO	World Health Organization

Introduction

As per UNOS (United Network for Organ Sharing), there are more than 100,000 patients awaiting renal transplantation as shown in Fig. 1. Living kidney donation can help lessen this widening gap. However, living donation rates have declined progressively for more than a decade. This decrease has largely been driven by a reduction in the number of living related kidney donations, from 4340 in 2004 to 2693 as per 2014 Scientific Registry of Transplant Recipients (SRTR) annual report (Fig. 2).

There are short- and long-term risks of living donor nephrectomy. In order to address this, the Organ Procurement and Transplant Network (OPTN) has defined policies which outline the minimum general and kidney-specific requirements for

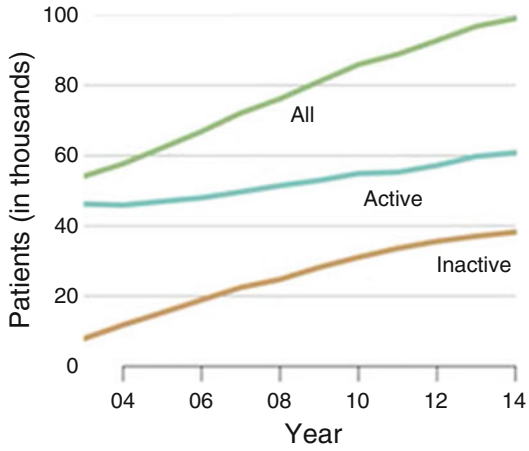

Fig. 1 Adults awaiting renal transplantation (Reference: American Journal of Transplantation Volume 16, Issue S2, pages 11–46, 11 Jan 2016 doi: 10.1111/ajt.13666. http://onlinelibrary.wiley.com/doi/10.1111/ajt.13666/full#ajt13666-fig-0001)

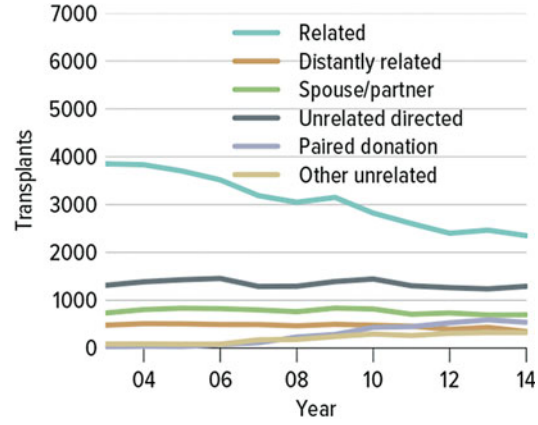

Fig. 2 Kidney transplants from living donors, by donor relation (Reference: American Journal of Transplantation Volume 16, Issue S2, pages 11–46, 11 Jan 2016 doi: 10.1111/ajt.13666. http://onlinelibrary.wiley.com/doi/10.1111/ajt.13666/full#ajt13666-fig-0001)

suitability as a living kidney donor. These minimum requirements along with additional criteria are generally incorporated into center-specific protocols that are based on local expertise and center-specific risk threshold and then targeted to individual donor candidates on a case-by-case basis. Policy 14 by OPTN pertains to living donation and extensively details all pertinent living donor requirements. It encompasses psychosocial evaluation of living donors, independent living donor advocate requirements, informed consent requirements, and medical evaluation. This chapter will primarily cover medical evaluation of living donor since other aspects are covered in detail elsewhere in this book.

The first step to evaluation of a living donor begins with checking the living donor and recipient blood type to assess compatibility. The blood type and crossmatch compatibility are the primary criteria for biological compatibility of the donor and recipient. HLA typing of the donor is also pursued to assess residual immunologic risk that may exist beyond verifying compatibility of anti-human globulin CDC and flow crossmatches. With this added information, often times a zero-mismatched donor is preferentially used in case there are multiple living donor options available. Also any low-intensity donor-specific antibodies can be picked up easily in the recipient once HLA typing of the donor is known. Those living donor recipient pairs which are biologically incompatible should be counseled about the options of living donor kidney exchanges and chains. Based on center-specific protocols, desensitization of the intended recipient for both ABO incompatibility and HLA antibodies may also be pursued.

According to a recent publication by Grams et al. (2016), for a 40-year-old person with a similar profile to age-matched healthy donors, the 15-year projections of the risk of end-stage renal disease (ESRD) in the absence of donation vary according to race and sex; the risk was 0.24% among black men, 0.15% among black women, 0.06% among white men, and 0.04% among white women. The 15-year observed risks after donation among kidney donors in the United States were 3.5–5.3 times as high as the projected risks in the absence of donation. An online risk assessment tool developed by the same authors is also available at www.transplantmodels.com/esrdrisk to evaluate, counsel, and accept living kidney donor candidates. The incidence of 90-day all-cause perioperative mortality is considered very low at 0.03% based on a study by Segev et al. (2010) of more than 80,000 living donors where 25 deaths were recorded. Table 1 shows a more recent cohort of living kidney donor deaths recorded in the United States and also lists the causes.

Table 1 Living kidney donor deaths from 2010 to 2014 (Adapted from Table 3.1 from SRTR 2014 Report)

	Days after donation		
Cause	**0–30**	**31–90**	**91–365**
Suicide	**1**	**1**	**4**
Accident/homicide	**0**	**0**	**5**
Medical	**3**	**2**	**1**
Cancer	**0**	**0**	**1**
Unknown	**0**	**1**	**1**
TOTAL	**4**	**4**	**12**

Medical Evaluation of Living Donor

General donor history requirements as specified by OPTN policy 14 pertaining to living donation are listed below. All living kidney donors should be queried for a personal history of significant medical conditions which include but are not limited to:

(a) Hypertension
(b) Diabetes
(c) Lung disease
(d) Heart disease
(e) Gastrointestinal disease
(f) Autoimmune disease
(g) Neurologic disease
(h) Genitourinary disease
(i) Hematologic disorders
(j) Bleeding or clotting disorders
(k) History of cancer including melanoma
(l) History of infections
(m) Active and past medications with special consideration for known nephrotoxic medications or chronic use of pain medication
(n) Allergies
(o) An evaluation for coronary artery disease

Additionally, potential living donors should be queried for kidney-specific personal history:

(a) Genetic renal diseases
(b) Kidney disease, proteinuria, hematuria
(c) Kidney injury
(d) Diabetes including gestational diabetes
(e) Nephrolithiasis
(f) Recurrent urinary tract infections

Family history should focus on the following elements:

(a) Coronary artery disease and any cancer
(b) Kidney disease
(c) Diabetes
(d) Hypertension
(e) Kidney cancer

Social history should include:

(a) Occupation
(b) Employment status
(c) Health insurance status
(d) Living arrangements
(e) Social support
(f) Smoking, alcohol and drug use and abuse
(g) Psychiatric illness, depression, suicide attempts
(h) Increased risk behavior as defined by the US Public Health Services (PHS) Guideline

Physical exam should focus on:

(a) Height
(b) Weight
(c) BMI
(d) Vital signs
(e) Examination of all major organ systems
(f) Blood pressure taken on at least two different occasions or 24-h or overnight blood pressure monitoring

General laboratory and imaging studies that need to be pursued include:

(a) Complete blood count with platelet count
(b) Blood type and subtype

(c) Prothrombin time (PT) or international normalized ratio
(d) Partial thromboplastin time (PTT)
(e) Metabolic testing (to include electrolytes, BUN, creatinine, transaminase levels, albumin, calcium, phosphorus, alkaline phosphatase, bilirubin)
(f) HCG quantitative pregnancy test for premenopausal women without surgical sterilization
(g) Chest X-ray
(h) Electrocardiogram (ECG)

Kidney-specific tests include:

(a) Fasting blood glucose.
(b) Fasting lipid profile (cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol).
(c) Glucose tolerance test or glycosylated hemoglobin in first-degree relatives of diabetics and in high-risk individuals.
(d) Urinalysis or urine microscopy.
(e) Urine culture if clinically indicated.
(f) Measurement of urinary protein and albumin excretion.
(g) Measurement of glomerular filtration rate by isotopic methods or a creatinine clearance calculated from a 24-h urine collection.
(h) Hospitals must develop and comply with a written protocol for polycystic kidney disease or other inherited renal disease as indicated by family history.
(i) Patients with a history of nephrolithiasis or nephrolithiasis (>3 mm) identified on radiographic imaging must have a 24-h urine stone panel measuring: calcium, oxalate, uric acid, citrate, creatinine, and sodium.
(j) Determine on kidney imaging study: size of both kidneys, presence of lesions (cyst, mass, stone), anatomical defects or variants, and assessment of which kidney is suitable for donation.

Transmissible Disease Screening

Infectious disease testing must be performed in a CLIA-certified laboratory or in a laboratory meeting equivalent requirements as determined by Centers for Medicare and Medicaid Services (CMS) using FDA-licensed, approved, or cleared tests. Testing must include all the following:

1. CMV (cytomegalovirus) antibody
2. EBV (Epstein-Barr virus) antibody
3. HIV antibody (anti-HIV) testing or HIV antigen/antibody (Ag/Ab) combination test as close as possible, but within 28 days prior to organ recovery
4. Hepatitis B surface antigen (HBsAg) testing as close as possible, but within 28 days prior to organ recovery
5. Hepatitis B core antibody (anti-HBc) testing as close as possible, but within 28 days prior to organ recovery
6. Hepatitis C antibody (anti-HCV) testing as close as possible, but within 28 days prior to organ recovery
7. HCV ribonucleic acid (RNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery
8. Syphilis testing
9. Assessment of tuberculosis risk in living donor and then test for latent infection using either intradermal PPD or Interferon Gamma Release Assay (IGRA)

Endemic Transmissible Disease Evaluation in Living Donors

Each living donor hospital must develop and follow a written protocol for identifying and testing donors at risk for transmissible seasonal or geographically defined endemic disease as part of its medical evaluation.

Cancer Screening in Living Donors

Recovery hospitals must develop and comply with protocols consistent with the American Cancer Society (ACS) or the US Preventive Services Task Force to screen for:

(a) Cervical cancer
(b) Breast cancer
(c) Prostate cancer
(d) Colon cancer
(e) Lung cancer

Imaging Studies

The type of imaging study to be pursued is center specific and may include either CT angiogram or magnetic resonance (MR) angiogram. Anatomic assessment of kidneys by imaging to assess equality of kidney size and evaluate for masses, cysts, stones, or other structural defects to help determine the kidney best suited for donation. Assessment of kidney volume should also be done to assess discrepancy since this information also needs to be factored in while making decisions on which kidney to use for donation.

The minimum exclusion criteria as defined for living kidney donation is defined by OPTN policy number 14 pertaining to living donation.

Living donor recovery hospitals may exclude a donor with any condition that, in the hospital's medical judgment, causes the donor to be unsuitable for organ donation. Living donor recovery hospitals must exclude all donors who meet any of the following exclusion criteria:

(a) Is both less than 18 years old and mentally incapable of making an informed decision
(b) HIV, unless the requirements for a variance are met
(c) Active malignancy or incompletely treated malignancy
(d) High suspicion of donor coercion
(e) High suspicion of illegal financial exchange between donor and recipient
(f) Evidence of acute symptomatic infection (until resolved)
(g) Uncontrolled diagnosable psychiatric conditions requiring treatment before donation, including any evidence of suicidality
(h) Uncontrollable hypertension or history of hypertension with evidence of end-organ damage
(i) Diabetes

Additional center-specific contraindications beyond those specified by OPTN may include:

(a) Proteinuria >300 mg in 24 h. Some centers also exclude microalbuminuria.
(b) Impaired renal function (defined as glomerular filtration rate (GFR) <80 mL/min/1.73 m^2 or inappropriately low function for age and sex).
(c) Marked urologic, renal vascular abnormalities, or multiple renal vessels.
(d) Any chronic, active viral infection such as HBV and HCV.
(e) History of malignancy, especially lung, breast, renal or urologic, gastrointestinal, or hematologic cancers and melanoma.
(f) Chronic illness (pulmonary, liver, autoimmune, neurologic, or cardiac disease).
(g) Nephrocalcinosis, bilateral kidney stones, or recurrent nephrolithiasis.
(h) Current pregnancy.
(i) Morbid obesity with BMI >35 kg/m^2.
(j) Active illicit substance or alcohol abuse.

Estimation of Renal Function

The most commonly used measure of evaluating GFR in clinical practice is based on a 24-h creatinine clearance and serum creatinine concentration. It is extremely important to ensure adequacy of 24-h urine collection. An incomplete urine collection leads to an underestimation of creatinine excretion and therefore of the GFR. The completeness of the collection can be estimated from knowledge of the normal rate of creatinine excretion. In adults under the age of 50 years, daily urinary creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women. After age 50, creatinine excretion falls progressively due to a decrease in muscle mass and may be as low as 10 mg/kg. A GFR >80 ml/min corrected to body surface area of 1.73 m^2 is generally considered acceptable for kidney donation. The Amsterdam Forum on the Care of the Live Kidney Donor (2005) consensus guidelines state that a GFR <80 mL/min or 2 standard deviations below normal (based on age, gender, and body surface area corrected to

1.73 m^2) generally precludes donation. OPTN criteria also states that an individual unsuitable for living donation includes creatinine clearance <80 mL/min per 1.73 m^2 or projected GFR with removal of one kidney at 80 years old of <40 mL/min per 1.73 m^2. In cases where there is doubt regarding the accuracy of GFR from estimation methods, a direct measurement of GFR is undertaken by exogenous clearance methods. Acceptable methods include a direct evaluation of the GFR by methods such as Cr-EDTA (nuclear GFR), iothalamate, iohexol, or inulin clearance although these methods may not be widely available. Study of practice patterns of US transplant centers by Mandelbrot et al. (2007) has revealed that about 90% of centers rely on measured creatinine clearance to estimate GFR and 10% use an exogenous filtration marker; and approximately 67% used a GFR ≥80 mL/min as cutoff to accept donors, while 25% used a threshold based on age and sex. As some older donors with lower GFR may be used, it is important to keep in mind as shown by Nordén et al. (2000) that cumulative graft survival in the recipient after adjusting for death-censored graft loss was significantly reduced in recipients of grafts from living donors with GFR <80 ml/min. Moreover, implications of letting these low GFR candidates donate do require additional considerations.

Need for Split Renal Function Testing

For most part, kidney function and size are correlated. As per Wang et al. (2014) and Glodny et al. (2009), the average kidney length and volume in healthy adults are approximately 12 cm and 300 ml, respectively, but vary based on age, sex, and body size. Moreover, the normal right kidney is approximately 5% smaller than the normal left kidney. As specified by KDIGO guidelines, asymmetry in kidney size is generally considered as a difference in kidney size >10% (e.g., a difference in kidney length >1.2 cm or kidney volume >30 ml). An equivalent difference in kidney function would be >10% (>55% vs. <45% of two kidney function on split testing). Radionuclide imaging is desirable before nephrectomy if there is substantial discrepancy in the size of the kidneys or anatomical abnormality is noted. In these situations, most centers would prefer to transplant the kidney with lesser function and leave the donor with the kidney with greater function after all technical considerations for surgical planning have been taken into account.

Evaluation of Proteinuria in Kidney Donor Candidates

Potential donors with 24-h urine protein >300 mg are usually excluded from donation. Some centers prefer a cutoff of 24-h urine protein >150 mg as a contraindication. Urinary protein comprises of small amounts of high molecular weight proteins (mainly albumin) that does not cross the glomerular filtration barrier and low molecular weight serum proteins that are normally filtered but subsequently undergo tubular reabsorption and finally proteins secreted by the urinary tract. Glomerular proteinuria demonstrated by albuminuria denotes glomerular hyper filtration or damage. Tubular proteinuria can be seen as an overflow proteinuria such as light-chain proteinuria (Bence Jones protein) due to overproduction of light chains as in lymphoproliferative disorders or due to lower urinary tract disease leading to tubular proteinuria. Patients with nephrolithiasis or tumors of the urinary tract may also have proteinuria.

In potential donors <30 years of age with proteinuria outside of acceptable range, orthostatic proteinuria should be ruled out by doing a split 24-h collection. Springberg et al. (1982) published that this entity can cause low-grade proteinuria, has a benign course, and should not be considered a contraindication to donation. In order to diagnose orthostatic proteinuria, it needs to be shown that there is only upright proteinuria with the absence of supine proteinuria. Specifically, the 8-h supine sample should contain <50 mg of protein to make this diagnosis.

Microalbuminuria is considered a sensitive indicator of glomerular pathology and should always be checked in addition to 24-h total protein. An early morning urine sample to measure

albumin excretion is preferred since the effect of diurnal variation is minimized. Furthermore, an albumin/creatinine ratio should be reported in the early morning sample since this overcomes variation due to urine concentration and dilution. An increased 24-h urine protein but normal urine albumin excretion should prompt search for non-glomerular etiology such as tubular or light-chain proteinuria or urinary tract disease. As per KDIGO clinical practice guidelines (2016), specific commercially available assays for α1-microglobulin, β2 macroglobulin, and monoclonal heavy or light chains can be used for this purpose. As recommended by KDIGO-CKD work group (2012), if a 24-h urine albumin excretion rate (AER) is measured, the cutoff usually recommended is AER threshold of <30 mg/day to routinely accept a donor candidate, which corresponds to total protein excretion of <150 mg.

Lastly, it is important to remember that proteinuria can be a result of altered renal physiology in conditions such as fever, exercise, or extreme cold. This is usually transient and can be ruled out on repeat testing.

Evaluation of Hematuria in Kidney Donor Candidates

All donor candidates should be screened for the presence of microscopic hematuria. If persistent microscopic hematuria is present, additional testing should be pursued to ascertain the cause. Microscopic hematuria can be from benign entities such as menstruation, endometriosis, benign prostatic hypertrophy, as well as strenuous exercise. Urinary tract infection can also cause hematuria and is not a contraindication to donation provided it is addressed prior to donation. Other conditions such as nephrolithiasis can be picked up on CT imaging, and donor suitability with this diagnosis is covered in detail under stone discussion. Finally, microscopic hematuria can be associated with conditions that preclude donation such as genitourinary or renal malignancy, polycystic kidneys, sickle cell disease, or glomerular disease. A urinary tract malignancy picked up during hematuria work-up will be a contraindication due to transmission risk. Further work-up usually involves CT urography and completion of cystoscopy along with focused clinical history for risk factors. Some glomerular diseases can also present with persistent isolated hematuria such as Ig A nephropathy, thin basement membrane disease, and Alport syndrome. A renal biopsy is usually needed in cases of unexplained persistent hematuria. Donor candidates with additional features such as low GFR, proteinuria, or hypertension are generally excluded from donation. Donors with isolated hematuria with a negative urologic evaluation and normal renal biopsy are generally acceptable for donation.

As per Cohen and Brown (2003), estimated prevalence of microscopic hematuria varies widely from 0.18% to 16%. The American Urological Association (AUA) states that a positive dipstick alone does not define micro hematuria, and evaluation should be based solely on findings of microscopic examination of urinary sediment as suggested by Davis et al. (2012). A commonly accepted definition is microscopic evidence of >2–5 red blood cells per high-power field of urinary sediment on 2–3 separate occasions in the absence of exercise, trauma, sexual activity, or menstruation (Cohen and Brown (2003), Davis et al. (2012), Sutton (1990), Vivante et al. (2011). This is because urine dipstick can give false positive results in the presence of contaminants, myoglobin, or hemoglobin.

As recommended by the AUA, micro hematuria work-up includes assessment of risk factors for urinary tract malignancies (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures); radiological evaluation (CT) urography, without and with intravenous (IV) contrast, or magnetic resonance urography; and cystoscopy in patients age 35 or older regardless of history of the use of anticoagulation therapy (Davis et al. 2012). Urine cytology and urine markers are not included in routine evaluation but may be considered in patients with persistent micro hematuria following a negative work-up or in those with other risk factors for urinary tract malignancies.

This section will cover relevant glomerular diseases in reference to hematuria-like thin basement membrane nephropathy (TBMN), Alport,

and Ig A nephropathy. Savige et al. (2013) have published expert guidelines for the management of Alport syndrome and TBMN and also cover living kidney donation. According to these guidelines: (A) "Individuals with TBMN may be kidney donors if they have normal blood pressure (BP), proteinuria, and renal function" and if a biopsy is done and Alport syndrome is excluded. Close monitoring and use of nephroprotective strategies are advised. (B) "Individuals from families with autosomal recessive Alport syndrome who have only one of the causative mutations (parents, offspring, some siblings) may be renal donors if they have normal BP, proteinuria levels, and renal function; if coincidental renal disease has been excluded by renal biopsy; and if X-linked Alport syndrome has been excluded by genetic testing." These guidelines recommended "discouraging affected mothers of males with X-linked Alport syndrome from renal donation because of their own risk of kidney failure." It is important to recall that carrier states for Alport mutations may present clinically as TBMN, and therefore it is important to confirm by doing genetic testing. High frequencies of eventual proteinuria (75%) and ESRD (8–30%) have been reported in female carriers of X-linked Alport syndrome mutations as per Jais et al. (2003). Glomerular pathology like Ig A nephropathy precludes kidney donation.

Evaluation of Kidney Stones in Donor Candidates

In a report from the National Health and Nutritional Examination Survey, the prevalence of kidney stones has increased in the United States from 3.8% in the period from 1976 to 1980 to 8.4% in the period from 2007 to 2010 (Scales et al. 2012, Stamatelou et al. 2003). Up to 16% of men and 8% of women will have at least one symptomatic stone by the age of 70 years (Scales et al. 2012). Over 80% of these stones will contain calcium, usually as calcium oxalate. Almost half of symptomatic stone formers will develop a recurrent stone in their lifetime. There are some factors which are associated with higher recurrence probability such as age at first stone detection <40 years, bilateral stones, deranged urinary biochemical profile, and presence of nephrocalcinosis. Sometimes, small 1–2 mm foci of calcification may be picked up on donor CT scan in the renal papillae which are known as Randall's plaque and are of undetermined prognosis.

Personal and family history of kidney stones should be queried in all live kidney donors. About 5–10% of potential donors will be diagnosed with asymptomatic kidney stones. These donors should have a detailed stone specific history and testing. A urine metabolic profile should be obtained to determine the cause and suggest corrective measures. Generally, donors with small unilateral kidney stone <15 mm with no history of recurrence may be accepted to donate. In most cases, the kidney with the stone is utilized for transplantation with ureteroscopy pursued in the operative field to remove the kidney stone from the explanted kidney. Such donors are encouraged to follow evidence-based dietary recommendations to minimize the risk of stone recurrence after donation. These recommendations include maintaining a urine output of 2.5 liters/day and low-salt and low-oxalate diet, cutting down on animal protein, and consuming average recommended calcium intake with avoidance of calcium supplements.

Evaluation of Obesity in Kidney Donors

All donors routinely should have a body mass index (BMI) assessment at their evaluation. However, there are inherent limitations on solely relying on BMI to convey body composition, and therefore additional measurement such as abdominal circumference may be used to convey body fat distribution and assess for metabolic syndrome. Donor candidates with morbid obesity (BMI ≥ 40 kg/m^2) should be excluded from donation. Obesity is a known risk factor for diabetes mellitus and may also cause direct kidney injury in the form of obesity-related focal segmental glomerulosclerosis. It is difficult to directly quantify the risk of kidney disease from obesity in isolation due to associated CKD risk factors such

as hypertension, diabetes, obstructive sleep apnea, and cardiovascular disease which may be also present. Per SRTR 2014 Annual report, most transplant programs have been accepting living donors with increasing donor body mass index (BMI); percentages of donors with BMI 25 to <30 and 30 to <35 kg/m^2 increased from 35.3% and 15.9% in 2004 to 41.2% and 19.7% in 2014. Gracida et al. (2003) and Ibrahim et al. (2009) examined associations of pre-donation BMI with post-donation renal function and found that BMI increase was correlated with modest reductions in estimated glomerular filtration rate (eGFR) at follow-up. They also examined pre-donation BMI with post-donation hypertension and found increased odds of hypertension requiring medication (OR per BMI unit: 1.12, 95% CI 1.02–1.23) or modest increases in mean arterial pressure (91.2 vs. 88.2 mmHg), respectively. Some other studies have looked at ESRD and mortality risk in obese donors. Mjoen et al. (2014) have reported that cardiovascular death is increased in donors with increasing BMI, but not risk of ESRD and all-cause mortality over a 15-year follow-up in a study involving a large cohort of 1900 living donors. Segev et al. (2010) have reported on over 4000 obese live donors with BMI ≥30 mg/m^2 at the time of donation compared to matched healthy controls and found no associations of BMI at donation with perioperative mortality or death over 12 years. Heimbach et al. (2005) have published their experience with obese donors and have shown that major surgical complications such as conversion to open or reoperation and length of stay are not different in comparison to ideal BMI donors. However, overall 9–10% wound complication rate for obese donors in comparison to 2–4% rate in nonobese donors was observed, and this should be disclosed to potential obese donors prior to surgery. Most centers use a threshold of BMI ≥35 kg/m^2 as an absolute or relative contraindication to live donation.

History of bariatric surgery in potential donors is usually not a contraindication to donation provided risk assessment for kidney stones and urine biochemical profile has been done. Most centers will not accept these donors if they have hyperoxaluria and or the presence of kidney stones. Most centers will also turn down obese donors who demonstrate metabolic syndrome, hypertension, obstructive sleep apnea, microalbuminuria, and/or hyperlipidemia. It is reasonable to set weight-loss goals in obese living donor candidates prior to donation. Finally, long-term risks of obesity and counseling to maintain a healthy body weight after donation should be stressed.

Evaluation of Diabetes in Kidney Donor Candidates

Potential donors with history of diabetes are generally excluded from living donation. Per UNOS/OPTN criteria, diabetes is an absolute contraindication to living donation. However, the British guidelines (2011) do not list this as an absolute contraindication but instead mentions "diabetics can be considered for kidney donation after a thorough assessment of the lifetime risk of cardiovascular and progressive renal disease in the presence of a single kidney." European best practices by Pascual et al. (2014) mention that certain donors with diabetes may be allowed to donate under "exceptional circumstances."

The World Health Organization (WHO) defines diabetes mellitus as fasting plasma glucose ≥126 mg/dl, random plasma glucose ≥200 mg/dl, or plasma glucose concentration >200 mg/dl 2 h after a 75 g anhydrous glucose load in an oral glucose tolerance test (OGTT) or a HbA1c ≥6.5% on standardized assays. Both WHO and American Diabetes Association (ADA) define impaired glucose tolerance as 2-h glucose levels of 140–199 mg/dl on the 75 g oral glucose tolerance test. However, they differ on the criteria for impaired fasting glucose with WHO defining it is 110–125 mg/dl for fasting plasma glucose (FPG), and ADA defines this as 100–125 mg/dl.

It is important to obtain family history of diabetes, personal history of gestational diabetes, or polycystic ovarian syndrome in all donors. In potential donors, the first step is to obtain a fasting blood glucose level. Additionally, 2-h glucose tolerance test and/or glycated A1c should be obtained in case of impaired fasting blood glucose, first-degree

relative with diabetes, history of gestational diabetes, or history of polycystic ovarian syndrome.

Some patients with prediabetes may be allowed to donate based on their predicted lifetime incidence of ESRD. Such candidates should be extensively counseled regarding their increased lifetime risk for developing diabetes and consequent end-organ complications and the importance of recognizing modifiable risk factors to reduce risks.

Evaluation of Blood Pressure in Kidney Donor Candidates

Hypertension is defined by office BP readings of systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg, or as per Chobanian et al. (2003) daytime mean ambulatory blood pressure monitoring (ABPM) or home measurements of SBP $\geq$135 mmHg or DBP $\geq$85 mmHg or the need to use drugs to control hypertension. Accurate blood pressure measurement with properly calibrated equipment is an integral part of living donor work-up. Blood pressure measurement should be done on at least two occasions. There should be low threshold to use ABPM for those potential donors who manifest high readings or known hypertensive donors to assess adequate control.

Potential donors with hypertension and end-organ damage such as myocardial infarction or stroke, microalbuminuria, hypertensive retinopathy, and/or evidence of left ventricular hypertrophy are universally excluded per most transplant center donor protocols. Moreover, donor candidates with hypertension requiring >1 or 2 drugs for adequate control are also generally excluded. Some centers only allow hypertensive donor candidates >50 years of age to proceed with donation with the rationale that kidney damage from hypertension likely would have manifested by this age. Mandelbrot et al. (2007) studied the practice of using hypertensive living donors across the United States and reported that 47% of transplant programs will not accept a hypertensive living donor. Another 41% will exclude donors if they are taking more than one drug to control hypertension, and 8% will exclude donors if they are on more than two drugs. A very recently published paper by Lentine et al. (2016) concluded that donor history of hypertension is not associated with increased perioperative complications which is in contrast to an earlier paper published by Segev et al. (2010) where donors with hypertension had a statistically significantly higher surgical mortality than did donors without hypertension (36.7 per 10,000 donors; 95% CI, 4.4–132.6; vs. 1.3 per 10,000 donors; 95% CI, 0.4–3.4). However, Segev et al. also concluded that the magnitude of the excess surgical risk was considered to be uncertain as indicated by the wide CI.

In normal healthy individuals, blood pressure tends to rise with aging. Kidney donation may accelerate the risk or progression of hypertension over time to a greater degree as a result of interplay between reduced GFR from donation, aging process, and compensatory hyperfiltration. Boudville et al. (2006) have published an estimated 6 and 4 mmHg higher systolic and diastolic BP in about 5000 primarily Caucasian donors in comparison to controls after an average of 7 years. Another study involving African-American donors by Doshi et al. (2013) reported higher rates of post-donation hypertension in comparison to race-matched healthy nondonor controls about 6 years post-donation. In general, all donor candidates should undergo extensive counseling on modifiable risk factors such as healthy diet, smoking cessation, weight reduction strategies, exercise, and salt restriction. They should also be counseled that blood pressure rises with aging and that donation may accelerate this process above and beyond what is expected with normal aging. This process may be more prominent in African-American donors which may result in need for antihypertensive treatment.

Finally, the Amsterdam guidelines (2005) provide some recommendations in using hypertensive living kidney donors and are similar to recommendations outlined in this section. According to them, BP >140/90 by ABPM are generally not acceptable as donors. BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings. Some patients with easily controlled hypertension who meet other

defined criteria (e.g., >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/ day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors. It should be stressed to these donors that long-term follow-up with a physician to monitor blood pressure control and renal function is important.

Assessment of Infection Transmission from Living Donors to Recipients

Living donor candidates should be rigorously screened for infections. This ensures that disease transmission risk is reduced, and health of the donor is protected. The risk of donor-derived disease transmission can be alleviated by obtaining detailed clinical, social, and travel history of the donor and pursuing blood testing. Some transmissions such as CMV and EBV are considered acceptable in the realm of both living and deceased organ donation and can be managed by adequate prophylaxis and center-specific monitoring protocol. Unanticipated and unacceptable infectious disease transmissions such as HIV and Hepatitis B and C through organ transplantation are rare in the era of current testing but may result in serious adverse outcomes and are a crucial focus of donor testing. The updated 2013 US Public Health Service (PHS) Guidelines by Seem et al. (2013) as outlined in Table 2 provide an evidence-based tool for this assessment. HIV transmission has occurred in living donor transplantation in 2009 in New York, and this case was confirmed to be donor derived based on testing of frozen specimens, tight phylogenetic clustering of HIV sequences from the donor and recipient, and lack of another HIV exposure risk in the recipient. The donor in this case was a high-risk male homosexual donor and was tested for HIV more than 2 months prior to donation with a negative result. After this case, transplant centers have started to screen living donors for HIV as well as Hepatitis B and C as close to the time of donation surgery and also provide counseling to potential living donors to reduce their risk of HIV and Hepatitis B and C exposure and acquisition. In the nutshell, the updated PHS 2013 Guidelines by Seem et al. (2013) recommend testing potential living donors for HIV and hepatitis B and C by both nucleic acid testing (NAT) and serological testing as close as possible to donation surgery. The window period by NAT testing as adapted from Humar et al. (2010) is highlighted in Table 3.

Per OPTN guidelines, microbiological testing as highlighted under transmissible disease screening previously is required on all donors. In addition,

Table 2 US Public Health Service (PHS) 2013 screening to assess increased likelihood of recent HIV, HBV, or HCV infection (Adapted from Seem et al. 2013)

1. Have you had sex with a person known or suspected to have human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections in the preceding 12 months?	2. If female: Have you had sex with a man with a history of male-sex-with-male (MSM) behavior in the preceding 12 months?
3. If male: Have you had sex with another man in the preceding 12 months?	4. Have you had sex in exchange for money or drugs in the preceding 12 months?
5. Have you had sex with a person that has injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months?	6. Have you injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months?
7. Have you been in lockup, jail, prison, or a juvenile correctional facility for more than 72 h in the preceding 12 months?	8. Have you been newly diagnosed with or have been treated for syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 months?
Donors who meet the following criterion should be identified as being at increased risk for recent HCV infection only: 9. Have you been on hemodialysis in the preceding 12 months?	**US PHS risk factors also include:** A child who is ≤18 months of age and born to a mother known to be infected with or at increased risk for HIV, HBV, or HCV infection. A child who has been breastfed within the preceding 12 months, and the mother is known to be infected with, or at increased risk for, HIV infection

Table 3 Estimates of window period length for HIV and Hepatitis B and C by different testing methods (Adapted from Humar et al. 2010)

Pathogen	Standard serology	Enhanced serology (fourth-generation or combined antibody-antigen tests)	Nucleic acid testing
HIV	17–22 days	~7–16 days	5–6 days
HCV	~70 days	~40–50 days	3–5 days
HBV	35–44 days	Not applicable	20–22 days

Table 4 Screening tool to assess geographically endemic infections and infections related to specific exposures (Adapted from OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee report 2014)

Geographic risks (including duration of time spent in a location)	Where was the potential living donor born (outside vs. inside the United States)? Home country/region? Prolonged residence outside home region, recent or distant? Close family members countries of origin Living donor recovery hospital region? Occupational or recreational travel to other countries and/or regions?
Occupational risks	Healthcare workers, vets/animal care workers Landscapers, park rangers, and other outdoor workers Peace Corps workers, international journalists Current or previous military service, particularly outside the United States Medical mission trips (consider a 3-month washout period prior to donation to allow identification of subclinical disease)
Seasonal risks	Particularly with warm weather and insect exposure – local West Nile virus, dengue, chikungunya virus transmission, local rickettsial infections, Lyme disease
Hobbies	Hunting/dressing game, taxidermy Time living outdoors including camping, swimming in lakes, drinking stream water, insect exposures Adventure sports Gardening
Significant animal exposure (wild and/or domestic)	Large numbers of cats or dogs or any unusual pets Laboratory/research animals Veterinarian/vet assistant
Family members and close contacts with potential risk factors	Geographic or seasonal infections previously diagnosed in close family members or other contacts may predict risk for subclinical infection in potential donor

urinary tract infection evaluation is typically pursued at donor evaluation and again close to actual donation surgery. UTI should always be treated prior to donation in the donor. Presence of UTI in a male donor candidate should prompt additional detailed urologic evaluation to rule out prostatitis, urethral stricture and seek history for predisposing conditions such as anal intercourse or family history of reflux nephropathy. Sometimes, female donors may have asymptomatic bacteriuria. Urinary tract infection in a living donor should be treated prior to donation.

Transplant centers are also required to evaluate and maintain a written policy for geographic, environmental, and occupational exposures in potential living donor candidates as per OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee (DTAC) guidance published in 2014 as highlighted in Table 4. Microbiological screening for additional infections to assess seasonal or geographic and endemic infections, implications of results, and strategies to prevent recipient infection as suggested by KDIGO and DTAC are highlighted in Table 5.

Table 5 Common seasonal and geographically endemic infections in organ donors (Adapted from OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee report 2014)

Pathogen	Target population for testing	Screening tests	Confirmatory/ additional tests	Implications of positive test for donation and management
West Nile virus (WNV)	Persons with history of mosquito exposure or blood transfusions; risk varies by geography and season	Anti-WNV Ab IgM is available, but NAT advised in initial screening	WNV NAT typically within 7–14 days of donation	Donation should be delayed for 28d when NAT screening is positive, followed by repeat NAT and IgM testing, with further decisions based on combined results
Mycobacterium Tuberculosis (MTB)	Born outside or prolonged residence outside the United States, homeless, alcohol or other substance abuse, prison time, healthcare worker, known TB exposure	Chest radiograph Histo Tuberculin skin testing (TST) or Interferon gamma release assay (IGRA)	Acid-fast bacilli (AFB) staining, culture and/or NAT testing for active infection	Donation is contraindicated from persons with active MTB infection. Consideration of donation after treatment of active MTB should be individualized Donation may be considered from persons with latent MTB infection after initiation of chemoprophylaxis in the donor before donation, informed consent of the recipient, and recipient monitoring after transplant
Strongyloides cruzi	Born or lived in tropical/ subtropical countries with substandard sanitation. Significant exposure to soil in the Appalachia or the southeastern United States including walking barefoot. Unexplained eosinophilia and travel to an endemic area. Prior history of *Strongyloides* infection	Anti-*Strongyloides* Ab (IgG)		Donation may proceed after treatment of the donor with an appropriate antiparasitic agent such as ivermectin
***Trypanosoma cruzi* (Chagas)**	Born or lived in endemic areas of Mexico, Central and South America. Children of woman who lived in endemic area. Recipients of blood transfusion in endemic areas. Prior history of Chagas	Anti-*T. cruzi* Ab (EIA or IFA test) NAT insensitive for chronic phase disease due to low levels of parasitemia		Donation may be considered from persons with chronic Chagas disease after treatment of the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant

(*continued*)

Table 5 (continued)

Pathogen	Target population for testing	Screening tests	Confirmatory/ additional tests	Implications of positive test for donation and management
Histoplasmosis	Born or lived in Midwestern US Mississippi or Ohio River valleys	Chest radiograph (may be suggestive but not diagnostic) Anti-histoplasmosis Ab (complement fixation, immunodiffusion or EIA)	Urine or serum antigen testing	Donation may be considered from persons with pulmonary-limited histoplasmosis after treatment of the donor candidate before donation, resolution of clinical signs/symptoms and of antigenuria/ antigenemia (if present at diagnosis), informed consent of the recipient, and recipient monitoring after transplant
Coccidioidomycosis	Born or lived in desert areas of Southwestern United States	Chest radiograph (may be suggestive but not diagnostic) Anti-*Coccidioides* Ab (complement fixation, immunodiffusion, or EIA)	Urine or serum antigen testing	Donation may be considered from persons with coccidioidomycosis after treatment of the donor candidate before donation, resolution of clinical signs/symptoms and of antigenuria/ antigenemia (if present at diagnosis), informed consent of the recipient, and recipient monitoring after transplant

Cancer Screening in the Donor

All living donors undergo routine age-appropriate cancer screening. These include screening recommendations for colon, breast, cervical, prostate, and lung cancer. This is done to protect donor health and to prevent malignancy transmission to the recipient. In general, any active malignancy except for some low-grade nonmelanoma skin cancers is considered an absolute contraindication to organ donation. Any history of choriocarcinoma, melanoma, lymphoma, and leukemia is also considered an absolute contraindication to donation as well. The malignancy subcommittee of DTAC was established to monitor probable transmissions and provide guidance to maximize organ usage in a safe manner. Nalesnik et al. (2011) summarized their report to minimize donor malignancy transmission as outlined in Table 6. In general, live kidney donation from candidates in minimal- and low-risk categories may be considered but with the caveat that recipient informed consent must be obtained as per OPTN policy 4.2.

Renal cancer, melanoma, lymphoma, and lung cancer are the most commonly transmitted donor cancers among kidney transplant recipients. In general, all donors with melanoma are categorized as high malignancy transmission risk donors, irrespective of stage or active versus past disease with the possible exception of in situ melanoma, where metastatic risk is low as per DTAC report by Nalesnik et al. (2011). The Israel Penn International Transplant Tumor Registry has previously reported a 75% transmission rate resulting in 62%

Table 6 Risk categories for donor tumor transmission risk (Adapted from Nalesnik et al. 2011)

No significant risk	Benign tumors in which malignancy is excluded
Minimal risk (<0.1% transmission)	Basal cell carcinoma, skin Squamous cell carcinoma, skin without metastases Carcinoma in situ, skin (nonmelanoma) In situ cervical carcinoma In situ vocal cord carcinoma Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage) (nonrenal transplant only)[a] Solitary papillary thyroid carcinoma ≤0.5 cm Minimally invasive follicular carcinoma, thyroid ≤1.0 cm (Resected) solitary renal cell carcinoma ≤1.0 cm, well differentiated (Fuhrman 1–2)
Low risk (0.1–1% transmission)	(Resected) solitary renal cell carcinoma, >1.0 cm ≤2.5 cm, well differentiated (Fuhrman 1–2)[b] Low-grade CNS tumor (WHO grade I or II) Primary CNS mature teratoma Solitary papillary thyroid carcinoma, 0.5–2.0 cm Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure
Intermediate risk (1–10% transmission)	Breast carcinoma (stage 0, i.e., carcinoma in situ) Colon carcinoma (stage 0, i.e., carcinoma in situ) (Resected) Solitary renal cell carcinoma T1b (4–7 cm) well-differentiated (Fuhrman 1–2) stage I[b] History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90 and 99%
High risk (>10% transmission)	Malignant melanoma Breast carcinoma >stage 0 (active) Colon carcinoma >stage 0 (active) Choriocarcinoma CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation, or extra-CNS metastasis CNS tumor WHO grade III or IV Leukemia or lymphoma History of melanoma, leukemia or lymphoma, small cell lung/neuroendocrine carcinoma Any other history of treated non-CNS malignancy either (a) insufficient follow-up to predict behavior, (b) considered incurable, or (c) with probability of cure <90% Metastatic carcinoma Sarcoma Lung cancer (stages I–IV) Renal cell carcinoma >7 cm or stage II–IV Small cell/neuroendocrine carcinoma, any site of origin Active cancer not listed elsewhere

[a]Does not apply to renal transplant, as lesions may be multicentric
[b]Assumes complete resection of tumor prior to transplant

recipient mortality in 28 recipients who were transplanted with organs provided by 13 donors. These 13 donors were deemed free of melanoma at donation (Penn 1996; Buell et al. 2004). Some donors with completely resected small renal cell cancers prior to implantation have minimal risk of transmission (Table 6) and may be considered as living donors after informed consent has been obtained.

Evaluation of Genetic Diseases in the Donor

It is important to ascertain the cause of ESRD in a transplant candidate not only to assess risk of recurrence but also to stratify the risk of renal disease in a biologically related donor.

Autosomal dominant polycystic kidney disease (ADPKD) results from mutations in one of two genes, PKD1 on chromosome 16 or PKD2 on 4. PKD1 mutations accounted for 85% of cases and PKD2 for 15% (Rossetti et al. 2007). PKD 1 mutations are associated with a faster progression to ESRD by the fifth decade of life versus individuals with PKD2 mutations that often do not develop ESRD until seventh decade. Based on the work of Ravine and Pei et al. (2009), updated ADPKD criteria are available for use in clinical scenarios in at-risk population in whom molecular testing is not available. Accordingly, ADPKD can be confidently excluded in the absence of cysts for at-risk individuals between ages 30 and 39 (negative predictive value [NPV] 98.3%) and in the presence of fewer than two cysts for patients ≥40 years (NPV 100.0%). Clearly, ultrasonography is limited in excluding ADPKD in at-risk individuals <30 years, even in the absence of cysts (NPV 90.8%), and a negative ultrasound does not exclude disease between the ages of 30 and 39 years in about 1.7% of those at risk. In a more recent study by Pei et al. (2014), the presence of fewer than five cysts on non-contrast MRI in both kidneys combined where all the cysts are also less than 1.0 cm in length excluded the disease in at-risk individuals aged between 16 and 40 years.

In individuals aged <40 years who are being considered as living related kidney donors, who have no cysts on renal ultrasound or five to ten cysts by MRI, genetic testing is a valuable additional tool to exclude ADPKD with certainty. Linkage-based genetic diagnoses of ADPKD using sequencing of microsatellite regions flanking ADPKD1 and ADPKD2 genes are now rarely performed except in cases of preimplantation diagnostics for pregnancy planning. Rather, direct mutation testing which involves sequencing of the entire coding regions of both *PKD1* and *PKD2*, including intron/exon boundaries, is the current method of choice for molecular diagnosis of ADPKD (Audrezet et al. 2012). The recipient is first screened for PKD1 and PKD2 mutations, and if a causal mutation is identified, then focused mutation detection can be carried out on the prospective donor. Up to 15% of patients with suspected ADPKD have a negative comprehensive mutation screen. In such cases where the mutation screening in the first-degree relative with ADPKD is negative, DNA testing is unhelpful in determining whether the donor candidate does or does not have ADPKD.

APOL1 genotype: The American Society of Transplantation (AST) held an APOL1 Consensus Building Meeting in December 2015 to bring experts in the field together to address the potential impact of the APOL1 gene variants on organ donation and transplantation. It is accepted that homozygosity or compound heterozygosity for the G1 and G2 alleles causes autosomal recessive predisposition to myriad manifestations of CKD such as focal segmental glomerulosclerosis and HIV-associated nephropathy, proteinuria, reduced GFR, and younger age at dialysis in African-Americans of sub-Saharan descent (Parsa et al. 2013). Having at least one *APOL1* allele risk variant confers resistance to lethal *Trypanosoma brucei* infections. Kidneys from African-American deceased donors that harbored two APOL1 risk variants have failed far more rapidly after transplantation than those with zero or one risk variant (Reeves-Daniel et al. 2011). The probability that an African-American in the general population carries two risk alleles is 12% and increases to about 72% in an African-American with FSGS. The offspring of two individuals, one without kidney disease and one with FSGS, has a 28% risk of carrying two risk alleles and a seven- to tenfold higher risk of developing FSGS or hypertensive CKD, even without donation (Kuppachi et al. 2015). However, at this time the utility of *APOL1* testing for living donation has not been described in current or prior living donor guidelines but is an intense area of intense interest.

Hereditary interstitial kidney disease: Autosomal dominant interstitial kidney disease is rare. Mutations in at least four genes are implicated: *MUC1* gene which encodes mucin1 (*MCKD1*), *REN* gene which encodes renin, *UMOD* gene which encodes uromodulin (*MCKD2*), and the *HNF1B* gene which encodes hepatocyte nuclear factor-1β (Hart et al. 2002; Kirby et al. 2013). HNF1B is implicated in causing the RCAD

(renal cysts and diabetes) syndrome which manifests as renal cysts and diabetes (MODY5). According to Thomas et al. (2008), mutations in HNF1B can have variable manifestations such as renal hypoplasia or agenesis, multicystic renal dysplasia, horseshoe kidney, and glomerulocystic kidney disease. Disease resulting from mutations in the UMOD gene has been called familial juvenile hyperuricemic nephropathy. MCKD1 is characterized by features of a chronic tubulointerstitial disease with occasional cortical cysts on renal imaging, minimal proteinuria, bland urinary sediment, and no other associated features other than progressive CKD. Potential biologically related living donors should undergo mutational testing if the intended recipient with kidney failure is confirmed to have the pathogenic mutation.

Atypical HUS: Current genetic testing is deficient in ruling out the presence of atypical HUS in a potential donor even when the mutation is known in the recipient. Although mutations in complement regulatory genes such as complement factor H (CFH), membrane cofactor protein (MCP), factor I (CFI), factor B (CFB), and complement C3 were initially identified in aHUS, the list of genes associated with aHUS has grown to include proteins in the coagulation pathway such as thrombomodulin and others according to Bu et al. (2014). Inheritance of an abnormal allele increases susceptibility to aHUS, and an environmental trigger such as pregnancy, infection, surgery, or drugs appears to be necessary for the disease to manifest. Given that as many as 30% of aHUS transplant candidate patients do not have an identifiable genetic mutation, a negative genetic screen cannot eliminate the risk for aHUS in a screened related living donor. Based on the known genetic risk of aHUS and the false-negative rate, it is wise to discourage at-risk candidates from donating.

Alport and Fabry Disease: Alport syndrome is most often an X-linked disorder (~80% of families), but can also be inherited in an autosomal recessive (~15% of families) and autosomal dominant fashion (very rare). There is little information on the outcomes of heterozygous women who proceeded with kidney donation (after confirming an absence of proteinuria, hypertension, low GFR, and other manifestations of the disease such as sensorineural hearing loss). If donation is entertained, it should only be done so in older women who have time to manifest kidney disease and after a careful deliberation and consideration of all other alternatives (including other living donors). In the evaluation of male potential living kidney donors, those >20 years of age without hematuria are very unlikely to have X-linked Alport syndrome.

Fabry disease is an X-linked lysosomal storage disease caused by deficiency of the lysosomal hydrolase, α-galactosidase A (α-Gal A), which results in systemic accumulation of trihexosylceramide (globotriaosylceramide [GL-3]) in the lysosomes of the vascular endothelium in multiple organs. ESRD is reached in the third or fourth decade of life in most affected males. Heterozygous females have variable clinical manifestations owing to lyonization (random X chromosome inactivation). Fabry disease is confirmed by biochemical and genetic testing. If the transplant candidate is known to have Fabry disease, all donor candidates at 50% or greater risk of disease, which includes siblings, mothers of affected children, fathers of affected daughters, and all children of an affected mother, should be screened for Fabry disease. All daughters of an affected father are at 100% risk and are not suitable living kidney donors. As with heterozygotes with Alport syndrome, if donation is entertained, it may only be acceptable in older women who have time to manifest any kidney disease and after a careful deliberation and consideration of all other alternatives.

Psychosocial Assessment of Living Donor

According to OPTN living donor policy 14, it is mandatory for all living donors to undergo psychosocial evaluation by a psychiatrist, psychologist, Masters-prepared social worker, or licensed clinical social worker prior to donation, including documentation of the following:

(a) Mental health issues that might complicate the living donor's recovery and could be identified as risks for poor psychosocial outcome.
(b) Assessment of behaviors that may increase risk for disease transmission as defined by the US Public Health Service (PHS) Guideline.
(c) Living donor's history of smoking, alcohol, and drug use, abuse, and dependency.
(d) The identification of factors that warrant educational or therapeutic intervention prior to the final donation decision.
(e) Determine that the living donor understands the short- and long-term medical and psychosocial risks for both the living donor and recipient associated with living donation.
(f) Assess whether the decision to donate is free of inducement, coercion, and other undue pressure by exploring the reasons for donating and the nature of the relationship, if any, to the transplant candidate.
(g) Assess living donor's ability to make an informed decision and the ability to cope with the major surgery and related stress. This includes evaluating whether the donor has a realistic plan for donation and recovery, with social, emotional, and financial support available as recommended.
(h) Review living donor's occupation, employment status, health insurance status, living arrangements, and social support.
(i) Determine that the living donor understands the potential financial implications of living donation.

Independent Living Donor Advocate (ILDA): Per OPTN requirements, living donor recovery hospitals must designate and provide each living donor candidate with an ILDA (one person or a team with a key contact) who is not involved with the potential recipient evaluation and is independent of the decision to transplant the potential recipient. Detailed role description of the ILDA is covered in the chapter Essential Components of the Living Donor Team.

Living Donor Follow-Up Requirements: OPTN policy 18.5A outlines the living donor follow-up requirements and policy 18.6A details reporting of living donor adverse events. This follow-up is needed for up to 2 years post-donation but certainly would be wise to perform this for lifetime. Failure to comply with these reporting requirements can lead to citation of the transplant program. Required kidney donor status and clinical information includes all of the following:

1. Patient status
2. Working for income and, if not working, reason for not working
3. Loss of medical (health, life) insurance due to donation
4. Has the donor been readmitted since last contact?
5. Kidney complications
6. Maintenance dialysis
7. Donor developed hypertension requiring medication
8. Diabetes
9. Cause of death, if applicable and known

Required kidney laboratory and other objective data includes *all* of the following:

1. Serum creatinine
2. Urine protein
3. BP reading

Conclusions

Potential living kidney donors are required to undergo a detailed medical, surgical, and psychosocial evaluation to ensure that their health status is optimal and their renal function and anatomy are suitable for donation. This evaluation also identifies and assesses infection and malignancy transmission risks from donor to recipient. It is also mandatory for all donors to meet with an ILDA who ensures that the donor is making an informed decision to donate, and all relevant information has been provided to the donor. OPTN has defined the minimum criteria for the medical and psychosocial evaluation of living donor candidates. All transplant centers are required to maintain a written living donor

inclusion and exclusion criteria which may have requirements above and beyond those defined by the OPTN minimum requirements. Based on this evaluation, the donor may be accepted, rejected, or need additional work-up to assess candidacy. This additional work-up may include ABPM, genetic testing to assess risk for inherited renal diseases, geographic and endemic diseases risk, and others. In general, all living kidney donors should be advised regarding modifiable risks of developing chronic kidney disease and should be counseled to adopt healthy lifestyles including weight reduction, smoking cessation, healthy diet, and regular exercise. Finally, it is difficult to quantify the short- and long-term risks of developing renal disease in a medically complex living donor post-donation. This decision-making process is quite intricate, and the final decision to accept or decline a donor depends on a composite of estimated post-donation ESRD risk based on demographic, clinical factors in addition to directly attributable risk from donation itself.

Cross-References

- A History of Kidney Transplantation
- Ethical Issues in Organ Transplantation
- Live Donor Nephrectomy
- Necessary Components of a Living Donor Team
- Organ Procurement Organization and New Kidney Allocation

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The Role of the Transplant Coordinator

Linda S. Wright

Contents

Abstract

Transplant programs are required to have at least one Clinical Transplant Coordinator, to coordinate the care of transplant candidates throughout all phases of transplant care. The Coordinator's specific role will vary, depending on the structure of the transplant program, with some managing patients from the beginning of the transplant evaluation through long-term post-transplant follow-up, and others being limited to a specific transplant phase. Additionally, depending on the size of the program, some Transplant Coordinators will manage the evaluation and care of live donors, in addition to transplant candidates/recipients, while others will focus on either donors or recipients. However, regardless of

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these differences that exist between transplant programs, Transplant Coordinators provide continuity of care for patients, and serve as a liaison between the various members of the multidisciplinary team. The different aspects of the Clinical Transplant Coordinator's role throughout all phases of transplant care are discussed, including the care of the live donor.

Keywords
Transplant Coordinator · Multidisciplinary team · Transplant phases · Transplant evaluation · Post-transplant · Education · Live donor · On-call

Introduction

The evaluation and management of kidney transplant and live donor candidates requires the involvement of a multidisciplinary team. The Transplant Coordinator plays a key role in this team, overseeing patients' progress during all phases of transplant care. In some transplant centers, the Coordinator manages patients regardless of their transplant phase, providing continuity of care for patients from evaluation and listing, through transplantation and long-term follow-up. Other transplant programs are structured so that Coordinators manage patients during a specific transplant phase, evaluation, listing, or post-transplant, with patients being assigned a new Coordinator as they move through the transplant process. Additionally, depending on the size of the program, some Transplant Coordinators will manage the evaluation and care of live donors, in addition to transplant candidates/recipients, while others will focus on either donors or recipients. Regardless of the program's structure, the Transplant Coordinator uses specialized knowledge of chronic kidney disease and the unique needs of this patient population, as well as an understanding of the various regulations that govern the contemporary kidney transplant program, to ensure that patient needs are met and all required elements of transplant care are addressed.

The Role of Transplant Coordinators

Transplant programs are required, according to Organ Procurement and Transplantation Network (OPTN) bylaws, to have at least one Clinical Transplant Coordinator on staff (Organ Procurement and Transplantation Network 2016a). The role of the Transplant Coordinator is to work with patients and their families, and to coordinate their care from the start of the evaluation process through transplantation (or donation) and ongoing follow-up (NATCO 2009). The Transplant Coordinator helps to assure continuity of patient care, while working with all members of the multidisciplinary team, but is also responsible for the completion of various forms of documentation that are required by the United Network for Organ Sharing (UNOS) and the Centers for Medicare and Medicaid Services (CMS). This role may be filled by a nurse practitioner, clinical nurse specialist, or physician assistant; however, it is most often filled by a registered nurse.

While the registered nurse Transplant Coordinator does not have the autonomous practice of an advanced practice nurse, the role of the Transplant Coordinator allows for, and requires, a more independent practice than that of the more traditional clinical nurse. Within the framework of program-specific protocols, the Transplant Coordinator functions independently, making decisions regarding a patient's need for additional testing or evaluation by specialty providers. The needs of the transplant candidate are complex, as is the degree of collaboration that is necessary, among members of the multidisciplinary transplant team as well as with other, nontransplant, health-care providers. The Transplant Coordinator plays a vital role in the gathering and synthesizing of patient information, and in presenting it to the various members of the patient's team so that the appropriate decisions can be made regarding the patient's care.

The specific responsibilities of the Transplant Coordinator are determined by certain characteristics of the transplant program (Donaldson 2003). These include the overall size of the program and which organs are transplanted at the center, as

well as whether the center transplants pediatric patients, adults, or both. The number of Transplant Coordinators on staff at any transplant center is generally correlated to the annual number of transplants performed, and the number of patients managed.

Regardless of whether a Transplant Coordinator cares for children or adults, for patients along the entire spectrum of the transplant process or in a specific transplant phase, pre- or post-transplant, the characteristics of the role are the same. These include a focus on long-term transplant outcomes, the ability to be a strong patient advocate and educator, and the ability to apply analytical and problem solving skills to unusual or unexpected situations (American Nurses Association and International Transplant Nurses Society 2016).

The Care of the Transplant Candidate

Transplant Referral and Evaluation

In the evaluation phase, the Transplant Coordinator plays an active role in the education of transplant candidates and their families. Coordinators must be able to provide education on a broad range of topics related to transplantation, including the following.

Evaluation Process

The evaluation process will differ from program to program. While much of the required testing is standardized, and even required by CMS and/or OPTN regulations, individual transplant programs may have established protocols which include diagnostic testing or professional consultations that would not be required by other centers. The Transplant Coordinator must be able to both guide the transplant candidate through the evaluation process, and provide education concerning the rationale for the various tests and consultations that are being required by the transplant team. Coordinators should also have an understanding of the ways in which their evaluation process may be unique, and be able to explain any differences to candidates who may have been evaluated at other transplant programs and may be confused or concerned about differences in requirements.

Indications and Contraindications to Transplantation

While qualifying criteria are set by OPTN policy, each transplant program must establish a set of selection criteria that candidates must meet in order to be transplanted at that center. Transplant programs will consider certain medical or psychosocial conditions to be contraindications to transplantation. Programs are free to establish their own practice, as long as the criteria are fair and nondiscriminatory. Differences in practice may be related to differences in team philosophies as well to differences in experience and expertise.

One such difference that has become important in recent years is related to body mass index (BMI). Some transplant centers have established BMI cutoffs, and will decline to transplant, or even list, candidates who have a BMI that is outside of their accepted range. Other transplant centers have no such BMI requirement. Transplant Coordinators must educate patients with regard to the transplant program's specific selection criteria, and be able to discuss ways in which their program's criteria differ from other centers. Coordinators must also provide education and support to candidates who are declined for transplant, even to the point of directing candidates to other transplant centers if they are not able to meet their program's requirements.

Benefits of Live Versus Deceased Donor Transplantation

Many transplant candidates and their families are unaware of the benefits of live donor transplantation. Patients will choose to wait on the deceased donor transplant list, and even decline potential live donor offers, because of various concerns for their potential donor. Often these concerns are based on misinformation concerning live donation, or a lack of understanding of their own prognosis. While it is the responsibility of each member of the transplant team to provide

information and education concerning the benefits of live donor transplantation, the Transplant Coordinator is uniquely positioned to provide and to reinforce this education, as the Coordinator will be the primary point of contact between the candidate and the transplant program, from the time of the initial evaluation until the time that the candidate is either transplanted or deemed not to be a candidate for transplantation.

The Organ Allocation System and OPTN Regulations

Most transplant candidates are not familiar with the specifics of the kidney allocation system. Transplant Coordinators provide education and clarification concerning the OPTN policies and regulations, and dispel candidate concerns and misunderstandings regarding deceased organ allocation. This aspect of the Coordinator role became even more important in recent years, with the implementation of a new kidney allocation system, and the many questions from transplant candidates and their families that came as a result of the changes.

Risks and Benefits of Considering Organs from High-Risk and Other Types of Deceased Donors

Along with other members of the transplant team, Transplant Coordinators educate candidates and their families concerning various types of deceased donors. These include donors with a high Kidney Donor Profile Index (KDPI), a feature of the new kidney allocation system, those who have tested positive for Hepatitis B or Hepatitis C, and those who have been determined to be at increased risk for the transmission of Hepatitis B and C and human immunodeficiency virus by U.S. Public Health Service (PHS) guidelines. Transplant Coordinators provide information and guidance regarding the risks and benefits of accepting organs from such donors, compared to the risks and benefits of declining such offers and delaying transplantation. This requires an understanding not only of the risk of graft failure or the transmission of an infectious disease, but also of waitlist mortality and the risks associated with remaining on dialysis.

Center-Specific Versus National Patient and Graft Survival Rates

Transplant programs are required to provide transplant candidates with data comparing center-specific graft and patient survival rates to national outcomes. Transplant Coordinators must be able to discuss these outcomes with patients, to ensure that patients are able to make an informed choice when selecting a transplant center.

What to Expect While Waiting on the Transplant List

Candidate experiences and processes while on the transplant list will vary based on the transplant program, the availability of a live donor, and the expected waiting time to transplantation. The Transplant Coordinator educates transplant candidates, so that they know what to expect during their waiting time. Coordinators provide information concerning the need for regular testing and reevaluation by the transplant team, as well as the need to inform the transplant program of any changes in their condition. Transplant Coordinators also provide ongoing education to transplant candidates as they begin to receive deceased donor organ offers, ensuring that they understand the process and the transplant program's expectations.

Transplant Process

Transplant Coordinators help to ensure that transplant candidates know what to expect at the time of transplant. They provide education concerning the admission process, perioperative period, and expected length of stay.

Post-Transplant and Ongoing Management

The specifics of the transplant candidate's post-transplant care and management will vary between transplant programs. The Transplant Coordinator will provide education concerning the structure of the program with regard to post-transplant care, such as whether the candidate can expect to be assigned to a new Transplant Coordinator, or if the same Coordinator will manage care throughout the transplant continuum. Candidates will also be informed of the transplant

program's expectations with regard to follow-up appointments and ongoing care. Some transplant programs continue to follow transplant recipients for the life of the allograft, while others refer recipients back to their community nephrologist at a certain point, and only see them again if and when a problem arises. The Transplant Coordinator also discusses the need for ongoing immunosuppression post-transplant, and the risks associated with nonadherence to the prescribed regimen, reinforcing the recipient's role in the success or failure of the transplant.

Organ Donor/Recipient Confidentiality

The Transplant Coordinator discusses issues regarding donor and recipient confidentiality. For some candidates, this will require education concerning the specific information that will and will not be shared with the transplant candidate concerning their potential live donor's evaluation and testing. For those without a potential live donor, however, this will entail education concerning the information that the candidate can expect to receive about a potential deceased donor at the time of any organ offer.

The Coordinator is responsible to ensure that the candidate completes all of the necessary diagnostic tests and consultations, so that the multidisciplinary team can make a determination regarding their suitability for transplantation. This also includes documentation of the candidate's blood type, according to OPTN policy (Organ Procurement and Transplantation Network 2016b), and the gathering and interpretation of serological test results, with an understanding of their implication and impact on the transplant process. The Coordinator also oversees communication between the transplant program and referring physicians and dialysis units, regarding the outcome of a candidate's evaluation, and status on the transplant waiting list.

Listing Phase

At the time of listing, the Transplant Coordinator is responsible to ensure that all OPTN requirements are met. The Coordinator then follows the candidate throughout the time spent on the waitlist, monitoring for ongoing suitability and readiness for transplant.

Documentation of Blood Type

OPTN policy requires that transplant candidates' blood type be drawn on two separate occasions prior to addition to the waitlist (Organ Procurement and Transplantation Network 2016b). The Transplant Coordinator ensures that candidates are not listed until the necessary documentation has been obtained. Additionally, OPTN policy requires that two different healthcare providers log in to the online database to document the candidate's blood type, to verify that the blood samples that were used meet the requirements, and that that the information that has been entered into the database matches the source documents. In some programs, two Transplant Coordinators perform this documentation and verification of a candidate's blood type. In others, where the actual entry of a candidate into the OPTN waitlist database is handled by someone other than the Transplant Coordinator, the Coordinator performs the second documentation.

Verification of Dialysis Start Date

With the change in the kidney allocation system that went into effect on December 4, 2014, transplant candidates are given credit for pre-registration dialysis time. The Transplant Coordinator ensures that documentation of dialysis start date is obtained and properly entered into the OPTN database.

Verification of Glomerular Filtration Rate

The glomerular filtration rate (GFR) is also used to qualify a candidate to start to accrue waiting time, but usually only for patients that are not on dialysis at the time of listing. While candidates may be listed with a higher GFR, they will not accrue waiting time until the GFR is $\leq$20 mL/min. The Transplant Coordinator ensures that a qualifying GFR is documented in the candidate's medical record at the time of listing. For candidates whose GFR is $>$20 mL/min at the time of listing, the Coordinator will monitor the candidate's kidney function until such time as there is a

qualifying GFR, at which point the candidate's listing will be updated to reflect the new GFR, to allow the candidate to begin to accrue waiting time.

Deceased Donor Acceptance Criteria

The Transplant Coordinator ensures that transplant candidates' UNOS listing accurately and properly reflects their acceptance or refusal of the different types of deceased donors. This includes donors having high KDPI scores, as well as those who have tested positive for Hepatitis B or Hepatitis C. While candidates must consent to receive an organ from a PHS increased-risk donor, willingness to consider such donors is not currently reflected in the UNOS listing. The Coordinator also ensures that the donor acceptance criteria are noted in the candidate's medical record, so that the information is available at the time of a deceased donor organ offer.

Waitlist Maintenance

During the often prolonged period of time that candidates are on the transplant waiting list, the Transplant Coordinator is responsible for monitoring their medical status, and assuring their ongoing readiness for transplant. The Coordinator ensures that patients complete their annual testing, per the center's protocols, and assesses for any abnormal findings or significant changes in medical condition, and coordinates any additional testing or evaluations that may be required. The Coordinator ensures ongoing communication with the patient, but also with referring physicians, dialysis units, and other members of the patient's care team. Additionally, the Coordinator responds to any perceived psychosocial or economic needs or changes, involving the appropriate members of the multidisciplinary team as needed. The Coordinator is also responsible to assess for knowledge deficits, with regard to the transplant process, and provide reeducation to transplant candidates and their families as needed.

Depending on the size and structure of the transplant program, the ongoing waitlist maintenance role may be fulfilled by the candidate's initial pre-transplant coordinator. Often, however, the management of waitlisted patients is transferred to a dedicated Waitlist Maintenance Transplant Coordinator, who assumes the responsibility for ensuring each listed candidate's continued suitability and readiness for transplant.

Perioperative Period

The Transplant Coordinator participates in the identification and selection of appropriate candidates in the case of deceased donor organ offers, in accordance with the specific protocols of the transplant center. The Coordinator uses an understanding of the candidate's medical condition, preferences with regard to high risk and other donor types, and any patient-specific considerations, to ensure the appropriate allocation of deceased donor organs, in accordance with OPTN policies. The Coordinator discusses relevant donor history or issues with potential recipients, while safeguarding the anonymity of the donor. The Coordinator also discusses any current or pertinent recipient issues with the transplant surgeon or physician, in order to ensure their suitability to receive the intended organ.

The Transplant Coordinator arranges for cross matching between the potential donor and recipient, ensuring a compatible result in advance of transplant. The Coordinator then serves as a liaison between the transplant surgery team and the patient, arranging for admission to the hospital, according to the individual transplant center's procedure, and the notification of all necessary parties, such as the operating room charge nurse, admissions office or emergency room, the tissue typing lab, and surgical residents.

Following the completion of the organ transplant, the Coordinator ensures the timely removal of the recipient from the transplant center's waiting list, in accordance with OPTN policy.

Post-Transplant

The Transplant Coordinator monitors the transplant recipient's progress throughout the hospitalization, and collaborates with nursing staff and

other members of the inpatient care team to ensure that discharge planning needs are addressed. Prior to discharge from the hospital, the Coordinator educates the recipient and their family with regard to various aspects of their post-transplant care.

Post-Transplant Education

Frequency and Location of Follow-up Visits

The frequency of follow-up visits will vary between transplant programs. The timing of the patients' referral back to their community nephrologist will vary as well, as will the level of involvement of the transplant program in the transplant recipient's ongoing care. Transplant programs will usually refer back to the referring nephrologist in the first 3–6 months post-transplant, with some programs choosing to share care by having the patient alternate visits between their local provider and the transplant program, while others prefer to have the local nephrologist manage the ongoing care, having the patient return only in the case of problems or complications.

Plan for Ongoing Laboratory Examination

As with follow-up office visits, the frequency of ongoing blood work, and the laboratory that the patient is required to use, will vary with the transplant program. For many laboratories, including national, commercial laboratories, the drug levels for the different immunosuppressive agents require at least 2 days for the results to be available. As a result, some programs will require transplant recipients to have blood work done at the hospital's own laboratory in the early weeks and months post-transplant, in order to ensure the timely receipt of results.

Process for Reporting Problems to the Transplant Program

Transplant recipients need to be aware of the transplant program's specific procedures for the reporting of any post-transplant problems. This should include basic contact information for different members of the transplant program, as well as emergency and after-hours contacts.

Signs and Symptoms of Rejection or Other Potential Complications

Patients are educated concerning common signs of rejection, such as fever, decreased urine output, and allograft tenderness, as well as other potential post-transplant complications. Teaching should include clear instruction regarding when and how to contact the transplant program, so that any and all complications can be addressed in a timely manner. The Transplant Coordinator will also educate the patient concerning the transplant program's policies and expectations regarding prescription refills and primary care activities, so that the patient has a clear understanding of when they should contact their primary care provider rather than the transplant program.

Medications

While protocols will vary between transplant centers, the Transplant Coordinator, in conjunction with the Transplant Pharmacist, should provide education concerning the purpose, appropriate dosage, and side-effects of immunosuppressants and other transplant-related medications. Teaching should include the risk of rejection that is associated with nonadherence with prescribed immunosuppressive regimens.

Expectation for Home Monitoring of Vital Signs

The Transplant Coordinator will provide teaching regarding the transplant program's expectations concerning the home monitoring of blood pressure, weight, and other vital signs. Programs, or transplant pharmacies, will often provide blood pressure monitors, scales, and thermometers, in order to facilitate patient self-monitoring. Patients should be given clear instruction regarding normal versus abnormal ranges, as well as the type of results which should be reported to the transplant program.

Any Restrictions in Diet or Activity

While the Transplant Dietitian will serve as the recipient's primary resource, Transplant Coordinators should educate patients about the basic

dietary restrictions associated with transplantation. This includes the need to avoid raw or undercooked meat, fish, and eggs, as well as unpasteurized milk and dairy products. The Coordinator should also educate patients about common food-drug interactions, in particular the need to avoid all forms of grapefruit due to its effect on the metabolism on the calcineurin inhibitor class of immunosuppressants.

Ongoing Management

Once the transplant recipient has been discharged from the hospital, the Transplant Coordinator is responsible to coordinate the patient's ongoing care. The Coordinator reinforces the education that was provided during the hospitalization, and reeducates the recipient as needed. The Coordinator monitors the patient's progress, assessing for changes in medical or psychosocial status, signs of infectious or other complications, medication-related issues, and adherence to treatment. The Coordinator collaborates with the transplant physicians, or other members of the team, to implement changes in the recipient's medications, and facilitates any necessary consultations or diagnostic testing. In addition, the Coordinator facilitates the transfer of information from the transplant center to community nephrologists and other members of the recipient's health care team, and addresses any need for urgent evaluation or treatment.

Reporting

The Transplant Coordinator may also be involved in the required ongoing reporting of recipient data to OPTN. Transplant programs are required by OPTN policy to complete transplant recipient follow-up reporting at 60 days post-transplant, 6 months post-transplant, and then at the time of the annual transplant anniversary for the life of the allograft. Reported elements include graft status and serum creatinine level, whether or not the recipient experienced rejection or required dialysis, immunosuppressive agents, post-transplant malignancies, functional and employment status, and primary insurance (Organ Procurement and Transplantation Network 2016b). Transplant Coordinators may actually complete the reports, or may assist with the collection of the required data.

The Care of the Living Donor

Evaluation

The Transplant Coordinator is similarly involved in the evaluation, and ultimate selection, of potential live kidney donors. The Transplant Coordinator screens potential donors, on initial referral to the program, to identify appropriate candidates for live donation, and coordinates their evaluation with the necessary members of the multidisciplinary team. The Coordinator is responsible to educate potential donors and their families on various aspects of live donation.

Evaluation Process

As with the evaluation of the transplant candidate, the live donor evaluation process will differ from program to program. While much of the required testing is standardized, or required by CMS and/or OPTN regulations, individual transplant programs may have established protocols which include diagnostic testing or professional consultations that would not be required by other centers. The Transplant Coordinator must be able to both guide the potential donor through the evaluation process and provide education concerning the rationale for the various tests and consultations that are being required by the transplant team. Coordinators should also have an understanding of the ways in which their evaluation process may be unique, and be able to explain any differences to candidates who may have been evaluated at other transplant programs and may be confused or concerned about differences in requirements.

Contraindications to Donation

Conditions that predispose an individual to developing chronic kidney disease are considered to be

contraindications to live donation. While certain conditions, such as diabetes mellitus, are an absolute contraindication, other conditions, such as hypertension or obesity, may be viewed differently by different transplant programs. For example, some programs may rule out any potential donor with hypertension, while other programs would consider a donor with hypertension, as long as their blood pressure is well controlled on one antihypertensive agent. Certain psychosocial issues could also be seen as a contraindication to donation. Programs are free to establish their own practice, as long as the criteria are fair and nondiscriminatory. Differences in practice may be related to differences in team philosophies as well to differences in experience and expertise.

Risks and Benefits of Donation

The Transplant Coordinator participates in the education of the potential donor concerning the risks and benefits of donation. Potential risks include those associated with the donor nephrectomy, but also long-term medical, psychosocial, and financial risks. For example, while the cost of the donor evaluation and ultimate surgery is not charged to the donor, there still may be out-of-pocket expenses for which the donor may be responsible, or other financial issues associated with donation. These include such things as lost wages, travel and child-care expenses, or even implications for future life and health insurance.

Donation and Hospitalization Process

Transplant Coordinators help to ensure that potential donors know what to expect at the time of surgery. They provide education concerning the admission process, perioperative period, and expected length of stay.

Recovery Period

The Transplant Coordinator educates potential donors concerning the post-operative recovery period. The Coordinator provides information about the need for time off from work post-donation, and any temporary restrictions in physical activity.

Short- and Long-Term Follow-Up Care

The Coordinator provides information regarding expected follow-up care and appointments. For donors who do not live near the transplant program, this should include the specific period of time that the donor is expected to remain in the area post-donation. Potential donors also need to be educated regarding the long-term follow-up that is required by OPTN policy (see the "Post-Donation" section that follows), and the expectation that they will participate in the required follow-up.

The Coordinator also works with the potential donor to identify learning and other needs, expectations, and commitment to donation and functions as the donor's advocate with other members of the multidisciplinary team. The Transplant Coordinator ensures that all necessary testing is completed, in the evaluation of the potential live donor, gathering and reviewing results with the multidisciplinary team, so that a determination can be made regarding the candidate's suitability to donate. The Coordinator then facilitates the hospital admission of the donor and transplant candidate, and notifies the team of the scheduled surgery.

Perioperative Period

The live donor Transplant Coordinator monitors the donor's progress throughout the hospitalization, and collaborates with nursing staff and other members of the inpatient care team as necessary, to insure that discharge planning needs are addressed. Prior to discharge from the hospital, the Transplant Coordinator is responsible to educate the live kidney donor on various aspects of post-donation care, according to the protocols of the specific transplant program. Education should include the following:

1. Frequency and location of follow-up visits
2. Process for reporting problems to the transplant program
3. Signs and symptoms of potential complications

4. Purpose, appropriate dosage, and side effects of any medications which may be prescribed by the transplant surgeon post-donation
5. Post-operative restrictions, and plans for return to full activity
6. Reinforce need for long-term precautions or lifestyle modifications post-kidney donation
7. Reinforce need for post-donation follow-up, according to OPTN policy

Post-Donation

Upon discharge from the hospital, the Coordinator assists the live donor with any issues that may arise relative to the kidney donation, serving as the primary point of contact for any complications that may arise in the post-operative period. However, it is also the Transplant Coordinator's responsibility to arrange for the donor's follow-up testing for a minimum of 2 years post-donation, according to OPTN policy. Transplant programs are required to submit follow-up reports at 6 months, 1 year, and 2 years post-donation. Required data elements include donor status and the presence of any complications, whether or not the donor developed hypertension or diabetes or required dialysis, any loss of medical insurance as a result of donation, and the donor's employment status. Transplant programs are also required to submit serum creatinine and urine protein levels (Organ Procurement and Transplantation Network 2016b).

The Transplant Coordinator educates the potential donor concerning their responsibility to participate in the required follow-up. This involves communication with the donor at prescribed intervals, providing all necessary prescriptions for testing, and gathering information about their post-donation status. It may also involve communication and coordination with the donor's primary care physician, or other appropriate member of the donor's health-care team, in order to obtain the required information. This is often a challenging part of the Transplant Coordinator's role. Living donors are, by definition, healthy individuals, and often do not see a need to have medical testing completed if they are not having overt health issues, despite having been educated pre-donation with regard to this need for mandatory follow-up.

The On-Call Role

The need to participate in an on-call schedule, and the exact nature of the on-call duties, varies from center to center. While some transplant programs require Transplant Coordinators to be on call for post-transplant patient issues, other Transplant Coordinators are on call for deceased donor organ offers only. Generally, the on-call responsibilities are shared by all of the Coordinators. In small programs where there is only one Transplant Coordinator, the duties may be shared with transplant fellows or other physicians.

On-call responsibilities can be a significant source of dissatisfaction among Transplant Coordinators. Additionally, the frequency of after-hours calls and the time spent managing organ offers can lead to a decrease in productivity and effectiveness during work hours, due to sleep deprivation. As a result, some transplant programs employ staff members whose primary job function is the coverage of the after-hours on-call schedule, and other programs contract with private companies for the management of their deceased donor organ offers and after-hours patient calls.

Conclusion

That the Transplant Coordinator plays a key role in the evaluation and management of transplant candidates, recipients, and live donors is evidenced by the fact that their role on the transplant team is mandated by UNOS and CMS. Coordinators use highly specialized knowledge to ensure that the varied needs of their patients are met, throughout all phases of the transplant

process, but also to ensure that the center fulfills the requirements set forth by the regulatory agencies that are charged with the oversight of the transplant system. The specific duties and responsibilities of the Transplant Coordinator vary, depending on the size and structure of the transplant program.

Cross-References

- Living Donor Evaluation and Selection
- Necessary Components of a Living Donor Team
- Recipient Selection for Kidney Transplantation

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Donor Selection: Deceased Donor

Ahmad Safra and Carlo Gerardo B. Ramirez

Contents

Abstract

Organs from donation after brain-stem death (DBD) donors have become the most common source of organs for transplantation with the establishment of the brain death guidelines. However, successful outcomes following transplantation have increased the disparity between demand and supply of available organs, creating a shortage of organs for transplantation. Consequently, many transplant centers and organ procurement organizations across the world have adopted methods to increase the donor pool, notably using organs from donation after cardiac death (DCD) donors, expanded criteria donors, Public Health Services (PHS) high-risk donors, and donors with positive serology for viral hepatitis. The significant variability in the quality of kidneys derived from these donors has a direct effect on the short- and long-term patient and allograft survival outcomes. Although DCD donor kidneys have twice the risk of developing delayed graft function (DGF) compared to

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DBD donor kidneys, they have similar reported graft survival rates. Transplantation of kidneys from hepatitis B virus (HBV) and hepatitis C virus (HCV) positive donors remains controversial but seems to be safe in the long-term based on single center and registry studies. On the other hand, the actual risk of disease transmission from Public Health Services (PHS) high-risk donors is reported to be very low. Finally, DBD kidneys procured from donors on ECMO have similar DGF rate, 1-year graft survival rate, and allograft function, compared to kidneys from non-ECMO donors, and, therefore, should be utilized to increase the donor pool.

Keywords

Brain death · Donation after cardiac death (DCD) · Donation after brain stem death (DBD) · Standard criteria donors (SCD) · Expanded criteria donors (ECD) · Hepatitis B core antibody positive (HBcAb+) donors · Hepatitis C antibody positive (HCV ab+) donors · Delayed graft function (DGF)

Introduction

Before the establishment of the brain death criteria, donation after cardiac death (DCD) donors and living related donors (LRD) were the only sources of transplantable organs. However, the use of organs from brain-dead heart beating (donation after brain-stem death or DBD) donors has become the most common source of organs for transplantation after the guidelines for determining brain death have been established in 1968. In succeeding years, the interest in using organs from DCD donors has decreased because of associated low yield of transplantable organs and generally inferior posttransplant outcomes compared with DBD donors. In recent years, the successful outcomes following organ transplantation have widened the disparity between demand and supply of available organs, creating an organ donor shortage. This has consequently revitalized the use of organs from DCD donors. The past decade alone has witnessed a significant increase in the number of DCD donors. Currently, DCD donors account for close to 10% of all transplants performed in the United States The increase in DCD donors has expanded the donor pool, which may have slowed down the number of patients dying on the waiting list in the USA (Pomfret et al. 2008).

History of Brain Death and Donation After Cardiac Death

Brain death (BD) is defined as complete and irreversible cessation of brain function. This implies the permanent absence of cerebral and brainstem capacity, and vegetative and respiratory activities. The earliest accounts concerning states resembling what would today be recognized as BD go back to the end of the nineteenth century, when several authors reported that following an increase of intracranial pressure (ICP) in experimental models and in patients, respiration suddenly stopped, whereas the heart continued to beat. In 1895, Horsely, a pioneering neurosurgeon, concluded that the immediate cause of death in patients with significant brain injury due to cerebral hemorrhage, brain tumors, and depressed skull fractures is due to respiratory failure and not to heart failure. This was corroborated by Cushing in 1902, who stated that, "in death from a fatal increase in intracranial tension, the arrest of respiration precedes that of the heart." In 1939, Crafoord stated that death was due to "cessation of blood flow to the brain and nothing else." At the end of the 1950s, neuroradiologists and neurosurgeons repeatedly reported the angiographic findings in cerebral circulation in patients with apnea and those who were in coma. In 1959, Wertheimer et al. and Jouvet characterized the "death of the nervous system." Some months later, Mollaret and Goulon coined the term "coma dépassé" for an irreversible state of coma and apnea.

While most countries have a legal vision of brain death, most institutions have protocols for diagnosing brain death. In the USA, specific criteria and mandatory regulations were formulated for the diagnosis of BD, especially when applied to organ donation.

Donation after cardiac death (DCD), also called non-heart beating donor, has become an accepted method of increasing the donor pool in many transplant centers and organ procurement organizations (OPO) across the world, although the exact definition of cardiac death and the timing of organ procurement remain controversial. All organs prior to the introduction of brain death into law in 1970s came from DCD donors. However, organs from DBD donors have better clinical outcomes. The growing demand of organs made transplant centers reconsider using organs from DCD donors to increase the pool of potential organs.

Maastricht system classification of DCD donors was developed in 1995 and revised in 2003 (Kootstra et al. 1995). This included the following patient categories: Category I. Brought in dead; Category II. Resuscitated unsuccessfully; Category III. Awaiting cardiac arrest; Category IV. Declared brain dead and developed a cardiac arrest; and Category V. In-hospital patients who developed a cardiac arrest. Only tissues such as heart valves and corneas can be taken from category I donors. Kidneys can be used from category II donors, and all organs except the heart can potentially be used from category III, IV, and V donors.

When a strict protocol for organ procurement is followed, the outcome of kidney transplantation (KT) from DCD donors compares well with that of KT from DBD donors in terms of survival and allograft function.

Evaluation and Management of Deceased Donors

Appropriate medical management of donors both before and after death is vital for the quality of the recovered organs and future transplantation outcomes. BD donors can be challenging despite maximal intensive care. The pathophysiology of brain death affects the homeostasis of many systems. Optimal medical management should anticipate and try to prevent or diagnose and treat all abnormalities that can cause permanent damage to the otherwise transplantable organs.

Potential organ donation should always be considered when caring for critically ill patients. The team work of the treating physician along with procurement coordinator provides the most effective approach to organ donation and that can be extended to coordination with organ procurement organizations and transplant centers and surgeons.

The optimal donor management aims to achieve hemodynamic stability, which maintains optimal viability of all potentially transplantable organs. The balance between interventions is extremely important to prevent injury to some organs while maintaining others. For example, restrictive management of fluid balance in a multiorgan donor supports adequate perfusion to vital organ systems even with a CVP <6 mm Hg. A strict fluid balance could avoid volume overload and neurogenic lung edema, increasing the rate of lung allografts available for transplantation without impacting either kidney graft survival or development of delayed graft function (DGF).

Other important considerations are the maintenance of proper ventilatory support, adequate pulmonary toilet, and appropriate infection prevention and treatment. Normothermia should be maintained passively on all brain-dead donors. Temperature less than 35 °C requires active rewarming modalities, such as a warm air blanket.

Many factors contribute to systemic hypotension in BD donors. These include: loss of sympathetic tone, adrenal insufficiency, intentional volume restriction, and central diabetes insipidus (DI). Bleeding in trauma patients can cause hypovolemia and hypotension, for which balanced volume resuscitation and closer monitoring of volume status are critically important. The use of vasopressors may be necessary in many instances, but attempts should be made to use the minimal dose of the least injurious agent first.

The loss of adequate levels of antidiuretic hormone (ADH) from the posterior pituitary gland in DBD donors can lead to the development of DI. This complication can lead to large volume diuresis and can be devastating if not treated adequately. Desmopressin and vasopressin are the drugs of choice in addition to adequate volume and electrolytes replacement. Other endocrine

abnormalities include low baseline cortisol levels and thyroid abnormalities (sick euthyroid syndrome) are very common. Levothyroxine therapy plays an important role in the management of hemodynamically unstable potential organ donors by decreasing vasopressor requirements and preventing cardiovascular collapse. This may result in an increase in the quantity and quality of organs available for transplantation.

In the setting of DCD, withdrawal of life-sustaining therapy is best performed in the operating room. This helps in decreasing the warm ischemic time. Prior to the loss of circulation, heparin should be administered to minimize the risk of thrombosis during circulatory arrest. Warm ischemic time can be calculated from the onset on hypoxemia and hypotension until the organs are cooled.

Donor Selection

Donation After Brain-Stem Death (DBD) Donors

There is a significant variability in the quality of deceased donor kidneys that are used for transplantation and that has a direct effect on the clinical outcome including patient and allograft survival. Organ Procurement and Transplantation Network (OPTN) is charged with developing policies and procedures for deceased donor organ procurement, allocation, and distribution in the USA. Historically, the OPTN allocation system has classified deceased donors into standard criteria donor (SCD) or expanded criteria donor (ECD).

Standard criteria donors (SCD) are donors who are under the age of 50 and have no significant comorbidities. In practice, all deceased donors who do not meet any of the criteria of ECD are considered as SCD.

ECD are donors who are more than 60 years old, or donors who are between 50 and 59 years old, and have any two of the following three criteria: (1) cause of death is cerebrovascular accident; (2) preexisting history of systemic hypertension; and (3) terminal serum creatinine of more than 1.5 mg/dL. By definition, KT using ECD kidney allografts has a 70% more chance of failure (odds ratio 1.7) compared to KT using SCD. However, recipients of kidneys from ECD generally have improved survival compared with matched dialysis-treated patients. By stratifying donor and recipient risk into the allocation and management algorithm, kidney allografts from ECD have been found to have excellent short-term outcomes. Ultimately, a number of important goals can be realized, including maximal and optimal utilization of ECD kidneys, minimizing kidney discard and waiting list deaths, improving rehabilitation and quality of life, controlling resource utilization, and respecting individual autonomy.

Since the expected kidney function within the ECD and SCD categories is widely variable, kidney allocation using the kidney donor profile index (KDPI) was introduced by the OPTN in December 2014. The KDPI combines several donor factors into a single number which can be a useful tool in deceased kidney donor evaluation. The KDPI can estimate how each kidney is expected to function relative to all of the kidneys recovered in the USA during the last year and can predict the likelihood of graft failure after deceased donor KT. Kidney allografts with lower KDPI scores are predicted to function longer, while those with higher KDPI scores are predicted to function for a shorter period of time. Based on OPTN figures, deceased donor kidney allografts with KDPI of 0–20% (low KDPI) are expected to function for an average of 11.4 years post-KT; those with KDPI of 21–85% (medium KDPI), which constitute the majority (65%) of kidneys, are expected to function for about 9 years post-KT; and those with KDPI >85% (high KDPI) are expected to function for more than 5.6 years post-KT (OPTN 2015).

Donation After Cardiac Death (DCD) Donors

It is important to differentiate between controlled DCD, wherein death and organ recovery can be predictably controlled following the withdrawal

of life support, and uncontrolled DCD, wherein cardiac arrest is unplanned and the timing of other aspects of organ recovery is not controlled.

Appropriate DCD donors include patients who meet the following criteria:

(a) The patient has a nonrecoverable illness or injury that has caused neurologic devastation and/or other system failure resulting in ventilator dependency.
(b) The family in conjunction with the medical staff has decided to withdraw life-sustaining therapies. Decisions concerning the treatment and management of the patients must be made separately from discussions of organ donation.
(c) The assessment of DCD suitability (to include the prediction of when the patient's death will occur that will allow for the recovery and transplantation of organs) will be conducted in collaboration with the care team.
(d) No systemic illnesses or contraindications that preclude donation.
(e) Must be dependent on life-sustaining treatment so that stopping would lead predictably and quickly to death.
(f) Other conditions that may lead to consideration of DCD eligibility include: cognitively intact persons with long-term neurological or cardio-pulmonary problems that have left them ventilator dependent (e.g., end stage degenerative disease like amyotrophic lateral sclerosis, high spinal injuries, or severe end stage respiratory or cardiac diseases). Although not dying, these patients decide that their quality of life is unacceptable and request to remove life-sustaining support.

The procurement coordinator will partner with the care team to conduct additional screening and assist in coordinating an appropriately timed discussion with the patient's attorney-in-fact or legal next-of-kin, as applicable, about the option of organ, tissue, and eye donation. Consent for DCD donation is an independent and separate decision from the decision to forego life-sustaining therapies. A procurement coordinator in collaboration with the care team, following the family's decision to withdraw support, will present donation options to the family. If necessary, separate consent will be obtained for any other surgical procedures or medical interventions that are required prior to the determination of death.

Standard care and comfort measures may be administered prior to the withdrawal of support at the discretion of the attending physician or his/her designee. In addition, Heparin (300 units/kg) will be administered at this time. Removal of life-sustaining treatments shall be done consistent with patient/family decision-making and with respect for patient autonomy. Withdrawal of life-sustaining therapies occurs in the operating room, or in a prearranged location. Care and comfort measures are carried out by the attending physician and done in accordance with usual practice.

The surgical recovery team usually prepares and drapes in a sterile fashion. Once the body is prepared and all necessary recovery equipment and preservation solutions are in place, the surgical recovery team leaves the room, and withdrawal of life support ensues. The physician who is certifying death should not have any involvement in the transplant or procurement team. Death will be pronounced by the attending physician according to applicable laws. The attending physician will determine when and how ventilator will be weaned, request and administer the medication, and manage the weaning process. He will determine when death occurs. He will pronounce the patient using the following criteria: zero pulse pressure, absence of heart tones, and any of the following ECG findings: 2 min of ventricular fibrillation, 2 min of asystole (i.e., no complexes, agonal baseline drift only), or 2 min of electromechanical dissociation. A 5-min waiting period is required after the pronouncement of death prior to the surgical recovery of organs. If removal of life support does not lead to the death of the patient within 1 h of stopping ventilation or "if organ ischemia is prolonged" in the judgment of the transplant surgeon, organ procurement may be canceled and the patient returns to a predetermined room where comfort care measures will be maintained.

The selection criteria used for transplantation of kidneys from DCD or DBD donors are similar.

Kidney allografts from DCD donors have twice the risk of developing DGF compared to kidney allografts from DBD donors (Summers et al. 2010). Although kidneys from DCD donors may have increased risk of DGF, the graft survival rates are reported to be similar to kidneys from DBD donors (Locke et al. 2007; Bernat et al. 2006).

Specific Donor Issues and Considerations

HBsAg, HBCAb+, HCV+ Donors

There is an increased interest in transplanting organs formerly considered marginal or undesirable. Reports from kidney transplantation from hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (HBcAb) positive donors suggest that patient and graft outcomes were not worse and there was no evidence of symptomatic hepatitis in the recipients (Mahboobi et al. 2012). HBV vaccination prior to transplant, with target hepatitis B surface antibody (HBsAb) titers >10 IU/L, has been demonstrated to be protective for renal recipients of HBcAb+ donors (Pilmore and Gane 2012). In a series of 356 KT recipients from HBcAb-positive donors, none of the recipients acquired HBsAg positivity, but four out of ten vaccinated patients sero-converted from HBcAb-negative to HBcAb-positive, without any clinical or biochemical signs of hepatitis (De Feo et al. 2006).

Transplanting an HBsAg-positive allograft into an HBsAg-negative recipient carries a significant risk of infection. Although the presence of preexisting acquired immunity after vaccination or after previous HBV infection should protect the recipient from primary de novo HBV infection, most transplant centers do not transplant kidneys from HBsAg-positive donors, and in most countries these donors can be transplanted only in matched HBsAg-positive recipients.

Although there are limited data regarding the HBV transmission risk following transplantation of kidneys from HBsAg+ donors into hepatitis B-immune recipients, current literature suggests that the risk of chronic infection in the recipient can be prevented by using antiviral agents or by boosting protective HBsAb levels. Transplantation of kidneys from HBsAG+ donors without HBV viremia to HBsAG-recipients with HBsAb titer above 100 mIU/mL provides excellent graft and patient survivals and without evidence of HBV transmission (Chancharoenthana et al. 2014).

While the prevalence of hepatitis C (HCV) infection in hemodialysis patients is declining in western countries due to advanced screening of blood and blood products, prevalence remains high in developing countries. Overall, prevalence of HCV in hemodialysis patients is greater than in the general population and those patients have a 25% increased risk of mortality on dialysis compared to the general dialysis population (Kalantar-Zadeh et al. 2007).

Studies have shown that HCV+ patients undergoing KT, despite a worse posttransplant outcome compared with HCV-patients, have better outcomes than those HCV+ patients remaining on the waiting list (Kucirka et al. 2012). These patients do experience more complications post-transplant, such as progressive liver disease, new-onset diabetes, and HCV-associated nephropathies. Of note, most mortality in these recipients is not liver-related, but the severity of HCV liver disease before KT is a key determinant of risk for liver-related mortality post-KT (Carbone et al. 2013).

Despite these complications, HCV infection should not be considered a contraindication to KT. However, only patients without cirrhosis or with early stages of cirrhosis are candidates. In regards to the use of HCV-antibody positive donor kidneys, transplantation should be restricted to HCV+ recipients as it is associated with a reduced time waiting for a graft and does not affect post-KT outcomes. Additionally, the use of direct acting antiviral agents (DAA) is both effective and safe after KT and will hopefully decrease the number of HCV+ donors in addition to decreasing the number of HCV+ patients on the waiting list (Coilly and Samuel 2016).

PHS High-Risk Donors

The Public Health Service (PHS) guidelines designate organ donors as "high risk" if they meet any of the criteria for high-risk behaviors that present an increased chance of human immunodeficiency virus (HIV) transmission. This is intended to alert and protect transplant candidates from the risks of infection, because even negative antibody testing of potential donors does not entirely eliminate the possibility of disease transmission due to the window period between infection and sero-conversion. The actual risk of false-negative disease transmission is likely very low. Although limited by a voluntary reporting system, current estimates suggest the combined risk of transmission of HIV, hepatitis B or hepatitis C from a sero-negative donor is less than 1% (Duan et al. 2010). Furthermore, studies have shown that utilizing nucleic acid amplification testing during the screening process can further reduce the risk of disease transmission, though the cost-benefit remains uncertain. An informed consent of transplant recipients is recommended by ethicists and required by Organ Procurement and Transplantation Network (OPTN) policy. Specific mechanisms of disclosure and informed consent are left up to each transplant center, and a study on this matter has demonstrated that significant within- and between-center variation exists in disclosure practices.

Donors on ECMO

Extra-corporeal membrane oxygenation (ECMO) has been commonly used to treat patients with overwhelming cardiac and respiratory failure. Still, not all patients on ECMO survive and that creates a new group of potential organ donors. However, the outcomes and function of kidneys procured from those donor need to be evaluated. Several studies have looked at that outcome and concluded that DBD kidneys procured from donors who were on ECMO perform similarly to kidneys from donors who were not on ECMO with regard to delayed graft function (DGF), 1-year graft survival, and function (Carter et al. 2014). Based on the current available data, kidneys from donors who were on ECMO should be utilized to increase the donor pool. More data will be emerging as more ECMO donors are being evaluated and accepted for donation.

Conclusion

Currently, organs from DBD donors still remain as the most common source of organs for transplantation. However, successful outcomes following transplantation have created a shortage of available organs for transplantation. Consequently, many transplant centers and organ procurement organizations have adopted methods to increase the donor pool, notably the use of organs from DCD, ECD, HBV and HCV positive, PHS high-risk donors, and donors on ECMO. Although kidney allografts from DCD donors have twice the risk of developing DGF, the graft survival rates are reported to be similar to kidneys from DBD donors. Current knowledge derived from single center and registry studies have shown that transplantation of kidney allografts from hepatitis B virus (HBV) and hepatitis C virus (HCV) positive donors remains controversial, but seems to be safe in the long term. Likewise, the actual risk of disease transmission from PHS high-risk donors has been reported to be very low. Finally, DBD kidneys procured from donors on ECMO have similar DGF rate, 1-year graft survival rate, and allograft function, compared to kidneys from donors who were not on ECMO, and therefore, should be utilized to increase the donor pool.

Cross-References

- ▶ Infection in Kidney Transplantation
- ▶ Living Donor Evaluation and Selection
- ▶ Organ Procurement Organization and New Kidney Allocation

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Organ Preservation, Preparation, and Procurement Surgery in Kidney Transplantation

Christina Jacovides and Warren Maley

Contents

Abstract

Optimizing kidney retrieval and preservation are essential to ensure that high-quality organs are available for transplantation to an ever-growing population of patients waiting for them. Key components of the retrieval process include the clear establishment of brain death in the donor (for donations after brain death), the complete evaluation of donor criteria to ensure targeting of organs to appropriate recipient populations, careful operative recovery to optimize technical surgical success of the organs, and the judicious use of preservation techniques to maximize graft survival.

Keywords

Brain death · Donor selection · Hepatitis C · Hepatitis B · Operative recovery · Kidney preservation · University of Wisconsin (UW) solution · Histidine-tryptophan-ketoglutarate (HTK) solution · Static cold preservation (SCP) · Hypothermic machine perfusion (HMP) · Normothermic machine preservation

Introduction

The majority of organ donors in the United States are donors after brain death (DBD). In these donors, the goal of retrieval efforts is to minimize

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the time it takes for the kidneys to go from warm and normally perfused to cold and asanguinous. The majority of the preservation of the organs is provided by the cold temperature, which restricts metabolic activity by inhibiting enzymatic function via cold-induced conformational changes of the active sites of metabolically important enzymes. Further inhibition of ischemic or preservation injury is provided by preservation solution, either in the setting of static cold preservation or machine preservation. Restricting graft injury during kidney retrieval and preservation is key to achieving optimal graft and ultimately recipient survival.

Brain Death

Most deaths result from etiologies which prevent organ donation, such as malignancy or heart disease that leads to cardiac arrest without resuscitation (Murphy et al. 2017). Few patients arrive at the hospital in a state of brain injury which will lead to brain death and the potential for organ donation. This highlights a large reason for the short supply of organs for transplantation in relation to the large volume of patients awaiting transplantation. Injury to the brain via trauma, hemorrhage, or anoxia leads to brain swelling and the development of what could be referred to as an intracranial compartment syndrome (Stocchetti and Maas 2014). Cerebral perfusion pressure is defined as the mean arterial pressure minus the intracranial pressure. Restriction of venous flow by rising intracranial pressure eventually blocks venous outflow, resulting in rapid development of a situation wherein the intracranial pressure rises to equal mean arterial pressure and cerebral perfusion pressure drops to zero (Stocchetti and Maas 2014). Brain death is defined as the complete and irreversible loss of all brain and brainstem function, essentially the death of all neuronal tissue superior to the foramen magnum.

Documenting the diagnosis of brain death requires certain prerequisites (Greer et al. 2016; Spinello 2015; Zuckier and Kolano 2008). The patient's system must be free of intoxicating or confounding substances which either they ingested as part of the process of becoming brain injured or which they were given as part of their medical care (e.g., anesthetic or paralyzing drugs for intubation or sedation). Metabolically, the patient's physiologic state must be sufficient to permit neuronal activity (if present) to be manifest on physical examination. Severe metabolic derangement may prevent the detection of persistent neurologic function. The patient to be examined must also be roughly normothermic, as hypothermia during cardiac arrest may preserve brain function, which may normalize after resumption of circulation and rewarming. Once these prerequisites are met, testing for the diagnosis of brain death can commence.

The minimum standards of testing are set by state law, but each medical institution may set parameters which can be more stringent than state law dictates. Most states require two clinical exams documenting the absence of all brain and brainstem function. The tests must be performed by two different physicians and separated by a period of time (usually 6 h). An apnea test demonstrating a lack of ventilatory effort in response to a $pCO_2 > 60$ mmHg or a 20 mmHg rise in the partial pressure of CO_2 above baseline is typically performed as part of the second clinical exam (Spinello 2015). Ancillary testing, such as electroencephalography (EEG) monitoring or documentation of a lack of cerebral blood flow, may be required by the individual hospital but is not generally mandatory under state law. A nuclear blood flow scan performed in two projections is the most common ancillary test performed. On such a scan, the absence of intracranial blood flow via the internal carotid in the lateral projection and the presence of flow to the facial structures via the external carotid support a diagnosis of brain death. Computed tomography angiography (CTA) has also been evaluated as an alternative to nuclear blood flow scans for its greater ease of performance. CTA may in fact be more sensitive than nuclear imaging, although the clinical significance of this increased sensitivity is unclear and nuclear testing remains the standard ancillary test for brain death evaluation (Berenguer et al. 2010).

Brain dead donors thus enter the operating room with a signed death certificate. It is vitally important for both the families of the donors and the operating room staff, many of whom may never have been involved in organ donation before, to understand this fact (Shah et al. 2015).

Donor Selection

Multiple aspects of donor history and laboratory findings must be examined to assess whether a particular brain dead individual will be a satisfactory kidney donor.

A first-order approximation of donor kidney suitability for transplantation and risk of graft loss can be obtained from the Kidney Donor Profile Index (KDPI) (KDPI Calculator – OPTN n.d.). The index is a score from 1% to 100%. The higher the score is, the greater the risk of graft loss. The reference population for the KDPI is all organ donors in the United States from whom a kidney was recovered during the prior calendar year. The KDPI is calculated by first determining the Kidney Donor Risk Index (KDRI). Only donor factors are utilized to generate the KDRI. Ten donor variables including age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C virus status, and donation after circulatory death status are assessed. The KDRI is then scaled to the reference population and a mapping table used to generate the KDPI. The KDRI only has a c-statistic of 0.60, making it a moderate predictor of donor risk (Rao et al. 2009). A full discussion of the many donor and recipient factors used to determine whether or not to utilize a particular donor kidney is beyond the scope of this chapter and hopefully will be further elucidated in other chapters within this volume.

Infectious considerations also play an important role in the assessment of potential donors. Serologic and nucleic acid testing (NAT) may determine to whom the kidneys can be directed. Prior to listing, potential kidney recipients should be educated about possible scenarios involving conceivable infectious transmissions. Specific consent is required prior to listing for both hepatitis C and hepatitis B core antibody waiting lists with the Organ Procurement and Transplantation Network (OPTN). Recipients should also be educated about their ability to elect to hear about donors who, despite negative serology and NAT, are deemed at increased risk for potential transmission of HIV according to Public Health Service criteria. Such donors are being encountered with increasing frequency given the near-epidemic proportions of heroin overdoses occurring throughout the United States (Goldberg et al. 2016; Hart et al. 2017). At the time of transplantation, moreover, recipients should be appraised of potential infectious risks of the specific donor under consideration as part of the surgical consent process.

Kidneys from donors testing positive for hepatitis C by antibody or NAT are currently distributed to recipients who are themselves hepatitis C positive by polymerase chain reaction testing. Hepatitis C positive recipients are transplanted at a more rapid rate than other patients awaiting renal transplantation (Scalea et al. 2015). With the increasingly widespread utilization of direct-acting antiviral therapy against hepatitis C in the dialysis population, fewer and fewer patients remain on the waiting list to receive hepatitis C positive kidneys. Care must be exercised to be certain that recipients cured of their hepatitis C infection by direct acting antivirals be removed from the hepatitis C accepting list as such individuals may be re-infected from the donor organ. Elimination of potential recipients who are themselves hepatitis C positive from the kidney waiting list and the tremendous effectiveness of current antiviral regimens have prompted some to test the feasibility of intentionally transplanting hepatitis C positive kidneys into hepatitis C negative recipients with planned postoperative antiviral treatment. One such preliminary study has met with good success – all recipients developed hepatitis C posttransplant, but all cleared the virus and had a sustained response to antiviral treatment (Goldberg et al. 2017).

Donors who were previously infected with hepatitis B but who have cleared the virus from their blood stream (as evidenced by hepatitis B core antibody positivity) can be utilized for

recipients who are themselves hepatitis B core antibody positive. Transplant into infection-naïve patients may be made safer by electing recipients who have been immunized against hepatitis B and formed surface antibody in adequate titer. Prevention of reactivation or infection of nonimmunized recipients can be markedly diminished by use of intravenous hepatitis B immune globulin and antiviral therapies (Pilmore and Gane 2012).

Numerous less common infectious and neoplastic diseases have been transmitted by transplantation. Any conditions which may be transmitted to the recipient must be communicated to the transplant center and the potential recipient prior to organ acceptance. These include any bacterial, viral, fungal, or parasitic infections in the donor, active or prior malignancies, etc. (Ison et al. 2009). Depending on the disease and its severity, the recipient team has a range of options, from foregoing transplantation to providing the recipient with a short course of therapy. Kidneys recovered from donors with serologic testing positive for syphilis, for example, should prompt treatment of the recipients for potential infection with a three-dose treatment course of penicillin.

Operative Recovery

Following the recovery surgeon's review of the brain death examinations, laboratory testing, confirmation of blood type, and serologic testing for potential sources of transmittable infectious illnesses, the organ recovery can commence. The brain dead donor is positioned supine with the arms tucked. Incision is made from sternal notch to pubis (even in the rare instances of kidney-only recovery, sternotomy facilitates exposure and final exsanguination of the donor at the end of the procedure). Multiple teams are frequently involved, typically with a different team for each of the various extra-renal organs. Upon opening the abdomen, the donor should be explored for evidence of infectious or neoplastic pathology. This process should continue throughout the retrieval procedure right up to the final closure of the skin. If the lungs are not recovered, they should be examined for potential malignancy by palpation, particularly as the age of the potential donor rises. Detection of masses, together with pre- or postretrieval frozen section, may prevent the transmission of a malignancy from the donor to the transplant recipient.

Isolation of the distal abdominal aorta just proximal to the common iliac bifurcation and control with two heavy tapes in preparation for aortic cannulation is done on entering the abdomen so that urgent flush and retrieval can be performed should the donor's heart arrest prior to exsanguination. Full mobilization of the right colon with Kocherization of the duodenum (the so-called Cattell-Braasch maneuver) exposes the entire vena cava and the surface of the right kidney. Likewise, the Mattox maneuver or left visceral rotation exposes the surface of the left kidney and provides access to the entire abdominal aorta. The right colon and entire small bowel up to the ligament of Treitz can be wrapped in a moist towel to better facilitate their retraction and the exposure of the vasculature. Mobilization of the kidneys themselves off of the posterior abdominal wall allows for better surface cooling when ice is packed into the abdomen during the cold-flushing of the organs. Excessively vigorous retraction during mobilization of the kidneys may lead to separation of the renal capsule from the parenchyma, particularly if this is done bluntly with the operator's hand. Exposure of the supraceliac aorta in the lower chest or through the diaphragmatic crura prepares for the isolation of the abdominal aorta and subsequent cold-flushing of the abdominal viscera once all surgical teams have performed the necessary dissection and assessment of their target organs for retrieval.

Following administration of diuretics (furosemide and mannitol) to promote urine flow prior to retrieval, heparinization is achieved at levels similar to that achieved for cardiopulmonary bypass. Typically, 300–400 units of heparin per kg is administered as a bolus. Following a circulation time of 3–5 min, the aorta is ligated above the bifurcation and cannulated in its distal-most segment with a large perfusion cannula. The inferior mesenteric vein is intubated as the flush inflow point for the portal vein. Once all of the teams are

prepared, the aorta is cross-clamped at or above the diaphragm, the patient is exsanguinated via an incision in the inferior portion of the right atrium, and the organs are flushed with the cold preservative solution. Topical cooling of the organs is also performed by placing sterile crushed saline ice around the abdominal organs to be retrieved. Once the donor's blood has been completely flushed from the organs and exchanged for the preservative solution, the organs are procured from the donor.

The organs are then retrieved according to their sensitivity to tolerate ischemia. Lungs and then the heart are removed from the thoracic cavity. The liver, small bowel, and pancreas are excised and moved to the back table for sterile packing in preparation for transport. The kidneys can then either be separated *in situ* or removed *en bloc* and divided on the back table. Separation of the two kidneys is facilitated by dividing the left renal vein at the cava. Leaving a small cuff of caval wall attached to the left renal vein greatly enhances the surgeon's ability to anastomose the vein in the recipient, given the greater strength of the caval tissue compared with the thin substance of the renal vein. The aorta is then bisected in the midline both anteriorly and posteriorly under direct vision to prevent injury to the orifices of the frequently multiple renal arteries. Final preparation of the kidneys, including possible extension of the right renal vein by creation of a caval conduit, is typically performed in the recipient operating room. Further flushing of the organs on the back table is dictated by the local organ procurement organization's standard practice.

Kidney Preservation

High quality kidney preservation is critical to ensure that a maximum number of organs with the least amount of damage possible are available for transplantation and that both graft and recipient survival is maximized. Key factors that contribute to the quality of the preservation (in addition to the donor criteria discussed above) include the cold ischemia time, the preservative solution used, and the method of preservation. Methods for assessing the quality of preservation include evaluation of short-term outcomes such as delayed graft function (DGF), which has been linked to increased risk of graft loss (Yarlagadda et al. 2009), and long-term outcomes such as overall graft and patient survival.

The kidney cold ischemia time is inversely related to graft survival, with significant decreases in graft survival in organs with greater than 18 h of cold ischemia time (Opelz and Döhler 2007). With a growing understanding of the importance of minimizing cold ischemia time has come a decrease in the fraction of transplanted organs that are subjected to extended cold ischemia times (Opelz and Döhler 2007).

Two major preservative solutions are utilized in the United States: University of Wisconsin (UW) solution or Viaspan (of which there are now several generic equivalents) and histidine-tryptophan-ketoglutarate (HTK) solution or Custodiol solution (Guibert et al. 2011). UW solution was proposed by Folkert Belzer as a preservative to prevent cell swelling and create an extracellular milieu similar to the constituents of the cytosol (Belzer et al. 1992; Hoffman et al. 1988; Kalayoglu et al. 1988). HTK was developed in Germany by Bretschneider as a cardioplegia solution (Bretschneider 1980; Preusse et al. 1981), eventually supplanting Euro-Collins as the standard preservative solution for kidney transplants in Europe (Opelz and Döhler 2007). Single-center data suggest equivalence (Klaus et al. 2007; Latchana et al. 2015) of HTK with UW solution in renal transplantation and some benefit from HTK in reducing biliary complications in liver transplantation (Mangus et al. 2008). However, registry data from the United Network for Organ Sharing (UNOS) database suggest that use of HTK is an independent risk factor for graft loss in deceased donor kidneys, particularly for grafts from extended criteria donors (ECDs), for grafts transplanted into African-American recipients (Stewart et al. 2009), and when preservation times exceed 24 h (Opelz and Döhler 2007).

The majority of procured kidneys are simply stored in the solution with which they were flushed in the donor. In the early history of kidney transplantation, it was postulated that continuous

perfusion of kidneys on a perfusion pump would improve preservation. Static cold preservation (SCP), however, which permits wider organ sharing and reduces up-front costs and material required for hypothermic machine perfusion (HMP), has supplanted the use of pumping in most organ procurement organizations. There has been recent renewed interest in the use of HMP, especially in expanding the use of ECD organs. This interest has been bolstered by several studies that have shown that HMP decreases the frequency of DGF (Deng et al. 2013; O'Callaghan et al. 2013; Wight et al. 2003) and improves the rate of decrease of serum creatinine posttransplant (O'Callaghan et al. 2013). HMP also may improve 1-year graft survival (Jochmans et al. 2010; Moers et al. 2009; Wight et al. 2003). Mixed results have been observed for the use of HMP with kidneys from donation after cardiac death donors (DCD), with some finding no differences in outcomes between HMP and SCP groups (Watson et al. 2010) and some demonstrating reduced DGF (Deng et al. 2013) and some demonstrating reduced DGF in HMP kidneys (Deng et al. 2013; Jochmans et al. 2010). There has been a steady increase in the utilization of HMP in all types of donors (standard criteria donation (SCD), ECD, and DCD) (Gill et al. 2014; Jochmans et al. 2015), although the highest percentages of use of HMP are seen in DCD donors with long cold ischemia times (Gill et al. 2014). Reductions in DGF and the need for postoperative dialysis may offset the cost of HMP and even make it cost-effective (Gómez et al. 2012; Groen et al. 2012; Jochmans et al. 2015).

Kidneys that undergo HMP demonstrate a progressive decline in vascular resistance over the first several hours of pumping (Jochmans et al. 2011). Increased resistance (Jochmans et al. 2011) and reduced perfusion flow index (PFI, e.g., flow divided by systolic pressure) (Sevinc et al. 2016) appear to be predictive of reduced graft survival, although the predictive value of each is low. Moreover, increased resistance appears to be an independent risk factor for DGF (Jochmans et al. 2011) and low PFI has been associated with decreased GFR (Sevinc et al. 2016). Timing of HMP may be of importance, especially in DCD donors, as long periods of cold ischemia time appear to blunt the positive benefits on DGF (Gill et al. 2014). There are no data suggesting that HMP can eliminate the negative effects of prolonged cold ischemic intervals. Thus, limited periods of HMP which do not significantly prolong the total cold ischemic interval would appear to be beneficial.

A number of investigators are currently studying the effects of oxygenated normothermic machine perfusion as a way to both improve preservation and potentially offer the possibility of "repair" of ischemically injured organs (Hosgood et al. 2015). These studies are as yet too preliminary to offer direction to clinical practice, although early clinical trials have shown significant reductions in DGF among ECD donors (Nicholson and Hosgood 2013). Efforts have also been made to use hypothermic and/or normothermic machine perfusion clinically in the transplantation of other organs, including liver and heart transplants, with the goal in all organs of expanding the donor pool and making possible the use of ECD organs that would otherwise not be able to be transplanted (Hameed et al. 2017; Macdonald et al. 2016; Schlegel et al. 2016).

Kidney retrieval and preservation should maximize the number of viable grafts available to be shared with patients waiting increasingly long intervals for transplantation. Every effort must be made to minimize ischemic insults to potential renal grafts which have already endured the negative effects of the donor's mode of demise and the further injurious brain dead state. Novel methods to improve organ preservation have been studied in animal models (including pharmacologic treatment and cellular therapies such as mesenchymal stem cells and regulatory T cells), although most of these methods have not yet been successfully translated to human clinical trials (Saat et al. 2016).

Conclusion

The number of patients on the renal transplant list far outstrips the number of potential donors, and patients continue to die from their renal disease prior to transplantation. As a result, there is an

ever-present need to expand the potential donor pool in transplantation. Refinement of techniques in preservation and recovery may significantly expand this pool and make transplantation possible, safer, and more effective for a broader range of transplant recipients.

Cross-References

- A History of Kidney Transplantation
- Donor Selection: Deceased Donor
- Ethical Issues in Organ Transplantation
- Organ Procurement Organization and New Kidney Allocation

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Recipient Kidney Transplantation Surgery

Cataldo Doria and Lauren Margetich

Contents

Abstract

After successful kidney transplantation, all recipients experience nearly a normal quality of life, and 75% of recipients return to work and gain independence and report an improved mental health and physical well-being. Potential recipients of kidney transplantation should be evaluated to determine their eligibility to be placed on the waitlist for a cadaveric kidney or for living donor kidney transplantation. Once a suitable donor becomes available, the recipient is prepared for kidney transplantation. The surgical technique of recipient kidney transplantation includes back table preparation of the kidney graft, and recipient kidney transplantation surgery. Back table preparation of the donor kidney provides adequate anastomoses for kidney recipient surgery and the surgical techniques are detailed in this chapter. The donor kidney is placed in the iliac fossa, due to its close proximity to the bladder and the iliac vessels. Numerous vascular anastomosis techniques during the surgery can be used and are selected based upon the surgeon's preferences; the various techniques are described in the chapter. Before closure, the kidney, renal vessels, and iliac vessels must be inspected for thrombosis and adequate blood flow.

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Kidney recipient · HLA-antibody · Back-table preparation · Surgical vascular anastomoses · Ureter reimplantation

Introduction

Four options are available for patients who require kidney replacement therapy, which include hemodialysis, chronic ambulatory peritoneal dialysis (CAPD), palliative care, or renal transplantation. Kidney transplant recipients enjoy an improved quality of life, a prolongation of life, and a more cost-effective method over dialysis (Flechner 2013). The surgical technique for renal transplantation has remained constant since its development in the 1950s and 1960s (Gruessner et al. 2014). As of the end of 2014, there were about 100,000 adult candidates on the waitlist for a kidney, and 14.7% of these patients have been waiting for over 5 years for a kidney transplant (Hart et al. 2016). In 2013, nearly 16,300 kidney transplants were performed with less than one-third transplanted from living donors (United States Renal Data System 2015). The demographics for kidney transplant recipients have stayed fairly constant for the last decade, with the exception of the percentage of the recipient's age increasing, see Table 1 (Hart et al. 2016).

Recipients of kidney transplantation have over a 90% 1-year survival rate after a kidney transplant from both living and cadaveric kidney donor. According to the United Network for Organ Sharing (UNOS) Scientific Renal Transplant Registry, graft failure rates have improved over the years with 5-year all-cause graft failure rates at 26.5% and 14.3% for deceased-donor and living donor transplants, respectively. From 2004 to 2014, there has been an increasing trend of deceased donation from less than 10,000 to about 12,500 and a decreasing trend of living donation from about 6,000 to nearly 5,000 (Hart et al. 2016). After a successful kidney transplantation, all recipients experience nearly a normal quality of life, and 75% of recipients return to work and gain independence and report an improved mental health and physical well-being (Shapiro et al. 1997). Studies show that the survival rate for a patient that has undergone a kidney transplant compared to dialysis is higher. According to the United States Renal Data System (USRDS), the annual death rate for transplant patients compared to patients on the waitlist undergoing dialysis was 3.8 versus 6.3 per 100 patient-years, respectively (Rossi and Klein 2016).

Table 1 Most recipients of a renal transplant are in their fifth–sixth decade. One of the biggest changes in demographical data is the increasing number of elderly recipients receiving kidney transplantations. However, older age can influence graft function and surgical outcome

Age	2004	2014
18–34	12.9	9.3
35–49	32.2	25.8
50–64	41.1	43.7
≥65	13.8	21.2

Potential Recipients

Potential recipients of kidney transplantation should be screened on the following studies listed in Table 2. These tests determine the eligibility of an individual to be placed on the waitlist for a deceased donor kidney or from a matched living donor kidney. Other tests can be added to the list, depending on the patient's health history.

The absolute contraindications for renal transplantations are: active infection, active malignancy, active substance abuse, reversible renal disease, and uncontrolled psychiatric disease; all other relative contraindications vary between transplant centers (Rossi and Klein 2016). Colon, prostate, and breast are the three most common cancers found in kidney recipients. Waiting times vary based on patient history on a case-by-case basis. Patients with history of cancer can have their medical record submitted to the Israel Penn Registry (https://ipittr.uc.edu) and the recommended waiting time is followed in most cases. Typical waiting times are either 2 or 5 years.

Modifiable risk factors vary by transplant centers and may postpone renal transplantation for

Table 2 TJUH potential kidney recipient work-up. All of these tests are to be repeated once a year. Exceptions include stress tests, pap smears, mammograms, and colonoscopy, as should be repeated based off the patient's history and US health guidelines. Blood type testing, as the ** indicates, must be repeated at two separate centers and/or on two separate days in order for the recipient to be placed on the waiting list. Bolded terms, CMV antibody, EKG, and Chest X-ray are to be repeated acutely preoperatively for the kidney transplant recipient

Potential kidney recipient work-up
Chemistry lab tests
Comprehensive metabolic panel
Lipid panel
Blood lab tests
Magnesium
Prothrombin time
PPT/partial thromboplastin time (activated)
CBC with Diff
Hepatitis A Ab
Hepatitis B core Ab
Hepatitis B surf Ab
Hepatitis B surf Ag
Hepatitis BE Ab
Hepatitis C Ab
RPR
Serum drug screen
Quantiferan Gold
Microbiology-HIV
HIV 1/2 Ab and Ag combo screen
Microbiology tests
Quantiferon MTB gold
CMV antibody IgM / IgG
Varicella IgG
Rubella IgG Ab
EBV Ab panel
Blood components and testing
Blood type check **
Antibody screen
Immunogenetics and tissue typing labs
HLA-ABC and DR typing
HLA cross-matching: T and B cell serological
Antibody screening: cytotoxic antibody screen (PRA)
Tests
EKG
Chest X-Ray
Renal ultrasound
Echocardiogram
Psychosocial Evaluation
Female pts: pap smear, mammogram, as per health guidelines
Patients > 50 years old: colonoscopy, persantine stress test
CT scan of abdomen and pelvis
Other: dependent on history of patient

potential recipients. Obesity has shown to delay graft function, decrease graft survival, increase cardiovascular mortality, and prolong hospitalization. Weight reduction to lower a BMI greater than 35 may be required before renal transplantation. Smoking accelerates the progression of atherosclerotic cardiovascular disease and can result in proteinuria, and therefore recipients must stop smoking prior to transplantation.

Major causes of death for transplant recipients include MI, Non-MI cardiac mortalities, CVA, septicemia, pulmonary complications, cancer malignancy, and withdrawal of treatment (Flechner 2013).

Non-renal disease high-risk factors for potential renal transplant recipients are older age, African American race, obesity, known psychiatric illness, and noncompliance. Survival of elderly patients post-transplant is largely due to careful selection and evaluation. Patients over 40–50 years old should regularly have echocardiography and patients over 50–55 years old should also have pharmacologic thallium studies. Dobutamine echocardiography may be used in place of pharmacologic thallium testing and echocardiography (Shapiro et al. 1997). For diabetic patients, a majority who cannot reach 70–80% of their maximum heart rate due to beta-blockers, autonomic neuropathy, and poor patient conditioning at the time of the study can give inadequate or false-negative thallium stress tests. Therefore, stress tests with or without thallium for diabetic patients show little predictive value. An angiography is recommended for all diabetic patients older than 45 years old; however, younger patients without a smoking history or without ST-T wave changes on ECG are advised to undergo a dipyridamole thallium stress test. Hypertensive African American patients, compared with reciprocal white patients, live longer on dialysis and have a worse allograft and patient survival rate post-transplant (Shapiro et al. 1997).

Diabetes is the predominate cause of renal failure and is present in more than one-third of kidney transplant patients. Two additional leading causes of renal failure leading to a kidney transplant include hypertension and glomerulonephritis.

Preoperative Evaluation

Immediately before the kidney recipient is taken to the operating room, the surgeon, nephrologist, and anesthesiologist meet with the patient. Serum potassium levels and volume status are evaluated. Potassium level not exceeding 5.0 mmol/L is needed for the patient to undergo surgery; a level of 6.0 mmol/L or greater requires the patient to undergo a preoperative dialysis. Refer to Table 3 for a list of potassium levels.

A CMV antibody, EKG, and Chest X-ray are ordered and reviewed for final evaluation before the recipient is taken to the OR. There are two types of cross-matches: virtual and flow cytometry. Virtual cross-matches compare the patient's HLA antibody profile with the potential donor's HLA antibody profile. Flow cytometry cross-matches allow for the detection of lower tier HLA antibodies and non-cytotoxic HLA antibodies. Repeat cross-matches usually do not delay transplantation. Every 2–4 weeks, the kidney recipient has his or her blood drawn either at the hospital or shipped to hospital till the donor presents. The blood sample will be tested quarterly and the other samples will be refrigerated and stored in case a potential donor is identified. All test results are sent to UNOS. Cross-matches are performed from the stored blood sample if deemed fresh enough, or a new sample will be taken while the recipient is waiting for the kidney donation. HLA cross-matching is used to determine the patient's Panel Reactive Antibody (PRA) level. The PRA measures the level of antibodies that could potentially compromise the transplant if the recipient has antibodies against the donor kidney. The lower the PRA level, the fewer antibodies and more compatible the recipient will be for the donor kidney; the higher the PRA level, the less compatible the recipient is for the donor kidney.

Table 3 Potassium levels are accessed before the patient receives his or her kidney transplantation. Levels between 5.0–6.0 mmol/L are up to the surgeon's discretion; for levels above 5.3 mmol/L a preoperative dialysis is recommended (Shapiro et al. 1997)

Potassium level	Action
≤5.0 mmol/L	Proceed to OR if all other tests are acceptable
5.1–5.3 mmol/L	Up to surgeon discretion, usually acceptable
5.3–6 mmol/L	Preoperative dialysis recommended
≥6.0 mmol/L	Preoperative dialysis

Back Table Preparation

The back table is located in a sterile field in the operating room where the kidney is cleaned and trimmed before transplantation. A one liter bag of crushed, frozen saline is placed in a shallow basin and covered with a clear sterile bag. The donor kidneys must have the excess muscle, connective tissue, and fat remove before transplantation. Ligation of vessels and vessel branches not leading to or from the kidney must also be performed prior to transplantation, as well as trimming the cuff of the aorta and vena cava to allow the vessels to be prepared for anastomosis with the recipient's vessels without difficulty. Excess donor vena cava may be used to extend the length of the shorter right renal vein to prevent kinking in the recipient, see Figs. 1 and 2. The excess donor inferior vena cava will be stapled or over sewn with 4-0 non-absorbable monofilament sutures. The extra lumbar veins are ligated off the donor inferior vena cava using 2-0 or 4-0 silk sutures (Ellison and Zollinger 2016).

The left renal vein is longer than the right renal vein, as the opposite is true for the arteries; the left renal artery is shorter than the right. The left renal vein has the following major branches: the suprarenal vein, inferior phrenic vein, lumbar vein(s), and testicular/ovarian vein (Netter 2014). These vessels from the kidney should be ligated using 2-0 permanent or 4-0 silk sutures (Ellison and Zollinger 2016; Shapiro et al. 1997). Branches off the renal artery and the right renal vein are less common; however, an adrenal artery may be present off the renal artery (Netter 2014).

In the case where multiple renal arteries supplying the kidney, reconstruction may be required, and use of 7-0 or 8-0 sutures are preferred. Vessel reconstructions that may be used include one or more of the following techniques: (1) creating an

end-to-end anastomosis (see Fig. 3), (2) implanting the transected polar artery into the main renal artery (see Fig. 4), and (3) shortening excess aorta between multiple renal artery cuffs (see Fig. 5) (Shapiro et al. 1997). Reconstruction occurs at the back table during preparation.

The venous system reconstruction can be more forgiving than the arterial system as long as the main renal vein remains undamaged and other venous branches can be ligated without serious damage.

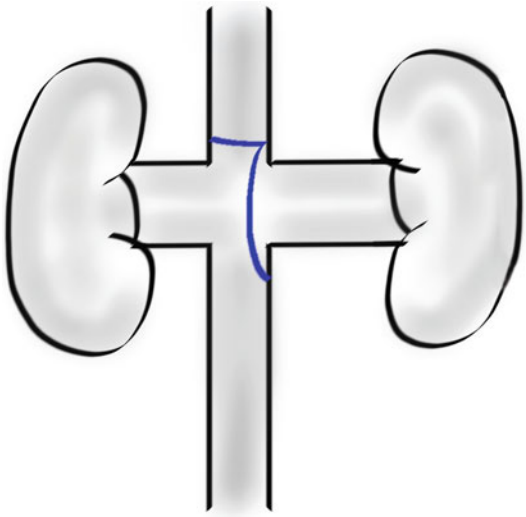

Fig. 1 Kidneys from deceased donors can use the donor's inferior vena cava to elongate the right renal vein. There are multiple techniques to achieve this elongation, this figure illustrates one technique, where the blue line indicates where the donor vena cava is to be cut

Peri-ureteral vessels and fat should be preserved on the ureter to prevent necrosis after transplantation; however, gonadal vessels should be removed. The ureter receives its blood supply from the renal branches, gonadal branches, branch of the aorta, and common iliac branches. Minor preparation at the back table is required for the ureter. Excess fat should be left on the kidney from the lower lobe to the hilum to ensure adequate blood supply for the ureter. All other excess fat can be removed from the donor kidney.

Procedure

The kidney recipient is brought to the operating room and positioned supine on the operating room table. The patient is placed under general anesthesia via endo-tracheal intubation, intermittent decompression devices are attached to both legs. A right or left internal jugular central venous line and right or left radial arterial line are placed. A 3-way Foley catheter is inserted with one port connected to Neosporin bladder irrigation bag and the other port to a sterile urine bag tubing. The bladder is distended by up to 200 mL of antibiotic solution and gravity and not by use of excess fluid as this could result in bladder rupture. Prior to the initial incision, the patient has his or her hair trimmed in the surgical field, then prepped with sterile Iodine or Chlorhexidine antiseptic solution and draped. Methylprednisolone IV and Thymoglobin IV immune-suppressive induction

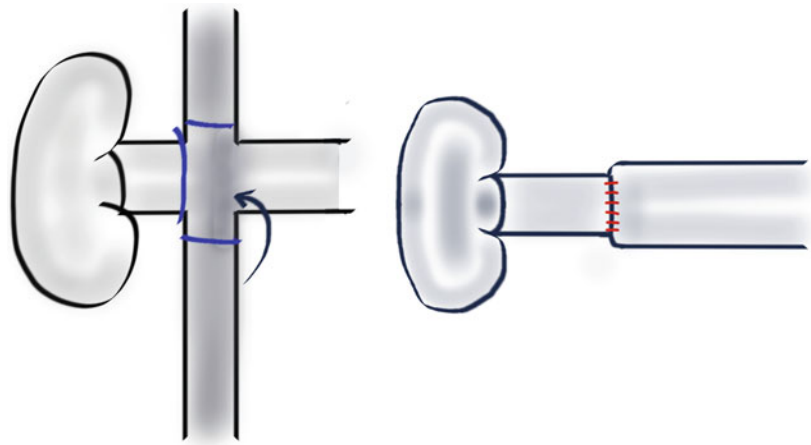

Fig. 2 An alternative technique than the one above for use of donor's inferior vena cava to elongate the right renal vein. The inferior vena cava should be cut and flipped to anastomose to the right renal vein. The blue indicates where the donor vena cava is to be cut and the red indicates the sutures

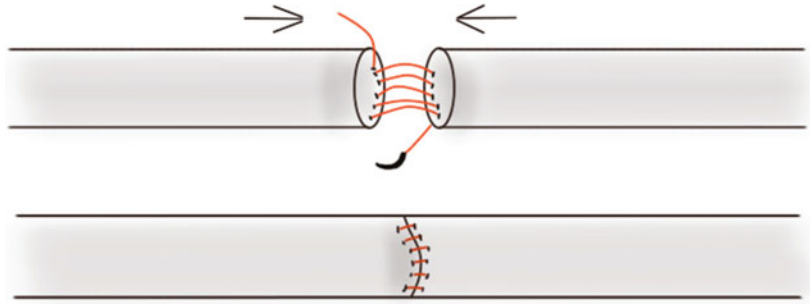

Fig. 3 End-to-end anastomosis. Vessel reconstruction can be accomplished via this technique where the two vessel ends are sutured together; this is a useful technique to elongate a vessel. As the arrows indicate bring the two vessels together when suturing

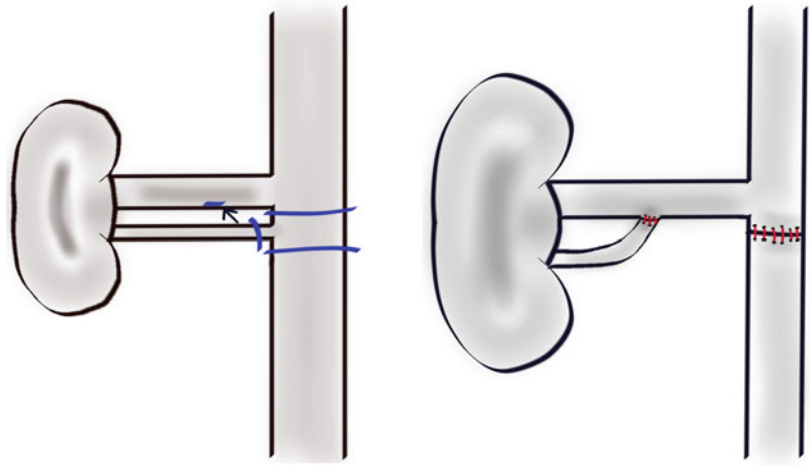

Fig. 4 When multiple arteries are supplying the kidney and are of different sizes, then the smaller one can be cut and attached to the larger main renal artery. This is a useful method to create one arterial cuff to attach to the external iliac artery. The blue indicates where to cut and the red indicates the sutures

therapy and antibiotic prophylaxis are also given to the patient at this time.

The recipient's two failed kidneys are not removed during the transplantation surgery. The donor kidney is placed in the iliac fossa, due to its close proximity to the bladder and the iliac vessels. The right iliac fossa has higher contact to the iliac vessels compared to the left side and its distance from the colon is advantageous since the colon can cause possible complications. The right iliac fossa is best utilized for left donor kidneys as well because the kidney will be flipped 180° to bring the ureter pointing toward the bladder. The renal pelvis is positioned against the peritoneal sac to allow the renal pedicle to be readily accessible intraperitoneally if a ureteral reimplantation is needed postoperatively. If a prior kidney graft from a previous renal transplant in the right iliac fossa has failed, the left iliac fossa may be used (Gruessner et al. 2014). The incision is frequently a curving right (or left) lower abdominal incision, which extends from midline, 1 cm above the pubic symphysis to a point 2–4 cm superomedial to the anterior superior iliac spine or a paramedian incision with a hockey-stick deviation to the midline inferiorly (see Fig. 6). Scalpel Blade is used for the incision and bovie cauterization is used to dissect to the external oblique fascia. The internal oblique and transversalis fascia are then opened lateral to the rectus abdominis muscle and exposed using the Bookwalter retractor.

Either incision should provide enough exposure to view the external iliac vessels. Mobilizing the peritoneum medially and ligation and division

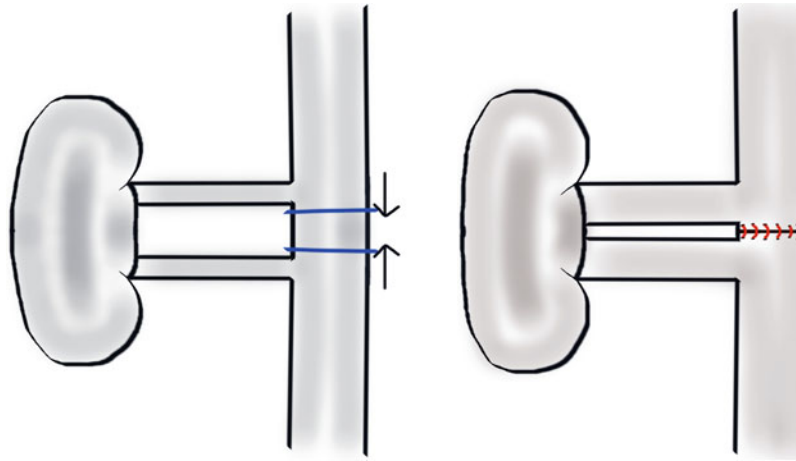

Fig. 5 When multiple renal arteries are supplying the kidney, the excess aorta can be cut, indicated by the blue, and sutured together. This is an alternative technique to make one aortic cuff to anastomose to the external iliac artery

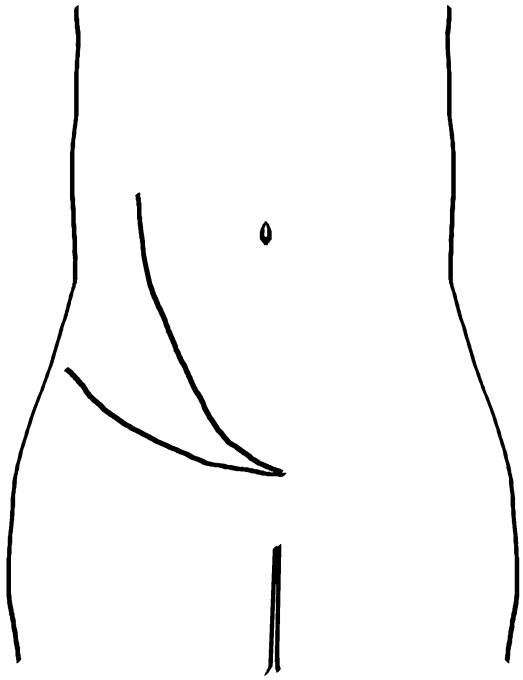

Fig. 6 Illustrations of surgical incision options. Both extend from 1 cm above the pubic symphysis to either (1) 2–4 cm superiorly and medially to the anterior superior iliac spine or (2) hockey-stick deviation extending just lateral to the rectus muscle and 1–2 cm medial to the anterior superior iliac spine (Kirk 2014)

of the inferior epigastric vessels expose the external iliac artery and vein. In females, ligation and division of the round ligament and inferior epigastric vessels should be performed using 2-0 silk ties. In males, the spermatic cord is displaced inferomedially and looped with a penrose drain. Bleeding is controlled by electrocautery. Further exposure of the vessels is based on surgeon preference. For teaching purposes, most of the external iliac artery and vein are mobilized to maximize exposure. The lymphatic vessels, which pass anterior to the external iliac artery, are ligated with Silk 2-0 ligatures and divided to reduce the risk of postoperative lymph leakage and lymphocele formation (Ellison and Zollinger 2016). The genitofemoral nerve, found lateral to the artery, should be identified and secured. Clamps or vessel loops should be placed proximal and distal to the intended anastomotic site on the external iliac vessels.

Numerous vascular anastomosis techniques exist and are selected based upon the surgeon's preference, these include: (i) the two-stitch technique (see Fig. 7), (ii) the four-stitch technique (see Fig. 8), (iii) suturing the back wall from within (see Fig. 9), and (iv) the single-stitch technique (see Fig. 10). In the procedure, the renal vein is anastomosed end-to-side to the external iliac vein first to minimize arterial clamp time, using 5-0 or 6-0 polypropylene sutures. Next, the renal artery is sutured to the external iliac artery end-to-side or end-to-end anastomosed to the internal iliac artery. Pediatric angle potts clamps are placed proximally and distally on the external iliac artery and an arteriotomy is made on the anterolateral aspect of the artery using a blade #11, and then, enlarged with a circular artery punch or with

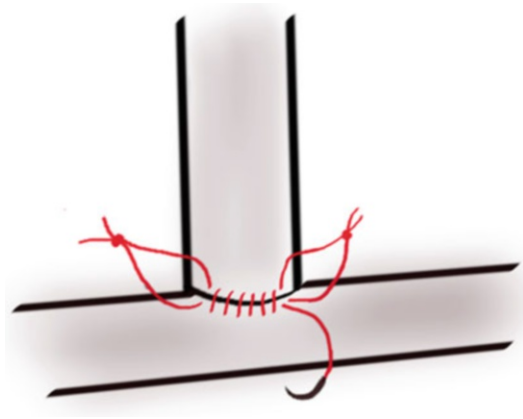

Fig. 7 The simplest approach to vascular anastomosis is shown above and represents an end-to-side anastomosis. It consists of placing two sutures at each corner of the vessel, 180° apart from each other. The two vessels are then anastomosed with a continuous suture on each side of the vessel

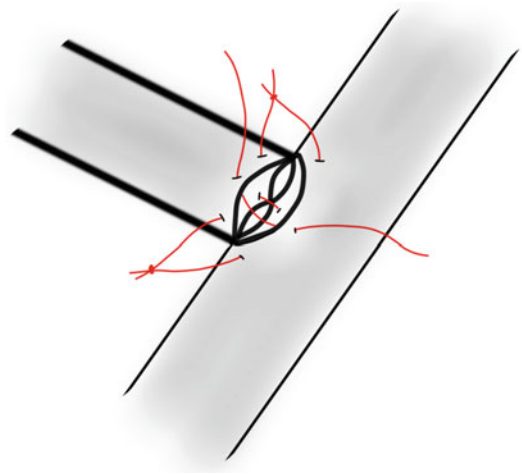

Fig. 8 Depicted above is an alternative to the two-stitch suture for vascular anastomosis. Similar in approach to the two-stitch suture, this approach consists of four sutures 90° apart and successive closing sutures between the four sutures

scissors. The anastomoses are completed using the four-stitch technique as described above (see Fig. 8), using 5-0 or 6-0 polypropylene sutures on each side. After the anastomoses are completed, the venous and arterial clamps are released.

In cases of multiple retransplantations, scarring may make exposure to the external or internal iliac vessels difficult, and in these circumstances the common iliac vessels or intra-adbdominal inferior vena cava and aorta anastomoses can be used. Living donor kidneys will not have extra cuffs from the aorta or the vena cava, and although the vascular anastomoses to the external iliac vessels are possible, end-to-end anastomosis to the internal iliac artery is sometimes preferred.

A newly reperfused kidney should turn pink and start producing clear urine immediately. During transplant, various methods may be used to keep the donor kidney cold and viable. One method involves wrapping the kidney in double sponges filled with crushed ice and secured with surgical clips during the anastomoses. During the renal vein anastomosis, administer continuous 1 g/kg IV mannitol and continuous 1 mg/kg IV Lasix over 30 min. Mannitol decreases damage from free radicals and Lasix induces diuresis. The suture lines are examined closely after the kidney has been reperfused. Small bleeding on the surface of the kidney should be controlled and stopped by electrocautery.

The most common ureteral reimplantation is extravesical. First, 2–3 cm of the detrusor muscle at the bladder dome is incised to expose the bladder wall mucosa, which is opened approximately 1 cm using an electro-cautery and a blade #11. The ureter is cut at an angle and anastomosed to the bladder mucosa with running or interrupted 6-0 polyglyconate sutures. The distal portion of the ureter is then sutured to the muscle layer of the bladder using interrupted sutures to limit reflux; this technique is called the Lich-Gregoir Technique and is depicted in Fig. 11 (Mobley and Pelletier 2010). The submucosal tunnel, adapted from techniques to correct reflux in children, is when the bladder muscle layer is the corrected length as to not constrict the ureter. An alternative technique is to telescope the ureter using a single suture rather than suturing the ureter into the bladder mucosa (Shapiro et al. 1997). Other methods of ureter reimplantation include: (i) ureteroureterostomy over a double J stent, (ii) extravesical single-stitch (U-stitch) technique, and (iii) the Politano-leadbetter transvesical ureteroneocystostomy (Mobley and Pelletier 2010).

When using a double J stent, insert the stent into the ureter with one end in the renal pelvis and the other end inserted in the bladder's incision. Close the ureter around the bladder opening using

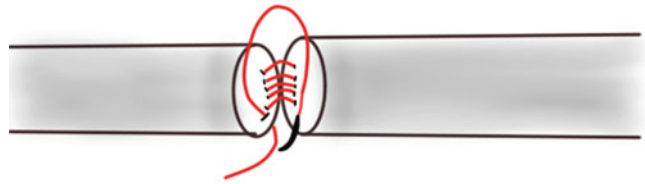

Fig. 9 Alternative technique to anastomose two vessels by starting to suture the back wall of the vessels together from within the vessel. This details a single continuous stitch. This intravascular technique may be used when the vessels location is difficult to reach from behind to complete one of the other extravascular techniques

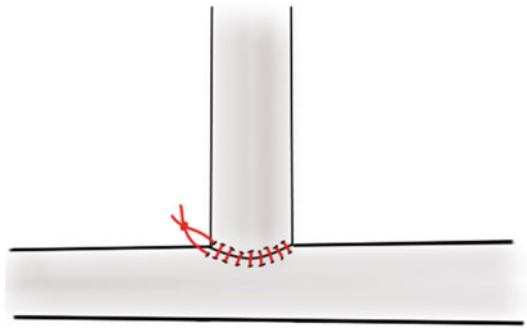

Fig. 10 The one stitch technique involves one suture followed by a continuous suture anastomosing the two vessels. This can be more difficult than the alternative techniques since there is only one stitch

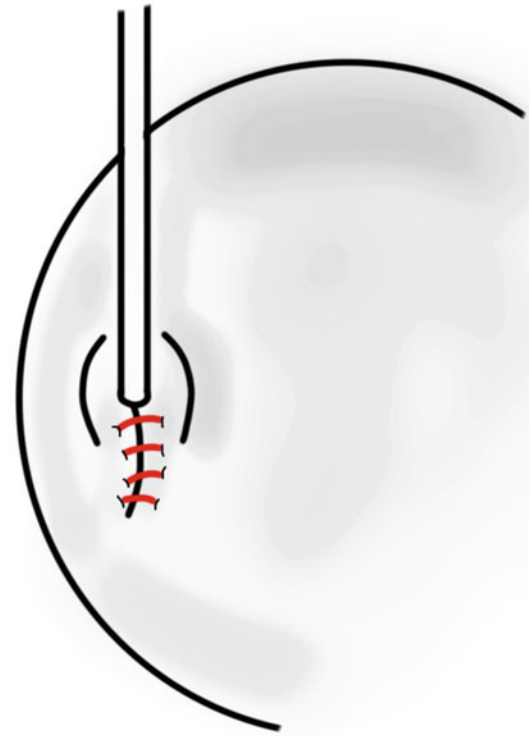

Fig. 11 Reimplantation of the donor's ureter into the recipient's bladder. This suturing technique creates a submucosal tunnel from the bladder's muscular wall to reduce reflux

PDS 6-0 running sutures after bladder irrigation was emptied. Using interrupted vicryl 3-0 sutures, form a tunnel over the anastomosis from the detrusor muscles.

An extravesical single-stitch (U-stitch) technique (see Fig. 12) involves one absorbable stitch at the distal tip of the ureter. In this technique, the ureter is secured to the bladder wall after the ureter is inserted into the bladder and the single stitch at the end of the ureter is stitched through the bladder wall.

The Politano-leadbetter technique (see Fig. 13) is an intravesical technique, whereby the ureter is sutured to the bladder mucosa from the inside of the bladder through a large cystotomy. This technique uses two cystotomies, first cranially to access the inferior bladder and second to insert and suture the ureter to the bladder mucosa. After the donor ureter is sutured to bladder mucosa, the detrusor muscle is closed over to create a tunnel similar to the Lich-Gregoir technique described above.

If the donor kidney has a double ureter, the surgeon may choose to implant the ureters separately or anastomose the ureters together to suture into the bladder as a single unit. Either option is acceptable provided the blood supply is not disrupted (Shapiro et al. 1997).

Before closure, the kidney, renal vessels, and iliac vessels must be inspected for thrombosis and adequate blood flow. The anesthesia team should evaluate the urine output. If the kidney perfusion and urine output appears adequate, abdominal closure can start. The iliac fossa should be irrigated with antibiotic solution before closure, and then all

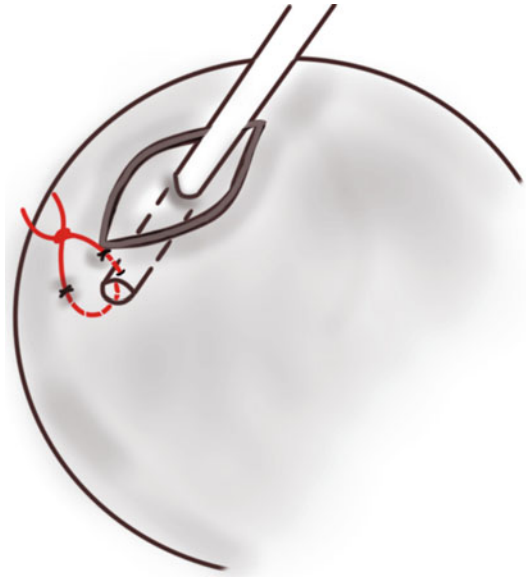

Fig. 12 An extravesical single-stitch (U-stitch) technique, also known as Taguchi extravesical technique. A single stitch is placed on the distal end of the ureter and secured to the bladder wall from within

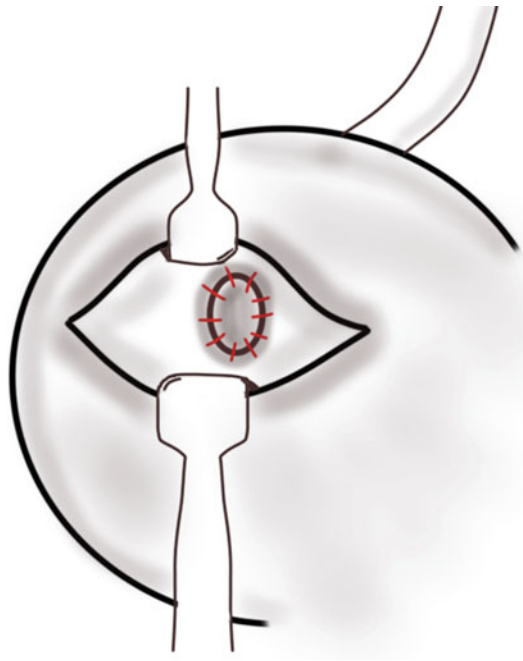

Fig. 13 The Politano-leadbetter technique is intravesicular. The retractors secure the view of the inside of the bladder to allow the donor ureter to be sutured from within the bladder

retractor blades removed. The abdominal wound should be closed in two layers by realigning the fascial and muscular layers using Nylon or Polydioxanone 1 running sutures; the subcutaneous tissues are closed using figure of 8 vicryl 3-0 sutures. The dermal layer is closed with staples or 4-0 polydecaprone absorbable subcuticular sutures.

Cross-References

- ▶ Immunology of Kidney Transplantation
- ▶ Kidney Transplantation: Surgical Complications
- ▶ Recipient Selection for Kidney Transplantation

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Live Donor Nephrectomy

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Contents

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Abstract

Live donor nephrectomy, first performed in the 1950s, has gained popularity over the last 30 years as an alternative option to increase organ availability for patients awaiting renal transplant. However, until the advent of laparoscopic donor nephrectomy in the mid-1990s, much controversy persisted over the ethical nature of living donor nephrectomy with respect to donor morbidity. Despite dramatically decreased morbidity and mortality for live donors today, controversy still persists over the long-term implications of live kidney donation, with clearly demonstrated disparities in outcomes based on various demographic factors. This chapter details the history of living kidney donation, followed by the risks and specific complications unique to living kidney donation and the effects of various demographic characteristics on these complications. Finally, a detailed review of operative technique and variations is also offered.

Keywords

Living donor · Living donation · Live donor · Donor nephrectomy · Laparoscopic donor nephrectomy · Kidney transplant · Renal transplant · Nephrectomy · Kidney donation

Introduction

History and Evolution of Live Donor Nephrectomy

Joseph Murray and the First Successful Living Donor Nephrectomy

The first living donor kidney transplant in humans was performed in 1952 by a French surgeon named René Küss within a team led by nephrologist Jean Hamburger. His recipient patient was a 16-year-old boy with a solitary kidney who had suffered a traumatic injury, requiring emergent nephrectomy. He underwent renal transplant, with his mother serving as the living kidney donor. Unfortunately, the graft failed after just 3 weeks due to rejection (Legendre and Kreis 2010). Two years later, an American surgeon named Joseph Murray performed the first successful human kidney transplant in Boston. The recipient underwent live donor renal transplant from his monozygotic twin, eliminating the need for immunosuppression, for which there existed only a limited understanding at the time. The recipient lived a total of 8 years post-transplant and his graft eventually failed due to recurrent disease. Murray was awarded the Nobel Prize for Medicine in 1990 for his accomplishments (Hatzinger et al. 2016).

Progress with Deceased Donor Kidney Transplant

Following Murray's success, much of the progress over the coming years would focus on deceased donor kidney transplantation. Immunosuppressive therapies were optimized to avoid rejection in non-HLA identical patients, while minimizing potential adverse effects such as infection, overwhelming sepsis, and malignancy. With improvements in immunosuppressive techniques, the number of successful deceased donor transplants grew at a rapid pace.

Organ Shortage and Emergence of Live Kidney Donation as a Solution

Kidney transplantation has been clearly demonstrated to be the optimal treatment for patients with end-stage renal disease (ESRD), with transplant recipients showing dramatic improvements in survival over patients remaining on dialysis (Rodrigue et al. 2013). However, organ availability

has proven to be the major obstacle to expanding the application of kidney transplantation for these patients, and expanding the donor pool became imperative as waiting times increased for potential recipients. As a paired organ, the kidney is ideally suited for living donation, and living kidney donation emerged as a potentially promising solution to organ shortage (Segev et al. 2010).

Since 1954, it is estimated that over half-a-million living kidney donations have been performed worldwide, with the majority of those coming from the United States and India (Reese et al. 2015). The introduction of laparoscopic donor nephrectomy in 1995 helped reduce much of the morbidity associated with open donor nephrectomy, contributing to the dramatic rise in living kidney donations over the coming years. In the United States, the number of living donor kidney transplants has increased from 1817 in 1988 to 6388 in 2009. This number has since dropped and plateaued, with 5632 procedures performed in 2016 as seen in Fig. 1 (Rodrigue et al. 2013; OPTN 2017a; Branger and Samuel 2015).

Benefits of Living Kidney Donation

Over the last 30 years, the benefits of living kidney donation for recipients have been clearly demonstrated in the literature. Given that time on dialysis is the strongest predictor of patient outcomes, and that decreased time on dialysis leads to longer graft survival, live donor kidney transplant (LDKT) outcomes have proven to be superior to deceased donor kidney transplant (DDKT) in patients with ESRD (Rodrigue et al. 2013; Meier-Kriesche and Kaplan 2002; Meier-Kriesche et al. 2004). Compared to DDKT, LDKT has been associated with decreased time on wait lists, prolonged kidney allograft survival, increased life-years after transplant, decreased length of stay, and decreased hospital costs (Terasaki et al. 1995; Smith et al. 2000; Mange et al. 2001; Meier-Kriesche and Kaplan 2002; Abecasis et al. 2008; Axelrod et al. 2010). With LDKT, patients are able to get off the transplant list sooner and to stay off of the list for a longer duration. This combination of effects has had a profound impact on containing the number of patients on the list at any given time (Rocca et al. 1995).

Considerations for Donors and the Rise of Laparoscopic Donor Nephrectomy

Despite the dramatic improvements in outcomes offered by LDKT to the recipient, there remained a major ethical debate regarding its implementation due to the morbidity, mortality, and costs incurred by living donors. In 1995, the University of Wisconsin published their 28-year experience with live donor open nephrectomy that included 681 patients from 1971 to 1991. At the time, there were 4000–5000 cadaveric donors per year, a

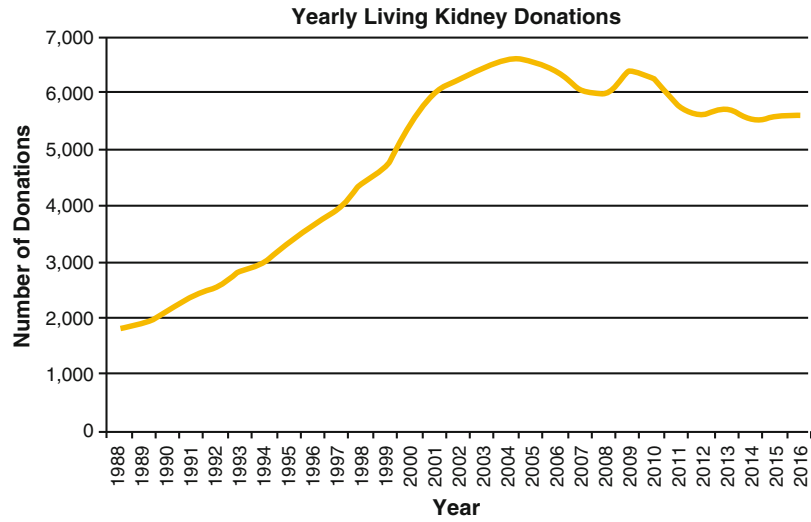

Fig. 1 Annual number of living kidney donations in the United States from 1988 to 2016

number that had remained relatively static despite the growing waiting list of recipients. They reported a 17% complication rate for donors, including pneumothorax, UTI, wound infection, pneumonia, and pulmonary embolus; only one death was reported, which was due to pulmonary embolism. In their experience, the live donor program accounted for one-third of the institution's volume. They placed great emphasis on the need to encourage living donations as a source of potential kidneys for the 27,000 listed potential recipients at the time (D'Alessandro et al. 1995).

The introduction of laparoscopic donor nephrectomy, first reported by Ratner et al. in 1995, offered the ideal solution to a number of logistical and financial disincentives to live donation (Ratner et al. 1995). Laparoscopic donor nephrectomy afforded less postoperative pain, shorter hospital length of stay, and postoperative convalescence for the donor patient with equivalent recipient outcomes compared to open donor nephrectomy. Overall complication rates were initially similar for laparoscopic versus open donation but were shown to decrease with improved surgeon experience (Ratner et al. 1997; Lee et al. 2000). Over the following decade, laparoscopy became the preferred technique at many institutions, leading to increased access to living donation for recipients (Flowers et al. 1997; London et al. 1999; Odland et al. 1999; Ratner et al. 1999).

Evaluation of Potential Living Donors

Requirements for Living Kidney Donation

According to the current guidelines from the Organ Procurement and Transplantation Network (OPTN), potential living donors must undergo extensive evaluation prior to donation. All living donors should undergo psychosocial evaluation to evaluate for any psychological and mental health issues, as well as to evaluate for behaviors that could place the donor at higher risk of poor psychosocial outcomes. Donors are also assessed for potential sources of coercion or external pressure for donation and must express understanding of the potential financial implications of living donation. The OPTN also requires the designation of an Independent Living Donor Advocate (ILDA). The ILDA is a third-party person or team that is completely independent from the recipient's medical team and whose main responsibility is to advocate for the living donor. Finally, an extensive medical evaluation must be completed and a thorough informed consent must be obtained prior to proceeding with living donation. The relative and absolute contraindications to living kidney donation vary based on guidelines and institutional protocols (Delmonico et al. 2005; Abramowicz et al. 2015; OPTN 2017b; Joint Working Party of the British Transplantation Society 2011). The evaluation of potential living donors is discussed in detail in chapter ▶ "Living Donor Evaluation and Selection."

Risks Associated with Living Kidney Donation

As the only operative intervention to offer no direct benefit to the patient, living donation offers a very unique set of challenges and ethical considerations not to be taken lightly. In addition to a rigorous preoperative workup, the operating surgeon should have an extensive discussion of the risks inherent to surgery as a whole, and also those specific to donor nephrectomy. Fortunately, an extensive amount of data has become available over the last 20–30 years regarding specific donor outcomes. However, these have often been limited by their retrospective nature, high loss to follow-up, and short time-frames. Furthermore, many of these studies have drawn comparisons to the general population, which is often not as thoroughly screened as the healthy living donor population (Ommen et al. 2006; Lentine and Segev 2013). Given these limitations and the many inherent biases to these studies, as well as their sometimes discordant results, it can be very difficult to convey the exact risks to patients. Further adding to the complexity of this discussion is the fact that many of the complications inherent to donor

nephrectomy can be dramatically influenced by various demographic and socioeconomic factors (Lentine and Segev 2013). For this reason, the discussion with patients should be highly individualized.

Morbidity and Mortality

Morbidity

The overall complication rate for donor nephrectomy is estimated to be between 7.9% and 22%, with major complications comprising an estimated 2.5–6% (Mjøen et al. 2009; Lentine and Patel 2012; Schold et al. 2013; Lentine et al. 2016). Lentine et al. found a 16.8% overall complication rate in the perioperative period, which consisted of 4.4% gastrointestinal complications, 3.0% bleeding, 2.5% respiratory, and 2.4% surgical/anesthesia related injuries, with all other complications comprising 6.6% (Lentine and Patel 2012). Schold et al. reported a 7.9% complication rate using data from the National Inpatient Sample (NIS) and the Scientific Registry of Transplant Recipients (SRTR) database, incorporating data for patients operated on between 1998 and 2010. The authors reported the proportion of significant complications as gastrointestinal (32%), respiratory (14%), puncture or laceration (11%), infectious (9%), and cardiac (4%). Importantly, the overall incidence of these complications declined over the study period (Schold et al. 2013). In a similar study evaluating hospital readmission, Schold et al. estimated 1- and 3-year rehospitalization rates to be 5% and 11%, respectively, with 21% of cases related to pregnancy, 14% digestive, 13% injuries and "poisoning," 8% genitourinary, 6% psychiatric, 5% musculoskeletal, 5% neoplastic, and 4% diseases of the circulatory system (Schold et al. 2014). Common factors associated with increased risk of complications are African American race (OR 1.26), male sex (OR 1.37), hypertension (OR 3.35), obesity (OR 1.55), hematologic conditions (OR 2.78), psychiatric conditions (OR 1.45), and robotic nephrectomy (OR 2.07) (Schold et al. 2013; Schold et al. 2014; Lentine et al. 2016). High-volume centers infer a protective effect, with centers performing more than 50 live donor nephrectomies per year showing decreased complications with an odds ratio of 0.55 (Lentine et al. 2016).

Mortality

Overall mortality after donor nephrectomy is extremely low. Evaluating a total of 80,347 live donors from the OPTN registry from 1994 to 2009, Segev et al. estimated a 90-day mortality of 3.1 per 10,000 live donors, which did not change over the 15-year observational period (Segev et al. 2010). Comparing 2028 Canadian living donors to healthy nondonors, Garg et al. estimated the risk of death and major cardiovascular complications to be lower in donors (2.8 vs. 4.1 per 1000 person years) over a median follow-up period of 6.5 years (Garg et al. 2010). Although most studies appear to indicate no increase in mortality with living kidney donation, there exists one study that demonstrates diminished survival in live donors (Mjøen et al. 2014).

Chronic Kidney Disease, End-Stage Renal Disease, and Other Renal Complications

Chronic Kidney Disease and End-Stage Renal Disease

Living kidney donation may elevate the risk of developing ESRD. However, despite the fact that half of the donor functional renal mass is removed at the time of donation, ESRD remains a very rare outcome in living donors. Intuitively, glomerular filtration rate (GFR) drops by approximately 50% immediately post-donation. However, because of compensatory hypertrophy and hyperfiltration by the remaining native kidney, GFR usually returns to approximately 70% within 3 months post-donation (Garg et al. 2006; Rook et al. 2006; Barri et al. 2010; Kasiske et al. 2013).

Although early literature seems to suggest equal risk for ESRD in living donors as compared to the general population (Cherikh et al. 2011), these early studies were limited by the fact that the general population was likely less healthy than the

heavily screened donors deemed suitable candidates for donation. More recently, Mjoen et al. found an incidence of ESRD of 0.47% in a population of Norwegian kidney donors with a median follow-up of 15.1 years (Mjøen et al. 2014). Muzaale et al., using a cohort of 96,217 live kidney donors in the US, found an incidence of ESRD of 0.31% at 15 years post-donation compared to 0.03% in matched healthy nondonors (Muzaale et al. 2014).

Evaluating Potential Donors for Renal Disease

Given the risk of developing ESRD, evaluating potential donors for baseline renal function remains an essential part of donor evaluation. Traditionally, most transplant centers in the United States only offered living donation to patients with a GFR above 80 mL/min/1.73 m^2, as this threshold was classically associated with lower graft failure rates in recipients (Nordén et al. 2000). Various methods of measuring GFR have been described and vary depending on institutional preferences. 24-hour urine collection is the most commonly used method, although measurement of urinary clearance of various tracers such as Iohexol, technetium 99mdiethylenetriaminepentaacetic acid (Tc99-DTPA), and other renally cleared tracers are gaining popularity (Mandelbrot et al. 2007). Recently, use of contrast-based imaging as a dual modality for anatomic evaluation and GFR measurement has been proposed, as some contrast media are strictly renally cleared, making them ideal for GFR measurement. However, this method of evaluating renal function has yet to gain a stronghold in donor evaluation (Rocca et al. 2012). In addition to GFR, potential donors are also screened for proteinuria, as this is a well-established risk factor for the development of CKD (Iseki et al. 2003) and is often considered a contraindication to donation. Hematuria is also evaluated since this may be an indication of underlying renal disease in potential donors.

Other Potential Kidney-Related Complications

Living kidney donors may develop other sequelae of decreased renal function, including a rise in serum uric acid and parathyroid hormone (Rossi et al. 2014; Kasiske et al. 2015). Lam et al. estimated an incidence of gout of 1.4% at 8 years post-donation, making living kidney donors 1.6 times more likely to develop gout post-donation than healthy matched nondonors (Lam et al. 2015b). African American race, older age, and male sex confer an increased risk of developing gout post-donation (Lam et al. 2015b; Lam et al. 2015a). Despite the rise in PTH and fibroblast growth factor-23 (FGF23) post-donation (Moody et al. 2016), Garg et al. demonstrated no increased fracture risk in donors as compared to healthy nondonors at a median of 6.6 years follow-up (Garg et al. 2012b).

Race and the Risk of ESRD Post-Donation

African American donors are at highest risk (four times higher) of developing ESRD post-donation, a trend that is consistent with that seen in the general population as compared to white individuals (Muzaale et al. 2014; Lentine et al. 2010). Gibney et al. found that 48% of living donors who require listing for kidney transplant themselves are African American (Gibney et al. 2007). Using a calculation tool to project estimated long-term incidence of ESRD based on various population characteristics, Grams et al. found a 15-year risk projection of 0.24% and 0.15% in black male and female donors respectively, compared to 0.06% and 0.04% in their Caucasian counterparts (Grams et al. 2016). In addition, black donors are also at increased risk of developing various renal complications including CKD, proteinuria, nephrotic syndrome, and other renal diagnoses (Lentine et al. 2015). Although these disparities can be partially explained by population-based socioeconomic factors and access to care, new evidence appears to suggest that genetic factors may play a role in this racial disparity (Gibney et al. 2007).

Hypertension

In addition to an increase in risk for ESRD, a rise in blood pressure is also a well-known complication of living donor nephrectomy. Boudville et al. estimated an increase in mean arterial blood pressure of 5 mmHg above the rise in blood pressure

expected by aging alone at 5–10 years post-donation (Boudville et al. 2006). Garg et al. found that at a mean follow-up of 6 years, 16.3% of donors developed a new diagnosis of hypertension compared to only 11.9% in a cohort of healthy adults (Garg et al. 2008). It is known that every 10 mmHg increase in systolic blood pressure and every 5 mmHg increase in diastolic BP confers a 1.5-fold increase in death from cardiovascular disease (Lewingston et al. 2002), theoretically increasing the risk of cardiovascular complications in the living donor population. Despite this fact, there has been no demonstrated increase in the incidence of cardiovascular disease in donors (Garg et al. 2012a; Moody et al. 2016).

Pathogenesis of Hypertension Post-Nephrectomy

Although the mechanism is poorly understood, it is thought that the compensatory hyperfiltration in the remaining native kidney and resultant alterations in renal blood flow and subsequent effects on the renin-angiotensin-aldosterone system may contribute to this increase in blood pressure. Additionally, more stringent long-term follow-up in donors is thought to potentially explain the increased incidence of the diagnosis of hypertension as compared to healthy matched controls (Garg et al. 2008).

Race and the Risk of Hypertension Post-Nephrectomy

Special mention should be made to specific patient populations with regard to hypertension post-kidney donation. Race has strong implications in the development of post-donation hypertension, with African American donors at highest risk of hypertension (Lentine et al. 2014b). Lentine et al. estimated an increased risk of 52% and 36% among African American and Hispanic donors respectively, as compared to white donors (Lentine et al. 2010). Similarly, African Americans are 37% more likely to be on antihypertensive medications post-donation (Lentine et al. 2014a). African American donors on Medicare are 2.4 times more likely to develop malignant hypertension than Caucasian Medicare donors (Lentine et al. 2014b). In a study of 103 African American donors, Doshi et al. showed a 40.8% incidence of hypertension post-donation compared to 17.9% in controls matched for age, sex, race, and baseline blood pressure at a median follow-up of 4.4 years, suggesting an unusually strong susceptibility to development of hypertension in African American donors (Doshi et al. 2013).

Pregnancy and Hypertension-Related Complications Post-Nephrectomy

Gender also has an impact on hypertensive complications after living donor nephrectomy. In comparing pre-donation pregnancies to post-donation pregnancies, Ibrahim et al. found an incidence of 5.7% gestational hypertension post-donation compared to 0.6% pre-donation, and an incidence of pre-eclampsia of 5.5% post-donation versus 0.8% pre-donation (Ibrahim et al. 2009). A similar study by Reisaeter et al. found an incidence of gestational hypertension of 5.7% post-donation compared to 2.6% pre-donation (Reisaeter et al. 2009). Both studies were limited by the simple fact that aging in women increases the risk of such pregnancy-related complications. In a retrospective cohort study matching 85 pregnant women post-donation to healthy matched controls, Garg et al. found an incidence of gestational hypertension or pre-eclampsia of 11% in donors compared to 5% in healthy controls. Importantly, there was no significant difference in maternal or fetal outcomes between the two groups (Garg et al. 2015).

Demographics and Other Considerations in Potential Live Donors

The increased risks associated with African American race and pregnancy have been clearly demonstrated, as detailed above. In discussing potential donation, other factors should be considered prior to proceeding.

Obesity

Another patient population deserving of particular mention is the obese population. Obesity is a well-established risk factor for the development of

hypertension and diabetes, both of which are known to contribute to the development of end-stage renal disease. Additionally, obesity itself has been shown to be a risk factor for the development of proteinuria and/or renal insufficiency after nephrectomy (Praga et al. 2000; Iseki et al. 2004; Kincaid-Smith 2004). It is this concern that has led transplant centers to adopt various cutoffs for BMI as part of the consideration for donation. In a 2007 survey of United States Transplant Centers, 10% of centers used a BMI of 30 kg/m^2 as a threshold for consideration, while 52% used a BMI of 35 kg/m^2, and 20% use a BMI of 40 kg/m^2 as a cutoff. Six percent considered BMI with other cardiovascular risks, and 12% had no cutoff at all (Mandelbrot et al. 2007).

Donor Age

Another important consideration in assessing potential donors is patient age. There has been growing concern in the use of young donors for living donation, as the lifetime risk of developing ESRD in young healthy patients has been estimated to be 2–3% in whites and 7% in African Americans. Currently, most guidelines will decline patients with risk factors for ESRD. Given that younger donors who are bound to develop ESRD in the future have not had the time necessary to exhibit many of those risk factors, the argument has been made that too much comfort is taken in using young "healthy" donors, as a significant number are destined to develop ESRD. Comparatively, older donors without risk factors for ESRD are themselves much less likely to develop ESRD, having lived many years without developing risk factors (Steiner 2010). It is in this young healthy donor population that better estimations of risk for donation based on variables such as race, gender, and socioeconomic status should be established more clearly.

Choosing the Right Versus Left Kidney

As elicited in the OPTN guidelines for evaluation of potential donors, detailed imaging should be obtained to assess donor kidneys for lesions that could prevent donation, such as masses, cysts, or stones. Imaging can also help determine which kidney to procure. CT and MRI are the most commonly used modalities to delineate renal and renovascular anatomy. Traditionally, the left kidney has been preferred for retrieval given its longer renal vein. Furthermore, procurement of the left kidney has been associated with decreased operative times and easier reimplantation in the recipient. However, recent literature suggests that with the advent of laparoscopy, using the right kidney leads to equivalent outcomes for both recipient and donor (Buell et al. 2001; Mandal et al. 2001; Bettschart et al. 2003; Kay et al. 2006; Narita et al. 2006; Hoda et al. 2010; Hoda et al. 2011). These findings were corroborated in a recent meta-analysis by Wang et al. (2015). Although retrieval of the left kidney is generally preferred, there should be no hesitation to use the right kidney, especially in cases where the left kidney may have questionable lesions or multiple arteries.

Surgical Technique

The laparoscopic donor nephrectomy has become the mainstay of living donation. While there is variability regarding the peculiarities of the operation at individual institutions, the operation proceeds in generally the same fashion. One major distinction that exists is hand-assisted vs. pure laparoscopic donor nephrectomy. Herein, the various techniques available for donor nephrectomy are described, beginning with a description of pure laparoscopic donor nephrectomy, followed by the hand-assisted approach. Finally, two other minimally invasive techniques have been described, namely the single incision laparoscopic surgery (SILS), and the robotic donor nephrectomy, which will be discussed below.

Pure Laparoscopic Approach

The technique of pure laparoscopic donor nephrectomy has been well described by Fabrizio et al., and the operative description for the left-sided

approach that follows, as well as the associated figures are taken directly from the authors' description with permission (Fabrizio et al. 1999).

Technique for Left-Sided Pure Laparoscopic Approach

After induction of general anesthesia, broad spectrum antibiotics are administered, a foley catheter is placed along with an orogastric tube to be removed at the completion of the case. Adequate intravenous (IV) access is mandatory and generally consists of two large bore peripheral IV lines. The patient is then positioned in a modified flank position, placing the torso in a 45° lateral decubitus position. To enhance exposure to the lower abdominal midline, the hips are rolled slightly backward. Next, the arms are brought to chest level in a semiflexed position and the patient is secured to the operating table with straps. Care is taken to appropriately pad the axilla and lower extremities, and the patient is appropriately flexed, as seen in Fig. 2. Next, proper configuration of the operating room is ensured, as noted in Fig. 3.

The authors prefer to establish pneumoperitoneum using a Veress needle, insufflating to a pressure of 15 mmHg. Using an optical trocar and zero-degree lens, the first 10–12 mm port is placed lateral to the rectus muscle midway between the umbilicus and iliac crest. Under direct visualization, the second 10/12 mm port is then placed at the umbilicus, followed by a 5 mm port, which is placed midline between the umbilicus and xyphoid process, as illustrated in Fig. 2. A 30-degree scope is used for the remainder of the procedure, using the umbilical port as the camera port during the dissection.

Starting at the splenic flexure, atraumatic graspers placed in the 5 mm port and a Ligasure device (Valleylab, Boulder, CO) placed in the lateral port are used to reflect the ipsilateral colon medially to the level of the sigmoid by incising the lateral peritoneal reflection (Fig. 4). To allow the colon to be completely reflected medially, the phrenocolic ligaments at the level of the splenic flexure must be completely divided. Next, the spleen is retracted superiorly by dividing the lienorenal and splenocolic ligaments at the inferior border of the spleen. Finally, the colorenal ligaments are divided, allowing full exposure of Gerota's fascia. Next, the kidney is freed within Gerota's fascia (Fig. 5). Care must be taken to avoid inadvertent injury to the kidney, spleen, and renal hilum, as this is one of the most challenging portions of the procedure. Electrocautery can be used, maintaining caution to avoid any thermal injury to the colon.

Next, attention is turned to mobilization of the kidney. The border of the upper pole is identified, making sure not to confuse lobulations for the border of the upper pole. Once properly identified, gentle elevation of the upper pole with a blunt instrument will facilitate dissection (Fig. 5). Regardless of the instrument chosen for retraction (a 5 mm irrigation/suction device is preferred), retraction should be performed under direct visualization, advancing the tip of the retractor along the sidewall so as to prevent inadvertent injury to the surrounding organs. The upper pole

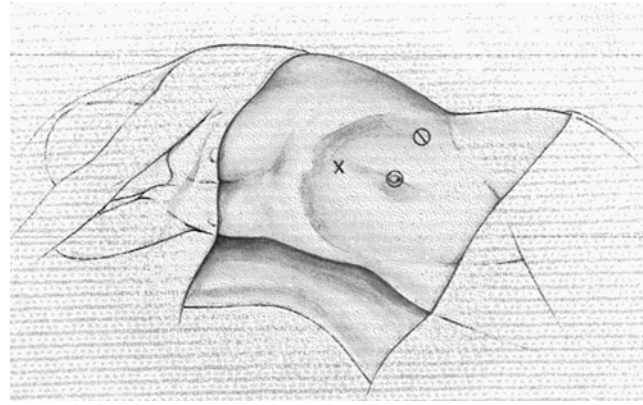

Fig. 2 Patient position. The arms are flexed and the hips rolled slightly posterior. The three port placements, 10/12 mm, 10/12 mm, and 5 mm, are noted

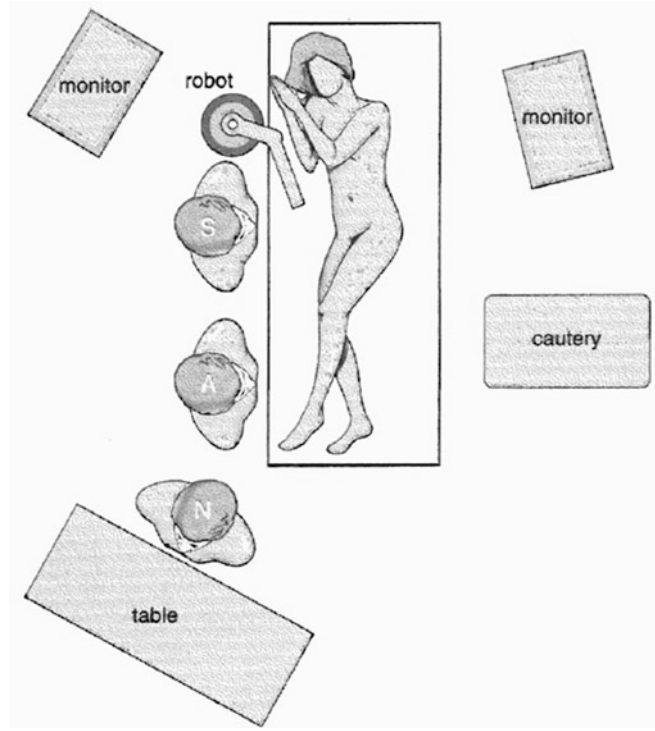

Fig. 3 Operating room configuration

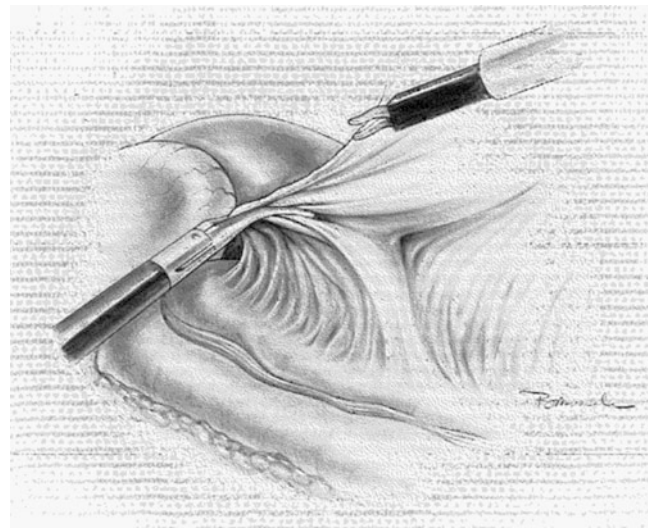

Fig. 4 Incising the lateral peritoneal reflection (line of Toldt) and reflecting the colon medially

attachments are completely freed using both blunt and sharp dissection, and attention is then turned to exposing the hilar vessels.

Incising Gerota's fascia medially should bring the renal vein into view. Next, the renal vein is completely isolated by freeing it from its adventitial attachments. The gonadal, adrenal, and lumbar veins are identified and are cauterized and divided using the Ligasure device (Valleylab, Boulder, CO) (Fig. 6). To facilitate exposure of

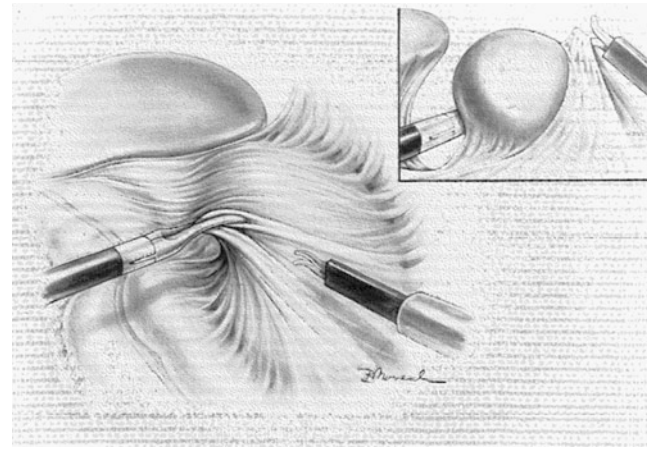

Fig. 5 Division of the colorenal ligament and exposure of Gerota's fascia. Inset illustrates the upper pole of the kidney which has been freed and elevated

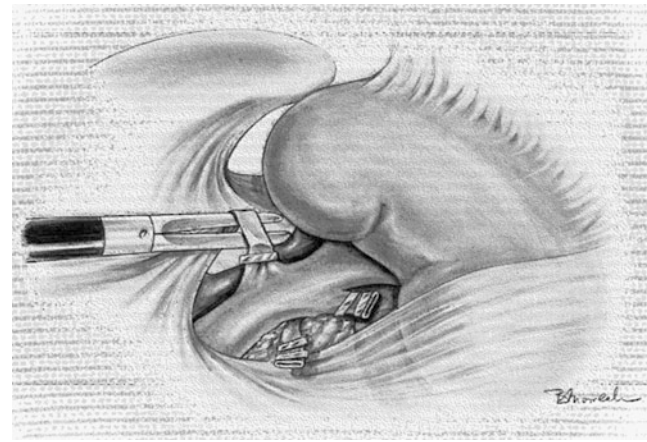

Fig. 6 After exposing the renal vein, the gonadal and adrenal veins are clipped and divided. Note the forceps under the adrenal vein

the lumbar veins, the renal vein can be lifted with gentle traction. Care should be taken during dissection of the renal vein, as overly aggressive dissection can result in bleeding from the adrenal vessels, which can be difficult to control. The renal artery, lying posterior to the renal vein can now be identified and isolated via sharp dissection to separate it from its extensive surrounding lymphatics. Here, the Ligasure device (Valleylab, Boulder, CO) is carefully employed to prevent lymphatic leakage. Lastly, the renal artery is completely dissected to its origin at the aorta to ensure maximal exposure, and the patient is administered 20 mg of IV furosemide.

To prevent torsion of the kidney on its dissected vascular pedicle, the lateral, posterior, and inferior attachments are left intact, forming a three-point fixation. Next, the ureteral dissection is commenced inferiorly. The gonadal vein is identified inferior to the renal hilum and a plane is created medially toward the side wall. The dissection then proceeds inferiorly and the gonadal vessels are transected at the level of the pelvis using the Ligasure device (Valleylab, Boulder, CO). Dissection of the ureter continues inferiorly to the level of the left iliac vessels, where it is divided using a clip applier and laparoscopic scissors (Fig. 7). Next, the inferior and lateral attachments to the kidney are divided. Lastly, the posterior attachments are divided using gentle elevation of the upper pole, leaving the kidney attached only by its vascular pedicle.

Prior to dividing the vascular pedicle, a 5 cm Pfannenstiel incision is made, extending the incision through fascia, without violating peritoneum

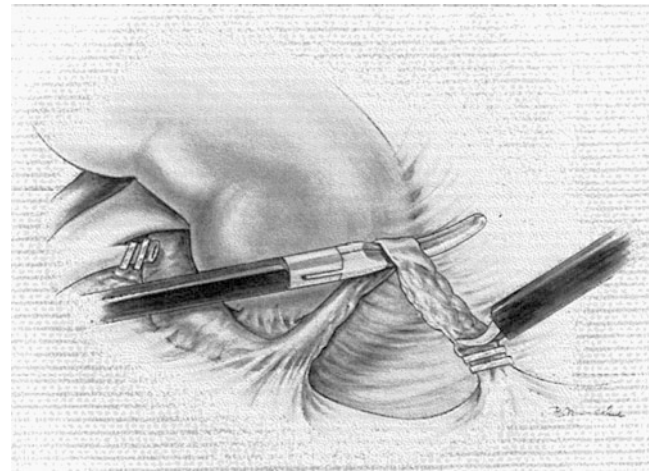

Fig. 7 Division of the ureter at the level of the iliac vessels. Care is taken to preserve abundant periureteric tissue

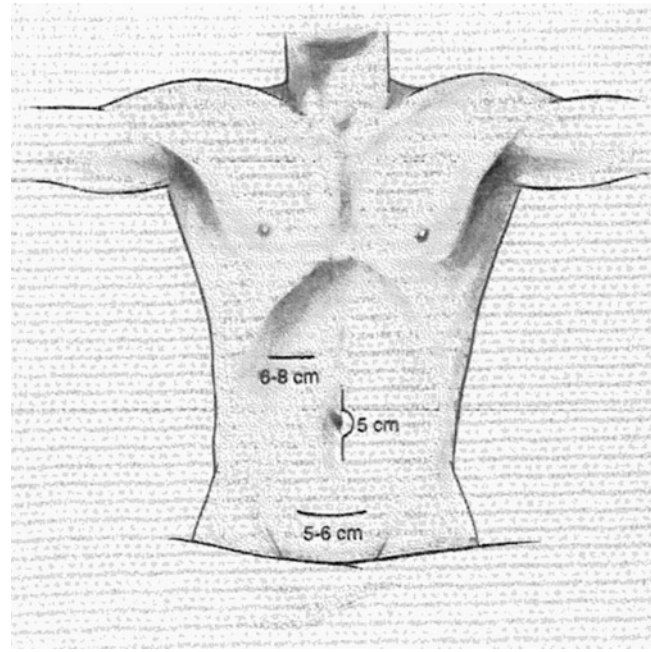

Fig. 8 The locations of the three possible incisions employed for delivery of the kidney. The right upper quadrant, midline, and Pfannenstiel incisions are noted

(Fig. 8). A purse-string suture is then placed into the peritoneum and a trocar is inserted to allow insertion and deployment of an Endocatch bag (Covidien, Mansfield, MA). The camera is then moved to the left lower quadrant port, and an Endo GIA stapler (Covidien, Mansfield, MA) is used to divide the renal artery first (Fig. 9), followed by the renal vein (Fig. 10). The free kidney is then reflected over the spleen by grasping the perirenal adipose tissue and is placed into a 15 mm Endocatch bag (Covidien, Mansfield, MA) inserted through the Pfannensteil incision. Up to this point, care should be taken to avoid violating the peritoneum so as to maintain pneumoperitoneum. Once the kidney is secured in the Endocatch bag (Covidien, Mansfield, MA), the peritoneum is incised and the kidney is delivered through the Pfannensteil incision, making

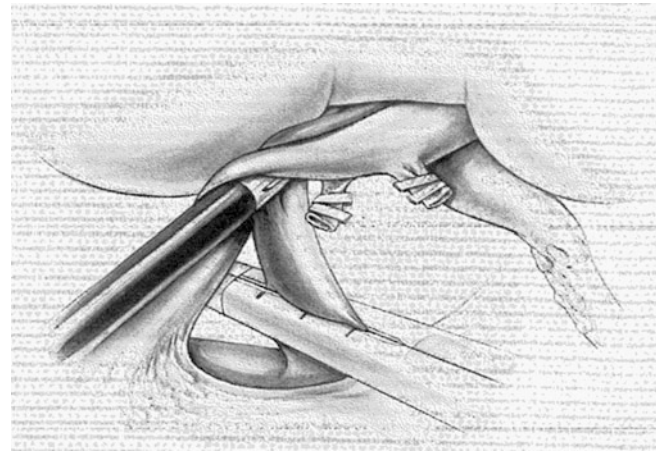

Fig. 9 Division of the vascular pedicle – division of the renal artery

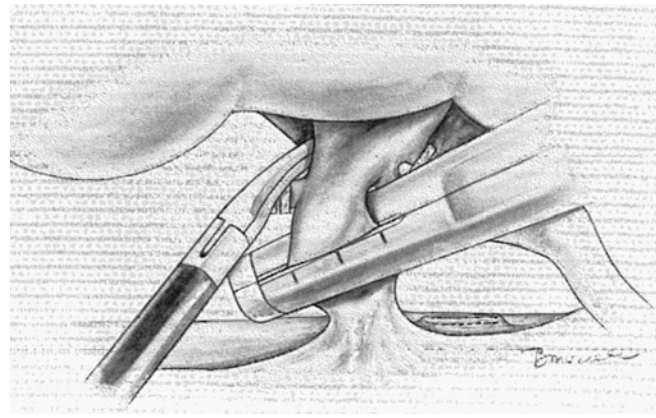

Fig. 10 Division of the vascular pedicle – division of the renal vein

sure to lengthen the incision as needed to ensure completely atraumatic delivery. The kidney is then transferred to the recipient team.

Number 1 polydioxanone (PDS) suture is used to close fascia in interrupted fashion, and pneumoperitoneum is reestablished. Hemostasis is ensured with careful examination of the renal bed, followed by the trocar sites. The lateral port site is closed under direct visualization using the Carter-Thomason closure device (CooperSurgical, Trumbull, CT) with 2–0 Vicryl suture. The camera is removed and pneumoperitoneum is evacuated via the periumbilical port. The umbilical port site is closed utilizing a figure of 8 suture. The skin is then closed with 4–0 Monocryl suture and adhesives are applied to the incisions (Fabrizio et al. 1999).

Technique for Right-Sided Pure Laparoscopic Approach

In the right-sided approach, as described by Chow et al., the patient is placed in the left lateral decubitus position. As in the left-sided approach, transperitoneal access is obtained and pneumoperitoneum established in the standard fashion. Ports are placed in the following locations: one halfway between the umbilicus and the xiphoid, one halfway between the pubic symphysis and the umbilicus, and a final port lateral to the rectus muscle on the right side at the level of the umbilicus. The right colon is mobilized and a Kocher maneuver is performed. The posterior and lateral attachments of the liver are released to allow it to be reflected to expose the right renal hilum. An

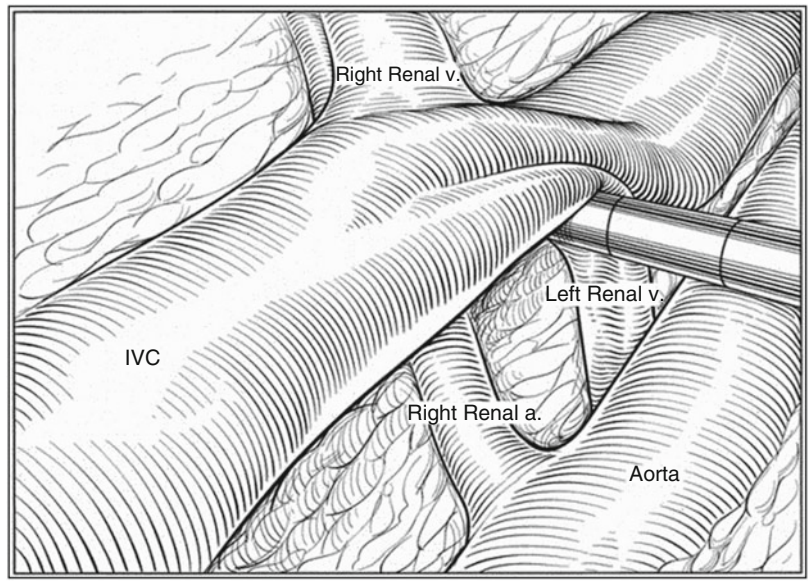

Fig. 11 Diagram illustrating anatomy of interaortocaval region. Superior retraction of the vena cava is used to expose the interaortocaval area (Image reproduced with permission by Chow et al.)

additional 3-mm port is placed in the subxyphoid area, and a locking grasper or liver retractor is utilized to assist in hepatic retraction.

The right renal vein is dissected and mobilized. This allows exposure of the right renal artery posteriorly. Blunt dissection in the interaortocaval area is used to identify the origin of the right renal artery. It is important to ligate or clip lymphatic tissue prior to division to prevent lymphocele. The retrocaval artery is mobilized by careful upward retraction of the vena cava and blunt dissection along the artery (Fig. 11). The lumbar veins should be identified and ligated to afford sufficient mobilization of the vena cava. The artery is then dissected free circumferentially, and the procedure proceeds in a manner similar to that of the left-sided approach. The vessels are transected with an Endo GIA stapler (Covidien, Mansfield, MA). The artery is incised at its take off from the aorta (Chow et al. 2001).

Hand-Assisted Donor Nephrectomy

Technique

The patient is brought to the operating room and placed on the operating table in the supine position with the flanks overlying the break in the table. General anesthesia is then induced with endotracheal tube placement. A foley catheter is placed. At this point, the patient is repositioned in the lateral decubitus position. In the case of a left donor nephrectomy, the right side is decubitus. Care is taken to adequately pad the head, so the neck is in a neutral position. An axillary roll is placed just inferior to the axilla. Two blanket rolls are utilized in conjunction with the draw sheet to secure the patient in the lateral position. Some centers utilize a suction beanbag, but the authors' approach offers a similar result with less complexity. The dependent arm is placed in the bent position and padded at the elbow. The left arm is suspended by way of an arm sling. The legs are positioned such that the dependent leg is bent and the nondependent leg is fairly straight. The knees and ankles are padded to ensure a neutral position. Towels are placed caudal and cephalad to the operative field, and the patient is secured to the operating table with 3-inch silk tape. The bed is then flexed approximately 15° to enhance the operative field. Upper and lower Bair-Huggers (3 M, St. Paul, MN) are placed.

The patient is then prepped and draped as is typical for a laparoscopic procedure. A periumbilical incision is made, typically 6.5 cm in length. Electrocautery is used to dissect through the subcutaneous tissue, open the fascia, and enter the peritoneum. Typically, a Gelport (Applied

Medical, Rancho Santa Margarita, CA) is placed at this incision and a 12 mm trocar is placed through the Gelport (Applied Medical, Rancho Santa Margarita, CA). The abdomen is insufflated through this port to 12 mmHg. A 10 mm camera is then inserted through this same port and the abdomen is inspected for any potential injury or adhesions. At this point, 5 mm trocars are placed in the lateral and subcostal positions. These are placed under direct visualization, and care is taken to avoid the epigastric vessels with the placement of the subcostal port. The camera is then switched to a 5 mm 30° scope, which is inserted through the subcostal port.

At this point, the dissection can move forward. The surgeon's left hand is inserted through the hand port and a Harmonic scalpel (Ethicon, San Angelo, TX) is typically utilized through the lateral 5 mm port. The dissection is initiated by mobilizing the left colon. The mesentery is mobilized by dividing the peritoneum just superficial to the white line of Toldt. This ensures that the dissection does not proceed posterior to the kidney. This dissection is carried down to the iliac vessels and extended cephalad to mobilize the spleen along with the colon in one unit. This will expose Gerota's fascia and the gonadal vein. Care is taken not to dissect too close to the pancreas to avoid inducing pancreatitis.

At this point, the surgeon is able to palpate the kidney and assess the extent of the upper pole, lower pole, and the location of the hilum. From here, there are two approaches to the hilar dissection. In the authors' dissection, the Gerota's fascia is entered directly and the renal vein is identified. It is important throughout the dissection to maximize the use of the left hand to gently retract tissue for division or provide counter tension. Once the anterior surface of the renal vein is dissected clear, the next step is to identify the insertion of the gonadal and adrenal veins. Through a combination of the Harmonic scalpel (Ethicon, San Angelo, TX) and the Maryland dissector, adequate length of the gonadal and adrenal veins are dissected out to allow double clip ligation and division of each vein. This allows for circumferential dissection of the renal vein towards the vena cava and exposure of the renal artery. The anterior surface of the renal artery is dissected clear utilizing the hook cautery or the Harmonic scalpel (Ethicon, San Angelo, TX). The hook cautery is preferred as it allows the careful division of overlying tissues without injuring the posteriorly located artery. The adrenal gland is then dissected free of the upper pole of the kidney. This dissection proceeds by identifying the adrenal gland and dissecting from the renal vein to the upper pole. The ureter is identified lateral to the gonadal vein near the lower pole of the kidney. It, along with the surrounding fat, is dissected out of the retroperitoneum down to the level of the iliac vessels.

Once the ureter has been circumferentially mobilized, the lower pole of the kidney can be mobilized out of the retroperitoneum. The dissection remains close to the surface of the kidney and proceeds from lower pole to upper pole, lateral to medial. The surgeon's hand may be utilized to gently retract the kidney away from the retroperitoneum to aid in dissection. Once the kidney is fully mobilized, the posterior aspect of the renal artery can be dissected clear of tissue. At this point, the kidney is fully mobilized and connected to the donor only via the renal artery, renal vein, and ureter. It is important during the dissection that the donor is kept normotensive, and the kidney should remain well perfused and fairly firm. Overmanipulation of the kidney or relative hypotension can result in the donated kidney becoming hypoperfused, leading to impaired immediate graft function. The ureter is then clipped distally and divided. To ensure immediate graft function, the surgeon watches the ureter for the production of urine. In the authors' experience, significant urine production after division of the ureter is a good marker of immediate graft function. Once the receiving surgeon is ready, the vessels can be divided. A stapling device is used to close and divide the renal artery first, followed by the renal vein. The kidney is then retrieved through the hand port and passed to the receiving surgeon.

Once brought to the backtable, the vessels are examined and the organ is flushed with preservation solution on ice until clear. During this time, the donor surgeon replaces the Gelport (Applied

Medical, Rancho Santa Margarita, CA) and insufflates the abdomen. The retroperitoneum is inspected and hemostasis is achieved through a combination of clips, cautery, and Harmonic scalpel (Ethicon, San Angelo, TX) as necessary. The origins of the renal artery and vein are examined to confirm hemostasis. Care must be exercised to examine the spleen and adrenal gland, as these can be a source of bleeding. Lastly, the area is examined to identify any potential lymph leak stemming from periaortic lymph channels, which are divided during the dissection and can leak. Failure to control lymph leaks prior to completing the operation can result in a lymphocele requiring further intervention.

Once the donor surgeon is satisfied, the abdominal contents are returned to their native positions and the ports can be removed. The 5 mm ports are removed under direct visualization to identify any port site bleeding prior to closure. The abdomen is then desufflated and the Gelport (Applied Medical, Rancho Santa Margarita, CA) is removed. The omentum is pulled inferiorly to cover the small bowel and to lay between the periumbilical incision and the bowel.

The peritoneum is closed with a 4–0 PDS suture. The midline fascia is then closed with number 1 PDS figure of eight sutures. All skin incisions are closed with 4–0 Monocryl running subcuticular sutures. Wounds are then dressed. The patient is repositioned in the supine position and anesthesia is discontinued.

Right nephrectomy is performed in a similar manner to that of the pure laparoscopic approach.

Single Incision Laparoscopic Surgery (SILS)

Technique

The SILS technique has been well described by Barth et al. in the detailing of the experience at the University of Maryland. The authors offer nephrectomy through a single transumbilical incision. In their experience, they have demonstrated equivalent complication rates, blood loss, and operating times. Despite a significant learning curve, the authors performed both laparoscopic and SILS surgery with equivalent outcomes by the completion of the study period (Barth et al. 2013). The operative description that follows is adapted from the description offered by LaMattina, et al. with permission (LaMattina et al. 2017).

After induction of general anesthesia, the patient is positioned in a lateral decubitus position. For left nephrectomy, a 2–3 cm SILS port (Covidien, Mansfield, MA) or a 4–5 cm Gelpoint (Applied Medical, Rancho Santa Margarita, CA) incision is made around the umbilicus. For a right nephrectomy, the Gelpoint (Applied Medical, Rancho Santa Margarita, CA) incision is always used. The abdomen is insufflated to 15 mmHg and is then visually explored. Next, using the Harmonic scalpel (Ethicon, San Angelo, TX) to minimize bleeding, the colon is mobilized from the splenic flexure to the pelvic brim. The kidney is then mobilized using blunt dissection.

Next, the ureter and gonadal vessels are dissected free from the renal hilum to the level of the iliac vessels. On the left side, this will expose the junction of the gonadal vein and renal vein. The lower border of the left renal vein and any lumbar vein are then exposed by gently elevating the lower pole with an atraumatic bowel grasper. Lumbar veins are divided with the Harmonic scalpel (Ethicon, San Angelo, TX), with larger veins potentially requiring division between clips. The Harmonic scalpel (Ethicon, San Angelo, TX) is then used to develop a plane between the adrenal gland and the kidney using lateral traction to facilitate the process. Next, the posterior renal attachments are freed and the renal artery is dissected circumferentially. Once isolated, the artery is dissected further up to its origin at the aorta and the renal vein is dissected past the level of the aorta. At this point, the left adrenal vein can either be left intact to be divided at the time of left renal vein division, or it can be dissected further and divided with a Harmonic scalpel (Ethicon, San Angelo, TX) to maximize left renal vein length.

When ready to explant the kidney, a 15 mm port is inserted through the single port device and an Endo GIA vascular stapling device (Covidien, Mansfield, MA) is used to divide the ureter and gonadal vein together at the level of the pelvic brim. Next, the renal artery and vein are divided

sequentially with the same stapling device and hemostasis is ensured at each staple line. The free kidney is then placed into a 15 mm Endo Catch bag (Covidien, Mansfield, MA) under direct visualization and the port is removed with specimen extraction. When using the SILS port, the skin incision needs to be extended by 1–3 cm depending on the size of the kidney, and the kidney is extracted in the bag atraumatically and transferred to the recipient team.

The fascia is partially closed, allowing for ports to be replaced and for pneumoperitoneum to be reestablished. The abdomen is explored one last time, ensuring hemostasis, and any mesocolonic defects are identified and repaired with metal clips or intracorporeal suturing. The ports are then extracted and pneumoperitoneum evacuated. The fascia is then closed with number 1 PDS suture. The skin is closed with 4–0 Monocryl suture and incisions are covered with adhesive dressings (LaMattina et al. 2017).

Again, this approach can be utilized for right donor nephrectomy, proceeding with similar adjustments to those made utilizing the pure laparoscopic technique.

Robotic Donor Nephrectomy

The University of Illinois-Chicago group published the largest series of robotic donor nephrectomy (Horgan et al. 2002). Their series essentially serves as a proof of concept for robotic donor nephrectomy as there currently exists no FDA-approved device for ligation and division of the renal vessels. In their series, they described a hand-assisted robotic approach that allowed the surgeon to utilize the superior optics and dexterity of the minimally invasive instruments to recreate the dexterity and hand-eye coordination experienced by the surgeon during open surgery. The operative times, complication rates, and lengths of stay were commensurate with those experienced in their own laparoscopic series. While this technique is in its infancy, this series does point to the possibility of robotic donor nephrectomy once robotic stapling and retrieval devices are perfected.

Complications

Complications after minimally invasive living donor nephrectomy have been described in numerous series. They are summarized in Table 1 based on descriptions by Ahearn et al. Among the most common minor complications are wound complications and infections. Major complications can include postoperative port-site hernias, intraoperative visceral injury, major hemorrhage, need for blood transfusion, and death (Ahearn et al. 2011). In addition, it is important to emphasize to the donor that, however rare, there may arise situations in which the operation is terminated or the kidney is sacrificed for the safety of the donor.

The most common complication after the SILS technique is a hernia at the umbilical port site, occurring in 3% of patients following donation.

Table 1 Complications of live donor nephrectomy with associated incidence

Major complications	Incidence
Readmission	1.0%
Blood transfusion	0.5%
Open conversion	0.3%
Lymph leak	0.3%
Port-site hernia	0.2%
Reoperation	0.2%
Renal insufficiency	0.2%
Rhabdomyolysis	0.1%
Minor complications	
Wound infection	1.9%
Ileus	0.5%
Urinary retention	0.4%
Urinary tract infection	0.4%
Pneumothorax	0.3%
Respiratory distress	0.2%
Pneumonia	0.1%
Intraoperative complications	
Splenic laceration	0.8%
Liver laceration	0.3%
Adrenal injury	0.2%
Venous injury	0.2%
Bowel injury	0.2%
Carbon dioxide embolism	0.2%
Ureteral injury	0.1%
Bladder injury	0.1%

Table derived from description by Ahearn et al.

In a series of 378 consecutive SILS nephrectomies, LaMattina et al. found that 92% of hernias occurred in women, and 73% of these women had had prior pregnancies. Fifty percent of donors who suffered a hernia had undergone prior transumbilical surgical procedures. Cross clamp time, estimated blood loss, BMI, age, and laterality of the donation were not associated with subsequent hernia formation. The hernias reported 13.5 months after donation were at the original port-site incision, with 2/3rd being repaired primarily and 1/3rd requiring mesh. 1.9% of patients required a return to the operating room for a variety of reasons, including internal hernia from a mesenteric defect in the mesocolon, wound infection leading to evisceration, bowel obstruction, bleeding, and persistent wound infection. There was a single open conversion, one intraabdominal abscess, and three patients who required a blood transfusion (LaMattina et al. 2017).

Postoperative Pain Control

There are multiple techniques for analgesia postdonation. With an increasing emphasis on early return to activity and shortened hospital stays, there has been a gradual turn away from narcotic-based analgesia plans. Many centers utilize multimodal nonnarcotic pain management regimens. These often include the use of local anesthetic or blocks, nonsteroidal anti-inflammatory medications, and acetaminophen.

Conclusion

Kidney transplantation is now well established as the best treatment modality for patients with ESRD. As the number of patients needing transplantation continues to grow, one of the major obstacles remains organ shortage. Living donor kidney transplantation has emerged not only as a way to give more patients access to kidney donation but also to improve outcomes in transplant recipients as compared to deceased donor kidney transplantation. As the only surgery to offer no direct benefit to the patient, a number of ethical issues have been brought up that are unique to living donation, specifically focusing on the risks to potential donors. With the advent of laparoscopy, laparoscopic donor nephrectomy has become the standard of care in suitable candidates and has significantly decreased the morbidity of living kidney donation. Nonetheless, outside of standard postoperative risks, specific lifetime risks remain in post-nephrectomy patients after donation. The lifetime increase in risks of developing ESRD and hypertension in donors is a concern in the literature. Further complicating the matter are issues such as the disparity in outcomes based on demographic and socioeconomic factors such as race, gender, BMI, and insurance status. These must all be taken into consideration when offering living kidney donation to patients, and the discussion of potential risks associated with surgery must be highly individualized and tailored to each patient. Such tools, as the risk calculator, devised by Grams et al. may be very useful adjuncts in the evaluation of individual donors for donation risks (Grams et al. 2016).

Cross-References

- ▶ Living Donor Evaluation and Selection
- ▶ Necessary Components of a Living Donor Team
- ▶ Organ Procurement Organization and New Kidney Allocation

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Renal Transplantation with Other Organs

Pooja Singh and Jerry McCauley

Contents

Abstract

Simultaneous kidney transplantation is sometimes pursued with other organs due to severe dual organ dysfunction or end stage failure. The most common dual organs transplanted together are kidney and pancreas. Patients in need of life saving organs such as liver, heart, or lung may also have chronic kidney disease and may be eligible for dual transplantation. There are advantages to multi-organ transplantation since there is immunologic exposure to only a single donor, avoidance of multiple surgeries, and the need to wait for a second organ is circumvented. However, the lack of standardized allocation criteria leads to variability in practices across the United States. This chapter covers kidney transplantation simultaneously with other organs such as pancreas, liver, heart, and lung. It also covers the current policies and existing criteria pertaining to synchronous kidney pancreas and liver

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kidney transplantation. It also discusses absence of standardized criteria with combined kidney heart and kidney lung transplantation. Finally, it provides some insight into ethics of dual transplantation and how it may sometimes undermine the principles of equity and utility.

Keywords

Combined transplantation · Simultaneous liver kidney transplantation · Simultaneous pancreas kidney transplantation · Heart kidney transplantation · Kidney lung transplantation

Introduction

Consensus about eligibility for combined renal and nonrenal transplantation is lacking. Patients listed for life saving organs such as heart, lung, or liver transplantation may suffer from chronic renal insufficiency and may require dual organ transplantation. In these cases, the kidney allograft gets allocated out of sequence to these very sick patients raising concerns about undermining utility and equity for over 100,000 patients awaiting kidney transplantation. Current practices for dual listing for combined transplantation in the USA are very heterogeneous which undermines fair and transparent allocation. Recently, UNOS approved the eligibility criteria for combined kidney and liver transplantation to help bring uniformity to this listing process. Furthermore, policy drafts must be developed using evidence-based and expert consensus opinion that can be vetted through the appropriate channels to help formulate national policies.

The most common simultaneous organ transplant is Simultaneous Pancreas Kidney (KP) transplantation with >19,000 transplants performed in the Unites States from 1998 to 2013 (Reese et al. 2014). On October 30, 2014, a new Kidney Pancreas allocation system came into effect. A major change with this allocation was establishment of qualifying criteria for KP candidates which had to be met to accrue wait time for the combined KP wait list. Previously, pancreas allocation policy allowed Organ Procurement Organizations (OPOs) several choices on pancreas allocation practice. They could allocate organs to kidney pancreas (KP) candidates based upon the KP match run, the kidney alone match run, or a combination of match runs. This has now changed with the new policy since KP candidates and pancreas alone candidates will be on a single match run.

The second most common simultaneous organ transplantation is liver kidney transplantation (SLK) with >5000 transplants performed from 1988 to 2013 (Reese et al. 2014). In 2012, 8.4% of all deceased donor liver transplants were part of multi-organ transplants (MOT) with 92% of these being SLK transplants (Fig. 1a, b). The **Model for End-Stage Liver Disease**, or **MELD**, is a scoring system used for assessing the severity of chronic liver disease. It incorporates serum bilirubin levels, serum creatinine, INR value, and dialysis dependency. Since its adoption in 2002 for liver allocation, the proportion of SLK transplants increased substantially and now averages about 400 transplants/year. In June 2016, UNOS approved the new SLK eligibility criteria. This eligibility criterion provides guidance on which patients with chronic kidney disease (CKD) or acute kidney injury (AKI) and liver disease should pursue dual transplantation.

In 2014, 103 simultaneous heart and kidney transplants were done which was about 4.5% of all heart transplants. Overall, dual transplantation remains uncommon. Similar to liver transplantation, heart transplantation is based on the candidate's degree of sickness and candidates are classified as status 1A or 1B based on ventilator requirements, need for mechanical assist devices, inotropic support, and expected survival without transplantation. Combined kidney and lung transplants are very rare and only 19 such transplants have been done between 2002 and 2013. Whenever combined transplantation is contemplated with candidates needing a heart, liver, or lung transplant, kidney is downgraded to nonprimary organ category status and allocation sequence is determined by the lifesaving organ. However, these kidneys being allocated as part of multi-organ transplants are among the highest quality organs as depicted in Fig. 2.

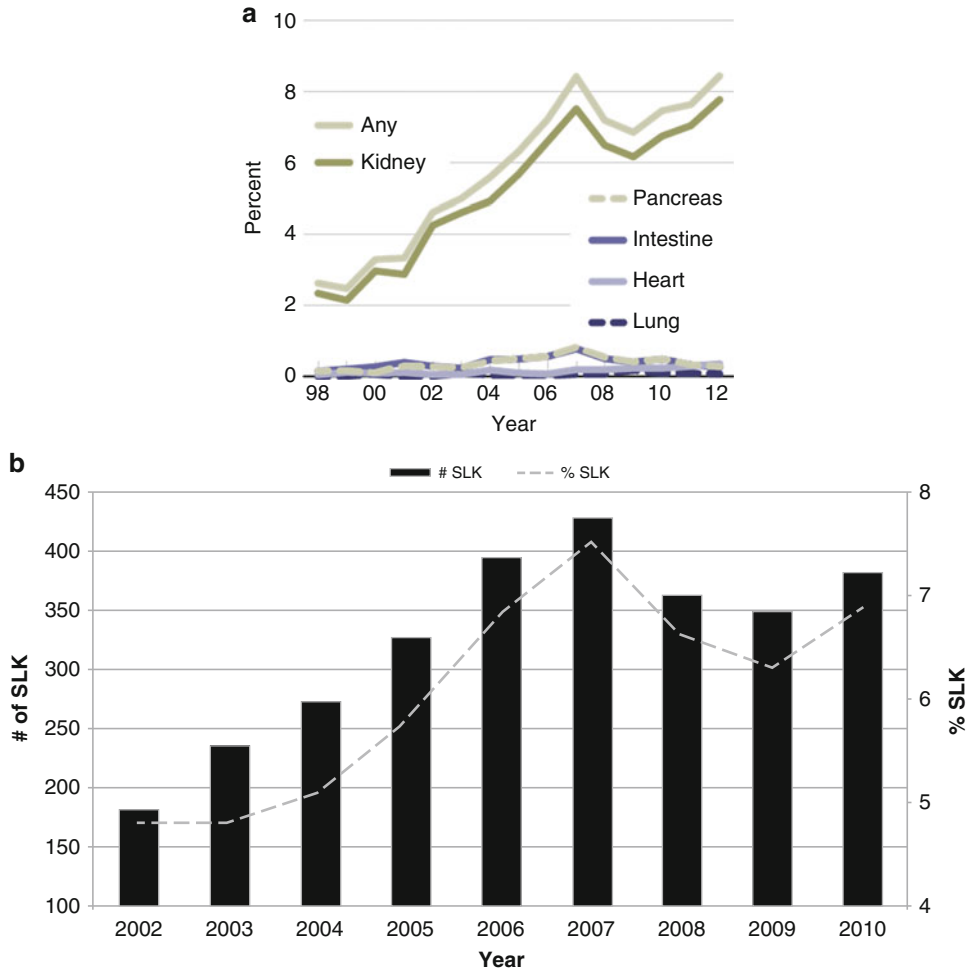

Fig. 1 (**a**) Liver transplants done as part of combined organ transplants (Data from http://srtr.transplant.hrsa.gov/annual_reports/2012/. Slide 34 SRTR report liver slides). (**b**) Total number and percentage of simultaneous liver-kidney transplantation (SLK) of all deceased donor, adult liver transplantation. Model of the end-stage liver disease (MELD) score was implemented in February 2002 (This figure is adapted from Nadim et al. 2012)

This chapter will cover kidney transplantation with other organs and address some controversies associated with dual transplantation.

Estimation of Renal Function

A thorough pre-operative evaluation for these candidates should be undertaken and this includes assessing for history of AKI including duration and prior reversibility. It should also include risk factors and stage of CKD and its expected progression to end stage renal disease. The first step involved in this process is a detailed history and physical examination, an accurate measure of kidney function, urine studies including urinalysis and urine protein/creatinine ratio, and renal ultrasonography. A renal biopsy may be pursued as clinically indicated.

Sarcopenia is not uncommon in liver, heart, or small bowel transplant candidates and consequently, low serum creatinine values are expected at baseline. Creatinine is derived from the metabolism of creatine produced by skeletal muscle and

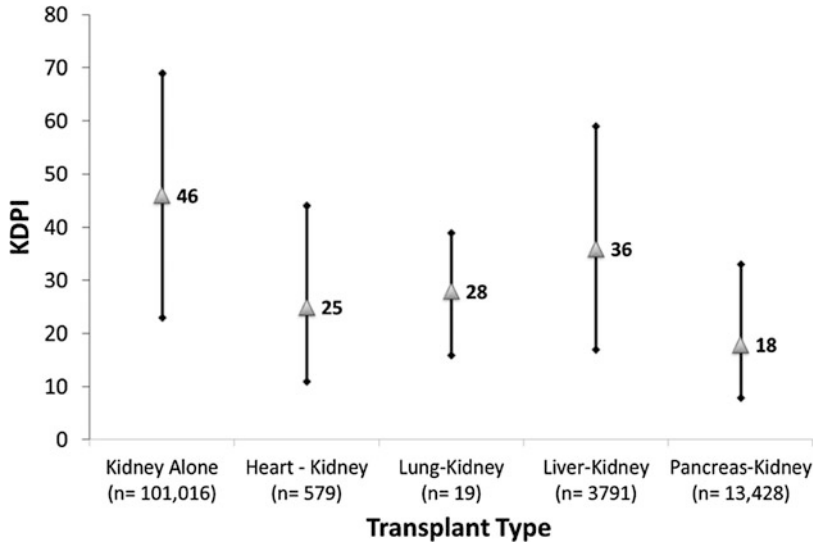

Fig. 2 Distribution of kidney donor profile index (KDPI) scores among recipients of kidney-alone and multi-organ transplant recipients. Based on Organ Procurement and Transplantation Network (OPTN) data and represents a cohort of adult (≥18 years) solid organ transplant recipients who received a deceased donor kidney transplant from February 2002 to April 2013. $p < 0.001$ for each comparison of kidney-alone recipients to each other multi-organ transplant group (Adapted from Reese et al., American Journal of Transplantation. Volume 14, Issue 1, pages 21–26, 19 DEC 2013)

from dietary meat intake. It is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, about 10–40% of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule (Shemesh et al. 1985). Under steady state conditions, creatinine excretion is usually a good clinical marker of renal function since its reabsorption and secretion as well as total production and excretion are equal.

Estimation of renal function is done by using a 24-h urine collection for Creatinine Clearance (Cr Cl) or serum Creatinine based estimation equations. However, there are some limitations present. Overestimation of glomerular filtration rate (GFR) is commonly encountered in end stage heart or liver failure since serum creatinine value is falsely low due to underproduction. Overestimation of GFR is also encountered in patients with CKD in whom the tubular secretion of creatinine is increased thus overestimating total creatinine clearance. Competitively inhibiting creatinine secretion by the administration of cimetidine which blocks the renal tubular secretion is not a foolproof method to increase accuracy since wide variability in its blocking property may make interpretation difficult (Van Acker et al. 1992). Finally, overestimation is also encountered due to extra renal creatinine elimination from increased intestinal bacterial overgrowth and increased creatininase activity in CKD stage 5 (Dunn et al. 1997). In conclusion, creatinine clearance represents an overestimation of GFR in these scenarios. GFR can be precisely estimated by using renal clearance of various radionuclide markers, like 99mTc-labeled diethylene triamine penta-acetic acid (DTPA), 51Cr-labeled ethylenediaminetetraacetic acid (EDTA), and 125I-labeled iothalamate (Tanriover et al. 2008). However, these methods are not widely available.

Simultaneous Pancreas Kidney Transplantation

Combined kidney-pancreas transplantation is an established, definitive treatment for selected diabetic patients with end stage diabetic

nephropathy. More than two-thirds of pancreas transplants are performed as simultaneous pancreas-kidney (SPK) transplants, with the remainder performed as sequential pancreas after kidney (PAK) transplant or pancreas transplant alone (PTA). The clear majority of pancreas-kidney transplants are in patients with type 1 diabetes, although a small number are done in patients with type 2 diabetes. While SPK most often employs grafts procured from a single deceased donor, some are simultaneous living-donor kidney and deceased-donor pancreas.

In 2014, some important changes and initiatives were incorporated to policies involving pancreas transplantation. Firstly, the new pancreas allocation system became effective in Oct 2014 and a pancreas qualifying criteria was launched. Per National Pancreas Allocation system, SPK candidates need to meet both a GFR and insulin requirement/C-peptide criteria. For kidney listing, SPK candidates must meet the requirement of GFR $\leq$20 mL/min **OR** dialysis dependency. For pancreas listing, insulin requirements and C peptide level are assessed and the candidates should meet the following criteria:

A. On insulin **AND** C-peptide $\leq$2 ng/mL **OR**
B. On insulin **AND** C-peptide >2 ng/mL **AND** BMI $\leq$30 kg/m^2

The BMI criteria is only applicable to those candidates with C-peptide >2 mg/mL. This BMI cut off labeled as maximum allowable BMI can be a moving target and may be changed by UNOS periodically based on data review.

As per SRTR annual report, total new listings (active and inactive) for pancreas increased to 1213 in 2014 compared with 1164 in 2013, again largely due to PTA and SPK listings (Fig. 3). However, the overall number of pancreas transplants continued to decline, to 954 in 2014 (Fig. 4). Early Pancreas graft failure is experienced in about 8.2% of patients. All-cause kidney

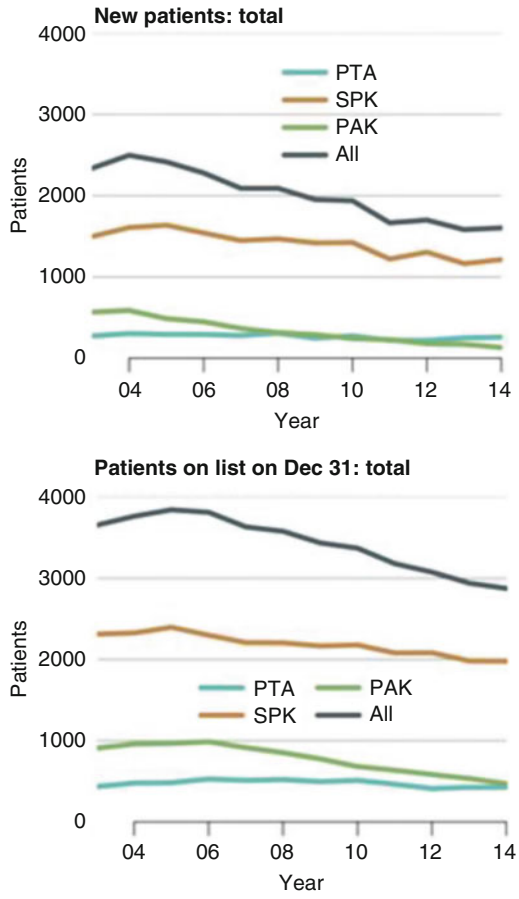

Fig. 3 **Adults waiting for pancreas transplant** (Adapted from American Journal of Transplantation. Volume 16, Issue S2, pages 47–68, 11 JAN 2016)

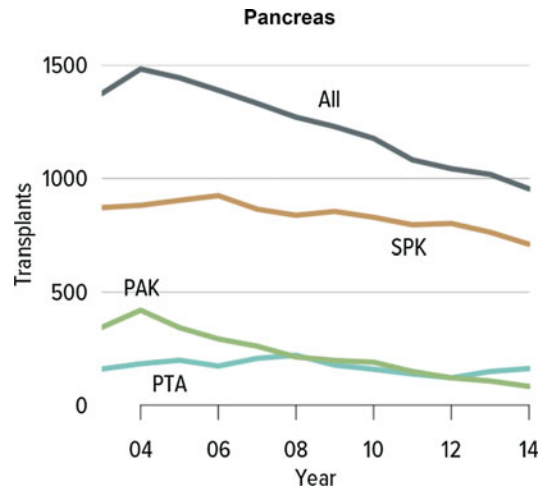

Fig. 4 **Total pancreas transplants** (Adapted from American Journal of Transplantation. Volume 16, Issue S2, pages 47–68, 11 JAN 2016)

graft survival in SPK at 1, 5, and 10 years is reported to be about 95%, 81%, and 61%. This compares favorably with non-SPK deceased donor kidney transplants survival at 93%, 74%, and 47%, respectively.

Similar to kidney transplantation, combined kidney-pancreas transplantation also confers decreased mortality and improvement in quality of life. Freedom from dialysis, insulin usage, and blood sugar monitoring are primary determinants for improved quality of life (Becker et al. 2001). In type 1 diabetes, SPK transplantation appears to confer better survival than kidney transplant alone, at least compared with a deceased-donor kidney transplant. A study of 18,549 patients with type 1 diabetes reported that 8-year survival was similar for SPK (72%) and living-donor kidney transplant recipients (72%), but higher than that observed for deceased-donor kidney transplant recipients (55%) (Reddy et al. 2003). It is unclear if SPK provides additional survival advantage over living donor kidney transplant but previously published data shows that the 12-month pancreas graft function significantly influences survival following simultaneous pancreas-kidney transplantation. In an OPTN analysis (Weiss et al. 2009), which stratified SPK recipients based on the pancreas function at 1 year, the 7-year post-transplant patient survival was highest in SPK recipients with a functioning pancreas graft 12 months post-transplant (89%), followed by living-donor KTA (80%), SPK recipients with a non-functioning pancreas (74%), and deceased-donor KTA (65%).

In summary, the main advantage of combined kidney-pancreas transplantation is decreased mortality and enhanced quality of life. It is generally accepted that this survival benefit is primarily driven by kidney transplantation. Lack of randomized controlled trials hinders conclusive evidence if an additional survival advantage exists when comparing SPK versus KTA. Potential benefits of combined kidney-pancreas transplantation include improved metabolic profile, reduced risk of recurrent diabetic nephropathy, and improvement in other complications such as autonomic neuropathy and retinopathy.

Simultaneous Liver and Kidney Transplantation

Renal failure was no longer considered a contraindication to liver transplantation after the first combined liver kidney transplantation was reported by Margreiter et al. in 1984. It is generally believed that liver transplant done as SLK protects the kidney from rejection. The underlying mechanism is believed to be secretion of soluble class I HLA antigens which have the ability to block HLA antibodies and also inhibit cytotoxic T lymphocytes (McMillan et al. 1997). Additionally, Kupffer cells are also involved in phagocytosis of HLA antibodies (Starzl et al. 1994). This immunoprotective effect has helped to overcome immunologic barriers in liver and SLK transplantation (Flye et al. 1990; Fung et al. 1988). This is the reason why pre-transplant cytotoxic crossmatches are not standard protocol in liver transplantation. According to Fung et al. (1987), a newly transplanted liver can convert a positive crossmatch to negative in a patient with pre-formed donor specific antibodies thereby allowing successful renal transplantation 8 h later. Furthermore, multiple studies have shown that renal rejection and graft loss are diminished after SLK in pre-sensitized recipients (Gonwa et al. 1988; Shaked et al. 1993; Vogel et al. 1988; Gil-Vernet et al. 1992). With greater technical proficiency and enhancements in immunosuppression, the indications for combined liver and kidney transplantation have evolved. The most common indications for SLK transplantation are shown in Table 1.

Liver transplant candidates frequently encounter renal dysfunction due to a myriad of causes. Functional renal failure such as hepatorenal syndrome is generally expected to improve after liver transplantation. Likewise, patients with acute renal failure without pre-existing renal insufficiency can be expected to regain normal renal function after liver transplantation but many variables such as duration of acute renal failure, recurrent renal insults, need for renal replacement therapy, and a complicated perioperative course may lead to permanent loss of renal function. The

Table 1 Most common indications for combined liver and kidney transplantation

Diseases synchronously affecting both organs	Hepatitis B or C causing cirrhosis and MPGN/membranous nephropathy/ cryoglobulinemia
Unrelated liver and kidney disease	Primary renal diseases (hypertension, diabetes) Primary liver diseases (alcoholic liver disease, PBC, etc.)
Noncirrhotic diseases with origin/ involvement of liver and kidney	Primary oxalosis, atypical HUS, familial amyloidotic polyneuropathy, end stage polycystic liver kidney disease
ESLD of any etiology with prolonged AKI	Most commonly acute tubular injury or hepatorenal syndrome with dialysis dependency of $\geq$6 weeks duration

MPGN membranoproliferative glomerulonephritis, *PBC* primary biliary cirrhosis, *HUS* hemolytic uremic syndrome, *ESLD* end stage liver disease, *AKI* acute kidney injury

decision to offer a simultaneous renal transplant to these patients may vary from being simple to quite complex. It is important in these cases to establish if the renal dysfunction is expected to be permanent. However, this may pose challenges since serum and urine creatinine based methods to assess renal function may not be accurate. Doing a renal biopsy in these candidates is risky due to increased bleeding risks in liver failure.

Etiology of Renal Dysfunction in Liver Transplant Candidates

Hepatorenal syndrome (HRS) represents the end stage of a sequence of reductions in renal perfusion induced by worsening liver failure. The pathophysiology involves arterial vasodilation in the splanchnic circulation because of over production of nitric oxide triggered by portal hypertension. However, the changes in the renal bed are the opposite marked by increase in renal vascular resistance as a result of renin angiotensin activation in response to systemic hypotension (Ginès and Schrier 2009; Wadei et al. 2006). Two forms of HRS have been described (Ginès and Schrier 2009). *Type 1 hepatorenal syndrome* has a rapid onset, fast progression, and is characterized by oliguria and twofold increase in serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks. *Type 2 hepatorenal* has slower onset, less severe renal impairment, and is clinically marked by diuretic resistant ascites. This syndrome can be precipitated by gastrointestinal bleeding and spontaneous bacterial peritonitis. Hepatorenal syndrome is a diagnosis of exclusion after first ruling out pre-renal azotemia, acute tubular injury, glomerulonephritis, and obstruction. This syndrome is marked by lack of hematuria and proteinuria and no improvement in renal function in response to normal saline infusion and/or albumin administration. Since hepatorenal syndrome is considered a functional form of renal failure, there is a reasonable chance that renal function will improve after liver transplantation.

Acute tubular injury or necrosis can be encountered due to nephrotoxic medications, iodinated contrast based imaging studies, and hemodynamic instability from bleeding or sepsis. Traditional laboratory parameters such as fractional excretion of sodium above 2% in tubular injury and $<$1% in pre-renal azotemia may not be accurate since this value may be $<$1% in cirrhotic patients who have persistent renal ischemia because of hepatic disease (Diamond and Yoburn 1982). The urinalysis can be deceptive since granular and epithelial cell casts may be seen with marked hyperbilirubinemia alone and not necessarily representative of tubular injury. Post liver transplantation, renal recovery can often be delayed due to recurrent insults during perioperative period and use of calcineurin inhibitors which promote persistent renal vasoconstriction. Those patients who end up needing dialysis modality can also have superimposed hypotensive episodes thus delaying renal recovery. Additionally, calcineurin inhibitor usage has also been incriminated in inhibiting proliferation of renal epithelial cells in dose dependent manner (McCauley et al. 1991).

Renal involvement may be seen with Hepatitis B and C as the etiology of liver disease.

Hepatitis B has been associated with membranoproliferative GN (MPGN), membranous GN, and polyarteritis nodosa (Johnson and Couser 1990; Lai and Lai 1991). Glomerular diseases associated with Hepatitis C virus infection include mixed cryoglobulinemia, membranous nephropathy, and polyarteritis nodosa (PAN) (Davis et al. 1994; Misiani et al. 1992). Finally, secondary IgA nephropathy due to impaired removal of IgA containing complexes by the Kupffer cells predisposes to IgA deposits in the kidney (Amore et al. 1994). Adults usually have no clinical manifestations of glomerular disease (Pouria and Feehally 1999) while up to one-third children may have asymptomatic hematuria or proteinuria (Noble-Jamieson et al. 1992). It is postulated that the lack of symptomatic presentation may be due to absence of concomitant IgG deposition which may minimize activation of complement and other inflammatory mediators (Emancipator 1990). Restoration of normal hepatic function after liver transplantation is adequate to allow dissipation of these deposits from the kidney and other sites and therefore IgA deposits on renal biopsies before liver transplantation can generally be viewed as a relatively benign finding.

Finally, a group of noncirrhotic metabolic disorders can also be considered for dual transplantation. These include metabolic disease such as methylmalonic aciduria, familial non-neuropathic amyloidosis, primary oxalosis, and atypical hemolytic uremic syndrome (HUS). These patients are usually referred for simultaneous liver and kidney transplantation under MELD exception provision.

Patients awaiting liver transplantation may also have *pre-existing chronic kidney disease from* causes unrelated to their liver disease. Pre-existing CKD is common before liver transplantation (McCauley et al. 1990; Gonwa et al. 1995). Diabetic nephropathy, hypertensive nephrosclerosis, and glomerular diseases not associated with viral hepatitis probably occur at the same frequency as the general population. It is imperative to consider the natural history of specific CKD etiology when deciding to offer a concomitant renal transplant. Figure 5 shows the most commonly reported kidney diagnosis as indication for dual liver and kidney transplantation.

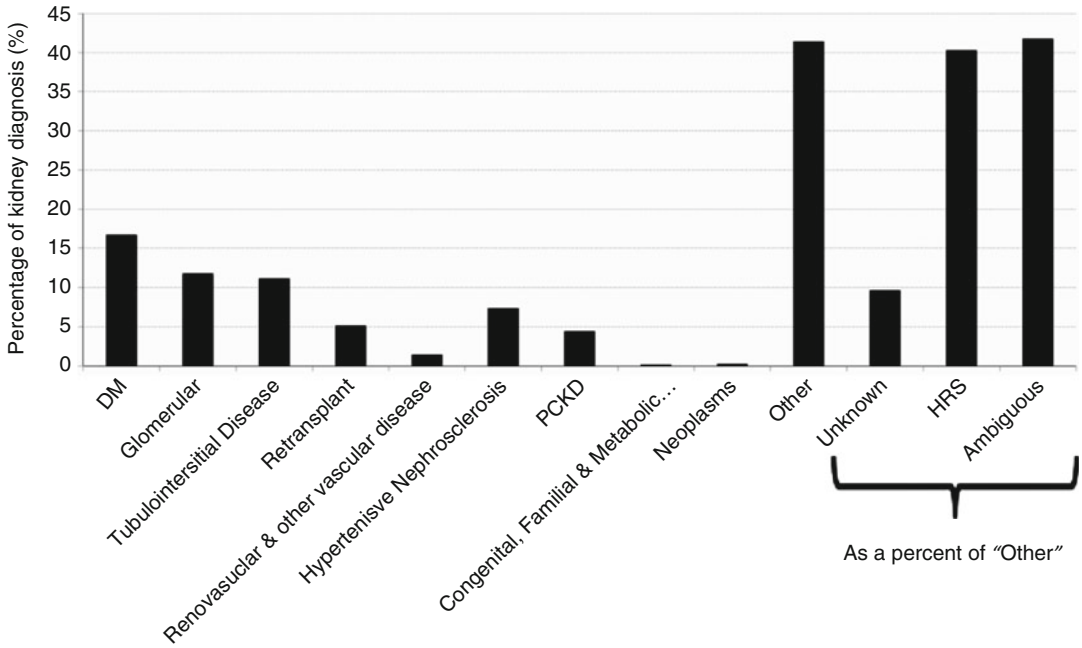

Fig. 5 Most commonly reported etiology for kidney disease in patients receiving simultaneous liver and kidney transplant from 2002 to 2010. Data from Organ Procurement and Transplantation Network (OPTN) as of June 2011 (http://optn.transplant.hrsa.gov) (Figure adapted from Nadim et al. 2012)

OPTN/UNOS launched initiatives to finalize the minimum eligibility criteria for liver kidney transplantation and it was released for public comment back in August 2015. The feedback obtained was reviewed by UNOS board and the final version of the medical eligibility criteria has been approved as of June 2016, and outlined in Table 2. In addition to meeting the eligibility requirement, the sign off from a transplant nephrologist for suitability for dual transplantation would also be needed. With an increase in the number of simultaneous liver and kidney transplants in recent years, it was felt that at least some kidneys are being allocated to liver candidates who likely would have regained native kidney function following a liver transplant alone. Moreover, it was also noted that these kidneys were of superior quality. The Kidney Donor Profile Index (KDPI) based on 10 donor characteristics is used to define deceased donor kidney quality. A lower score translates into a better-quality kidney showing superior kidney allograft survival (Rao et al. 2009). Review by OPTN has shown that almost half of SLK recipients received a kidney with a KDPI <35% based on allocation priority of liver. Essentially, some of the best quality kidneys were allocated in conjunction with dual transplantation thus diverting these kidneys from other patients on the kidney list.

It has been previously shown that a serum creatinine level of 2.5 mg/dL or higher is the cut off at which survival advantage with dual liver and kidney transplantation can be expected (Fong et al. 2012). Applying four variable MDRD formulas for a 50-year-old white male with a serum Cr of 2.5 mg/dL equates to an eGFR of 30 mL/min. This is the rationale for incorporation of this eGFR value for CKD criteria as shown in Table 2. An interesting fact noted by Formica (2016) showed that applying these eligibility

Table 2 Medical eligibility criteria approved by UNOS/OPTN Board

If the candidate's transplant nephrologist confirms a diagnosis of	Then the transplant program must report to the OPTN Contractor and document in the candidate's medical record
Chronic kidney disease (CKD) with a measured or calculated glomerular filtration rate (GFR) less than or equal to 60 mL/min for greater than 90 consecutive days	At least *one* of the following: 1. That the candidate has begun regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent nonhospital based, or home setting 2. At the time of registration on the kidney waiting list, that the candidate's most recent measured or calculated creatinine clearance (CrCl) or GFR is less than or equal to 30 mL/min 3. On a date after registration on the kidney waiting list, that the candidate's measured or calculated CrCl or GFR is less than or equal to 30 mL/min
Sustained acute kidney injury	At least *one* of the following, or a combination of *both* of the following, for the last 6 weeks: 1. That the candidate has been on dialysis at least once every 7 days 2. That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 mL/min at least once every 7 days If the candidate's eligibility is not confirmed at least once every 7 days for the last 6 weeks, the candidate is not eligible to receive a liver and a kidney from the same donor
Metabolic disease	A diagnosis of at least *one* of the following: 1. Hyperoxaluria 2. Atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I 3. Familial non-neuropathic systemic amyloidosis 4. Methylmalonic aciduria

criteria to patients who received dual transplantation in previous years would have in fact reduced the number of dual transplants by 19%. Another important component of this proposed policy is to introduce the concept of **safety net to** impart kidney transplant priority for those liver transplant recipients with severe renal dysfunction or dialysis dependency post liver transplant who did not undergo dual transplantation. The idea here is that providing safety net provision may deter overzealous dual listing and hopefully will provide a realistic chance of minimizing SLK in those who may regain native renal function post liver transplantation.

Combined Renal and Heart Transplantation

The first report of a combined heart and kidney transplantation was described in 1978 by Norman et al. With advances in perioperative management, simultaneous heart and kidney transplantation has been performed although no official guidelines for dual listing were formulated. The next big milestone was an article by Narula et al. (1997) which showed similar survival between heart-kidney and heart only recipients. Subsequently, Russo et al. in 2009 made the first attempt to define pre-transplant characteristics and survival outcomes between heart-kidney and isolated heart transplant. Factors associated with diminished survival included peripheral vascular disease, recipient age older than 65 years, non-ischemic etiology of heart failure, dialysis dependence at the time of transplantation, and usage of a ventricular assist device as bridge therapy. Only low-risk patients with eGFR <33 mL/min and heart failure seem to gain a survival benefit from combined transplantation. Even today, consensus or evidence based recommendations to establish the indications, contraindications for combined heart and kidney transplantation are lacking.

Tables 3 and 4 outline the wait list and transplant characteristics for combined heart and kidney transplantation. A straight forward indication for combined heart and kidney transplantation is a candidate with end stage heart failure meeting criteria for heart transplantation, who also has end

Table 3 Characteristics of adults on the heart transplant waiting list on December 31, 2004, and December 31, 2014 (Adapted from SRTR Annual Report 2014, Table HR 1.1)

		2004		2014	
		N	%	*N*	%
Multi-organ	Heart only	2,775	93.3	3,403	93.6
	Heart-kidney	54	1.8	165	4.5
	Heart-lung	135	4.5	39	1.1
	Other	9	0.3	28	0.8
All candidates		2,973	100.0	3,635	100.0

Table 4 Characteristics of adult heart transplant recipients, 2004 and 2014 (Adapted from SRTR Annual Report 2014. Table HR 3.2)

		2004		2014	
		N	%	*N*	%
Multi-organ transplant	Heart only	1,671	95.1	2,130	93.9
	Heart-lung	32	1.8	17	0.7
	Heart-kidney	44	2.5	103	4.5
	Heart-liver	9	0.5	18	0.8
	Other	2	0.1	1	0.0
All recipients		1,758	100.0	2,269	100.0

stage renal disease. What may be contentious is combined transplantation for end stage heart failure with nondialysis-dependent renal insufficiency. About 30% of patients with New York Heart Association stage 3 or 4 end stage heart failure have evidence of CKD (McAlister et al. 2004). The extent of renal dysfunction can influence wait list mortality with dialysis-dependent patients listed for heart transplantation doing worse than patients with nondialysis-dependent renal dysfunction (Singh et al. 2012). A more recent analysis suggested that patients listed for heart transplantation with eGFR less than 37 mL/min had increased survival after combined heart and kidney transplantation in comparison to heart transplantation alone (Karamlou et al. 2014). Unlike, SLK eligibility criteria, there are no formal guidelines to guide combined heart and kidney transplantation. In general, it is important to establish reversible from irreversible renal failure. A clear majority of patients with renal insufficiency and end stage heart failure have cardiorenal syndrome and heart transplantation alone should alleviate the renal insufficiency. It can be challenging to ascertain underlying etiology of renal failure in some cases, and a combination of renal ultrasonography, presence of risk factors for CKD, proteinuria, fluctuations in renal function trends, and or/renal biopsy may help clarify. Most centers depend on multidisciplinary approach involving transplant nephrologists, cardiologists, and surgery to make the final determination about dual listing for heart and kidney transplantation. A recent UNOS analysis by Schaffer et al. (2014) has shed light on wait list and post-transplant outcomes. The 3-month wait list mortality for patients on dialysis listed for isolated heart or combined heart-kidney transplantation is 31% and 21%, respectively. In those with renal insufficiency not requiring dialysis, the 3-month wait list mortality is about 12% and 7% for isolated heart versus combined heart and kidney transplantation. Five-year post-transplant survival was improved in combined transplant recipients compared with isolated heart recipients for both patients with dialysis-dependent (73% vs. 51%, $p < 0.001$) and nondialysis-dependent renal failure (80% vs. 69%, $p < 0.001$). While this does show that recommending combined transplantation improves survival for end stage heart- and dialysis-dependent patients, this recommendation for renal dysfunction not needing dialysis must be weighed against the possibility of renal recovery with isolated heart transplantation and societal benefit of transplanting two organs into two different recipients.

Recently, combined liver and kidney transplant eligibility criteria were approved by UNOS. Once implemented, this should streamline the listing practices of all transplant centers. The concept of safety net has been introduced which provides a priority listing for kidney after liver transplantation. Similarly, it is prudent to make alternative plans for kidney transplantation if renal failure persists post heart transplantation since prognosis of such patients is poor (Cassuto et al. 2010). Possibility of staged live donor kidney transplants if available should be strongly pursued in addition to listing for deceased donor kidney transplant.

Combined Kidney and Lung Transplantation

Advanced kidney disease is usually an absolute contraindication for lung transplantation due to the problematic management issues of these patients in the post-operative period. Combined heart-lung and liver-lung transplants have been done and reported with overall good clinical outcomes as previously described (Barshes et al. 2005; Orens et al. 2006). Although performed very rarely, combined kidney and lung transplantation could be offered to selective patients with renal and pulmonary dysfunction. The first case of a double lung-kidney transplant was published in 1998 in a patient with pulmonary lymphangioleiomyomatosis and renal angiolipomas after a unilateral nephrectomy (De Perrot et al. 1998). In a nutshell, it is a viable option for some selective patients but it is expected that the post-operative management will be complicated since the strict fluid restriction required to prevent pulmonary edema must be balanced with the need for abundant fluid intake for adequate renal perfusion

Table 5 Simultaneous heart-kidney and lung-kidney transplants in United States from 1987 to 2010 (Adapted from Wolf et al. 2013)

	Simultaneous heart-kidney		Simultaneous lung-kidney	
Date range	Listed	Transplanted	Listed	Transplanted
1987–1990	20	21	0	0
1991–1995	128	62	5	1
1996–2000	267	131	8	3
2001–2005	399	198	10	4
2006–2010	606	272	18	10
Totals	1420	684	41	18

and function in a new kidney transplant. Lung transplant patients are typically maintained on higher calcinuerin inhibitor dosages to counteract rejection and these need to be optimized to minimize nephrotoxic effects. Another report published in 2013 summarized successful double lung and kidney transplantation in a 38-year-old male patient with cystic fibrosis who at 46 months follow-up maintained excellent pulmonary and renal function (Borro et al. 2013). Reich et al. (2015) recently published an OPTN/UNOS analysis of all combined kidney and lung transplants and reported that 31 combined transplants were performed between 1995 and 2013. Patient survival after lung kidney transplantation was 92.9%, 71.0%, and 71.0% at 1 month, 6 months, and 1 year, with a median survival of 95.2 months. One- and five-year survival of 71.0% and 59.9%, after combined lung kidney transplantation, were similar to 81.7%and 51.4% after lung transplantation ($n = 23{,}913$) ($P = 0.061$ and 0.55 respectively). However, this was inferior to 1- and 5-year survival of 94.9% and 82.8% after kidney transplantation alone ($n = 175{,}269$), ($P < 0.0001$), respectively. In summary, patient survival after lung kidney transplantation was similar to isolated lung transplantation, and these results suggest that lung kidney transplantation is a reasonable option for lung transplant candidates with significant renal dysfunction.

Table 5 shows the details of the waitlisted and transplanted counts for both heart kidney and lung kidney candidates spanning from 1987 to 2010. Table 6 outlines the etiology of underlying organ dysfunction in these simultaneous heart-kidney and lung-kidney wait list groups.

Ethics of Dual Organ Transplantation

With a scarce organ supply, the principles of utility and equity must be considered for all waitlisted patients with the caveat that some of these dual transplantation candidates will have competing needs against the candidates listed for single organ transplantation. It is quite likely that the candidates listed for single organ transplantation may have greater potential benefits by receiving the nonprimary organ of the dual transplant candidate. These groups include individuals such as children, highly sensitized individuals, and those where the risk of death may be higher without transplantation. Kiberd et al. (2011) studied patient survival by allocating a liver and kidney transplant to two separate individuals versus allocating the two organs to one individual. The conclusion was that cumulative survival was better with separate allocation unless a high probability of reaching ESRD existed within 1 year of liver transplantation. This question of dual versus single organ transplantation would not be raised so frequently if organ supply was not scarce. It is agreed upon that certain advantages to dual transplantation do exist since surgery and induction immunosuppression is only needed once. One bypasses the waiting time to get another organ transplant and immunologic exposure is limited to only one deceased donor. Also, in SLK transplantation, it is generally felt that the risk of rejection for kidney is lessened due to protective effect of liver as shown by Creput et al. (2003) and Ruiz et al. (2006).

Currently, transplant center quality metrics do not include dual organ transplant outcomes and

Table 6 Etiology of organ dysfunction in simultaneous heart-kidney and lung-kidney wait list groups (Adapted from Wolf et al. 2013)

	Simultaneous heart-kidney	Simultaneous lung-kidney
n	1420	41
Etiology of end-stage renal disease		
Diabetes	196	2
Tubular and interstitial diseases	165	10
Glomerulonephritis	159	5
Hypertensive nephrosclerosis	143	4
Retransplantation/graft failure	75	2
Polycystic kidney	43	0
Renovascular diseases	38	3
Other/unspecified by UNOS	591	15
Etiology of lung failure		
Cystic fibrosis or immunodeficiency disorder	–	6
Pulmonary vascular disease	–	10
Restrictive lung disease	–	20
Obstructive lung disease	–	4
Other/unspecified by UNOS	–	1
Etiology of heart failure		
Nonischemic cardiomyopathy	576	–
Ischemic cardiomyopathy	519	–
Retransplant/graft failure	192	–
Valvular heart disease	33	–
Other/unspecified by UNOS	100	–

Table 7 Proposed reforms to policy and practice of renal transplantation with other organs (Adapted from Reese et al. 2014)

Reforms	Ethical implications
1.Establish minimal clinical criteria for listing of nonprimary organ(s)	Improves equitable distribution and access to organs Improves utility via lesser allocation of organs to MOT candidates who derive less benefit from additional organs than other candidates on the waiting list
2. Restructure current allocation of multi-organ transplant candidates	
Consider downgrading the allocation priority of multi-organ transplant candidates for their additional organs versus the priority of children	Promotes equity by prioritizing children as "the worst off" (in terms of potential life years) and utility since children typically derive excellent survival benefit from transplant
Consider downgrading the allocation priority of multi-organ transplant candidates for their kidneys versus the priority of sensitized candidates	Promotes equity by recognizing the claims of individuals who have waited for an organ, or who have limited opportunities for a compatible match, and whose health is likely to deteriorate during the delay in transplant
Consider downgrading the allocation priority of multi-organ transplant candidates for their kidneys versus the priority of individuals with prolonged waiting times	
3. Include multi-organ transplant outcomes in center quality metrics	Improves transparency and accountability Improves utility by discouraging inappropriate use of nonprimary organs for MOT Promotes equitable access to organs by discouraging inappropriate diversions from recipients of single organs

such reporting should be encouraged with appropriate adjustment made to account for greater degrees of sickness for such candidates. Reese et al. (2014) have also proposed some policy approaches to improving ethical practice of multiple organ transplantation as shown in Table 7.

Conclusion

Transplantation of kidney with other organs is pursued in some selected cases. For SPK transplants, UNOS has clearly defined listing criteria which is already implemented. For SLK transplantation, UNOS has approved eligibility criteria which have recently been implemented. Minimum dual listing criteria for renal transplantation with heart or lung do not exist currently but these dual transplants in general are very few. Variable listing and subsequent dual transplantation practices have limited high-quality data that can be used to add value to the concept of dual transplantation versus single organ transplantation. Additionally, there are no randomized controlled trials comparing dual to single organ transplantation. There are advantages to dual organ transplantation but outcomes metrics are currently neither measured nor reported by UNOS. In summary, the practice of renal transplantation with other organs is becoming more prevalent but there exist striking differences in listing practices across different transplant centers.

Cross-References

- ▶ Ethical Issues in Organ Transplantation
- ▶ Organ Procurement Organization and New Kidney Allocation
- ▶ Recipient Selection for Kidney Transplantation

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Anesthesia Management in Kidney Transplantation

George Hsu and Yoogoo Kang

Contents

Abstract

Excellent anesthetic care of renal transplantation consists of a detail understanding of end-stage renal disease (ESRD), thorough preoperative assessment, intraoperative maintenance of recipient hemodynamics and donor organ perfusion, and diligent postoperative care with medications and fluids. Coupled with

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good surgical practice, excellent anesthesia may lead to successful transplantation.

Keywords
Anesthesia · Renal transplant · End-stage renal disease · Pathophysiology · Induction · Monitoring · Drugs · Pressors · Fluids · Transfusion · Reperfusion

Introduction

End-stage renal disease (ESRD) and its associated comorbidities present unique challenges to the anesthesiologist. Detailed preoperative evaluation of the patient and optimization of various organ functions, especially the cardiopulmonary system, are prerequisites prior to transplantation. During transplantation, maintenance of hemodynamics of the recipient and perfusion of the transplanted organ plays a critical role in achieving successful transplantation. Vigilant postoperative care to maintain adequate hydration and renal blood flow, satisfactory analgesia, and immunosuppression are all important to achieve a positive outcome.

Pathophysiology

ESRD affects many major organ systems (Rabey 2001). Uremic encephalopathy ranges from altered mental status, decreased mentation, and frank coma. Neuropathies, both peripheral and autonomic, are also prevalent due to deposition of calcium phosphate and other toxins to the nervous tissue (Fraser and Arieff 1988). In the cardiovascular system, ESRD predisposes to hypertension, accelerated atherosclerosis, and hyperlipidemia. As a result, patients may develop coronary artery disease, cerebrovascular accidents, cardiomyopathy, and heart failure. Diabetes and arterial disease (hypertension and atherosclerosis) are the two most common causes of ESRD, with prevalence of over 30% and 80% in ESRD, respectively. These underlying pathophysiological processes also lead to coronary disease in up to 25% of patients with chronic kidney disease (Schmid and Jungwirth 2012). Pulmonary edema and pleural effusion also ensue secondary to volume overload and heart failure. Delayed gastric emptying, from diabetes or autonomic neuropathy, is also common. Acidosis and hyperkalemia, hyperphosphatemia, and hypocalcemia are typical of ESRD without dialysis or after delayed dialysis. Osteodystrophy and soft tissue calcification (due to altered parathyroid hormone level, hyperphosphatemia, calcium catabolism, and excessive vitamin D) are also prevalent secondary to accumulation of toxins as well as from coexisting diabetes (Thomas et al. 2008). Decreased level of erythropoietin causes anemia, while the low levels of von Willebrand factor decrease platelet count and platelet function.

Preoperative Evaluation

Given the extensive comorbidity associated with ESRD, a thorough preoperative evaluation is mandatory to identify further need for optimization prior to surgery. In addition, medical evaluation quantifies perioperative risk and the degree of necessary monitoring. Preoperative evaluation begins with history and physical examination.

The electrocardiogram (ECG) should be reviewed for ischemia. Prolonged Q-T intervals appear to be more frequent in ESRD (Genovesi et al. 2008). A chest X-ray could identify pulmonary edema or evidence of fluid overload. Patients with any cardiac symptoms or signs, such as decreased exercise tolerance, exertional chest pain, abnormal ECG, and chest X-ray, or those with three or more coronary disease risk factors (see list below), should undergo further cardiovascular testing with echocardiogram or stress test. Repeated cardiac assessment may be warranted for high-risk conditions such as unstable coronary syndrome, heart failure, significant arrhythmias, and severe valvular disease, since patients are often on the waiting list for an extended period of time (Kapoor et al. 2007).

Risk factors associated with coronary disease:

Diabetes mellitus
Known coronary artery disease

Dialysis > 1 year duration
Left ventricular hypertrophy
Age > 60 years
Hypertension
Dyslipidemia

Airway examination may also reveal stiff joint syndrome, especially for patients with insulin-dependent diabetes mellitus. The "prayer sign," the inability to oppose palms, may also suggest atlantoccipital fixation and difficult tracheal intubation (George and Jacob 2003).

Laboratory tests, including complete blood cell count, electrolytes, and coagulation profile, are also mandatory. If moderate anemia is present (6–8 gm/dL), erythropoietin may be administered before transplantation. If severe anemia is present (<6 gm/dL) or if transplantation is imminent, transfusion may be necessary to ensure adequate oxygen delivery. Though patients with ESRD often have varying degrees of hyperkalemia and are relatively resistant to medical management, a potassium level of <5 mmol/L is ideal prior to transplantation (Morgan et al. 2006). Excessive hyperkalemia should be aggressively treated medically using glucose and insulin infusion or Kayexalate, or by hemodialysis prior to transplantation. Metabolic acidosis may also develop since acids are accumulated in the absence of renal function. Patients with moderate to severe metabolic acidosis may also require hemodialysis before transplantation. Blood products should be readily available since patients with anemia or coagulopathy may require blood transfusion (Rabey 2001).

Intraoperative Management

Anesthesia and Induction

General anesthesia, regional anesthesia (spinal and epidural anesthesia), and a combination thereof are all feasible anesthetic techniques. However, general anesthesia is usually preferred due to the emergent nature of the surgery, high aspiration risk, the prolonged duration of surgery (usually >3 h), the frequent use of invasive monitoring, and risk of underlying coagulopathy. Induction of general anesthesia is followed by tracheal intubation. Propofol (2 mg/kg) is the most commonly used induction agent, while etomidate (0.2–0.3 mg/kg) is chosen for patients with less cardiopulmonary reserve. Various muscle relaxants can be used safely to facilitate tracheal intubation; succinylcholine (1 mg/kg), rocuronium (0.6–1.2 mg/kg), or cisatracurium (0.2–0.3 mg/kg). Succinylcholine may worsen preexisting hyperkalemia, although patients with renal failure are often resistant to hyperkalemia and the increase in serum potassium level of 0.5–1 mmol/L is no more than that of patients without renal dysfunction (Morgan et al. 2006). Rocuronium is primarily excreted via the biliary system, but a prolonged duration of neuromuscular blockade may occur. Cisatracurium is degraded through nonenzymatic Hoffman elimination (ester hydrolysis) and is, therefore, ideal for patients with renal failure (Schmid and Jungwirth 2012). In the setting of high risk of aspiration, either succinylcholine or rocuronium may be chosen to secure the airway and then cisatracurium for maintenance (Rabey 2001). If difficult airway is anticipated or if the patient is at high risk of aspiration, an awake fiber-optic intubation is preferred.

Monitoring

Monitoring begins with standard monitoring defined by American Society of Anesthesiologists (ECG, pulse oximetry, blood pressure, capnography, and temperature). Due to lack of urine output as a measure of preload, central venous pressure (CVP) monitoring is essential to assess intravascular volume. Although CVP may vary depending on other factors (i.e., positioning, intra-abdominal pressure, the use of PEEP (Positive end expiratory pressure), and myocardial compliance), its trends over time may still be helpful as a surrogate for preload. For patients with left ventricular dysfunction, the use of a pulmonary artery catheter and/or transesophageal echocardiography is preferred to assess left-sided cardiac function, cardiac output,

and contractility. However, patients on dialysis through central veins or those with previous central venous access may develop central venous thrombosis or stenosis, making placement of central venous catheter rather challenging and rarely impossible (Rabey 2001). Though not essential, an intra-arterial catheter may be placed for beat-to-beat monitoring of blood pressure and frequent determination of the arterial blood gas tension and acid-base status, hemoglobin level, and coagulation profile.

Maintenance of Anesthesia and Other Drugs

A balanced technique with inhalational agents and opioids provides amnesia, analgesia, and some muscle relaxation during surgery. Potent inhaled anesthetics, such as sevoflurane, desflurane, and isoflurane, can be safely used. Sevoflurane has not shown any harmful effect in the clinical setting, although Compound A, produced when sevoflurane is in contact with soda lime absorber, can cause renal impairment in rats. A rapid increase in the plasma level of desflurane may cause tachycardia and is undesirable in patients with coronary artery disease. Enflurane, an older inhalation agent, is best avoided due to generation of potentially nephrotoxic fluoride ions. For analgesia, fentanyl is effective at normal doses, as it mainly undergoes hepatic metabolism and excretion. Morphine should be titrated very carefully due to potential for accumulation of active metabolite, morphine-6-glucuronide (Schmid and Jungwirth 2012). Hydromorphone, a longer acting potent opioid, also provides excellent analgesia, especially for patients on chronic opioids and/or with high opioid tolerance.

Positioning

Typically patients remain in the supine position for the duration of the renal transplantation. Because of the high incidence of diabetes and peripheral neuropathy in renal patients, care should be taken to avoid compression or stretch injury to peripheral nerves. Arms are abducted less than 90° and preferably padded by gelpads or blankets. AV fistula or graft must be free of compression, and a warming device may be placed around the AV fistula or graft to avoid thrombosis. A noninvasive blood pressure cuff is placed on another limb to avoid occlusion of arterial flow and venous stasis (Rabey 2001). Initial palpation for pulse and/or thrill followed by periodic assessment of the AV fistula until the conclusion of surgery is recommended.

Drugs

Antibiotic prophylaxis, with intestinal anaerobic coverage, should be dosed appropriately since renal patients are at high risk of infection due to altered immune system and subsequent use of immunosuppression. Typically, prior to graft reperfusion, immunotherapy (frequently with steroids and basiliximab), is initiated to prevent graft rejection.

Diuretics

Furosemide (10–40 mg) and mannitol (0.5–1 mg/kg) may be administered to promote urine production and to flush renal tubules. Studies on efficacy of diuretics have not shown significant benefit (Schmid and Jungwirth 2012), but diuretics are relatively benign without significant side effects.

Pressors

Vasopressors, such as norepinephrine, cause renal vasoconstriction and are therefore undesirable during renal transplantation (Richer et al. 1996). Although low-dose dopamine may enhance renal blood flow via D1 receptors, studies thus far have not shown a clear benefit of its use in patients with acute renal failure or undergoing renal transplantation (Kellum and Decker 2001; Kheterpal et al. 2007). In fact, there is good evidence suggesting the contrary; therefore, the use of dopamine during renal transplantation is discouraged (Ciapetti et al. 2009; Holmes and Walley 2003). However, a

small dose of dopamine may increase cardiac output and improve renal perfusion (Dalton et al. 2005). The use of other vasopressors also cannot be recommended, but inotropes may be needed to maintain renal, coronary, and cerebral perfusion.

Antihypertensive Drugs

Some hypertensive patients may have persistent hypertension intra- or postoperatively. The use of beta-blockers (labetalol and metoprolol) is discouraged, because they may cause hyperkalemia (Bakris et al. 2006). Hydralazine or other vasodilators (nitroglycerine) may be used to control hypertension.

Fluids

During transplantation, euvolemia is critical in maintaining stable hemodynamics of the patient and optimal perfusion of the newly grafted kidney. Isotonic crystalloid solutions, such as normal saline, lactated Ringer's, and Plasmalyte-A® (Travenol, Skokie, IL) have all been used successfully (Trujillo et al. 2015). Infusion of a large volume of normal saline (>4 L) may cause hyperchloremic metabolic acidosis and subsequent hyperkalemia due to its lower pH (about 5.5) (O'Malley et al. 2005), while lactated Ringer's and Plasmalyte-A® solutions are still relatively hypotonic compared to blood. The efficacy of colloids in renal transplantation compared to crystalloids is unclear. Besides cost, albumin has the potential for anaphylaxis and infectious contamination, while dextrans and hetastarch have also been associated with anaphylaxis and bleeding complications. Therefore, the use of colloid during renal transplantation should only be considered when large amount of crystalloid is detrimental or when high oncotic pressure is needed (Schmid and Jungwirth 2012).

Transfusion

Since significant blood loss during renal transplantation is infrequent, blood transfusion is rarely necessary and may lead to a higher incidence of acute graft rejection (Schmid and Jungwirth 2012). Moreover, renal patients are often accustomed to chronic anemia, compensated by increased cardiac output and 2, 3-DPG, and are already on iron replacement therapy and/or erythropoietin. Therefore, the hemoglobin level which triggers transfusion may be lower than those without renal failure (Kapoor et al. 2007), although it is still affected by the overall physiologic reserve and comorbidity of the patient.

Reperfusion

Reperfusion occurs when the vascular clamps are removed. Hypotension may occur due to vasodilation and acidosis, and usually is restored by fluids, sodium bicarbonate (0.5–1 mEq/kg), and small doses of inotropes. Occasionally, ischemia of the renal graft or residual organ preservation solution may cause hyperkalemia, which should be aggressively treated with sodium bicarbonate, calcium, insulin and glucose. Immediately after reperfusion, a friendly physiologic environment for the newly grafted kidney is imperative in ensuring immediate and long-term renal function (Rabey 2001). As renal function is dependent on renal perfusion, maintenance of optimal preload, cardiac output and renal perfusion is critical and cannot be overemphasized. A target CVP of 10–15 mmHg and a systolic blood pressure of 120–140 mmHg (as a surrogate of good cardiac output and perfusion) maybe reasonable parameters (Kapoor et al. 2007). Furthermore, normalization of acid-base state and glucose control contribute to homeostasis of the renal graft and successful outcome of the renal transplantation.

Postoperative Care

Continuous and close postoperative monitoring of the patient, whether in the postoperative anesthesia care unit (PACU) or the intensive care unit (ICU), is paramount for good patient outcome. Aside from supportive care with supplemental

oxygen, intravascular volume is maintained to avoid hypovolemia by CVP monitoring. A close frequent monitoring of urine output is essential, and additional boluses of isotonic fluids may be administered to maintain intravascular volume and urine output. A chest X-ray is routinely obtained to ascertain proper positioning of the CVP catheter and look for evidence of volume overload (Rabey 2001). Careful titration of IV opioids, through boluses or PCA or epidural anesthesia, provides adequate analgesia and mitigates the development of tachycardia and hypertension, both of which could lead to increased myocardial oxygen demand and myocardial ischemia. Continuation of immunosuppression decreases the risk of graft rejection (Schmid and Jungwirth 2012), and avoidance of nephrotoxic agents, including NSAIDs, may minimize graft dysfunction in the long term (Rabey 2001).

Special Considerations: Anesthesia for Living Donors

Due to the advantages of the elective nature as well as increased graft survival, living donation of the kidney is an alternative to cadaveric kidney transplantation (Kapoor et al. 2007). Preoperatively, living donors are evaluated medically and psychologically to ensure full informed consent without coercion. Living donors should be in good health (ASA I or II) without significant systemic disease. General anesthesia with tracheal intubation is usually preferred, especially for laparoscopic nephrectomy, which involves creation of pneumoperitoneum in the lateral position. In patients with laparoscopic nephrectomy in the lateral position, the positioning must be carefully assessed to avoid compromise of ventilation and nerve and soft tissue injury. Typically, standard ASA monitors (ECG, pulse oximetry, and cuff blood pressure) are employed without invasive monitoring, and two large bore IVs are sufficient for surgery. Cefazolin, a first generation cephalosporin, is typically used for surgical antibiotic prophylaxis. Prior to vascular clamping of the renal vessels, heparin (100 U/kg) is given for thrombotic prophylaxis, which may be reversed later with protamine (mg/100 U of heparin) if needed. Same as with the anesthetic management of the recipient, renal perfusion (both the donor kidney and the remaining kidney) is maintained via optimal fluid administration. The goal of fluid management is to maintain stable circulation, positive fluid balance, and good donor urine output (>1 mg/kg). Diuretics, such as mannitol (0.5 g/kg), are often given in conjunction with proper hydration. Postoperatively, patient centered analgesia (PCA) with an opioid is standard and NSAIDs are best avoided (Kapoor et al. 2007).

Conclusion

Anesthesia for renal transplantation presents unique challenges to anesthesiologists and requires a thorough understanding of the pathophysiology of ESRD and its comorbid disease processes. First, a detailed preoperative evaluation allows identification of pathology and optimization of disease process prior to surgery. Intraoperatively, graft function is better preserved by maintaining homeostasis and optimizing renal perfusion. Lastly, postoperative close monitoring of circulation and fluid balance, adequate analgesia, continuation of immunosuppression, and avoidance of nephrotoxic agents lead to successful transplantation.

Cross-References

▶ Pathology of Kidney Transplantation

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Organ Procurement Organization and New Kidney Allocation

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Contents

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Abstract

Early attempts at kidney transplantation were plagued by technical difficulties; however, as the efficacy of renal transplant increased, so did the demand for the therapy. Organ Procurement Organizations came into being because of the considerable resources required to support deceased donor procurement and ultimate

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transplantation. On several occasions US legislation has been critical in assisting the build of transplantation infrastructure with the most noticeable piece being the 1984 National Organ Transplant Act which created the Organ Procurement and Transplantation Network (OPTN) as the main body to oversee transplant-related services. With the increasing demand for donor kidneys in the United States, the OPTN continually attempts to optimize the use of recovered organs while still ensuring fair access to transplantation for those on the waitlist. The most recent of these reforms came in December of 2014, with the implementation of the new Kidney Allocation System which brought nine new changes to the rules. The two most important changes are allowing dialysis time to be captured as waiting time for those candidates referred after dialysis initiation and the reliance on the Kidney Donor Profile Index score in directing kidney allocation.

Keywords

Organ Procurement Organization (OPO) · Kidney Allocation System (KAS) · Organ Procurement and Transplantation Network (OPTN) · National Organ Transplant Act (NOTA) · United Network for Organ Sharing (UNOS) · Kidney Donor Profile Index (KDPI) · Kidney Donor Risk Index (KDRI) · Calculated Panel-Reactive Antibody (CPRA) · Zero Mismatch Policy

Introduction

With half of a million people living in the United States with end-stage renal disease (ESRD) today, it is hard to fathom that 75 years ago kidney failure was almost always quickly fatal. For most of the twentieth century, kidney failure was synonymous with mortality unless the patient's kidneys somehow recovered. Multiple initial forays into the development of renal replacement therapies were unsuccessful, and it is probably true that many of these well-intentioned failures have been lost to medical historians. Peritoneal dialysis, hemodialysis, and kidney transplantation share a common theme in that their early development began with tentative applications and required multiple tweaks over a course of least two decades before widespread use of these therapies could begin. In addition, access to hemodialysis presaged problems with accessing kidney transplantation and foreshadowed the costs and hurdles from limited resources that continue to vex ESRD care today.

Because of the less technical machinery requirements and the lack of need for anticoagulants, peritoneal dialysis was the first successful renal replacement used in humans. Dr. Georg Ganter of the University Würzburg first reported on two cases of peritoneal dialysis in 1923, one being a woman with ureteral obstruction from uterine cancer. Unfortunately, with the rise of the Nazis, Dr. Ganter was forced into retirement soon after he nobly advocated for the rights of Jewish patients. By the time of his death in 1940, only 13 patients worldwide had been treated with peritoneal dialysis (Teschner et al. 2004).

Notable forays into developing hemodialysis technology also had roots in Germany, where in 1924, at the University of Giessen, Dr. Georg Haas became the first physician to try this therapy in human patients (Paskalev 2001). However, it would be almost another 20 years before it was used again by Willem Kolff in the World War II-ravaged Netherlands to treat patients with acute kidney injury (Kolff et al. 1944 reprinted 1997). Unfortunately, but understandably, with only a few hemodialyzer prototypes available to meet the needs of the many patients with kidney failure, careful patient selection was necessitated, leaving many to succumb until more dialyzers could be made (Blagg 2007).

It is commonly accepted that the first long-term successful kidney transplant was performed by Dr. Joseph Murray at the Brigham and Women's Hospital on December 23, 1954. The transplant occurred between the Herrick brothers and could only proceed because the recipient and donor were proven to be identical twins. The transplanted graft lasted 8 years and subsequent identical twin transplants were successful. However, dealing with rejection episodes in non-

homozygous donor and recipient pairs presented an enormous hurdle. Developing the means to avoid rejection, primarily with immunosuppressing medication, became the principal driver to widening the application of kidney transplantation. Thus, it took more than 20 years before kidney transplantation could assume its preeminence in ESRD care for all patients and not just those with an immunologically well-matched living donor.

Despite the inferior outcomes of unmatched kidney transplants in 1967, renal disease experts recognized the value of kidney transplant and positioned it at least in the same tier as dialysis therapy in terms of clinical importance. The report of the Special Committee on Chronic Kidney Disease chaired by Carl W. Gottschalk definitively established for practicing US doctors that transplantation and dialysis therapies for renal failure were no longer experimental, even though high rates of difficult to treat rejection were still common with transplant therapies. This report, although read only by select audiences, had an undeniable influence in revising Medicare legislation to include the End-Stage Renal Disease Entitlement in 1972, ensuring dialysis patient and kidney transplant patient coverage (Rettig 1991). In 1968, the Uniform Anatomical Gift Act was enacted which helped to better standardize the organ donation process which up to that time varied state to state (NCCUSL 1968). At approximately the same time, the first Organ Procurement Organization (OPO) in the United States, the New England Organ Bank, came into being. Other OPOs were established not long after this as transplant professionals tried to increase the availability of deceased donor organs. As the vast majority of hospitals in the United States did not and still do not have transplant surgery capabilities, OPO assistance in organizing resources for organ procurement was essential to its occurrence, and this continues to be true today. The additional duties of OPOs with regard to deceased organ donation are to provide comfort for surviving family and friends during the death process and to obtain and communicate critical medical information that may affect organ quality and allocation.

During this time period, kidney transplantation from deceased donors was a rare occurrence, especially when compared to today's standard. It had been accomplished by Drs. Joseph Murray, the same surgeon who worked with the Herrick twins, and David Hume in 1962, but proving its superiority to dialysis therapies was far from being the case. Unlike the living kidney transplant scenario where immunologic matching was often easier because of genetically related family members, deceased donor transplants faced much more complicated routing if they were going to find an immunologically well-matched home. In addition, if the matching was not strong, the outcomes suffered significantly, and the recipient could be worse off than if they had remained on dialysis.

Many attempts were made to overcome the immune-mediated rejection of transplanted allografts, including severe bone marrow suppression with total body irradiation, 6-mercaptopurine, cyclophosphamide, and azathioprine (Starzl 2000). However, the specific advancement that finally tipped the scales in favor of kidney transplantation over dialysis was the introduction of cyclosporine in the late 1970s. The extract from the fungi *Cylindrocarpon lucidum* and *Trichoderma polysporum* was found to preferentially target T lymphocytes without the accompanying bone marrow suppression or organ toxicity as seen with azathioprine and cyclophosphamide (Dreyfuss et al. 1976; Borel et al. 1977). Thus, cyclosporine dramatically reduced rejection rates even for highly unmatched grafts, and it quickly became apparent that transplant recipients fared much better than their dialysis requiring cohorts (Port et al. 1993).

The improved outcomes of kidney transplant recipients, as well as the unscrupulous behavior by some who hoped to profit from developing an organ trade, prompted increased federal government inquiry and oversight (Sullivan 1983). In October 1984, through bipartisan efforts and sponsorship by Representative Al Gore and Senator Orrin Hatch, the National Organ Transplant Act (NOTA) was signed into law by President Reagan. The most straightforward accomplishment of this new legislation was the outlawing of buying and selling organs. More importantly

it seized the opportunity to advance the infrastructure that was needed to allow deceased donor transplantation to grow. Thus, the Organ Procurement and Transplantation Network (OPTN), which acts as the main umbrella organization for transplantation in the United States, was created (Neylan et al. 1999). Today OPTN membership includes all transplant centers, OPOs, and transplant histocompatibility laboratories.

NOTA also allowed the adaptation of an already present program into more prominent infrastructure. This was the conversion of the Southeastern Organ Procurement Foundation (SEOPF) into United Network for Organ Sharing (UNOS). SEOPF was originally formed by a group of transplant professionals in 1968 with the goal of determining where deceased donor kidneys could best be utilized (Stegall 2017). However, as the number of patient awaiting a deceased donor kidney increased and the knowledge of immunologic matching improved, the complexity of this problem became daunting. In 1977, SEOPF became the first organization to use a computerized database named "United Network for Organ Sharing" to help with deceased donor kidney allocation. In 1982, SEOPF established a call center in Richmond, Virginia, to assist with organ placement in the same location of today's UNOS headquarters. UNOS was formed in 1984, as a nonprofit organization, and was awarded the contract to operate the OPTN in 1986, and it has since been the sole entity to manage the contract (UNOS 2017).

With UNOS managing the OPTN, a transparent methodology was established for how all the processes behind deceased donor procurements and transplantations would be conducted. This included rules on how OPOs would operate and how waitlists for various organs would be constructed. Committees were established for each organ system and for other specific concerns to help manage the OPTN. A principal effort was directed toward developing a system that would maximize safe deceased donor organ usage for transplantation. Waitlist construction for each organ system for biologic reasons was and is still organized by blood type. In terms of deceased donor kidneys, other factors would be taken into consideration. Most importantly, the human leukocyte antigen (HLA) makeup of both donor and recipient has significant relevance in waitlist construction; thus the individual candidate rankings were and are frequently quite different even for donors of the same blood type. In 2007, DonorNet® was disseminated in the United States, and organ offers started to be made in a computerized fashion over the Internet. This allowed easier viewing of the specific match run for each organ offer and provided greater dissemination of information on both donors and potential recipients. In 2013, in an attempt to eliminate disparities in access for ethnic minorities and highly sensitized candidates, as well as provide comprehensive data about kidneys in an effort to guide transplant decision-making, the UNOS board approved the Kidney Allocation System or KAS. This new strategy went into effect on December 5, 2014, and contained nine major revisions to the kidney allocation policy with the goal of maximizing the utility of every donated kidney without diminishing access, particularly for high-risk groups.

Summary of the Kidney Allocation System Changes:

1. Waiting time will capture prior time spent on dialysis (section "Living Kidney Transplantation and Living Kidney Exchange Programs").
2. Simultaneous local and regional offers of kidneys with higher parenchymal risk (i.e., KDPI score greater than 85%) (section "Geographic Considerations").
3. Elimination of OPO-specific variances (section "Geographic Considerations").
4. Elimination of the Payback Policy (section "Geographic Considerations").
5. Kidney Donor Profile Index (KDPI) score used for allocation over the old definitions of SCD, ECD, and DCD (section "The Development of Calculators and the Reliance on the Kidney Donor Profile Index (KDPI) Score for Allocation").
6. Longevity matching for the top 20% adult posttransplant survival candidates (EPTS score $\leq$20%) for kidneys with a 20% or better KDPI (section "Utility Concerns and the Estimated Posttransplant Survival Score").

7. Sensitization addressed in a stratified fashion with special measures for the highly sensitized (section "The Development of the Calculated Panel-Reactive Antibody (CPRA) and the Very Highly Sensitized").
8. Improved access for blood type B candidates using A2 and A2B donors (section "Improved Access for Blood Type B Candidates").
9. Defining living donors by procurement not transplant (section "Living Donor Defined by Procurement").

Living Kidney Transplantation and Living Kidney Exchange Programs

Living kidney transplantation is usually considered as the best option for any patient needing a transplant. However, the reasons today are somewhat different than they were during the early history of kidney transplantation. In the early years of kidney transplantation, immunologic matching of genetically close family members was given a strong preference over other therapeutic choices with the ideal option of having an identical twin or sibling as an immunologic match. Haplo-identical matches from parents donating to children, children donating to parents, or siblings donating to siblings were also given preference.

With improvements in immunosuppression, familial matching lessened in importance, and spousal and friend donation has become more common and is now highly encouraged. In addition, as the number of patients awaiting a kidney transplant increases, the need for access to a living donor transplant is of paramount importance, regardless of the degree of immunologic matching. Also, as the collective knowledge of kidney disease pathology and genetics has progressed, it has become possible to better standardize the evaluation process of living donors. The persistent pressure to increase the number of living donors has led many centers to consider using individuals as donors with medical conditions that would have previously disqualified them (i.e., obesity, hypertension, and age >60) (Rao and Ojo 2009).

Another method of overcoming the massive shortage of living donor kidneys is the invention and building of infrastructure for living donor exchange programs. This type of program was first proposed in 1986, when kidney transplantation had proven its superiority over dialysis for the definitive treatment of end-stage renal disease (ESRD) (Rapaport 1986). However, functional living kidney exchange programs in the United States did not become fully operational until the 2000s, with its strongest US proponents being transplant surgeons at Johns Hopkins Hospital in Baltimore (Akkina et al. 2011). In contrast, South Korea, which faced greater struggles with developing a deceased donor infrastructure than in the United States, began the earnest operation of a living donor exchange program as early as 1991 (Park et al. 1999). One of the reasons for the relatively slow adoption of living donor exchanges in the United States was that the original NOTA legislation of 1984 prohibited the profiteering from organ procurements. Thus federal regulations needed improved language to ensure that living donor exchange programs could function legally. This did not occur until 2007, with the Charlie W. Norwood Living Donation Act, which established that paired donation is not considered valuable consideration (an inducement to enter into a contract that is enforceable in the courts) (Akkina 2011). With this improved legislation and the widespread acceptance of the United States transplant community of its potential benefit, robust exchange programs are now operational with at least one of the programs managed by UNOS. It is fairly clear now that US exchange programs offer a very functional and usually successful solution for patients needing a transplant who have one or several medically and socially suitable but incompatible donor(s). The one area where the current exchange programs are less functional is if the recipient is extremely sensitized. For the extremely sensitized, the need for a large number of potential donors to find a compatible situation can be a daunting challenge and may require a number beyond the scope of today's US exchange program enrollment. Because of the transportation issues involved in exchange programs, including the need to box organs and ship

them on flights, local OPOs have played a critical role providing logistical support. Many of the same processes necessary with deceased donor kidney transplantation have had to be adapted to assist with living kidney exchanges. Yet despite the strong emphasis on living kidney donation, improved abilities to deal with immunologic incompatibilities, and a modest broadening of the living donor criteria, living donors made up less than 30% of the kidneys transplanted in the United States in 2017 (OPTN 2017).

Deceased Donor Kidney Scarcity and Waiting Time

The invaluable resource that deceased donors have provided was recognized at the outset of their use, but the ever-increasing disparity in the limited supply versus the ballooning demand has necessitated multiple informational campaigns to target the lay public (Chatterjee et al. 2015). Public policy adaptation to the precious resources of deceased donor organs has led to being able to designate oneself as an organ donor when applying for a driver's license in all states and the District of Columbia as of 2017 (Department of Health and Human Services 2018). A look at trends does show that the number of deceased donor kidneys available to transplant has increased considerably during UNOS's history. In 1988, there were slightly more than 4,000 deceased donors nationally, whereas in 2016, which was record year in deceased donation, there were just under 10,000 (OPTN 2016). Reasons for this increase are multifactorial and include education to the public on the benefits of deceased donor transplants, updated legislation to bar revoking of a deceased donor's consent to donate made while the donor was alive, and standardization of practices on how deceased donor families should be approached. This increase, however, pales in comparison with the increased number of patients awaiting a kidney transplant not to mention all patients requiring dialysis. In 1988, the number of candidates awaiting a kidney transplant was 10,000. By October 2017, the number had grown to over 96,500 (OPTN 2017). In addition, the dialysis population in the United States has approached 500,000 patients by 2017 (USRDS 2017). Putting this information together describes the dominant trend in kidney transplantation need. Since the establishment of the OPTN, there has been an almost 2.5× increase in deceased donation, but there has also been a greater than ninefold increase in the number of patients awaiting a deceased donor kidney. The principal area of growth is the increased number of patients being listed at greater than 50 years of age (OPTN/UNOS 2008). Thus, the number of patients needing a deceased donor kidney transplant has always outnumbered the number of kidneys available, and the gap between the resource and demand is widening. Despite the concentrated effort toward raising awareness for living kidney donation, deceased donor kidney transplants have outnumbered living donor transplants in the United States by more than two to one over the last 30 years of OPTN data (OPTN 2017). Considering these realities, patients needing a kidney transplant and who do not have a living kidney option face an obligate wait of potentially many years for a deceased donor kidney.

Following ethical principles of equity (fairness), how long a particular candidate has been waiting for a kidney transplant has been consistent, and is often the deciding factor in allocation, with each year of time waited being worth a point and each second waited being added incrementally to a candidate's score. How this time is accrued has changed dramatically with the latest revisions to the national kidney allocation policy in 2014. Historically, time accrual only began once two conditions were satisfied: (1) the candidate's glomerular filtration rate was documented as at or below 20 cc a minute, and (2) the candidate had been listed by a transplant program. This meant that some patients might be on dialysis for a long period of time before being able to accrue allocation points. For patients who were diagnosed with ESRD on presentation, the functionality of getting onto a kidney transplant waitlist immediately could be an impossible endeavor. Many transplant programs refused to complete inpatient evaluations, necessitating the new

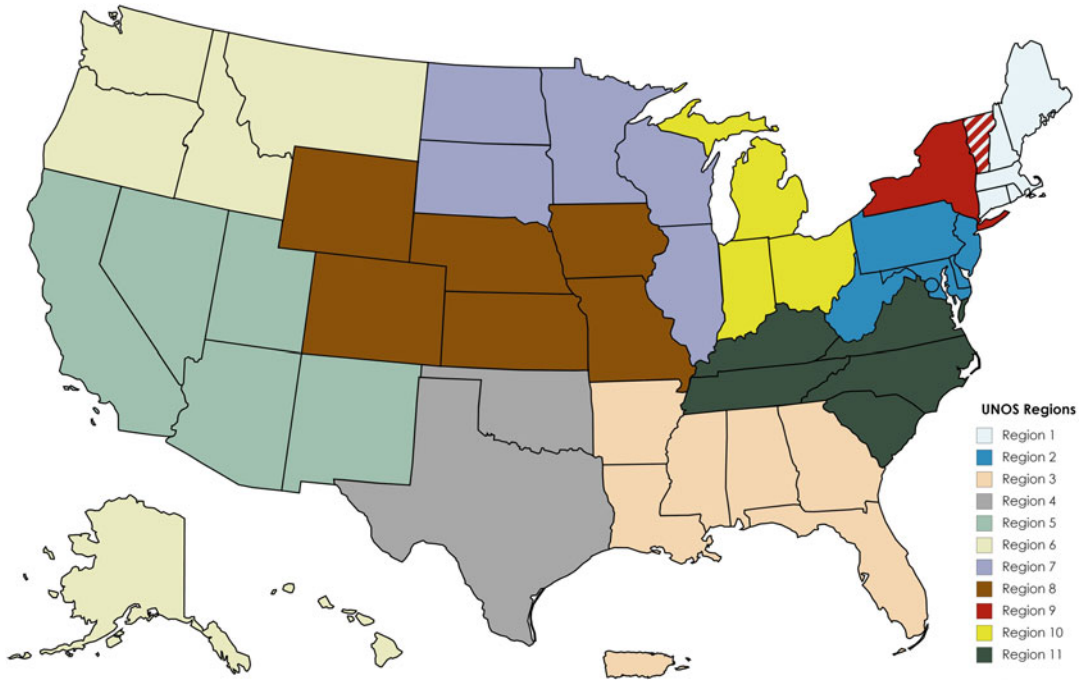

Fig. 1 This map illustrates the 11 regions of the United States and Puerto Rico set forth by the OPTN. The largely geographic divisions help to facilitate transplantation and are each individually represented on the Board of Directors and all OPTN standing committees. Important to note, a portion of Northern Virginia is included in Region 2 and Vermont is divided into Eastern and Western halves being serviced by Regions 1 & 9 respectively

ESRD patient return for outpatient appointments after they had left the hospital. A monumental change made with KAS is that for all candidates referred to transplant centers after initiating chronic dialysis, their waiting time would include all time since starting on chronic maintenance dialysis, as determined by the information on the Centers for Medicare and Medicaid Services form 2728 (OPTN 2014). This change was made to improve fairness in accessing deceased donor kidneys recognizing that many candidates were unfairly penalized by late referral to a transplant center.

Geographic Considerations

Initially, the allocation of organs from deceased donors was based on chance, with geographic location being the dominant or often the only consideration. Deceased donor kidney allocation today is still predominantly influenced by geography. The reasons for this are multifactorial and, in part, due to precedent. The United States is divided into 11 regions by UNOS (Fig. 1). Each region currently contains between 2 and 10 OPOs, with there being a total of 58 OPOs covering the United States and Puerto Rico. Each OPO covers a specific donor service area (DSA) which includes transplant centers and other hospitals in the area. Processes have been developed that are operational in all US hospitals so that patient deaths are referred to the local OPO for consideration of organ procurement. Certainly, in the codified rules of deceased donor kidney allocation, there is a preference for local use, i.e., within the same donor service area in which they are procured, to allow those organs to service the same community which provided them. Other factors that favor local organ use are concerns of long cold ischemia times engendered by travel and the general desire to have the same surgical teams responsible for the transplant to be involved in the recovery.

Between 1998 and 2000, the US Department of Health and Human Services amended NOTA to include the "OPTN Final Rule" in order to preference national use of procured organs over local use if the acuity of waitlisted patients warranted it (Smith et al. 2012; Stegall et al. 2017). The impact on kidney allocation was initially minor as an established alternate therapy in the form of dialysis was readily available; thus increased severity of illness could not be readily justified as a reason to transport kidneys nationally. Nevertheless, with the latest major changes in kidney allocation put into effect in December of 2014, there have been three modifications made to support the regional and national sharing of deceased donor kidneys. The impact of these changes created an increase of the number of deceased donor kidneys used outside the local DSA/OPO from 21% pre-KAS to 32% during the initiation of KAS, with regionally distributed kidneys increasing from 8.8% to 12.7% and nationally distributed kidneys increasing from 12.6% to 18%.

The three changes that increased travel of deceased donor kidneys with the implementation of the new KAS were the elimination of OPO-specific variances, the regional sharing of higher parenchymal risk kidneys based on the individual donor's Kidney Donor Profile Index (KDPI) score being greater than 85%, and the regional and national sharing of kidneys to meet the need of highly sensitized waitlist candidates. OPO-specific variances, which existed pre-KAS, allowed routing of deceased donor kidneys in manners that did not follow UNOS rules and often had a strong localism aspect in their design (Weimer 2010). For example, the Gift of Life™, the OPO that services Delaware, the eastern half of Pennsylvania, and parts of New Jersey, directed deceased donor kidneys from the Harrisburg/Pocono area preferentially to patients listed at transplanted centers located close to these areas during the pre-KAS years. The effect of eliminating these variances does not impact regional or national sharing but does change routing within the OPO's DSA. The impact of immediately channeling higher KDPI kidneys (KDPI >85%) regionally has resulted in more regional transport of these organs, with local transplantation rates dropping from 69.2% to 50.9% after KAS intiation. Local transplants of kidneys with best parenchymal quality, a KDPI between 0% and 20%, changed very little from 23% pre-KAS to 22% post-KAS (Stewart et al. 2016). KAS mandates regional sharing of kidneys for waitlisted candidates who had a Calculated Panel-Reactive Antibody (CPRA) of 99% or greater and national sharing for candidates with a CPRA of 100%. This change in the allocation rules under the KAS led to an initial bolus in transplantation for these broadly sensitized candidates and increased movement of deceased donor kidneys out of the local OPOs. Of note, the new rules removed the difficult to track, and difficult to enforce, Payback Policy which existed pre-KAS where OPOs would accrue a kidney "debt" to the OPOs from which they imported a kidney. This aspect of the KAS was the one component that would decrease travel of deceased donor kidneys.

Both in the pre-KAS and post-KAS, geography still plays a dominant role in accessing deceased donor organs and kidneys. Today, in many OPOs the median waiting time cannot even be calculated because the majority of listed patients have not and will not achieve transplantation. In other OPOs, access to transplantation is much easier with some areas of the country having median access to deceased donor transplant in as little as 1 year (SRTR & OPTN 2012; Zhou et al. 2018).

The Acquisition of Data Leading to the Expanded Criteria Donor Category

Early on in deceased donor kidney transplant, it was acknowledged that deceased donor kidney quality was variable, and kidney graft life could be impacted by certain donor factors (Kasiske 1988). With the creation of the OPTN, data collection via a registry of transplant recipients and donors was established. This Scientific Registry of Transplant Recipients (SRTR) began collecting data in October 1987, on every transplant that occurred in the United States. By 1993, there was voluminous data available that definitively demonstrated deceased donor kidney transplantation's superiority over dialysis despite the

increased short-term morbidity and mortality risk associated with the additive surgery. By day 117 posttransplant, death rates between remaining on dialysis and receiving a deceased donor kidney became equivalent, and by day 325, transplantation began to demonstrate a consistent widening and improvement in survival (Wolfe et al. 1999). Broadening of criteria for who could be a deceased donor occurred during the 1990s, but as deceased donors with more complicated medical histories became commonplace, it became increasingly clear that the outcomes of these higher-risk transplants did suffer. Discard rates of already procured kidney also began to increase among certain types of donors.

In October of 2002, OPTN policy began to distinguish Expanded Criteria Donor (ECD) kidneys to allow a specific routing of these organs and to encourage a greater use of them in the appropriate recipients. ECD donors were defined as any donor 60 years old or older or a donor aged 50–59 with two of the following: a history of hypertension, a serum creatinine greater than or equal to 1.5 mg/dl, or death resulting from a stroke. These factors were found to have an increased relative risk of graft loss of 1.7 in comparison with a well-selected Standard Criteria Donor (SCD) reference group. Five-year graft survival for ECD kidneys was 51% in comparison with 68% for non-ECD kidneys (Wynn et al. 2004). Between 2002 and December 2014, pre-KAS, there were four specific deceased donor kidney allocation groups:

1. Kidneys from donors younger than 35 years of age being preferentially allocated to pediatric candidates (implemented in 2005)
2. ECD kidneys allocated to recipients who consented to receive these organs
3. Donation after cardiac death (DCD) kidneys being allocated according to a sequence that valued placement within a local distribution to lessen cold ischemia time
4. All remaining SCD kidneys being offered to all candidates on the waiting list

The specific concept regarding the ECD kidneys was an acknowledgment that these organs did have a shorter graft life, but the waiting time to obtaining them would be shorter than SCD grafts.

The Development of Calculators and the Reliance on the Kidney Donor Profile Index (KDPI) Score for Allocation

Liver allocation in the United States underwent major changes in early 2002. Prior to 2002, the Child-Turcotte-Pugh score and the candidate's location (home, hospital, or ICU) were the principal metrics used to define a candidate's level of illness and thus his/her position on the waitlist (Christensen et al. 1984). It became commonly agreed upon among liver experts that there was a lack of objectiveness in these measurements in defining the degree of liver decompensation. Ultimately, the liver transplant community decided that the Model for End-Stage Liver Disease (MELD) score, which was initially only studied for risk of transjugular intrahepatic portal-systemic shunt (TIPSS) placement, was a far superior measurement and decided to use this score in liver allocation (Desai et al. 2004; Smith et al. 2012). This began the use of calculators, sophisticated mathematical formulas, in allocation and would soon be duplicated in the coming decade in deceased donor kidney transplantation.

Further data accumulation in the SRTR, along with improved statistical methodology and a refined consensus of what impacted graft survival, allowed transplant researchers to develop formulas for the relative impact of different factors in graft and recipient survival. This was first accomplished for liver transplantation in 2006, when Sandy Feng published what would be known as the Liver Donor Risk Index (LDRI) which incorporated both donor and transplant variables in predicting the likelihood of liver transplant success (Feng et al. 2006). After Dr. Feng's publication, creating an analogous risk index for kidney transplantation became an objective for many researchers, and in 2009, Rao et al. published the Kidney Donor Risk Index (KDRI) (Rao et al. 2009). This initial KDRI score estimated the relative risk of posttransplant kidney graft failure for

the average adult recipient of a deceased donor kidney. Specifically, it ranged in value from 0.48 to 4.2, and descriptively a kidney with a KDRI score of 1.30 would have a relative risk of graft failure of 1.3 times the median kidney from the study time interval (Rao et al. 2009; Friedwald et al. 2013). It was also analogous to the LDRI in that it used both donor and transplant variables and thus was not immediately appropriate for use in kidney allocation, since transplant variables could only be known after completion of a transplant. The initial transplant variables for the KDRI were the level of HLA-B and HLA-DR matching between the donor and recipient, the cold ischemia time, and whether a dual deceased donor kidney transplant was performed. Soon the KDRI was adapted to be exclusive to the ten donor variables to make it readily useable for allocation (Rao et al. 2009). There are six binary and four complex donor variables:

1. Whether or not the donor's cause of death was stroke related
2. Donor history of hypertension
3. Donor history of diabetes
4. Donor hepatitis C status
5. Whether the donor is African-American or not
6. If the donor is a DCD donor
7. Donor height
8. Donor weight
9. Terminal serum creatinine level
10. Donor age

Variables 7 through 10 have a more complex impact on the score with the donor's height in centimeters and weight in kilograms having a linear inverse effect on the score with taller and heavier donors having a lower score (Rao et al. 2009). For all donors weighing greater than or equal to 80kg, the impact of weight is equivalent and thus there is no further reduction to the KDRI for these donors. Terminal serum creatinine also has a generally linear inverse relationship with the KDRI, but the impact of values greater than 1.5 mg/dl is lessened somewhat recognizing that many of the high creatinine donors are a simple manifestation of acute and recoverable donor kidney injury. Finally, the impact of the donor age is the most complex with both the young and old donors having higher KDRI scores (Rao et al. 2009).

Kidney Donor Profile Index (KDPI) is a simplified scoring system mapped from the KDRI and has a range of values from 0% to 100%, with 100% being the most risky deceased donor kidney transplants and lower scores being associated with higher donor quality and increased expected longevity. The reference group to which each kidney is mapped is the population of all deceased donor in the previous calendar year. KDPI began to be reported on DonorNet® in June of 2013, and ultimately was incorporated into determination of kidney allocation in December 2014. It was immediately apparent that the KDRI and its subsequent offspring, the KDPI, provided a much more granular and consistent metric on kidney quality than the SCD/ECD dichotomy (Friedwald et al. 2013). Figures 2 and 3 depict graft survival for kidneys of various KDPI scores.

With the initiation of the KAS, similar to the previous allocation system, there are four distinct pathways for kidney allocation within the new scoring system, namely, Sequence A for KDPI less than or equal to 20%, Sequence B for KDPI greater than 20% but less than 35%, Sequence C for KDPI greater than 34% but less than 86%, and Sequence D for KDPI greater than 85%. Within each of the sequences, candidates are rank-ordered according to points granted for circumstances such as waiting time, sensitization, being a prior living organ donor, or being a pediatric candidate. The specific criteria for routing in each sequence are detailed in Table 1. As previously mentioned, higher-risk kidneys with a KDPI score greater than 85% are offered locally and regionally with the hope that this will enable appropriate routing of these organs which face high discard rates. For kidneys with a KDPI score less than 21%, the new allocation rules have a special provisions for these organs, based primarily on utility concerns, routing them to be used in specific candidates who are expected to have the longest posttransplant survival.

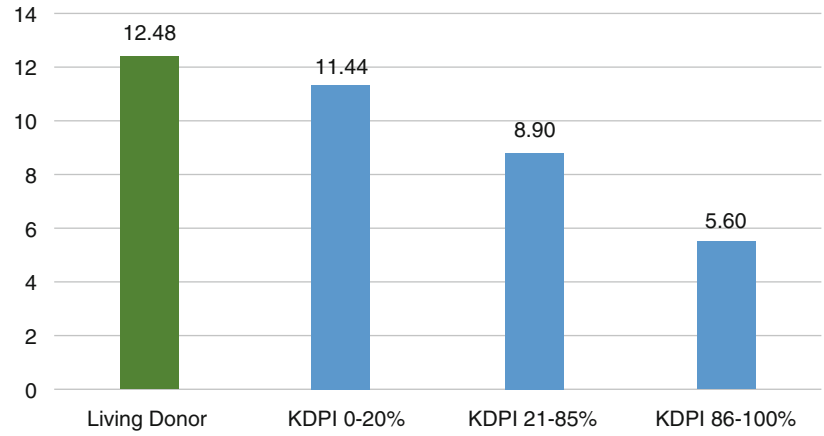

Fig. 2 This graphic compares the estimated half lives (i.e. the time it takes for ½ of the grafts functioning at one year to subsequently fail) of different donor kidney grafts in terms of years. The numbers used are based off of OPTN data as of March 21, 2018. (OPTN/HRSA 2018)

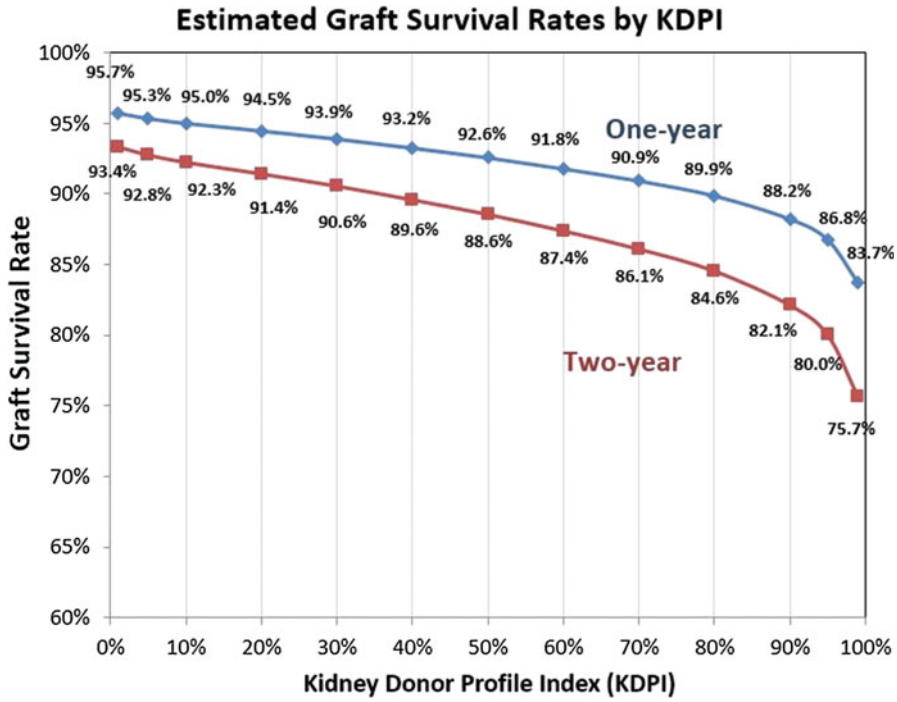

Fig. 3 The graphic illustrates both one-year and two-year estimated graft survival rates for donor kidneys based on their KDPI. The numbers used are based off of OPTN data as of March 4, 2016. (DonorNet 2018)

Utility Concerns and the Estimated Posttransplant Survival Score

As with allocating any scarce resource, two dominant principles have guided policy development in deceased donor kidney transplantation. Equity is a principal in which all candidates have a fair opportunity of accessing a resource, in this instance a deceased donor kidney. Utility is a principal based on the fact that society's benefit will be different depending on how the scarce resource is distributed. Prior to the changes introduced with KAS in December 2014, the deceased donor Kidney Allocation System focused

Table 1 This table shows a simplified summary of the current routing algorithm under KAS for deceased donor kidney grafts based on their KDPI as of March 2018. Within each of the sub-categories (e.g. local pediatrics) under a given sequence, transplant candidates are ranked in order of their allocation points

Sequence A (KDPI 0–20%)	Sequence B (KDPI 21–34%)	Sequence C (KDPI 35–85%)	Sequence D (KDPI 86–100%)
CPRA 98–100%	CPRA 98–100%	CPRA 98–100%	CPRA 98–100%
0-ABDR mismatch (EPTS 0–20%)	0-ABDR mismatch (all)	0-ABDR mismatch	0-ABDR mismatch
Local prior living donors	Local prior living donors	Local prior living donors	Local SLK safety net
Local pediatrics	Local pediatrics	Local SLK safety net	Local (all)
Local A2/ A2B into B (EPTS 0–20%)[a]	Local SLK safety net	Local (all)	Local (dual opt-in)[b]
Local (EPTS 0–20%)	Local (all)	Regional (all)	Regional (all)
0-ABDR mismatch (EPTS 21–100%)	Local A2/ A2B into B (all)[a]	National (all)	Regional (dual opt-in)[b]
Local A2/ A2B into B (EPTS 21–100%)[a]	Regional pediatrics	Local (dual opt-in)[b]	National (all)
Local (EPTS 21–100%)	Regional A2/ A2B into B (all)[a]	Regional (dual opt-in)[b]	National (dual opt-in)[b]
Regional pediatrics	Regional (all)	National (dual opt-in)[b]	
Regional pediatrics	National pediatrics		
Regional A2/A2B into B (EPTS 21–100%)[a]	National A2/A2B into B (all)[a]		
Regional (EPTS 21–100%)	National (all)		
National pediatrics			
National A2/A2B into B (EPTS 0–20%)[a]			
National (EPTS 0–20%)			
National (EPTS 21–100%)			

Stewart et al. (2016), Merola et al. (2017), OPTN (2018b) and OPTN/UNOS (2018)
SLK simultaneous liver-kidney
[a]For centers that perform A2/A2B into B transplants
[b]Kidney allocation policy changes scheduled to take effect in the third quarter of 2018

principally on equitable access with utility concerns only being prioritized for pediatric considerations, the Zero Mismatch Policy, and point boosts for specific HLA-B and HLA-DR matches. Research on models where utility is given the dominant weight in the allocation system was conducted by many, and it became increasingly clear that the number of life years gained in the allocation system dominated by equity was reduced in comparison with systems where utility was prioritized (Wolfe et al. 2008; Segev 2009).

The desire to alter kidney allocation with a greater focus on utility concerns became a perennial concern of the OPTN's Kidney Committee starting as early as 2003 (Friedwald 2013). By this time, it was becoming increasingly apparent that the waitlist's growth was predominantly among candidates greater than 50 years old with an increasing number being over 70 years old. Various proposals submitted to the OPTN's Kidney Committee were rejected because they were overwhelming ageist (OPTN/UNOS 2008). One eventual driver to changing policy was the recognition that younger waitlist candidates who received inferior-quality deceased donor kidneys were likely to return to the waitlist pool and require retransplantation and thus further deplete the number of organs available. Therefore, in December 2014, KAS introduced longevity matching as a policy tweak in which there would be routing of deceased donor kidneys with a KDPI score of $\leq$20% toward adult candidates who had the best 20% estimated posttransplant survival (EPTS) score. This score is only for candidates 18 years

or older and ranges from 0% to 100%, with higher scores having a worse posttransplant survival. Since data on the entire waitlist is required to generate a score, it utilizes a web-based calculator that requires input of four pieces of information. The date of birth of the candidate and the start date of chronic maintenance dialysis, if the candidate has started, are the two date variables required. The other two variables are binary in their effect on the score and are the candidate's diabetes history (either diabetic or not diabetic) and the candidates prior transplant history (either no prior transplants or a prior transplant). In its current form, the web-based calculator does allow the specific number of transplants to be entered and gives three different diabetes options, but none of choices alters the score. These four variables were selected by UNOS Board of Directors due to their objectivity and simplicity in an attempt to increase transparency of the process for the general population (Clayton et al. 2014).

The impact of longevity matching in adult patients for the EPTS $\leq$20% has likely been siphoned somewhat by the increasingly common scenario where another organ transplant pulls a desirable and likely low KDPI deceased donor kidney. For example, 2017 was a record year for both liver-kidney and heart-kidney transplants with 739 and 187 being done, respectively (OPTN 2017).

Pediatric Candidates

NOTA's initial language makes special provisions for pediatric patients, and there are multiple stakeholders in pediatric care that have lobbied for the protection of children and have placed their welfare as an objective of paramount importance. It also has been accepted by the transplant community that the benefit that a child can receive from an organ transplant may have long-standing health consequences over that individual's life and thus lead to a considerable gain in quality life years. Thus, the allocation system has consistently awarded children candidates with 4 points (i.e., 4 years of time) for those 10 years old or younger, with an additional point added if the donor has a KDPI score of <35% (OPTN 2018b). For those candidates between 11 and 17 years of age, 3 points have been awarded (Neylan et al. 1999; Smith et al. 2012; OPTN 2018b). Pre-KAS, deceased donors under the age of 35 years old were specifically directed toward pediatric recipients. Under KAS, preferential pediatric access is maintained, but routing is directed by a KDPI <35 instead of using donor age (Friedwald et al. 2013). Data post-KAS implementation has demonstrated only a modest negative effect on pediatric candidates' access to transplantation, despite many changes that would advantage adult candidates (OPTN 2016).

Early Immunologic Concerns, the Development of the Zero Mismatch Policy, and HLA-DR Matching

The surgical technique of kidney transplantation surgery was resolved long before the immune system's response to receiving another human being's organ was understood. The history of early kidney transplantation even a decade after the successful Herrick twin transplant was fraught with frequent failures that would be considered disgraceful by today's standards. Many early kidney transplants were lost due to preformed antibody against the donor that could not be recognized at the time (Kissmeyer-Nielsen et al. 1966). Going across blood groups was something that was occasionally tried and sometimes successfully, but the majority of researchers in the field abandoned these endeavors in the 1960s (Starlz 2000). In addition, it was becoming increasingly apparent that preexisting antibodies could lead to early graft loss even if blood typing was convincingly compatible and the surgical technical was flawless (Starzl et al. 1964). The human leukocyte antigen (HLA) was first discovered in 1958, but its true characterization continues to be a daunting challenge to researchers even today (Dausset 1958; Terasaki et al. 1965). Initially, what was simpler and easier to accomplish was to figure out if an immediate reaction was likely, and this could be done by mixing donor white cells with recipient serum (van

Rood et al. 1958; Patel and Terasaki 1969). Over time, characterizing the HLA became increasingly possible, and with improved understanding of this point of high variability, its importance in kidney graft survival when well-matched was undeniable (Mickey et al. 1971). In addition, it became increasingly apparent that certain patients were likely to have multiple antibodies to different HLAs and this presented an immunologic barrier to safe transplantation.

The importance of HLA matching was well known to the OPTN upon its creation, and in 1987, UNOS mandated sharing of HLA-A, HLA-B, and HLA-DR matched deceased donor kidneys as a major utility measure designed to prolong kidney graft survival. Curiously, the technology behind class II HLA (-DR and -DQ) typing had at least a 25% rate being inaccurate at that time (Burlingham et al. 2010). However, with improvements in polymerase chain reaction (PCR) technology and a better understanding of the HLA, UNOS was able to revise its mandated matched sharing policy in 1995, to adapt to possible situations in which there might be HLA homozygosity at one, two, or three of the loci (Leffell and Zachary 1999). Thus, this new policy required obligate sharing of deceased donor kidneys when there was an instance of zero ABDR mismatches (0-MM) between the recipient and donor at the HLA-A, HLA-B, and HLA-DR loci (Leffell and Zachary 1999). During this time, more than 15% of deceased donor transplants nationwide were allocated and transplanted under the Zero Mismatch Policy (Burlingham et al. 2010). In addition, points were awarded for the quality of HLA-B and HLA-DR matching, with the maximum amount of points being seven for 0-MM at these four alleles (Leffell and Zachary 1999; Neylan et al. 1999). The Zero Mismatch Policy did lead to increased travel of kidney and longer cold ischemia times. The Payback Policy also in effect mandated that for every 0-MM kidney that traveled, there was a likely payback kidney that returned to the donating OPO. However, studies of transplant outcomes of these traveling kidneys were favorable in terms of overall survival despite the increased cold ischemia times. The Zero Mismatch Policy was also an avenue for the more sensitized patients to be transplanted with 47% of the grafts going into patients who had panel-reactive antibodies of $\geq$80% (Stegall et al. 2002). In 2003, when it became increasingly apparent that African-Americans were being particularly disadvantaged because of low likelihood for this group to receive any benefit from HLA-B matching, B matching points were eliminated (Gill 2011; Hall et al. 2011). HLA-DR matching, however, was maintained and continues to be in use today, with 0-MM at the DR loci being awarded 2 points and 1-MM being awarded 1 point and the majority being 2-MM and being awarded no points. In 2008, for multiple reasons including phenomenal growth of an aging part of the waitlist, UNOS decreased the 0-MM sharing obligations to exclude patients whose CPRA was less than 20% (Burlingham et al. 2010).

The Development of the Calculated Panel-Reactive Antibody (CPRA) and the Very Highly Sensitized

One of the most important changes in immunologic testing in kidney transplantation in the last decade is the transition from Panel-Reactive Antibody (PRA) to the more epidemiologically refined CPRA. The PRA test delivers a broadness of sensitization of a particular candidate and traditionally is reported as a value of between 0% and 100%, with candidates who are non-sensitized having values of less than 20% and most often 0%. Sensitized candidates typically have PRAs $\geq$20%, but there is clustering of candidates at the highest PRA values of >95% (Keith and Vranic 2016). The causes of sensitization are typically prior pregnancies in female candidates, prior blood transfusions, prior transplants, in rare instances infection or immunization, and prior tissue interactions such as from an islet transplant (Campbell et al. 2007). It was readily apparent that patient with PRA values $\geq$80% faced a considerable barrier to kidney transplantation. Thus, for at least two decades preceding KAS, candidates with PRA's $\geq$80% were awarded 4 points in deceased donor kidney allocation (Graham 1995; Leffell and Zachary 1999).

The initial development of PRA tests was recognized as not necessarily being reflective of the population of donors and lacked the sensitivity of future tests. Over time PRA panels improved in sensitivity and became increasingly reflective of donor population. In addition, improved understanding to the HLA allowed testing of potential recipient serum against specific antigens, allowing the characterization of antigens that should be avoided for a particular transplant candidate. In 2007, the United Network for Organ Sharing (UNOS) Board of Directors approved a measure by the OPTN's Histocompatibility Committee to implement a new system of a Calculated Panel-Reactive Antibody (CPRA). The CPRA is based on the frequency of HLA antigens in approximately 12,000 United States deceased kidney donors from 2003 to 2005 (Cecka 2010). The score is calculated based on the percent chance of a positive crossmatch between a donor and recipient based on the known unacceptable HLA antigens for a recipient. A calculator for transplant professionals is available on the OPTN website to give the percent value for the avoids listed (Calculator 2018). In effect, the entering of CPRA avoids creates a path through which compatible crossmatches are much more likely to occur. Initially, the CPRA did not allow HLA-DQ and HLA-DP avoids to be reported, and this led to some unanticipated positive crossmatches (Singh et al. 2016). These loci have subsequently been added, but the allele expression of avoids is still imperfect, and thus positive physical crossmatches are still possible in that most deceased donors only have low to medium resolution typing. Virtual crossmatches are now frequently done by tissue typing labs before a kidney is shipped any distance to minimize the possibility that it be destined for a candidate for whom it is incompatible.

When the CPRA calculator was first introduced, credit for sensitization was Boolean in that only patients with a CPRA $\geq$80% would receive 4 points so there was understandable concern that certain patients who had been characterized as highly sensitized in the old PRA system would lose points. This was in fact the case for roughly 12% of highly sensitized patients by PRA values at the time (Cecka 2010). However, the converse was also true in that for the moderately sensitized by PRA (20–79%), roughly 20% were discovered to have a CPRA $\geq$80% (Cecka 2010). The CPRA system which required reporting avoids dramatically changed match runs for any specific deceased donor kidney in that in the prior PRA system, all the highly sensitized candidates were often on the top of every match run and were only removed following testing. These changes had a stifling effect on using desensitization to access a deceased donor kidney in that if desensitization was successful in dropping CPRA avoids below the $\geq$80% threshold, the 4 point boost on the candidate's rank would be lost, and the candidate place on any match run for any organ would also drop similarly (Singh et al. 2010). This effect has persisted through KAS and desensitization for deceased donor kidneys are rarely pursued today. Ultimately, these concerns were replaced by a respect for the new technology that eliminated many positive crossmatches. In addition, with changes introduced with KAS, a graded boost in points for entering of CPRA avoids, sensitization transitioned from being an obstacle to organ access to often a driver to improve access.

Historically, highly sensitized candidates have waited considerably longer than non-sensitized candidates. The pre-KAS Boolean sensitization points did help highly sensitized candidates, but it did so in a fashion that was strongly preferential to the group of patients whose CPRA was between 80% and 84% (Cecka et al. 2011). Instances where individuals with a CPRA of >98% were offered a transplant were extremely rare and, if they occurred, were often contingent on a 0-MM kidney being available (Stegall et al. 2017). To help address this issue, KAS in December 2014 implemented a continuous, graded sliding scale for all candidates with a CPRA $\geq$20% (Friedwald et al. 2013) (Table 2). Under the new sliding scale, candidates with a CPRA of >90% would receive a significantly greater amount of points, ranging from 6.71 for 90% to 202.1 for CPRA of 100% (Formica et al. 2014). Other notable changes included access to regional and national sharing for a CPRA of 99% and 100%, respectively. Early statistical analysis of OPTN kidney transplant

Table 2 At the time of writing, the table shows the current number of allocation points awarded to an individual based on their CRPA score. Compared to pre-KAS where 4 points were awarded to all transplant candidates with a CPRA of ≥80, under KAS, potential transplant candidates receive points based on a continuous, graded sliding scale. These numbers are accurate based on OPTN policies as of March 1, 2018

CPRA score	Allocation points
0–19	0
20–29	0.08
30–39	0.21
40–49	0.34
50–59	0.48
60–69	0.81
70–74	1.09
75–79	1.58
80–84	2.46
85–89	4.05
90–94	6.71
95	10.82
96	12.17
97	17.3
98	24.4
99	50.09
100	202.1

OPTN 2018b

data also demonstrated an immediate success of increasing the proportion of transplants for individuals with a CPRA of 99–100%, increasing from 2.4% pre-KAS (December 2013–2014) to 13.4% post-KAS (December 2014–2015). However, during the same time period, proportional transplant rates for candidates with CPRAs of 0–79% and 90–94% experienced moderate declines, while individuals with a CPRA between 80% and 89% experienced a severe decline of greater than 60% from pre-KAS to post-KAS (Stewart et al. 2016).

Improved Access for Blood Type B Candidates

After the succession of failed kidney transplants across blood group barriers of the late 1950s and early 1960s, the OPTN organized deceased donor kidney allocation along blood group compatibilities. It soon became apparent that blood group AB recipients were significantly advantaged compared to other groups. Blood group A also fared better in comparison with blood groups O and B. Because of this, many type B candidates face a longer wait for a transplant. Minorities, especially African-Americans, make up a disproportionate amount of listed type B candidates when compared to the waitlist of other blood types. As the type B waitlist is composed of over 70% of minority populations, but makes up less than 15% of deceased donor kidneys available, UNOS has attempted on multiple occasions to address this disparity (OPTN 2018a). The first attempt to improve access to kidney transplantation for blood group B patients was in 2001, where UNOS policy dictated type B kidneys to be directed away from blood group AB recipients (with an exception being for cases of Zero Mismatch Policy) (Bryan et al. 2016). While this change in policy allowed a modest increase in transplantation of blood group B patients, blood type B patients still faced lower deceased donor kidney transplant rates compared to other blood types. Therefore, to better combat this problem, the new KAS implemented in 2014 allows for non-A1 A and non-A1 AB blood type kidneys to be transplanted into B candidates. Approximately, one fifth of blood type A is non-A1, most often A2. Non-A1 A and non-A1 AB individuals express significantly lower amounts of A antigen than normal type A1 individuals, allowing the safe use of these organs in B candidates who are not sensitized against A antigen. This policy was enacted to increase the potential donor pool for type B candidates with a minor impact on transplant rates on A and AB candidates. A critical stipulation is that B candidates must also demonstrate consistently low anti-A titers of $\leq$1:4 every 90 days, with any recorded titer of $\geq$1:8 being considered prohibitively high (Bryan et al. 2016). Analysis of long-term (7 year) follow-up data from the Midwest Transplant Network OPO showed that B candidates that received an A2 or an A2B had non-inferior outcomes when compared to traditional B to B transplants. However, one important consideration is that if a B type individual who had received an A2 or A2B organ could only receive plasma from AB donors

as plasma from a potentially sensitized B type source can initiate an antibody-mediated rejection.

Of all the changes made with KAS, the improved access for blood type B candidates has been the one area where transplant centers have truly struggled to build the necessary processes and infrastructure to advantage their blood type B waitlist. It is generally agreed that the results for non-A1 A and non-A1 AB into B are comparable to all other transplants if the blood type B candidate has a low A titer; however, this type of transplant requires an additional consent from the prospective candidate. Monitoring anti-A1 titers while the candidate waits on the list presents another challenge, and as of June 2016, only 18% of transplant centers have performed these transplants (OPTN/UNOS Minority Affairs Committee 2017).

Living Donor Defined by Procurement

Of the changes implemented with KAS, defining a living donor by the procurement surgery rather than by transplant of the organ has high symbolic significance but likely will have the least impact on actual transplant numbers. Historically, living donation was defined by the occurrence of a transplant. Unfortunately, there have been circumstances where a procuring surgery takes place, but a subsequent transplant does not happen. Kidney donors represent the overwhelming majority of living donors with greater than 95% of all living donors being of this type. The next most common living organ donated is a portion of liver, and by February 8, 2018, there have been 6,406 living liver donors in the United States recorded by the OPTN compared to the 145,629 living kidney donors. Thus, as living kidney donation relative risk for developing ESRD is approximately 7.9 when compared to matched controls who did not donate, this can present a significant problem if access to transplantation is unavailable to prior donors (Grams et al. 2016). Therefore, under the new KAS policy, a prior living donor is still awarded 4 allocation points if they ever need to be listed for a kidney transplant, but now they have the assurance that they will be considered a donor whether or not a transplantation has actually taken place after procurement (OPTN 2018b). Fortunately, the absolute risk of developing ESRD after living kidney donation is still much lower than that of the general population's (90 per 10,000 vs. 326 per 10,000) (Abimereki et al. 2014).

Conclusion

Despite the many limitations of the prior Kidney Allocation System, it operated for nearly 30 years and facilitated close to a quarter of a million deceased donor kidney transplants. It did pose a considerable obstacle to patients who learned of their kidney failure late in the disease course, since it required listing at a transplant center before waiting time could be accrued. It also was overly simplistic in its characterization of deceased donor kidney quality using dichotomous descriptors instead of the numeric KDPI score. In addition to these areas of improvement, the new Kidney Allocation System also improved access for sensitized candidates and has provisions to improve access for blood type B candidates. KAS also has an improved focus on utility of the deceased donor kidney transplant directing the best kidneys into the best adult candidates without significantly compromising pediatric candidate access. KAS has also attempted to decrease discard rates by implementing local and regional offering of higher KDPI organs. Despite these changes, geographic iniquity is still extremely prevalent and remains a dominant determinant in access to deceased donor kidney transplantation.

Cross-References

- A History of Kidney Transplantation
- Donor Selection: Deceased Donor
- Immunology of Kidney Transplantation
- Pediatric Transplantation
- Renal Transplantation with Other Organs
- The Regulatory and Legal Environment of a Contemporary Kidney Transplant Program

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Necessary Components of a Living Donor Team

Linda Wright and Pooja Singh

Contents

Abstract

Live donor kidney transplantation represents approximately one third of the kidney transplants performed each year in the United States. The Organ Procurement and Transplantation Network and the Centers for Medicare and Medicaid Services have developed specific requirements with regard to the evaluation of potential live donors. The required members of the live donor team include the transplant surgeon and physician, transplant coordinator, financial coordinator, transplant pharmacist, social worker, dietitian, and independent living donor advocate. Their roles and others are discussed, along with the necessary elements of the live donor informed consent process.

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Live donor kidney transplantation · Live donor evaluation · Live donor transplant team · Donor champion · Informed consent · Independent living donor advocate

Introduction

Kidney transplantation using live, volunteer donors began in 1953, when a 16-year-old boy received a kidney from his mother, after trauma necessitated the surgical removal of what was later determined to be a solitary kidney. The allograft functioned well for 3 weeks but was ultimately rejected (Hamburger et al. 1962). The following year saw the first successful kidney transplant between identical twins, Ronald and Richard Herrick, performed by Dr. Joseph Murray, a plastic surgeon who went on to share the Nobel Prize for Physiology/Medicine in 1990 with E. Donnall Thomas for their discoveries in the field of organ transplantation. The subsequent experience with identical twin transplantation throughout the 1950s led to an increase in knowledge regarding the surgical care of the patient with renal failure, as well as research concerning host immune responses (Tilney 1986). It also led to ethical discussions which are still ongoing in the modern era of kidney transplantation.

History

Live kidney donation would seem to violate a basic tenet of medical ethics which is to do no harm. In the early days of kidney transplantation, uncertain recipient outcomes only added to the ethical concern. Was it truly justified to expose an otherwise healthy individual to the risk of a surgical procedure which would be of no personal benefit, to remove a healthy, vital organ, when a good long-term outcome for the recipient was far from a guarantee? After being debated in ethics conferences, journal publications, and courts of law, consensus was reached in the 1970s, when it was argued that donors could find emotional benefit in the act of donating and that their well-being was, in a sense, dependent on that of the intended recipient. It was additionally noted that there was the potential for psychological harm to one who was prevented from donating an organ when the life of a loved one was at stake (Murray et al. 1976; Starzl and Marcos 2007). Long-term benefits to live kidney donors were, then, linked to the benefits to the recipients. At the same time, legislation in the early part of the 1970s established a mechanism for covering the evaluation and operative care of live donors, thereby providing support for live donor transplantation.

As live donor kidney transplantation became more common in the United States, there were ongoing ethical concerns, with staff at some transplant centers opting not to participate in live donor surgical procedures. As donor and recipients were often referred to transplant programs as a unit, it became unclear who was overseeing the donor and advocating for their welfare. Additionally, there were complications occurring at every phase of the donation process, from the evaluation through the postoperative period, including multiple donor deaths, many of which were not formally reported. Concern about the ethics of live donor transplantation continued to be so strong that, in 1986, the 11th Congress of the International Transplantation Society entertained formal debate on the topic. The argument in favor of live kidney donation centered on the growing need for organs and predicted that, even if all of the potentially available deceased donor organs were used, there would still be a shortage of organs which would lead to the deaths of many people who might otherwise have been able to return to an active and vital place in society. Live donation was seen as a means of advancing a policy of preserving life. The con side of the debate centered on concerns regarding emotional and physical risks to the donors, but also raised the issue of coercion, and the difficulty in guaranteeing that donors were not proceeding with donation under duress. Another part of argument against live kidney donation was a concern that it could lead to a decreased interest in deceased donor transplantation and might even serve as disincentive for the use of deceased donor organs (Starzl and Marcos 2007).

When the National Organ Transplant Act of 1984 (NOTA) established the Organ Procurement and Transplantation Network (OPTN), its main objective was to establish an equitable system for the allocation of deceased donor organs and the creation of a registry for the collection of recipient data. There were no specific rules governing the practice of live donor transplantation. At that time, most live kidney donors were blood relatives of the recipient and were close immunologic matches. Throughout the next decade, however, as deceased donor waiting times increased, studies demonstrated better long-term graft survival in live donor transplant recipients than in recipients of deceased donor organs, even when the live donor transplants involved significant mismatching of histocompatibility antigens. As a result, increasingly, potential live donors were not related to the intended recipient by blood, but rather shared an emotional or social relationship. At the same time, protocols for donor exchanges were starting to be developed, and the Internet was providing the means for live donor transplants to be arranged between individuals who had never met and had no previous relationship. The ability to solicit the public for an organ led to new ethical concerns regarding inequity of access to transplant, as well as the potential for illegal financial arrangements between live kidney donors and their recipients. Additionally, reports of donor complications, including, on rare occasions, donor deaths, led to increased public scrutiny of live kidney donation and a desire to ensure that donors were properly educated and screened and then monitored for complications post-donation (Brown et al. 2009).

In a 2006 notice in the Federal Register, the Health Resources and Services Administration (HRSA) directed the OPTN to develop policies regarding live organ donors and recipients. HRSA further determined that failure to comply with these policies would carry the same consequences for OPTN members as noncompliance with policies related to deceased donor organ transplantation. Centers performing live donor transplants were required to develop, and adhere to, policies concerning all phases of live donation, from evaluation through the postoperative period, as well as the timely submission of data.

The following year, for the first time, the Centers for Medicare and Medicaid Services (CMS) issued conditions of participation for transplant centers (2007). It established a system of minimum requirements, as well as an oversight process, for the purpose of protecting and promoting patient health and safety. The conditions of participation required transplant centers to follow protocols for the evaluation of living donors and to have an individual, or a team of individuals, charged with advocating for the specific interests of the live donor. They also required transplant centers to submit certain donor and recipient data to the OPTN. Failure of transplant centers to meet the conditions of participation would result in penalties, up to and including the loss of Medicare certification.

Also in 2007, the OPTN approved new bylaws for transplant centers with live donor programs, requiring written protocols for the evaluation and follow-up of live donors. Member centers were also required to follow a process of informed consent that would ensure that donors were aware of risks, benefits, and alternatives, of transplant center and national outcomes, and were proceeding without coercion. Additionally, centers were required to provide an independent donor advocate, an individual knowledgeable of the transplant process but independent of the medical team involved in the care of the intended recipient. This individual would serve the sole purpose of advocating for the interests and needs of the live donor.

Team Components

OPTN bylaws (2016a) and CMS regulations contain specific personnel requirements for transplant programs, in order to ensure the delivery of quality patient care. Programs that perform live kidney donor organ recoveries must meet all requirements of a kidney transplant program but must also have additional protocols and resources for the evaluation of live donors. Table 1 provides an overview of the roles and responsibilities of each member of the live donor team.

Table 1 The roles and responsibilities of each member of the live donor team

Team member	Role
Physician/ nephrologist	Evaluate prospective donor, without consideration of issues related to the intended recipient
	Oversee evaluation
	Provide education
	Participate in decision regarding donor candidacy
	Participate in perioperative and post-donation care as needed
Donor surgeon	Evaluate prospective donor with regard to surgical risks
	Consideration of patient-specific issues and donor anatomy
	Provide education related to the surgical procedure, risks, and recovery period
	Provide education on surgical procedure, risks, and recovery
	Participate in decision regarding donor candidacy
	Provide care in perioperative period, with post-donation follow-up as needed
Transplant coordinator	Education of prospective donor
	Evaluation process
	Surgery and recovery
	Risks
	Recipient options
	Coordinate the completion of the evaluation and all necessary testing
	Assist with the scheduling of donor surgery and hospitalization
	Coordinate postoperative care and post-donation follow-up
Financial coordinator	Review intended donor's insurance benefits
	Educate donor with regard to insurance reimbursement for live donation and any possible out-of-pocket costs which may be incurred
Pharmacist	Evaluate pre- and post-donation medication regimens
	Patient education as needed
Social worker/ psychologist/ psychiatrist	Psychosocial evaluation of prospective donor
	Provide education
	Recipient options
	Available support services
	Available resources to assist with out-of-pocket expenses related to donation
	Potential adverse outcomes: loss of income, post-donation complications, allograft failure
	Assessment of donor motivation and potential for coping with adverse outcomes post-donation
	Assess for informed decision-making
	Assist with plans for perioperative and recovery period
Dietician	Assess nutritional status or prospective donor
	Provide counseling and education as needed
Independent living donor advocate	Function independently from the recipient team
	Advocate for the rights and interests of the prospective donor
	Ensure that the donor has been adequately educated and is proceeding with donation voluntarily and free of coercion

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) Living Kidney Donors Work Group. KDIGO (2015)

Primary Transplant Surgeon and Physician

Transplant programs are required to identify a primary transplant surgeon and primary transplant physician, who will be responsible for the operation of the program and its ongoing compliance with OPTN policies and bylaws. The qualifications and training requirements for the primary surgeon and physician are specified by the OPTN. Additional transplant surgeons and physicians may be designated by the transplant center

but must be able to function independently to provide transplant services and manage the care of transplant patients.

In addition, transplant programs that perform live donor organ recoveries are also required to identify a primary open living donor kidney surgeon and a primary laparoscopic living donor kidney surgeon. The same surgeon can serve both roles if all qualifying criteria are met. Qualifications and training requirements, including a specified number of successful open and laparoscopic donor nephrectomies performed, are specified by OPTN bylaws.

Live Donor Surgeon and Physician

In the case of live kidney donation, the surgeon may be a transplant surgeon or a urologist. The live donor surgeon is responsible to discuss the possible risks and complications of a donor nephrectomy and to ensure that the potential donor is suitable, from a surgical standpoint, to proceed with organ donation.

The transplant physician/nephrologist is responsible for the medical evaluation of the potential donor. The nephrologist's role is to ensure that the donor does not have existing kidney disease or an increased risk of developing chronic kidney disease in the future. An assessment for future development of chronic kidney disease should be made based on a composite of potential donor demographics, risks associated with clinical history, and post-donation-associated/attributable risks. A detailed evaluation for the presence of any communicable diseases which could be transmitted from donor to recipient at the time of transplant should also be performed.

Transplant Coordinator

The transplant coordinator works with patients and their families, providing education and coordination of care, from the start of the evaluation process to transplantation and ongoing follow-up, both for potential living donors and their intended recipients. Based on the size of the transplant program, multiple living donor or recipient coordinators may be involved in this process. The transplant coordinator is most often a registered nurse but may also be a nurse practitioner, a clinical nurse specialist, or a physician assistant. In situations where the transplant coordinator is a physician assistant, CMS does require nursing participation in the multidisciplinary transplant team. The specific responsibilities of the transplant coordinator are discussed more fully in the chapter entitled "The Role of the Transplant Coordinator."

Financial Coordinator

The financial coordinator works with donors to clarify the financial aspects of the donation process. In most cases, costs associated with the live donor nephrectomy are covered by the recipient's insurance. However, donors may be responsible for expenses related to travel and housing, as well as lost wages and childcare costs. Complications or future health issues which arise as a result of donation may not be covered by the recipient's insurance, depending on the specific terms of the recipient's coverage. Additionally, the routine follow-up physical examination and laboratory testing, required by OPTN at specified intervals post-donation, will not be covered by the recipient's insurance. The financial coordinator works to identify all financial options and to help ensure that potential donors have the resources that are needed in all phases of the donation process. Specifically in the case of live donation, the financial coordinator reviews the potential recipient's insurance benefits to ensure that there is provision for the coverage of live donor surgical costs.

Clinical Transplant Pharmacist

Transplant pharmacists work in collaboration with the multidisciplinary transplant team, evaluating pre- and posttransplant medication regimens and participating in patient education as

necessary. The pharmacists' involvement with live donors may be "phased out," per CMS guidelines, if no specific needs are identified during the evaluation or are anticipated at later stages of the donation process.

Mental Health and Social Support

Transplant programs are required to have a masters-prepared, licensed clinical social worker to coordinate the psychosocial needs of live donors, transplant candidates and recipients, and their families. The social worker is responsible for assessing and intervening with regard to any psychosocial issues that may impact illness and recovery and for providing emotional support and guidance to patients and their families.

The psychosocial evaluation of potential live donors may be performed by a masters-prepared or clinical social worker but may also be performed by a psychiatrist or psychologist. Per the OPTN living donation policy (OPTN policy 14.1), the evaluation must include the following:

- Evaluation for any psychosocial or mental health issue which could either complicate the donor's recovery or pose a risk for a poor psychosocial outcome
- Evaluation for behaviors which would suggest an increased risk of disease transmission from donor to recipient
- Assessment of the potential donor's smoking history, as well as any history of alcohol and/or drug use or abuse
- Ensuring that the donor understands the long- and short-term risks of donation and is proceeding without "inducement, coercion, enticement, and other undue pressure," through evaluating the reasons for wanting to donate as well as any relationship between the donor and prospective recipient
- Assessment of the donor's ability to deal with the physical and emotional demands of donation, as well as the ability to make an informed decision
- Assessment of the donor's employment and insurance status, living arrangements, and availability of social support and determination that the donor understands any financial implications of donation

Nutritional Services

While OPTN bylaws do not require transplant programs to have a dietician, CMS guidelines do specify that nutritional services must be represented on the multidisciplinary transplant team. The transplant dietician is responsible to coordinate the nutritional counseling and education of live donors, as well as pre- and post-transplant patients. In some circumstances, the dietician may provide vital input for those potential living donors who have been provided weight loss goals in early phases of living donation work-up. However, nutritional services' involvement with live donors may be "phased out," per CMS guidelines, if no specific needs are identified during the evaluation or are anticipated at later stages of the donation process.

Independent Living Donor Advocate (ILDA)

Transplant centers are required to provide an ILDA to anyone who is being evaluated as a potential live organ donor. In cases where the live donor and the recipient are being evaluated by separate transplant programs, the ILDA must be provided by the center that will be responsible for performing the living donor nephrectomy. The ILDA may be an individual or a donor advocate team, but must not be involved in the care of, or the decision to transplant, the potential recipient. In cases where an independent donor advocate team is utilized, each donor must be given a specific individual who will be his or her primary contact. The ILDA must meet the transplant center's requirements with regard to knowledge of the organ donation process, transplantation, informed consent, medical ethics, and the effect of personal, family, or other external pressures on the decision

to proceed with donation. The responsibilities of the ILDA include the following:

- Function independently of the intended recipient's team.
- Advocate for the needs, interests, and rights of the live donor.
- Assess if the potential donor has been educated on the informed consent and evaluation process; the proposed surgical procedure; the medical, surgical, and psychosocial risks of donation; and the requirement for, and the benefits of, post-donation follow-up.
- Assist patient in getting additional information, if needed.
- Documentation of each of the above elements of the evaluation.

Live donor transplant centers are required to develop and adhere to written policies with regard to the composition of the ILDA team, if a team model is utilized, as well as the qualifications and required training of the ILDA. Centers are also required to have policies regarding the duties and responsibilities of the ILDA, which must include the items above, as well as the mechanism by which the ILDA can file a grievance with the recovery hospital, if needed in order to protect the interests of the donor, and the process to be used by the hospital in addressing an ILDA grievance.

Additional Resources

While not required as dedicated members of the transplant program, CMS regulations do require that transplant programs demonstrate the availability of other clinical disciplines, as needed, for the provision of transplant-related patient care. These disciplines include internal medicine, anesthesiology, infectious disease, pathology, immunology, radiology, and blood banking services.

Living Donor Champion

For more than two decades, according to OPTN data, there have been approximately twice as many additions to the kidney transplant wait list each year than the total number of transplants performed (Fig. 1). While live donor kidney transplantations increased throughout the 1990s, the number remained stable through the 2000s and actually decreased over the past 5 years. Barriers to live donation have been described and include a lack of knowledge about live donation, but also a reluctance to initiate a conversation about live donation, and a lack of knowledge on the part of potential recipients concerning how to ask someone to donate a kidney. While transplant candidates may be reluctant to discuss their need for a kidney transplant, friends and family members are

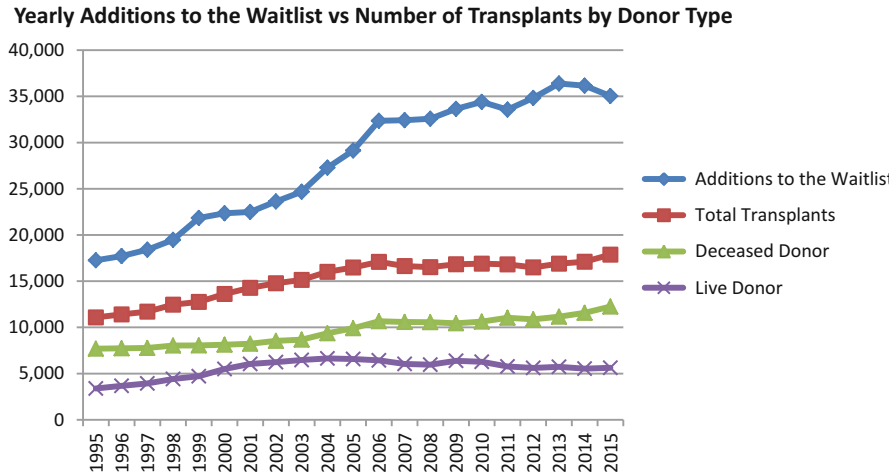

Fig. 1 Based on OPTN data as of April 8, 2016 (Source: https://optn.transplant.hrsa.gov)

often quite willing and are empowered through the act of advocating on behalf of their loved one.

A donor champion is an individual, within a transplant candidate's sphere of family and friends, who is willing to make people aware of the candidate's kidney disease and to provide information about kidney disease, the available treatments, and live kidney donation. The concept of the donor champion emerged from research into the use of a structured educational program, with the friends or family members of transplant candidates, which addressed the most common barriers to the identification of a live donor. The program led to increased comfort, on the part of these friends and family members, in initiating conversations about kidney transplantation and live donation and a significant increase in the identification of potential live donors. The donor champion has been described as an inexpensive way to decrease transplant wait times through increasing the live donor pool (Starzl and Marcos 2007). It also shifts the responsibility for finding a live donor from the transplant candidates and relieves them of the need to have what are often awkward and uncomfortable conversations in which they are asking a loved one to donate a kidney. Donor champion education should include information about kidney disease and transplantation, and some suggested components are illustrated in Table 2. The transplant center should impart training to these advocates on how to initiate conversations with potential live donors and possible strategies for making people aware of the candidate's need for a transplant.

Table 2 Suggested content for donor champion education

Topic	Suggested content
Introduction to kidney transplantation	Chronic kidney disease
	Treatment modalities with pros and cons
	Live donor versus deceased donor kidney transplant
Introduction to live donation	Live donor selection criteria
	Contraindications to live kidney donation
	Risks associated with donation (physical, psychosocial, financial)
	Evaluation process
	Surgery and recovery period
	Post-donation follow-up
The donor champion role	What is a donor champion?
	Who can be a donor champion?
	Expectations/responsibilities of a donor champion
Starting the conversation	Sample conversation starters
	Opportunity for role-playing
Making the need known	Acceptable options: places of worship, family gatherings, social media
	Unacceptable options: solicitation (may vary from center to center), reimbursement (money or goods/services), coercion
A successful champion	Examples of successful methods
	Story of donor champion and resulting transplant

Informed Consent

OPTN policy (2016b) contains specific requirements for recovery centers with regard to the informed consent of potential live organ donors. All potential donors must sign a document which confirms that they are willing to proceed with donation; that they are doing so of their own free will, without coercion or inducement; that they understand the medical and surgical risks; and that they have been informed that they may withdraw their consent to donate at any time. The following information must be provided to all potential live donors:

- The donor is able to withdraw from the donation process in a protected and confidential manner.
- The transplant center will take every reasonable precaution to protect the privacy of the donor and recipient. However, the same reporting requirements exist with regard to information obtained during the donor evaluation as exists for all medical records, and the evaluation could reveal a condition which would be required to be reported to public health agencies.

- The recovery center is required to submit follow-up information to UNOS, at specific intervals post-donation. Potential donors must commit to post-donation follow-up testing at the intervals specified by UNOS. Any malignancy or infectious disease within the first 2 years post-donation, which is pertinent to the care of the recipient, will be reported to the OPTN and the recipient's transplant center and may need to be reported to public health agencies.
- The potential donor must undergo a medical and psychosocial evaluation.
- In the event that the donor is declined by the transplant center, they must be informed of the potential of being accepted at another center, as each center has their own selection criteria.
- There are risks associated with undergoing an evaluation for live donation. Risks include the possible discovery of reportable conditions or serious medical conditions, the discovery of unknown genetic conditions, allergic reactions to intravenous contrast material, and the discovery of medical conditions which could necessitate additional testing, at the expense of the donor, or which could result in an unforeseen decision by the transplant team.
- Live donation is associated with medical, surgical, psychosocial, and financial risks which may be temporary but which could also be permanent. OPTN policy specifies the risks, in each category, which must be included in the informed consent.
- National 1-year patient and graft survival data, as well as the survival data for the recovery center, and the recipient center if known, and notification of any unmet CMS requirements. Donors must also be given the recipient center's 1-year live donor recipient patient and graft survival data, when the recipient center is known.
- Education about expected kidney function post-donation and how chronic kidney disease (CKD) or end-stage renal disease (ESRD) might potentially affect them in the future. Specifically, potential donors must be made aware that, while donation is associated with a permanent 25–35% loss in kidney function, the risk of developing ESRD is comparable to, or better than, that in the general population. However, as CKD is generally a condition that develops in midlife, the evaluation of a younger donor cannot provide an accurate lifetime risk of developing chronic or end-stage disease. Live donors may be at higher risk of developing CKD, if they experience injury to their remaining kidney, and may progress to ESRD more quickly than if they had two kidneys. Dialysis will be required in the event of ESRD; however, the current practice is to give priority to live donors who themselves become transplant candidates.

The education of potential donors may be completed using any available media and may consist of individual or group education sessions. Live donor recovery centers are responsible to obtain informed consent and must maintain documentation in the donor's medical record.

Conclusion

The basic composition of the live donor transplant team is mandated by OPTN and CMS policy. Increasingly, the content of donor education, and specifically the informed consent process, is also dictated by these governing bodies. Live donor transplant programs must be knowledgeable regarding these requirements and are required to ensure that all necessary elements are included, throughout all phases of the donation process. While also ensuring that recipients receive appropriate organs, the regulations that have been put into place are ultimately meant to ensure that live organ donors are fully protected and proceeding with a complete understanding of the implications of donation.

Cross-References

- ▶ A History of Kidney Transplantation
- ▶ Ethical Issues in Organ Transplantation
- ▶ Living Donor Evaluation and Selection
- ▶ Organ Procurement Organization and New Kidney Allocation

- ▶ Psychosocial and Personal Financial Aspects of Transplantation
- ▶ Quality Measurement of a Contemporary Kidney Transplant Program
- ▶ The Role of the Transplant Coordinator

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Medical Complications After Kidney Transplantation: Early

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Contents

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Abstract

Kidney transplant recipients need meticulous post-transplant medical care to avoid short-term and long-term complications, and to prolong graft and recipient survival. Multi-disciplinary care involving transplant surgeons, transplant nephrologists, social workers, dieticians, and transplant coordinators are essential for optimal care and successful outcomes. Living donor transplant outcomes continue to be superior to deceased donor outcomes. Both living donor and deceased donor 1 year graft survival have steadily improved over the last 10 years, and in 2013 were 97% and 92%, respectively (USRDS data 2015). Improvements in immunosuppression management, prevention, and early detection of rejection have reduced rejection rates. Prevention of hospital-acquired infections may reduce infection rates. Close post-transplant follow up and tailoring of immunosuppression when indicated may prevent infections and complications of BK polyomavirus and CMV disease. Pretransplant cardiac risk stratification and improving medical outcomes in diabetic patients have reduced post-transplant cardiovascular complications. Educating patients early on the risks of post-transplant obesity and post-transplant diabetes is more important now than ever before as we reach a peak in the obesity epidemic. This chapter will focus on the above issues, as well as more details of potential and commonly occurring complications in the first year post-kidney transplantation.

Keywords

Complications · Cardiovascular · Post-transplant diabetes · Infections · Graft dysfunction · Hemodynamic issues · Delayed graft function · Readmissions · BK polyomavirus

Introduction

The first 3 months after kidney transplantation are known as the early post-transplant period. For the completeness of post-kidney transplant care, this chapter shall focus on complications in the first 12 months, as with the use of new immunosuppressant medications, and higher risk recipients undergoing transplantation, some complications linger on well into the first post-transplant year.

Rejection and infections are most common in the first 3 months. High levels of immunosuppression are used during this early period and the side effects are more marked during this period than they are later on.

For the patient, this time is exciting and stressful. Patients need to keep daily logs of their blood pressures, urine outputs, and blood glucose at a time when they are recovering from surgery. It is important for the transplant team to provide support to patients and their caregivers during this time. The care for the transplant patient should ideally be a combined effort by medical and surgical teams, ideally by making combined rounds on patients to make decisions about patient care. It is useful to document all the events during the first admission in a manner that can easily be transmitted to the outpatient clinic.

Some patients need readmissions in the first month post-transplantation and verbal and written communication between those caring for the patient and the inpatient team is crucial to inpatient care. Recent literature reports readmission rates of 31% during this period (McAdams-Demarco et al. 2012). In our current health care climate, tremendous attention is placed on readmission and length of stay. Assessing Early Hospital Readmission (EHR) of the transplant recipient is a complex task due to the multiple comorbidities End Stage Renal Disease (ESRD)

patients are burdened with, along with the toxic drug regimens they are exposed to at the time of transplantation. In addition, kidney transplant patients have undergone a surgical procedure which independently increases their risk of readmission. Very specific factors come into play when deciding to readmit a patient. Studies show patients with readmissions are not unexpectedly older, have underlying congestive heart failure, delayed graft function, diabetes, ischemic heart disease, received induction therapy, older donor age, hepatitis C, peripheral vascular disease, cerebrovascular disease, history of arrhythmias, African American race, and a higher body mass index. A comprehensive review of risk factors can be found at Li et al. (2016) (Table 1).

The recovery of the transplanted kidney dictates the management of the kidney transplant patient in the first 3 months. Various complications may ensue and for the sake of this review, the complications have been divided into separate entities. It is possible for several complications to occur concurrently, and it may require some investigation to find out the etiology of graft dysfunction.

Delayed Graft Function

Delayed Graft Function (DGF) is defined as the renal failure necessitating renal replacement therapy within the first week of kidney transplantation. The causes of DGF are listed below:

Acute tubular necrosis
Intravascular volume depletion
Arterial occlusion
Venous thrombosis
Ureteric obstruction
Catheter obstruction
Urine leak
Acute rejection
Nephrotoxicity
Recurrent and De novo *glomerular disease after transplantation*

The decision to initiate renal replacement therapy (RRT) should be decided by both the transplant nephrologist and transplant surgeon. Indications to start RRT are hyperkalemia, volume overload, and metabolic acidosis usually in an oligoanuric patient. While RRT is supporting the patient, ongoing care to address and reverse the cause of DGF should be addressed daily.

Acute tubular necrosis (ATN) is the most common cause of DGF. ATN is primarily a clinical diagnosis and can be confirmed by kidney biopsy.

ATN may occur from ischemic-reperfusion injury, which occurs when oxygen is again available to the tissues, and results from the high concentration of oxygen free radicals that develop during anaerobic metabolism. It is not infrequent for the newly implanted kidney to initially diurese well, followed by the onset of oliguria as the kidney becomes more swollen and inflamed after reperfusion.

ATN may also be preexisting from the donor. The use of high Kidney Donor Risk Index (KDPI) score kidneys may have a greater risk for ATN (chapter ▶ "Donor Selection: Deceased Donor"). Cold ischemia time should be kept as short as possible. Perioperative dehydration and

Table 1 Summary of causes and outcomes of readmissions in kidney transplant and kidney/pancreas transplant recipients (Adapted from Li et al. 2016)

	Top causes of readmission	National (USA) outcomes
Kidney Transplant recipients	a. Kidney, ureter, prostate and bladder procedures b. Infection c. Endocrine disorders	Increased risk of graft loss and death (HR 1.4–1.54) in DDKT and LDKT
Kidney/pancreas transplant recipients	a. Rejection b. Infection c. Pancreas specific morbidity (dehydration,hematuria, pancreatitis)	No data available

HR hazard ratio, *DDKT* deceased donor kidney transplant, *LDKT* living donor kidney transplant

hypotension should be avoided. Good hemodynamic control is key during surgery (Fig. 1).

Acute Rejection

Acute cellular rejection (ACR) in the first week of transplantation is rare due to the widespread use of induction agents to prevent rejection in the first week. It can occur in patients within the first 3 months especially in patients who are not absorbing their immunosuppressant from vomiting, nonadherence, or subtherapeutic levels. ACR is suspected when the creatinine rises from unclear etiology, fails to fall post-transplantation, or elevated creatinine in the setting of low levels of immunosuppressant/nonadherence. Treatment of ACR will depend on biopsy results but usually always includes high dose steroids +/− thymoglobulin (chapter ▶ "Pathology of Kidney Transplantation").

Acute antibody mediated rejection (AMR) can occur in sensitized patients within the first 3 months and close monitoring of creatinine, immunosuppressant levels, and donor-specific antibody (DSA) levels in patients who are highly sensitized is recommended. Treatment of AMR also depends on biopsy results plus levels of DSA. Treatment is center dependent and may involve plasmapheresis, rituximab, and intravenous IgG (chapter ▶ "Immunology of Kidney Transplantation").

The incidence of rejection in the first year has decreased dramatically over the last 15 years due to improvements in induction therapies and immunosuppressants. Figure 2 below reveals trends from 1996 to 2013. In 2013, 7.3% of DDKT and 7.5% Living donors experienced at least one rejection in the first year post-transplantation

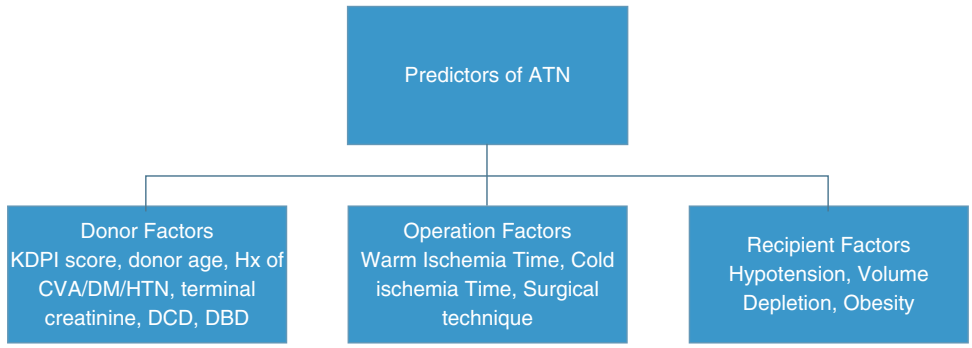

Fig. 1 Predictors of ATN include *CVA* (cerebrovascular accident), *DM* (diabetes mellitus), *DCD* (donation after cardiac death), *DBD* (donation after brain death)

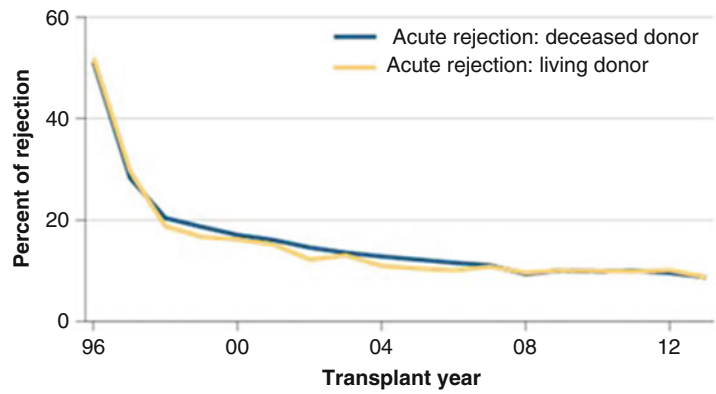

Fig. 2 Acute rejection within the first year post-transplant for kidney transplant recipients, 1996–2013 (Adapted from USRDS: volume 2, ESRD chapter 7, Fig. 7.18 (2015))

(chapter ▶ "Epidemiology of End-Stage Renal Disease and Kidney Transplantation").

Recurrent and De Novo Glomerular Disease After Transplantation

Recurrent focal segmental glomerulosclerosis (FSGS) can present within hours to days to weeks post-transplantation and presents with acute massive proteinuria and leg edema with or without an elevation in creatinine. Up to 30% patients with ESRD from FSGS develop recurrent FSGS in the transplant. Patients who receive a 2nd transplant because of allograft failure from FSGS have almost 100% recurrence in the 2nd transplant. Treatment with pre and post-transplant plasma exchange and rituximab may be promising but there are no trials to date studying outcomes with this therapy (Ponticelli et al. 2014).

Patients with Alport's syndrome can develop antiglomerular basement membrane (GBM) nephritis early post-transplant or within the first year. Clinically de novo anti GBM disease in a recipient with X-linked Alport's syndrome presents with a rapidly progressive glomerulonephritis. The diagnosis is based on detecting circulating anti-GBM antibodies and renal biopsy, which shows a diffuse crescentic nephritis with IgG immunofluorescence. The prognosis is poor. Plasmapheresis and rituximab may be attempted to remove the anti-GBM antibodies but only a few patients respond to treatment. Apart from the few patients who develop anti-GBM disease, the majority of Alport's syndrome recipients do very well.

Thrombotic microangiopathy (TMA) can occur in the setting of calcineurin inhibitors (CNIs), AMR, hypertensive crisis, viral infections, and drugs like valacyclovir or clopidogrel and in the presence of antiphospholipid antibodies. The clinical presentation of TMA may be insidious. Anemia, elevated lactate dehydrogenase (LDH), decreased haptoglobin, and schistocytes may be absent. Graft loss is frequent in patients with clinical features of HUS. In isolated glomerular TMA, the prognosis is less severe. Specific antiviral treatment is recommended in case of viral infection. Withdrawal or reduction of CNI/MTOR inhibitors may lead to remission in milder cases. Plasma exchange in addition to CNI withdrawal can contribute to graft salvage. Cases of remission with eculizumab in post-transplant de novo TMA in the transplant have been reported (Ponticelli et al. 2014).

CNI Toxicity

Calcineurin inhibitor toxicity can lead to slow graft function, acute kidney injury, and DGF as well as other effects such as uncontrolled hypertension, elevated liver enzymes, pancreatitis, and neurologic issues including tremors, altered mental status, seizures, hyperuricemia, and gout. The acute kidney injury is from efferent and afferent glomerular vasoconstriction leading to reductions in renal blood flow and reduction in eGFR and endothelial damage. Low-dose tacrolimus is less nephrotoxic than cyclosporine as demonstrated by the Elite Systemic Toxicity Elimination (ELITE) Study (Ekberg et al. 2007). The low-dose tacrolimus group was also associated with the lowest rejection and highest graft survival rates at 3 years. Rarely, glomerular thrombotic microangiopathy can be seen on kidney biopsy in which case the CNI dose can be reduced, or the CNI can be changed or stopped depending on the clinical scenario.

Surgical Complications of Kidney Transplantation

Lymphoceles are collections of lymph caused by leakage from severed lymphatics surrounding the renal hilum or the iliac vessels. Lymphoceles can be asymptomatic or cause AKI from ureteric obstruction, pain, and swelling of the leg around the graft or scrotum. Further management is discussed in chapter ▶ "Kidney Transplantation: Surgical Complications."

Renal Artery Thrombosis is most often seen in patients with thrombotic tendencies or low-flow states and is diagnosed by ultrasound which shows absence of renal artery blood flow.

Renal vein thrombosis can occur from kinking of the renal vein or venous anastomosis stenosis or a hypercoaguable state.

Transplant renal artery stenosis *(TRAS)* is suspected in patients with AKI/DGF, uncontrolled HTN and a "tardus-parvus" waveform on renal artery Doppler. If stenosis is suspected in the first month, then surgical revascularization is recommended.

Urine leaks may be a result of distal ureteral ischemia because the allograft ureter receives blood supply solely from the renal artery. Therefore, the preservation of a lower pole donor renal artery is essential to ensure the viability of the ureter. The general presentation is increasing wound drainage, decreasing urine output, abdominal pain, or leg swelling. The diagnosis is made by elevated creatinine of the fluid compared to the serum. The diagnosis is confirmed by cystogram, nuclear medicine scan, or antegrade nephrostogram.

Ureteral obstruction includes blood clots, extrinsic ureteric compression, ureteral stricture, stones BPH, or catheter blockage.

Electrolyte Abnormalities Post-Kidney Transplantation

Hyperkalemia is common post-transplantation. Urinary potassium excretion is primarily derived from potassium secretion in the collecting tubules via potassium channels in the luminal membrane. This process is stimulated by sodium reabsorption (which, unless chloride follows the sodium, creates a lumen-negative electrical gradient that promotes potassium secretion), aldosterone (which increases the number of open sodium channels in the luminal membrane), and by the basolateral Na-K-ATPase pump (which removes reabsorbed sodium from the cell in exchange for potassium, thereby increasing the size of the potassium secretory pool). CNIs cause decreased potassium excretion from decreasing the activity of renal angiotensin aldosterone system and impairing tubular responsiveness to aldosterone. Calcineurin inhibitors decrease the activity of the Na-K-ATPase pump and also decrease the activity of the potassium secreting cells in the collecting tubule. Other medications which contribute to hyperkalemia include Trimethoprim-sulphomethoxazole, which is used for antibacterial prophylaxis post-transplantation. The trimethoprim blocks the sodium channel in the collecting tubule which contributes to hyperkalemia. The hyperkalemia is usually mild and can be treated with low-potassium diet. Occasionally additional measures such as a low-dose diuretic (if volume status allows) and fludrocortisone may be indicated.

Hypophosphatemia is commonly caused by the renal phosphorus wasting of calcineurin inhibitors. Patients are advised to stop all phosphorus binders and advised to consume a diet high in phosphorus (mainly dairy). Potassium phosphorus supplements can also be given in patients who do not have hyperkalemia. Deleterious consequences of severe hypophosphatemia such as rhabdomyolysis are rare.

Hypomagnesemia is a result of renal magnesium wasting from CNIs and/or diarrhea. This has been linked with development of post-transplant diabetes mellitus (Huang et al. 2016). It is commonly treated with magnesium supplements such as Magnesium Oxide. In patients with adequate GFR and normal potassium levels, a high Magnesium diet is recommended (Many high magnesium foods also have high potassium content).

Metabolic acidosis can occur from diarrhea and/or CNI toxicity which may lead to acute kidney injury. The underlying cause should be treated. Sodium Bicarbonate can be given.

Hypocalcemia is less common but can occur in the setting of decreased glomerular filtration, especially when continuation of pretransplant medications like cinacalcet occurs. Hypercalcemia is actually more common and is due to tertiary hyperparathyroidism or volume depletion. Intravascular volume should be corrected first. If it is severe, cinacalcet can be initiated. Evaluation for parathyroid adenoma should be considered if hypercalcemia is severe.

Hyponatremia can occur and is usually in the setting of hypervolemia. It can also occur in the setting of adrenal insufficiency or volume depletion. The treatment is no different to the nontransplant population.

Hematologic Complications Post Kidney Transplantation

Anemia

Post-transplant anemia (PTA) has been reported in up to 45% of renal transplant recipients and is a predictor of graft loss. In addition to its clinical symptoms, PTA can exaggerate left ventricular hypertrophy. Unrecognized iron deficiency is a frequent cause, and gastrointestinal bleeding should be ruled out. Azathioprine, Mycophenolate, and sirolimus can cause anemia. Reduced renal function is also a common cause. Renin Angiotensin Aldosterone (RAAS) blockade may also contribute. Parvovirus infection can cause refractory anemia, which can be treated with intravenous immune globulin. Hemolysis is rare but can occur in the setting of drug-induced factors (CNIs), hypertensive urgency, or antiphospholipid antibody syndrome. Anemia should be treated in the same way as nontransplant patients, paying particular attention to reversibility of potential causes. Anemia in the early post-transplant period can be from bleeding postoperatively or hemodilution from volume overload, and particular attention should be paid to patients with anemia with underlying cardiovascular disease. These patients may need blood transfusions prior to discharge. The guidelines and indications for the use of erythropoietin in renal transplant recipients is the same as in the CKD population.

Erythrocytosis

This can occur in up to 20% patients, usually within the first 2 years and the pathogenesis is not well understood. Post-transplant erythrocytosis may be a manifestation of renal artery stenosis. The cause of erythrocytosis is related to a defect feedback regulation of erythropoietin metabolism. Activation of the renin angiotensin system and angiotensin II appears to stimulate erythropoiesis and may contribute to post-transplant erythrocytosis. Angiotensin II stimulates growth of erythroid progenitors and augments erythropoietin secretion. In this regard, activation of the angiotensin II receptor may enhance erythropoietin production in the graft or the native kidneys and directly activate red cell precursors in the bone marrow. As in other cases of erythrocytosis, 10–30% patients experience thromboembolic events; and 1–2% patients eventually die of associated complications if untreated and if erythrocytosis does not spontaneously remit. The diagnosis is made based on demonstration of a hemoglobin >17 g/dL and/or hematocrit $>51\%$ that persists for over 6 months after transplantation and by the exclusion of common causes of nontransplant-associated erythrocytosis, including malignancies and in select patients chronic obstructive pulmonary disease. ACE-inhibitors or ARBs can be used to treat post-transplant erythrocytosis successfully and in some cases avoid the need for phlebotomy.

Leukopenia

Leukopenia is a common early post-transplant complication which is usually medication induced. If this is the case, the drug dose may be reduced or held. Mycophenolate mofetil (MMF), azathioprine, and valgancyclovir are well known culprits. Lymphocyte depleting induction therapies such as thymoglobulin, OKT3, and alemtuzumab can cause severe neutropenia which can persist for several weeks after completion of treatment. Infections which commonly cause leukopenia such as CMV, parvovirus, severe sepsis must also be sought after.

Pancytopenia

Lymphocyte depleting agents can cause pancytopenias during infusion and daily monitoring of Complete Blood Count (CBC) is recommended, with dose reduction by 50% if the white blood cell count and platelet counts drop significantly. CNIs and MMF can also cause pancytopenias as well as viral infections such as parvovirus.

Hypercoaguable States

Known hypercoagulable states prior to transplantation should be addressed at the time of listing, and a plan made on what (if any) anticoagulation will be used intraoperatively to reduce the risk of thrombosing the graft. Close follow up with hematology is recommended as well as collaboration with the transplant team.

Infectious Complications Post Kidney Transplantation

Infections are more common in transplant patients during the early post-transplantation period when the immune system is most suppressed. During the first month, nosocomial infections (pneumonia, catheter-related urinary tract infection (UTI), c-difficile colitis) and post-surgical infections (wound, anastomotic leaks, abscesses) are most common. Donor derived infections also occur during this time. Fungal infections are common in patients on high dose steroids, but uncommon otherwise. In the absence of prophylaxis, Herpes Simplex Virus (HSV) infection can occur. Prophylaxis is universal in all transplant programs and includes trimethoprim/sulphamethoxazole (for 6–12 months) for antibacterial, nocardia and listeria coverage. Valgancyclovir is used to prevent Cytomegalovirus (CMV) infections in moderate to high risk patients. Some programs use acyclovir in low-risk CMV patients to prevent HSV infections. Oral nystatin is commonly used to prevent thrush and is usually tapered off once patients are off steroids. Pancreas transplant recipients are commonly on fluconazole to prevent fungal infections. Further infections are described in chapter ▶ "Infection in Kidney Transplantation."

BK Virus

BK polyomavirus (BKV) is the major cause of polyomavirus-associated nephropathy (Py-VAN) putting 1–15% of kidney transplant patients at risk of premature allograft failure (7). BKV and JC polyomavirus infections are widespread in the general population. Primary infection with BKV occurs in the first decade of life via the respiratory or oral route. Subsequently, BKV colonizes the renourinary tract as the principal site of latent infection. The presentation of PyVAN is inconspicuous with no clinical or laboratory signs other than high-level viruria as defined by decoy cell shedding and BKV viremia. Detecting BKV can guide more specific histopathology studies and impact therapeutic management. Occasionally, clinical symptoms may include hematuria, ureteral stenosis, slow elevations in serum creatinine, i.e., a "creeping creatinine." Most centers perform kidney biopsy in setting of elevated creatinine levels and/or if there is a concern for rejection. A minimum of two biopsy cores should be taken preferably containing medullary tissue as PyVAN can be quite patchy, and there is up to a 35% chance of sampling error. Definitive diagnosis of PyVAN is made by demonstrating PyVAN cytopathic changes confirmed by immunohistochemistry or in situ hybridization (Table 2).

Table 2 Screening and intervention for BKV replication and nephropathy (Adapted from Hirsch et al. 2013, Table 1, p. 182)

Testing		Diagnosis possible	Diagnosis presumptive	Diagnosis proven
Urine	High level viruria decoy cells, BKV DNA load $>7\log_{10}$	+	+	+
Plasma	Viremia BKV DNA load $>4\log_{10}$	–	+	+
Biopsy	Viral cytopathic changes, inflammatory infiltrates, tubulitis, IF/TA		–	+
Therapy		No	Yes	Yes

Please refer to chapter titled ▶ "Pathology of Kidney Transplantation"

Effective antiviral treatments are lacking, and therefore screening for BK virus in the blood (PCR assay) and/or urine (presence of urinary decoy cells) is the key recommendation to guide the reduction of immunosuppression. This intervention curtails BK replication in the graft and enhances clearance of BK viremia in 70–90% of patients. Post-intervention rejection episodes occur in 8–12%, most of which are steroid responsive. Late diagnosis is complicated with irreversible functional decline, poor treatment response, and graft loss. Two strategies have been used in reducing immunosuppression: Strategy (1) First dose reduction of the CNI by 25–50% in one to two steps (aiming for tacrolimus levels less than 6, and cyclosporine levels less than 150), followed by reducing the antiproliferative drug by 50% (mycophenolate mofetil daily dose <1000 mg/day), and followed by discontinuation of the antiproliferative drug. Strategy (2) First reducing the antiproliferative drug by 50% followed by reducing CNI by 25–50%, followed by discontinuing the antiproliferative drug. Oral prednisone is reduced to 10 mg daily. Immunosuppression is further adapted according to the plasma and the course of serum creatinine concentration. Most centers reduce immunosuppression and monitor BK viral loads every 2–4 weeks and serum creatinine levels every 1–2 weeks. Both protocols appear safe and effective for preventing polyomavirus nephropathy (PyVAN) and clearing BKV viremia. However, follow up data are lacking at this time. In one study, half of the patients cleared BKV viremia after a one-step intervention. The other half required two-step interventions, with overall mean clearance achieved by 4 months (Schaub et al. 2010). Despite preemptive BKV viremia guided reduction of immunosuppression, proven PyVAN still occurred in one third of cases. Proven PyVAN was characterized by higher plasma BKV loads, longer median time to clearance of BKV viremia, and three steps of reducing immunosuppression in one third of patients.

In patients with sustained high level plasma BKV viral load despite adequately reduced immunosuppression, the adjunctive use of antiviral agents may be considered. Adjunct therapies such as cidofovir, leflunamide, and intravenous immunoglobulins have been used, but the benefit has not been documented in clinical trials. Retransplantation after PyVAN is largely successful but requires close monitoring for recurrent BKV viremia. Cidofovir has been administered intravenously for PyVAN in doses from 0.25 to 1.0 mg/kg at 1–3 weekly intervals, without probenocid. These patients should be followed closely by serial measurements of serum creatinine concentration, leukocyte counts, eye symptoms, and vision. Anterior uveitis has been described in up to 35% patients receiving this drug. Leflunamide is orally administered as a replacement for discontinued mycophenolic acid with a loading dose of 100 mg for 5 days, followed by an initial maintenance dose of 40 mg. Regular blood counts and liver function tests are advisable once a month for all patients on leflunamide, as well as plasma BKV loads once every 2 weeks. Hepatitis, hemolysis, TMA, bone marrow suppression, and fungal pneumonia have been described in patients on leflunamide. Intravenous immunoglobulin (IVIG) preparations contain high titers of BKV neutralizing antibodies and have been administered in doses ranging from 0.2 to 2.0 g/kg in conjunction with reduced immunosuppression. Fluoroquinolones can inhibit BKV replication via an effect on the helicase activity of virus encoded large T antigen. Treatment of well-established PyVAN may not be effective. If acute rejection is diagnosed in allograft biopsies, after clearance of plasma BKV DNA and PyVAN by histology, anti-rejection treatment is indicated and a judicious increase in maintenance immunosuppression be considered.

Screening for BK virus should be done at least every 3 months post-transplantation for the first 2 years, and then annually until 5th year post-transplant. This ensures that at least 80–90% patients at risk of PyBK Nephropathy have been screened prior to significant renal dysfunction occurring. More frequent screening will pick up additional cases and should be based on center-specific incidence. A negative screening test eliminates the risk for Py-BK Nephropathy. Monthly plasma screening for BK via a BK Virus PCR for the first 6 months, then every 3 months until 2 years post-transplant has been employed successfully in

many centers. Alternatively, biweekly urine cytology for decoy cells for the first 3 months until 2 years post-transplant followed by plasma testing for BK viremia if positive can be employed.

Malignancies After Transplantation

Malignancies develop three to five times more commonly in the transplant population compared to the general population (Dantal and Pohanka 2007). For most common tumors, e.g., lung, colon, prostate, stomach, pancreas, ovary, and breast cancer rates have been reported to be roughly twofold higher after kidney transplantation compared with the general population. Melanoma, leukemia, hepatobiliary tumors, cervical and vulvovaginal tumors were each approximately fivefold more common. Testicular and bladder cancers were increased approximately threefold, while kidney cancer was approximately 15-fold more common. Kaposi's sarcoma, non-Hodgkin's lymphoma and nonmelanoma skin cancers were more than 20-fold increased than in the general population (Kasiske et al. 2004). Compared with patients on the waiting list, several cancers have been reported to have a higher incidence post-transplantation ($p < 0.01$); nonmelanotic skin cancers (2.2-fold), Kaposi's sarcoma (ninefold), non-Hodgkin's lymphoma (3.3-fold), cancer of the mouth (2.2-fold), and cancer of the kidney (39% higher). Cancer should continue to be the major focus of prevention post-kidney transplantation. However, there are no evidence-based guidelines on benefits of general screening in kidney transplant patients beyond what is already recommended in the general population. All patients should have annual skin examinations by an experienced health professional and advised to minimize sun exposure lifelong using protective clothing and effective ultraviolet blocking agents. Patients with a history of renal cell cancer or complex renal cysts may need yearly or bi-yearly renal ultrasounds. Reduction of immunosuppression in kidney transplant recipients (KTRs) with cancer may be considered. mTOR inhibitors should be used along with a reduction in overall immunosuppression.

Post-transplant Lymphoproliferative Disorder (PTLD)

Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and/or plasmacytic proliferations that occur in the setting of solid organ or allogenic hematopoietic transplantation. They are among the most fatal and most serious complications post-transplantation. The majority of PTLD appears to be related to the presence of Epstein-Barr virus (EBV); however, EBV negative disease does occur. Three types of PTLD have been described:

1. Early lesions: plasmacytic hyperplasia or an infectious mononucleosis like PTLD. This presents as an acute illness like infectious mononucleosis characterized by polyclonal B cell proliferation with no evidence to suggest malignant transformation.
2. Polymorphic PTLD are polyclonal or monoclonal lymphoid infiltrates that demonstrate evidence of malignant transformation but do not meet all of the criteria for B cell or T cell or NK cell lymphoma recognized in immunocompetent individuals.
3. Monomorphic PTLD are monoclonal lymphoid proliferations that meet the criteria for B/T/NK cell lymphomas in immunocompetent patients.

These conditions lie along a continuum of disease and are classified by the 2008 WHO classification of PTLD (Swerdlow et al. 2008). Importantly, small B cell lymphoid neoplasms (follicular lymphoma, small lymphocytic lymphoma) and marginal zone (MALT) lymphomas that occur post-transplantation are not considered PTLD.

The 1 year incidence of PTLD in KTR is about 1%, which is 30–50 times greater than in the general population. EBV seropositive status and the degree of T-cell suppression is directly linked with an increased risk of PTLD development. It is most common in the first year post-transplantation, with the risk of PTLD decreasing by 80% after the first year. Constitutional symptoms such as fever, fatigue, and weight loss can be

presenting symptoms. Other symptoms can be viral symptoms with lymphadenopathy, dysfunction of the involved organs, or compression of surrounding structures. More than half of PTLD patients present with extra nodal masses. Involved organs include the GI tract, skin, lungs, and liver. About 25% patients present with CNS involvement or involvement of the transplanted organ. Risk factors include the overall state of immunosuppression, and the EBV status of the recipient. The degree of T-cell immunosuppression appears to be more important than the degree of overall immunosuppression in the development of PTLD. Interestingly, MMF and alemtuzumab have not been linked with PTLD, whereas tacrolimus is associated with a greater risk of PTLD than cyclosporine. Lymphocyte depleting agents are associated with a greater degree of PTLD in the first year (after induction) when T cells are immunosuppressed maximally. A diagnosis of PTLD requires a high index of suspicion. Patients should undergo an evaluation if they present with B symptoms (fever, weight loss, night sweats) and/or unexplained abnormal hematologic markers and/or features suggestive of infiltration of extralymphatic tissues. Radiologic evidence of a mass and elevated LDH is suggestive of PTLD. A CT of the chest, abdomen, and pelvis is recommended for initial evaluation and staging prior to treatment. A rising EBV load may also be suggestive of the diagnosis. Some centers have protocols for antiviral treatment with ganciclovir in high risk patients for prevention of PTLD and a retrospective study showed that this reduced PTLD incidence by 38% (Funch et al. 2005). A tissue biopsy is required to make the diagnosis. Treatment involves tapering of immunosuppressive therapy, immunotherapy with rituximab (which is only effective in CD20 positive PTLD), chemotherapy, radiation therapy, or a combination of these.

The prognosis of PTLD has been described in retrospective studies and case series. The mortality in monomorphic PTLD is as high as 80%. Overall survival rates are between 25% and 35%. The largest study on PTLD is a French registry in KTRs and they published prognostic indicators associated with a poor survival: Older age (greater than 55), serum creatinine greater than 1.5, location of tumor (CNS or serous membrane invasion), elevated LDH, and monomorphic PTLD or T cell histology.

Post-transplant Diabetes

The incidence of PTDM has been reported in studies to vary between 10% and 74% in kidney transplant recipients. This large variation is due to different transplant centers reporting their rates, differences in age, BMI, underlying risk factors, and using different criteria for diagnosis of PTDM (Shivaswamy et al. 2016).

The first International Consensus Guidelines for new-onset diabetes after transplantation (NODAT) were published in 2003 and they reflected the same criteria adopted by WHO at that time. Diagnosis of NODAT could result from a fasting glucose greater than or equal to 126 on more than one occasion, random glucose >126 mg/dL on more than one occasion, random glucose greater than or equal to 200 with symptoms, or a 2 h glucose level after a 75 g oral glucose tolerance test (OGGT) of greater than or equal to 200 mg/dL.

In October 2013, a 2nd international consensus panel met to update the criteria and other criteria regarding NODAT and to evaluate the utility of HbA1C as a criterion, as it had been defined by the American Diabetes Association in 2010 in non-transplant adults:

Diagnosis of PTDM

Fasting Glucose >126 mg/dL on more than one occasion
Random glucose >200 mg/dL with symptoms
2 h glucose after a 75 g OGTT of >200 mg/dL
HbA1c >6.5%

Three major changes occurred with the new criteria: (a) they changed the name from NODAT to PTDM as many cases first identified after transplant are likely not new. Most transplant centers use fasting glucose or HbA1C to diagnose diabetes for screening candidates. These methods are less sensitive than the OGTT for identifying

diabetes in patients with renal failure (Armstrong et al. 2006). (b) The consensus panel recommended delaying the diagnosis of PTDM until the recipient has been discharged from the hospital, is stable, and had tapered to likely chronic immunosuppression doses. With greater inpatient glucose screening, there is increasing awareness of the number of transplant recipients who have glucose intolerance or could be diagnosed with PTDM during this immediate post-transplant period (Hecking et al. 2012; Sulanc et al. 2005). Because the hyperglycemia does not always persist after discharge, and the diagnosis of diabetes in most nontransplant populations is generally reserved for outpatient settings, the consensus panel recommended delaying the evaluation for and diagnosis of PTDM until the recipient had been discharged from the hospital. (c) The 3rd recommendation concerned the use of HbA1c for the diagnosis of PTDM. For many reasons, including reduced red blood cell survival after transplant, HbA1C is less reliable for identifying significant glucose intolerance in the first 12 months after transplant (Shabir et al. 2013).

Risk Factors for PTDM

The well-known risk factors for DM in nontransplant patients still holds true for the transplant patients and are described in Fig. 3.

Role of Immunosuppressant Agents

Corticosteroids cause hyperglycemia by inducing or worsening preexisting insulin resistance, increasing hepatic gluconeogenesis, and in long-term by stimulating appetite and weight gain (Wauters et al. 2012; Mathew et al. 2003; Joss et al. 2007). The impact is dose dependent. Most centers use high-dose corticosteroids for induction, and this has much greater impact than chronic low-dose corticosteroids that are common

Fig. 3 Pretransplant and post-transplant risk factors for post-transplant diabetes mellitus

to many maintenance immunosuppression protocols. A study using early steroid withdrawal compared to long-term low-dose prednisone (5 mg/day) showed that the incidence of PTDM was minimally impacted (Pirsch et al. 2015).

Azathioprine or mycophenolate mofetil have not been shown to have a major role in PTDM as they have not been shown to have a major impact on insulin action or glucose metabolism.

Tacrolimus and Cyclosporine and mTOR inhibitors (sirolimus or everolimus) may contribute to PTDM. Initially it was thought that CNIs did not cause PTDM as less hyperglycemia was observed with the use of lower doses of corticosteroids. However, after the initiation of tacrolimus, an association between this drug and insulin resistance. Tacrolimus increased DM risk in patients who were already at highest risk, such as African Americans and those with a prior history of HCV (Bloom et al. 2002; Neylan 1998). Tacrolimus appears to increase the risk for PTDM more than cyclosporine (18% vs. 8%) (Woodward et al. 2003). Multiple mechanisms have been described for CNI-associated PTDM. CNIs have been shown to impair insulin secretion (Duijnhoven et al. 2001). Tacrolimus has also been shown to reduce B-cell mass, increase islet cell apoptosis, and affect insulin production (Shivaswamy et al. 2014). Pancreas allograft biopsies of pancreas transplant recipients have also demonstrated reversible cytoplasmic swelling and vacuolization of islets with tacrolimus and cyclosporine treatment (Drachenberg et al. 1999). CNIs may contribute to hyperglycemia via hypomagnesemia (Navaneethan et al. 2006; Vannini et al. 1999). Hypomagnesemia alone can impact insulin signaling (Pham et al. 2007), is a well-known side effect of CNIs, and is associated with an increased risk of PTDM (Huang et al. 2016). A retrospective analysis showed that patients who developed PTDM had lower serum magnesium levels in the first month after transplant compared to non-PTDM recipients, and those with the lowest magnesium levels developed PTDM more rapidly (Van Laecke et al. 2009). Further studies are still needed to assess the impact of magnesium supplementation on the prevention of PTDM.

Sirolimus has also been associated with glucose intolerance after organ transplantation, and it is independently associated with an increased risk of PTDM (Flechner et al. 2011). Several mechanisms may be involved. Sirolimus treatment can reduce B-cell mass of human and rat islets through apoptosis (Bell et al. 2003), and it can also affect insulin signal transduction (Arvisais et al. 2010; Hashimoto et al. 2010). Further information regarding transplant immunosuppression can be found in chapter ▶ "Transplant Immunosuppression."

Role of "Stress," Inflammation, and Infection

Inflammation and "stress" have been associated with type II DM (Hotamisligil 2006). Deceased donor kidney transplantation express higher levels of proinflammatory cytokines compared to living donor kidney allografts and have been linked to a fourfold greater risk in PTDM (Gourishankar et al. 2004). Infections are another source of inflammation. HCV and CMV infections have been linked with a higher risk for PTDM in kidney transplant recipients. Insulin resistance has been shown to develop sooner in patients with the highest HCV levels (Anonymous 1994). A meta-analysis reported an increased risk of developing PTDM in kidney transplant recipients with HCV infection compared to HCV-negative recipients (odds ratio 3.97; 95% confidence interval, 1.83–8.61) (Shihab et al. 2008). The risk of PTDM is even higher in those who have HCV and are treated with tacrolimus based immunosuppression, compared to either risk factor alone (Bloom et al. 2002). A meta-analysis suggested that CMV positive recipients were at greater risk for PTDM (Einollahi et al. 2014). And a prospective observational study showed that CMV infection was an independent risk factor for PTDM, whether or not the patients were symptomatic, as assessed by OGTT at 10 weeks after transplant (Boots et al. 2002). Mechanisms for these CMV effects remain to be elucidated but may involve proinflammatory cytokine production or leukocyte-mediated destruction of B cells (Hjelmesaeth et al. 2005).

Other Potential Risks for PTDM

Vitamin D deficiency has been shown to increase the risk of DM in nontransplant patients but no data has been published in transplant recipients yet, and there are trials underway testing this hypothesis. Statins are commonly used post-transplantation to treat hyperlipidemia and have been shown to increase the risk of new-onset DM outside of transplant groups. In renal transplant recipients, patients treated with atorvastatin had more IFG and PTDM than those on fluvastatin (Choe et al. 2014).

Treating PTDM

The treatment of diabetes in hospitalized transplant recipients requires attention to a multitude of factors that are unique to transplantation. First, diabetic patients, who may not have required insulin while on dialysis, may develop significant hyperglycemia post-transplantation secondary to changes in renal function and increased nutritional intake. Second, high-dose corticosteroids and CNI toxicity can induce hyperglycemia. The inpatient rounding transplant teams (transplant nephrology and surgery) must pay close attention to blood glucose levels with frequent monitoring, and these patients may need IV insulin drips and endocrinology consultation for optimal management. Oral hypoglycemic are generally avoided in the hospital setting for the same reasons as in the nontransplant population.

Outpatient diabetes management involves subcutaneous insulin in many patients especially if there is preexisting obesity. However oral hypoglycemics can also be used in conjunction with insulin or alone if the glucose levels are acceptable. Metformin is often used in the nontransplant population. Animal studies show that metformin may reduce exocrine cell apoptosis that is induced by immunosuppressants (Shivaswamy et al. 2013), therefore some have suggested it be used post-transplantation. However, with the frequency of impaired renal function, use of contrast agents, and infection, metformin should be used with caution due to the rare risk of lactic acidosis with reduced renal function. A recent review of 47,000 kidney transplant recipients in the SRTR suggests that 10% of transplant recipients filled at least one prescription of metformin, although nearly 40% of the metformin users had serum creatinine level above the FDA approved cutoff (Stephen et al. 2014).

Cardiovascular Disease Post-transplantation

Cardiovascular disease is a leading cause of morbidity and mortality after transplantation. KTRs have a significantly lower risk of cardiovascular complications than patients on the transplant wait list, but a higher risk compared to the normal population. Cardiovascular disease is also the leading cause of death with functioning graft post-kidney transplantation. Around 50–60% deaths post-kidney transplantation are linked to a cardiovascular cause (Ojo 2006) (Table 3).

The table above shows the prevalence of cardiovascular risk factors of dialysis patients, transplant candidates, and transplant recipients. Even though many risk factors have led to the renal

Table 3 Prevalence of cardiovascular risk factors of dialysis patients, transplant candidates, and transplant recipients (Ojo 2006, p. 604)

Risk factor	Dialysis patients (%)	Transplant candidates (%)	Transplant recipients (%)
Systemic HTN	80	75	80
Diabetes mellitus	40	35	55
Hypercholesterolemia	25	25	60
Obesity (BMI >30)	14	20	32
Tobacco use	18	24	20
LVH	75	75	52
Anemia (Hct <30)	32	25	40

failure necessitating dialysis, these risk factors do not dissipate post-kidney transplantation due to the additional burden of immunosuppressants, patient lifestyle, renal dysfunction post-kidney transplantation, and intercurrent illnesses. Novel cardiovascular risk factors such as hyperhomocysteniemia, oxidative stress, systemic inflammation, lupus anticoagulant antibodies, and advanced glycosylation end-products have been implicated in the pathogenesis of CVD in kidney transplant recipients.

Kidney Transplant recipients are unique in their protoplasm as they have the traditional cardiovascular risk factors of ESRD patients (hyperphosphatemia, sudden cardiac death, hypertension/hypotension, vascular calcification, etc.), the well-known "U-shaped" curve with risk of death, along with the traditional risk factors such as smoking, diabetes, hyperlipidemia, hypertension, obesity, in addition to, transplant factors which include immunosuppressant medications which increase the risk of hyperlipidemia, proteinuria (an independent CVS risk factor), and hypertension (Fig. 4). Further details on recipient selection can be found in chapter ▶ "Recipient Selection for Kidney Transplantation."

Pretransplant factors that increase risk of cardiovascular death

Post-transplant factors that increase risk of cardiovascular death

Uncontrolled HTN

In 2009, Kidney disease improving global outcomes (KDIGO) extrapolated from the general CKD population and recommended aiming for SBP <130 and DBP <80 in kidney transplant recipients. As optimal blood pressure in KTRs remained uncertain, a recent analysis of the FAVORIT trial cohort studied associations of blood pressure with pooled cardiovascular disease outcome and all-cause mortality (Stoumpos et al. 2015). The study revealed that lower systolic BP was associated with a significantly lower risk of cardiovascular disease and mortality with no increased risk of adverse outcomes associated with even the lowest systolic BP values. In contrast, lower levels of diastolic blood pressure are associated with increased rates of cardiovascular outcomes and all-cause mortality. A recent study (Carpenter et al. 2014) showed that cardiovascular risk reduction in established kidney transplant recipients is suboptimal, and despite KTRs receiving specialized care, blood pressure and lipid goals are not being met. The reasons for this are most likely multifactorial and complex, ranging from difficulties in treating resistant hypertension, medication side effects causing significant hyperlipidemia, medication adherence, patient adherence issues with healthy diets, as well as systematic issues of suboptimal quality improvement measures addressing these outcomes. Blood pressure targets post-kidney transplantation vary depending on the time from transplant and how well the graft is functioning. Early in the postoperative course, stringent blood pressure control is avoided to avoid decreased perfusion to the graft. Elevated blood pressures are also avoided to avoid rupture of the arterial and venous anastomosis. Generally, in the first 24–48 h, systolic blood pressures are maintained in the 120–150 range. Early intraoperatively and postoperatively, patients are aggressively hydrated. Patients with significant cardiovascular issues are usually kept no more than 2–3 kg above their dry weight. This may result in volume-mediated hypertension. Close attention to volume status and blood pressure control is imperative to avoid complications after discharge. Patients with delayed graft function who remain on dialysis after their discharge should aim for a dry weight about 2 kg above their dry weight prior to kidney transplantation. Most transplant centers would agree to avoid overzealous blood pressure control in these patients. This is to avoid hypotension at dialysis and prevent additional renal insults and a delay in renal recovery. After discharge, patients may have fluctuating weight changes, which may affect their blood pressure significantly secondary to volume-mediated HTN or they may develop hypotension from poor oral fluid intake and increased urine outputs. Patients should keep a detailed log of their daily weights, blood pressures twice daily, and urine outputs in the first few weeks post-transplant to aid management of volume status and hypertension.

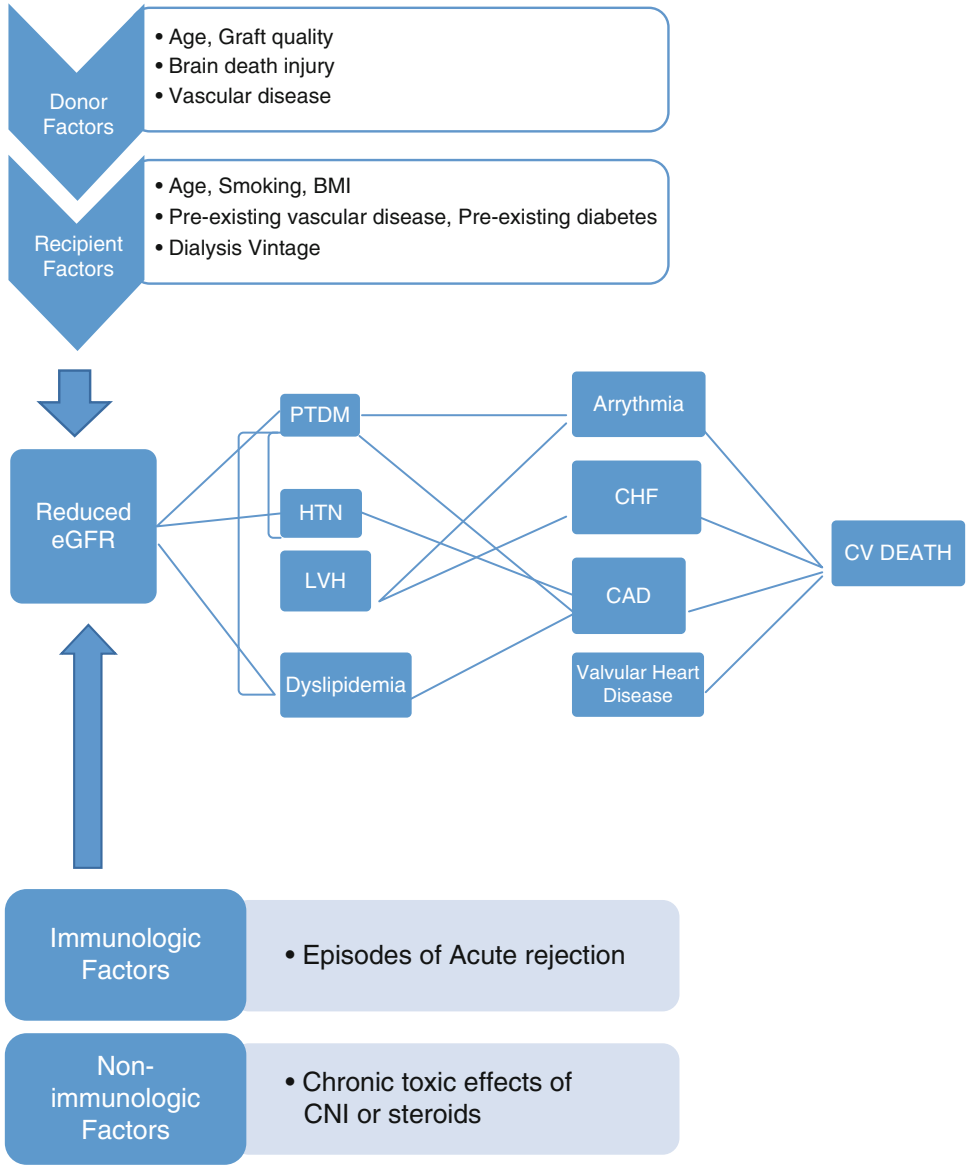

Fig. 4 Pre- and post-transplant factors in ESRD patients that increase risk of CV death (Stoumpos et al. 2015, p. 15)

Choice of Antihypertensive Agent

The commonest agents used to control blood pressure post-kidney transplantation are the non-dihydropyridine calcium channel blockers (nifedipine XL or amlodipine) and beta-blockers as they do not affect the renal function. Diuretics are generally avoided in the first few months post-transplantation unless the patient is hypervolemic. Most studies show that about 30–40% kidney transplant recipients are on a diuretic. Diuretics, ACE-inhibitors, and angiotensin receptor blockers may affect the renal function, and the fear is that the rise in creatinine, which may be from the diuretic/RAS blockade, may in fact be from a rejection. Therefore medications that affect the renal function are generally avoided in the early post-transplant course. Beta blockers may mask hypoglycemia and cause bradycardia. Non-dihydropyridine CCB may elevate the CNI levels and dose

reductions of CNI may need to be instituted. A recent randomized controlled trial in kidney transplant recipients revealed that ramipril did not slow decline in GFR, ESRD, or reduce mortality (Knoll et al. 2016). Therefore, the latest recommendations favor use of calcium channel antagonists. In transplant patients with hypertension and proteinuria, data suggest that ACE inhibitors and ARBs are unlikely to confer benefit over other agents. ACE-inhibitors are helpful for treating post-transplant polycythemia, so hypertension in the presence of polycythemia might make them a good treatment choice.

Hyperlipidemia

Dyslipidemias are abnormalities in circulating lipoproteins that are associated with an increased risk of cardiovascular disease. The incidence and prevalence of hyperlipidemia is high in KTRs largely due to the fact that immunosuppressive therapies such as CNIs and mTOR inhibitors have side effects of elevating the cholesterol and triglycerides. Lipid lowering measures lower the risk of cardiovascular mortality by up to 35% (Jardine et al. 2004) and reduce the LDL cholesterol up to 32% (Table 4).

Anemia

Anemia can worsen the severity of many cardiovascular disorders (CHF, CAD, and PVD) in the general population, in CKD patients and also in kidney transplant patients. Studies show that anemia is an independent risk factor for post-transplant LVH and CVD events (Rigatto et al. 2003). Cardiovascular events are 35% less likely in the first 6 months after transplantation in diabetic transplant recipients with hematocrit >30% compared to those with lower hematocrit levels (Djamali et al. 2003). The etiology of anemia is multifactorial; female gender, CNIs, MMF, sirolimus, poor graft function, older age group, acute rejection episodes, recent infection, Fe, folate, B12 deficiency, angiotensin interrupting drugs. The management of anemia post-transplant has been suboptimal in reported studies (Mix et al. 2003) and show that only 36% patients with anemia have Fe studies checked, and less than half of patients are receiving EPO or Fe repletion. However, caution is warranted against liberal use of EPO as studies show that EPO shortened the time to achieving the target Hct but did not have a significant impact on the achieved level of Hct compared to non-EPO treated randomized controls (Van Biesen et al. 2005).

Proteinuria

It is well established that proteinuria is an independent risk factor for cardiovascular disease. Studies reveal that the presence of proteinuria in KTRs significantly increases the prevalence of cardiovascular disease post-kidney transplantation (Ojo 2006).

Older studies show that ACE-inhibitors or ARBs conferred benefit in reducing the degree of proteinuria and preserving GFR and reducing CVS risk. However, more recent evidence suggests that ACE-inhibitors and ARBs do not preserve renal function or slow the decline in GFR in

Table 4 Management of hyperlipidemia post-kidney transplantation (Aadapted from Riella et al. 2012, p. 1976)

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG >500 mg/dL and LDL <100 ml/dL	TG <500 mg/dL	TLC	TLC + niacin	Fibrate or statin
LDL 100–129 mg/dL	LDL <100 mg/dL	TLC	TLC + low dose statin	Ezetimibe or niacin
LDL >130 mg/dL	LDL <100 mg/dL	TLC + low dose statin	TLC + 50% max dose statin	Ezetimibe or niacin
TG >200 mg/dL and non-HDL >130 mg/dL	Non-HDL <130 mg/dL	TLC + low dose statin	TLC + 50%max dose statin	Ezetimibe or niacin

patients with proteinuria (Knoll et al. 2016). These medications do however reduce proteinuria and continue to be prescribed for this indication.

Other risk factors for CVS disease include obesity which is a significant burden in KTR. A comprehensive weight loss program should be undertaken when excessive weight gain is observed in the post-transplant period as data shows an independent increased risk of both glucose intolerance and CVS disease in recipients with a high BMI. Left ventricular hypertrophy, hyperhomocysteinemia, inflammatory cytokines, and CD4 lymphopenia are all associated with increasing degrees of obesity.

Secondary Prevention

Results of coronary revascularization procedures in KTRs with ischemic heart disease are comparable to that of the general population. Studies have compared percutaneous transluminal coronary angioplasty (PTCA) with surgical revascularization and long-term results appear to favor surgical revascularization (Ferguson et al. 1999; Herzog et al. 2004) without compromising renal function.

One Year Post-transplant Mortality

Trends in kidney transplant patient survival 1 year post-transplant have continued to improve over the last 12 years. In DDKTs, the probability of all-cause graft failure in 2013 was 8% (an improvement from 14% in 1997), and probability of death was 4% (improvement from 6% in 1997). In living donor transplant recipients, 1 year post-transplant graft failure probability was 3% in 2013 (compared to 7% in 1997) and 1 year mortality was 3% in 2012, compared to 7% in 1997 (USRDS data 2016).

Factors associated with poorer patient survival include older recipient age, severity of comorbid conditions, smoking, and degree of immunosuppression, frailty, gender, and race. Measures to reduce 1 year post-kidney transplantation mortality involve meticulous kidney transplant evaluation and re-evaluation and thorough post-transplant medical care as mentioned in this chapter.

Conclusion

Complications in the first year post-kidney transplantation vary, with rejection, infections and risk factors and complications of cardiovascular disease being the commonest. Outcomes in 1-year kidney transplantation are far superior now to several decades ago. Future challenges to reduce early complications will be to reverse the post-transplant obesity epidemic, optimize long-term preservation of the renal allograft with optimal control of blood pressure, hyperlipidemia, and proteinuria, as well as discovering effective long-lasting treatments for antibody-mediated rejection and chronic transplant glomerulopathy.

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Kidney Transplantation: Surgical Complications

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Contents

Abstract

Kidney transplantation (KT) can be complicated by medical or surgical complications. Surgical complications after KT may cause kidney graft dysfunction and may have similar clinical manifestations as medical complications. Surgical complications include hemorrhage, vascular complications (renal artery and vein thrombosis or stenosis), urinary complications (urine leaks or ureteral stricture), lymphocele, and wound infection. Hemorrhage is uncommon after KT, and usually resolves spontaneously with conservative management. Renal vascular thrombosis is an uncommon, but serious complication, usually leading to graft loss. Renal artery stenosis (RAS) is a treatable surgical complication post-KT that can cause hypertension and allograft dysfunction. Urologic complications, manifesting as urine leaks or ureteral obstruction, affect about 2–10% of kidney transplant recipients, and are associated with high morbidity, graft loss, and mortality. Lymphoceles occur with an incidence of 0.6–18%, and commonly develop a few weeks to months after KT. Surgical site

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infections (SSIs), which are one of the most common complications after KT, usually occur within the first month after KT. Surgical complications post-KT can cause significant morbidity that requires early recognition, diagnosis, and immediate treatment to optimize outcomes and graft survival.

Keywords
Kidney transplantation · Immunosuppression · Kidney graft loss · Stenosis · Thrombosis · Urine leak · Ureteral stricture · Lymphocele · Wound infection · Hemorrhage

Introduction

Kidney transplantation (KT) is the treatment of choice for patients with chronic kidney disease. In the last decades, several major advances in surgical techniques of organ procurement and recipient transplantation, introduction of better preservation fluid, and more potent immuno-suppressive drugs have led to improved patient and graft survival post-KT. These advances have significantly reduced the incidence of post-KT surgical complications to 5–10%, compared to liver or pancreas transplantation. However, to minimize the deleterious effect of these surgical complications on the kidney graft and to reduce the significant morbidity to the KT recipient, early recognition, diagnosis, and immediate treatment of these surgical complications should be emphasized, when they occur. The incidence rates, clinical presentation, diagnosis, and treatment of various surgical complications after KT are discussed below.

Vascular Complications

Hemorrhage

Hemorrhage is an uncommon complication after KT. Common clinical presentation includes abdominal or flank pain, decreasing hemoglobin, tachycardia, and hypotension in occasional severe cases. Risk factors for bleeding include extensive dissection due to recipient obesity, and use of antiplatelet drugs or anticoagulants. Majority of cases resolve spontaneously with conservative management. However, patients may be considered candidates for surgical exploration if they develop manifestations of ongoing bleeding (decreasing serial hemoglobin or requirement for multiple blood transfusions), abdominal CT scan, or ultrasound findings of compressing perigraft hematoma, or those who become hemodynamically unstable. Often times, no obvious bleeding site is identified on exploration. However, those with overt bleeding identified usually arise from bleeding small blood vessels within the graft hilum or retroperitoneal surface, and occasionally, at the vascular anastomotic site.

Renal Graft Thrombosis

Renal vascular thrombosis, which includes renal artery thrombosis and renal vein thrombosis, is an uncommon serious complication with an incidence of 0.3–6.1% (Hedegard et al. 2009). They often occur in the first 2 weeks after KT and usually lead to graft loss.

Renal artery thrombosis (RAT) has an incidence of 0.5–3.5% and usually occurs within the first month after transplantation (Rouviere et al. 2002). It is usually due to technical complications like intimal dissection, and arterial kinking or torsion. Other reported risk factors include post-transplant hypotension, hypercoagulable state, multiple renal arteries, prolonged ischemia time, hyper-acute or refractory acute rejection, and severe recipient atherosclerosis. RAT developing later after post-KT is uncommon and is usually associated with refractory acute rejection or high-grade graft renal artery stenosis. Common clinical manifestations of RAT include: sudden cessation of urine output, graft pain and tenderness, increasing serum creatinine, hyperkalemia, and rarely, consumption thrombocytopenia. Diagnosis is made with Doppler ultrasound studies showing absence of blood flow in the renal artery, with the presence of intraluminal filling defects.

Renal vein thrombosis (RVT) is usually caused by proximal propagation of a lower extremity deep vein thrombosis or venous compression by a fluid collection around the kidney graft. Patients with RVT may present with allograft dysfunction associated with oliguria or anuria, hematuria, and abdominal wound pain and tenderness. The Doppler ultrasound findings of RVT include swollen kidney graft, and failure to demonstrate venous flow within the transplant kidney or its pedicle. The arterial waveforms show high resistive index in every definable vessel and at the arcuate arteries of renal pyramids with reversal of diastolic flow (Giustacchini et al. 2002).

Treatment for renal vascular thrombosis is urgent surgical exploration and thrombectomy. However, since the kidney transplant graft does not have any collateral vessels and has poor tolerance to ischemia, most grafts are nonsalvageable by the time of diagnosis, and most patients end up requiring graft nephrectomy.

Nonsurgical approach to treatment of renal graft thrombosis using transcatheter thrombolysis has been reported with successful outcomes in selected cases (Rouviere et al. 2002). This procedure involves percutaneous placement of a catheter tip within the thrombus, about a centimeter distal to the vascular anastomosis. Then, a 200,000 IU bolus of thrombolytic agent, i.e., urokinase, is injected through the catheter, followed by an infusion at a rate of 2500 IU/kg/h. Systemic IV heparin infusion at 500 IU/kg/d is given in conjunction with the thrombolytic agent infusion. However, the authors suggested that this treatment is mainly effective in limited cases such as segmental arterial thrombosis, less-extensive thrombosis, or high-risk surgical candidates (Ismail et al. 1997; Rouviere et al. 2002).

Renal Artery Stenosis

Renal artery stenosis (RAS) is an important treatable surgical complication post-KT that can cause hypertension and allograft dysfunction. It is a late complication that is mostly diagnosed in the first few years post-KT with an incidence of 3–12%. There are two types of RAS: true RAS and pseudo-RAS. True RAS is more commonly located at the donor-recipient arterial anastomotic site. However, it may occur at the main renal artery or at the segmental renal artery due to small vessel disease. RAS can be caused by donor or recipient arterial injury, intimal dissection, recipient arterial atherosclerosis, improper suturing techniques, kinking of a long artery, and mechanical arterial compression. Pseudo-RAS is due to inflow obstruction secondary to recipient aortoiliac atherosclerosis. Pseudo-RAS becomes more prevalent with advanced age and has an incidence of less than 3% (Voiculescu et al. 2003). Recipients with RAS may present with kidney allograft dysfunction, poorly controlled hypertension, and peripheral edema. However, several differential diagnoses for hypertension after kidney transplantation, such as calcineurin inhibitor toxicity, rejection, and recurrent glomerulonephritis, should be ruled out. Doppler ultrasound is the initial screening tool used because of its high sensitivity and specificity. Furthermore, this diagnostic modality can also identify the location, length, and morphology of the RAS, and assess the hemodynamic changes across the stenosis. Characteristic Doppler findings of RAS include peak systolic velocity >2–2.5 m/s, low pulsatility index of 0.9 ± 0.1, and a parvus et tardus waveform with systolic acceleration time of ≥ 0.1 s (Gottlieb et al. 1995). Magnetic resonance imaging (MRI) with or without contrast-enhanced magnetic resonance angiogram or CT angiogram can be used to confirm the diagnosis. However, percutaneous transcatheter angiography remains the gold standard in the diagnosis of RAS.

Percutaneous transluminal balloon angioplasty (PTA) with or without stent placement is the first-line treatment of choice for clinically significant RAS. Angiographic approach to the stenotic lesion may be determined by the type of arterial anastomosis, with an end-to-end anastomosis to the internal iliac artery better approached from the contralateral femoral artery, while an end-side anastomosis with the external iliac artery preferably approached on the ipsilateral femoral approach (Hedegard et al. 2009). A nonselective aortoiliac arteriogram is performed first to exclude

any pseudo-RAS using CO2 for the initial aortogram and iliac arteriogram. This is followed by a selective contrast-enhanced digital subtraction angiogram of the recipient's iliac artery to transplant graft renal artery. The technical success rate of this treatment, as defined by a residual stenosis of 20–30% post-angioplasty, is about 60–94%. On the other hand, the clinical response rate, as defined by >15% reduction in serum creatinine and diastolic blood pressure (DBP) with no change in antihypertensive medication or >10% decrease in DBP and antihypertensive medications, is more than 80% (Patel et al. 2001). The complication rate is reported to be 4–8%. Potential complications of angioplasty include arterial dissection, rupture, and thrombosis, which can lead to graft loss (Benoit et al. 1990). The incidence of recurrent stenosis after angioplasty is about 10–12%, mostly developing within the first 9 months post-angioplasty (Hedegard et al. 2009).

Surgical management of RAS is reserved for recurrent strictures post-PTA, unsuccessful PTAs, and long strictures or severe distal strictures which are inaccessible or not amenable to PTA. Although the success and recurrence rate of surgical treatment is similar to PTA, surgery is associated with increased graft loss and ureteral injury and higher mortality rate of up to 5% (Hurst et al. 2009). Several surgical techniques have been used to repair RAS, none of which has been proven to be superior to the other. These have included: resection of stenotic segment with revision of arterial anastomosis, renal artery patch angioplasty, localized endarterectomy, and renal artery bypass graft using either recipient saphenous vein or internal iliac artery (Bruno et al. 2004). One center reported their experience using preserved, blood type-matched, cadaveric donor iliac artery grafts to reconstruct the renal artery (Shames et al. 2003).

Urologic Complications

Urologic complications, manifesting as urine leaks or ureteral obstruction, affect about 2–10% of kidney transplant recipients, and are associated with high morbidity, graft loss, and mortality (Shoskes et al. 1995). Risk factors for urologic complications include donor age, multiple donor renal arteries, and delayed graft function. Urine leaks and strictures are believed to be due to ischemic necrosis or fibrosis of the allograft ureter secondary to disruption of arterial blood supply to the distal ureter, i.e., thrombosis of inferior polar renal artery or stripping of the ureteral mesenteric blood supply during organ procurement surgery. The terminal allograft ureter or ureterovesical anastomosis is the most commonly affected site because it derives its blood supply solely from the kidney allograft. The most common presentation of urologic complications is kidney graft impairment, which should be differentiated from other causes of graft impairment, such as acute rejection, calcineurin inhibitor (CNI) nephrotoxicity, etc.

Urine Leaks

Urine leaks, which can lead to urinoma or urine ascites, usually develop in the first few weeks post-KT at a rate of 1.8–5% (Berli et al. 2015). They are most commonly seen at the distal ureter and usually due to technical reason such as nonwater tight ureterocystostomy anastomosis. They may also be caused by excessive tension at the anastomotic site or an injury to the ureter during organ procurement surgery. Patients commonly manifest with kidney allograft impairment associated with fever, pain, wound swelling, and wound drainage. Diagnosis is made by ultrasound or CT scan showing a perigraft fluid collection, with elevated creatinine level of the fluid sample from the collection. An antegrade nephrostogram can demonstrate a leak. Initial treatment options include percutaneous nephrostomy catheter placement, with percutaneous drainage of urinoma. Long-term treatment options include placement of a nephroureteral stent, or surgical repair. Surgical revision of the ureteral anastomosis with ureteral reimplantation is the best treatment option for large leaks, or leaks that are refractory to conservative management. Surgical treatment allows for restoration of urine outflow and prevention of continuous allograft damage which can lead to graft loss.

Ureteral Strictures

Ureteral strictures are the most common cause of ureteral obstruction post-KT. They usually develop early after transplantation with an incidence of 2–7% (Berli et al. 2015). Kidney graft dysfunction is the most common urinary clinical manifestation of obstruction. Patients do not experience the classic colicky pain because the kidney graft is not innervated. Diagnosis is made by ultrasound which shows hydronephrosis. This can be confirmed by percutaneous antegrade nephrostogram, which typically demonstrates hydronephrosis with narrowing of the obstructed ureter, most commonly at the anastomotic site. The first line of treatment is percutaneous nephrostomy catheter placement to divert urine and decompress the kidney graft, allowing for recovery of kidney graft function. The obstructed ureter may also be approached by retrograde pyelography with double-J ureteral stent placement via cystoscopy. A balloon ureteroplasty may be indicated if there is a high grade, short anastomotic stricture. This is done by inflating a 5–8 mm angioplasty balloon to 10–17 atm. For 30–120 s repeatedly, until the balloon can be filled without any residual waist formation (Hedegard et al. 2009). A nephroureteral stent is placed at the end of the procedure. To minimize the potential risk of urinary tract infection, and discomfort for patients, this stent may be switched and internalized to a double-J ureteral stent, which can then be removed by cystoscopy in 6–12 weeks. Complications of percutaneous ureteroplasty include infection, ureteral perforation, urine leak, hematuria, and rarely, graft loss (Hedegard et al. 2009).

Other less common causes of ureteral obstruction include edema, kinking, stones, tumors, and external compression by hematoma or lymphocoele. Early obstruction, which is usually due to ischemia, commonly occurs at the distal or ureterovesical anastomosis, and has a favorable response to percutaneous ureteroplasty. On the other hand, late onset urologic obstruction is most often due to rejection, recurrent infections, or BK virus infection. It is more commonly located proximally, and has much worse response rate of 33% (Bhagat et al. 1998). Overall, both nonsurgical approaches have reasonable short-term success rates of 70–80%. However, the long-term outcomes are marginal due to recurrent urinary tract infections, and high rate of recurrent stenosis.

Surgical treatment is the treatment of choice for extrinsic strictures, strictures longer than 2 cm, or strictures that failed to respond to percutaneous ureteroplasty. The abdomen is best approached through a midline incision as this permits better exposure and easier access to the transplanted ureter. Identification of the transplanted ureter can be facilitated by preoperative placement of a nephro-ureterocystostomy tube, which can be shortened and converted later on to a nephrostomy tube. Preoperative placement of a double-J ureteral stent in the ipsilateral native ureter may also be performed to avoid the potentially difficult placement of a stent through the native ureter and into the bladder, intraoperatively. The same stent can then be passed across the ureteroureterostomy or ureteropyelostomy anastomosis. Once the transplanted ureter has been identified, and isolated, either of the following surgical options can be performed to bypass the stricture: direct ureteral reimplantation to the bladder, or for high strictures, reimplantation of the renal pelvis to the bladder or the ipsilateral native ureter. The contralateral ureter may be used in patients without an ipsilateral native ureter, while an ileal conduit may be utilized in the absence of a native ureter or a functional bladder. The double-J ureteral stent can be removed 4–6 weeks postoperatively, after a nephro-cystogram confirms free flow of dye into the bladder without extravasation. The nephrostomy tube can be pulled out later after a nephrostogram confirms no anastomotic leak (Berli et al. 2015).

Lymphoceles

Lymphoceles are lymph fluid collections around the kidney graft due to leakage of lymph fluid from lymphatic vessels that were severed while dissecting the iliac vessels during renal transplantation. They occur with an incidence of 0.6–18%

in KT recipients, and commonly develop a few weeks to months after KT (Von Sonnenberg et al. 1986). Most lymphoceles, especially small ones, are clinically asymptomatic. However, big lymphoceles or those larger than 3 cm, and lymphoceles that are small, but located close to the ureter or iliac vein, can produce symptoms. Lymphoceles can compress the ureter, causing ureteral obstruction, or the iliac vein, causing leg swelling or deep vein thrombosis. Rarely, they can compress the bladder, causing urinary incontinence. The presence of perigraft fluid collections can be confirmed by an ultrasound or CT scan, which typically shows a round, simple or septated fluid collection. Hydronephrosis may be present if there is ureteral compression. Percutaneous aspiration and sampling of the fluid collection will differentiate a lymphocele from hematoma or abscess based on fluid appearance, or a urinoma based on fluid creatinine level.

Lymphoceles can be minimized by ligation of lymphatic vessels, which are located along the iliac vessels, when isolating the iliac vessels during recipient KT. Most small lymphoceles resolve spontaneously over time, and, therefore, do not require any treatment. However, big and symptomatic lymphoceles will require nonsurgical or surgical drainage. Nonsurgical management includes simple aspiration or percutaneous drainage with or without sclerotherapy. Repeated fluid aspiration is not advisable as it is associated with increased risk of infection, and 80–90% recurrence rate. On the other hand, percutaneous drainage with sclerotherapy has been found to be highly effective and associated with less recurrence than simple aspiration or drainage alone (Von Sonnenberg et al. 1986). This procedure entails percutaneous placement of a catheter within the lymphocele, and injecting sclerosing agents, i.e., povidone iodine, tetracycline, alcohol, bleomycin, or fibrin glue, through the drainage catheter into the lymphocele. Patients may require multiple sclerotherapy treatments to minimize recurrence and achieve full resolution of the lymphocele. Surgical treatment is the treatment of choice for persistent or recurrent lymphoceles after percutaneous drainage and sclerotherapy, or those that are not amenable to percutaneous drainage. This can be done by open or laparoscopic marsupialization (unroofing) of the lymphocele to drain lymphatic fluid into the peritoneal cavity, where the fluid can then be absorbed. Care must be taken to confirm the absence of urine leak before performing the procedure to avoid draining urine into the peritoneal cavity leading to peritonitis.

Surgical Site Infections (SSIs)

SSIs, one of the most common complications after KT with an incidence of about 5%, usually occur within the first month after KT. Although they rarely lead to graft loss, they can cause significant morbidity, and can increase the length of hospital stay, and significantly raise health-care costs. Predisposing factors to SSIs include: the use of highly potent immunosuppressive drugs, i.e., sirolimus; and the clean-contaminated nature of KT, wherein urine can contaminate the operative field during bladder anastomosis. Age, delayed graft function, urine leak, reoperation, diabetes, sirolimus-based immunosuppressive regimen have been identified as risk factors for developing SSIs (Lynch et al. 2009; Ramos et al. 2008). However, obesity is probably the most consistently identified risk factor for developing SSIs post KT (Harris et al. 2015).

The treatment for deep SSIs includes percutaneous or surgical drainage, and antibiotics. Superficial SSIs are treated by opening the wound, followed by regular wound dressing changes until the wound heals by secondary intention. However, if there is significant wound drainage, a negative pressure (vacuum) wound dressing may be utilized to promote wound healing. A full course of antibiotic coverage may not be necessary unless the patient has systemic symptoms or there is associated significant cellulitis.

Conclusion

Most surgical complications occur early after KT and can cause significant morbidity and can lead to graft loss. Therefore, early recognition,

diagnosis, and treatment of post-KT surgical complications are critical to successful short- and long-term graft and patient survival outcomes after KT.

Cross-References

- ▶ Infection in Kidney Transplantation
- ▶ Radiology of Kidney Transplantation
- ▶ Recipient Kidney Transplantation Surgery
- ▶ Transplant Immunosuppression

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Medical Complications After Kidney Transplantation: Late

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Contents

Abstract

Over the years, the length of stay post-kidney transplantation (post-KT) has significantly reduced, leading to most of the post-KT care in an outpatient setting. With introduction of current immunosuppression rate of early rejection has declined, but inherent side effects in

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the long term have escalated. Hence, the long-term graft dysfunction and graft loss among post-KT patients have not changed significantly. Furthermore, the new kidney allocation policies and increased use of high kidney donor profile index (KDPI) kidneys have pushed the boundaries further, leading to new challenges in the management of post-KT recipients. These KT recipients, who have already been dealing with problems related to comorbidities prior to KT, now have to face new challenges resulting from the effects of immunosuppression. The type of comorbid illnesses post-KT determines the morbidity, as well as their short- and long-term patient and graft survival outcomes. This chapter summarizes late post-KT medical complications, focusing on the importance of early diagnosis and efficient management of these complications in the outpatient setting in improving outcomes. The goal is to identify causes of graft dysfunction, graft loss, and patient mortality post-KT and to devise strategies to improve patient and graft survival.

Keywords

de- novo DSA · Surgical complications · Aretrial thrombosis · Mortality · Hyperlipidemia · Hypertension · Cytomegalovirus · Post transplant · Lymphoproliferative disease · Post transplant diabetes mellitus · Tertiary hyperparathyroidism · Post transplant erythrocytosis · Recurrent and *de novo* glomerular disease · CKDT · Allograft nephrectomy

Introduction

Renal transplantation is the most successful and frequently performed form of organ replacement and has improved quality and survival in chronic kidney disease (CKD) and/or end stage renal disease (ESRD) population. The short- and long-term graft and patient survival rates of renal transplantation are superior to those for liver, heart, and lung transplantation (Rana et al. 2015). Earlier in the history of renal transplantation, length of hospital stay for recipients was approximately 1 month for postsurgical care and immunosuppression administration. Improvements in surgical technique, immunosuppressive drugs, and medical management led to progressive reductions in morbidity and mortality, which allowed a steady decline in hospital stay. Average length of stay for uncomplicated renal transplantation patients now is less than a week after surgery. Transplant teams now have a detailed understating of potential medical or surgical problems encountered during the early postoperative period (Ronco, Critical care nephrology textbook, 2nd edition).

Improvements in short-term patient and graft outcomes using better surgical techniques and more potent immunosuppressive drugs do not translate to better long-term outcomes, though. The following factors may play a role in the lack of improvement in long-term outcomes post-KT: the use of kidney allografts from high KDPI donors, occurrence of polyoma virus nephropathy, goals of immunosuppression, incomplete functional recovery after rejection episodes, and chronic inflammatory changes in the kidney allograft. Other factors such as cardiovascular disease, infections, and malignancies may also shorten patient survival and, therefore, may reduce the functional life of a kidney allograft (Meier-Kriesche et al. 2004a, b; Mannon 2004).

Short-Term Complications and Management

Medical Complications

Early graft dysfunction occurring during the first few weeks post-KT is more commonly related to delayed allograft function secondary to ischemic acute tubular necrosis. Rejection typically does not develop before 7–10 days after surgery unless there are preformed antibodies against donor antigens that have been present prior to KT. The following are predisposing factors to development of early acute rejection: presence of preformed donor-specific antibodies (DSA), ABO mismatches, and prior sensitization. Rarely, patients with unacceptable antigens (e.g., de novo DSA),

which were not defined preoperatively, may be at risk for early acute rejection. Other causes of early allograft dysfunction include: volume depletion due to overzealous use of diuretics or ultrafiltration with hemodialysis. Furthermore, the use of kidney allografts from high kidney donor profile index (KDPI) or recurrent kidney disease in the allograft, i.e., atypical hemolytic uremic syndrome (aHUS) and recurrent focal segmental glomerulosclerosis (FSGS), may increase the risk of allograft dysfunction. Calcineurin inhibitor (CNI) toxicity, thrombotic microangiopathy (TMA), or nephrotoxic agents should be sought when renal dysfunction cannot be explained. Angiotensin-converting enzymes inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) should be delayed in early posttransplantation period particularly in volume-depleted patients. BK viremia, hypertension, noncompliance, ongoing humoral injury, new renal disease, and post-transplant diabetes can also lead to early and delayed graft dysfunction (Djamali et al. 2006).

Causes of short- and long-term graft dysfunction

Pre-renal
- Decreased effective circulating volume
- Volume contraction
- Congestive heart failure
- Liver failure
- Renal transplant artery stenosis
- Drugs: CNI, ACE-I, ARB, NSAIDs

Renal
- Urinary tract infection and/or pyelonephritis
- Acute rejection (prior sensitization/histocompatibility mismatch)
- Acute interstitial nephritis
- Acute tubular necrosis
- Recurrent/de novo glomerular disease

Postrenal
- Hydronephrosis

Late allograft loss
- Chronic allograft nephropathy (CAN)
- CNI nephrotoxicity
- Polyoma (BKA) virus nephropathy
- Recurrent/de novo glomerular disease
- Chronic rejection (immunologic)
- Acute rejection

Patient death with functioning graft
- Cardiovascular disease
- Infectious complications
- Malignancies
- Others

Surgical Complications

Most surgical complications may be encountered after discharge from hospital but seldom are seen 1 month after transplantation. Potential surgical complications post-KT are listed below:

Short- and long-term surgical and urological complications after renal transplantation

Hematomas
Renal artery or vein thrombosis
Deep vein thrombosis
Arteriovenous fistulas and pseudoaneurysms
Urinary obstruction
Urinary leaks
Ureteral strictures
Lymphocele
Infection and abscess
Renal artery stenosis
Infarction
Renal calculi
Renal cancer
Wound infection
Gastrointestinal complications (like Ogilvie Syndrome or pseudo-obstruction)

Localized hematomas can be common and may arise within days after surgery or may develop at any time due to allograft biopsy or trauma. Large hematomas (requiring four or more units of blood transfusion within 48 h) that are rapidly expanding or causing obstruction of vessels or the ureter should be evacuated immediately along with repair of bleeding vessel. Late profound hematomas can result from rupture of mycotic aneurysm. Old hematomas found during an evaluation of fever may require aspiration to rule out infection. The diagnosis is typically made with ultrasound or computed tomography. Pre-transplantation coagulation parameters and medications should be paid special attention.

Arterial thrombosis often occurs within 2–3 days posttransplantation, mostly in patients with thrombotic tendencies, multiple renal arteries, or significant atherosclerosis. Venous thromboses typically develop in the early post-KT period as well as may develop from renal vein kinking, anastomosis stenosis, hypotension, hypercoagulable state, and acute rejection. These usually present with loss of allograft function, acute kidney injury, hematuria, or pain over the allograft. It is best diagnosed with Doppler ultrasound. If there is no flow, urgent surgery should be performed and patients with tendency for thrombosis should be anticoagulated in the perioperative KT period. For venous thrombosis, urgent thrombectomy with revision of anastomosis should be attempted. Renal transplant patients are at moderate risk for developing deep vein thromboses. If present, patient may require 3–6 months of anticoagulation, starting with heparin and later bridged to coumadin.

Arteriovenous fistulas or pseudo-aneurysms are usually complications of allograft biopsy or caused by partial disruption of an arterial anastomosis. These problems may develop at any time after first postoperative week. Most centers delay renal biopsies until after the first week, because the risk of complications is greater and rejection is seldom seen before the first week. These lesions are usually asymptomatic but may cause mild to severe hematuria and hypotension. The diagnosis can be made with Doppler ultrasound, but magnetic resonance imaging may be needed in technically difficult cases. Most arteriovenous fistulas and pseudo-aneurysms can be managed conservatively, but progressively expanding pseudoaneurysms may require embolic therapy such as absorbable gelatin sponges (gel foam) or steel coils.

Urinary leaks may be result of distal ureteric ischemia as allograft ureter receives blood supple solely from renal artery. Stented ureteric anastomosis to bladder has low incidence of urinary leaks.

Patient Mortality

The causes of death after transplantation are listed in Table 1 (Morales et al. 2012). During the first year, the risk of death due to infection or hemorrhage is greater; the late mortality risk is greater for malignancy and other causes. Cardiovascular and cerebrovascular disease is more common in patients older than 60 years of age and is rare in those 25 years of age or younger. During the early or late periods, mortality is strongly associated with number and type of comorbid illnesses. The greatest mortality occurs in older patients with significant comorbidity who receive higher KDPI organs.

Long-Term Complications and Management: 1 year Posttransplantation

The long-term follow-up of post-KT recipients entails continued management of comorbid illnesses, disease progression, and KT associated

Table 1 Causes of death after transplantation based on age group (5 year mortality)

Causes	<40% (%)	40–60 (%)	>60 (%)	Total (%)
Infection	25.0	20.8	24.5	22.9
Cardiovascular disease	33.9	35.6	31.0	33.9
Cerebrovascular accident	18.8	8.9	7.3	8.8
Ischemic heart disease	6.3	7.9	8.2	7.9
Other heart causes	12.5	11.9	8.2	10.1
Sudden death	6.3	6.9	7.3	7.0
Liver disease	0.0	1.0	4.5	2.6
Cancers	12.5	13.9	11.8	12.8
Accidental	0	1.0	0.0	0.4
Uncertain	0	5.0	4.5	4.4
Other	12.5	16.8	17.3	16.7
Unknown	6.3	5.9	6.4	6.2

Table 2 Timing and frequency of posttransplantation laboratory and clinical evaluations after 1 year

	Basic (mo)		Desired (mo)		Potentially advantageous (mo)	
Years after transplantation	Clinical	Laboratory	Clinical	Laboratory	Clinical	Laboratory
Year 2	Every 3	Every 3	Every 2	Every 2	Every 1	Every 1
Year 3–5	Every 6	Every 3	Every 4	Every 2	Every 2	Every 1
Year 6+	Every 12	Every 6	Every 6	Every 3	Every 4	Every 2

medical problems. This would require a collaborative effort between the transplant center, community nephrologist, and primary care physicians. The suboptimal long-term outcomes post-KT may be attributed to the use of kidney allografts from high KDPI donors, BK viremia, under immunosuppression, and chronic allograft nephropathy (CAN). In recent years, there were several attempts to set up clinical guidelines to standardize long-term care of KT recipients (Djamali et al. 2006; Saifu et al. 2005). The Lisbon conference was an international meeting convened to develop recommendations aimed at improving long-term outcomes in renal transplant recipients (Saifu et al. 2005; Abbud-Filho et al. 2007). Table 2 illustrates the suggested timing and frequency of clinical and laboratory evaluations. However, the frequency of laboratory studies should be tailored based on individual patients. Follow-up is different in different transplant centers. Unstable patients should be seen as frequently as their clinical condition dictates.

All renal recipients should benefit from age appropriate routine screening studies to detect malignancy, conduct skin cancer screening, and prevent progression of cardiovascular disease. It is the primary care physician's role to perform most of these studies. However, it is the transplant physician's responsibility to monitor and ensure that these studies are being performed and that he is informed of the study results. In these instances, close cooperation between the nontransplant physician and the transplant center is vital.

Hypertension

Hypertension is common in dialysis patients and in renal transplant patients. Table 3 lists potential causes of hypertension after transplantation.

Table 3 Causes of hypertension in renal transplant recipients

Causes	Examples
Preexisting hypertension	
Immunosuppressive therapies	Steroids Calcineurin inhibitors (acute vascular effect)
Disease in the renal allograft	Chronic allograft nephropathy Chronic calcineurin toxicity Recurrent diabetic nephropathy
High renin output in native kidneys	Renal artery stenosis of native kidneys
Recurrent essential hypertension	Recurrent/persistent systemic disease Transplantation of a predisposed graft

Patients with systolic blood pressure (SBP) >140 mmHg at 1 year posttransplantation but controlled to ≤140 mmHg clearly had significantly improved long-term graft outcome compared with patients with sustained high-SBP (Opelz and Dohler 2005). The American Society of Transplantation (AST) recommends target blood pressure levels of <140/90 mmHg (Kasiske et al. 2000). Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends blood pressure targets of <130/80 mm Hg in KT patients (KDOQI clinical practice guidelines 2004; Midvedt and Hartmann 2002).

Mailloux 1998, National Kidney Foundation (NKF) task force on cardiovascular disease recommends that the goal for antihypertensive therapy should probably be ≤135/85 mmHg for KT recipients without proteinuria and should possibly be ≤125/75 mmHg for patients with proteinuria.

European best practice guidelines (EBPG), published in 2002, recommend blood pressure goal of <130/85 mmHg without proteinuria and <125/75 mm Hg with proteinuria.

Lifestyle modifications are necessary and should include weight reduction, a DASH (dietary approaches to stop hypertension) eating plan, dietary sodium reduction, and physical activity (Chobanian et al. 2003). No preferred agent is offered by any of the guidelines for blood pressure control. Initially efficacy suggested that calcium channel blockers might have greater benefit in achieving BP control and limiting graft loss (Midvedt and Hartmann 2002; EBPG 2002), but it has not been shown to have a clear benefit over ACE-I on long-term kidney allograft function and survival (Midvedt et al. 2001). ACE-I have potential advantage of delaying progression of renal disease and proteinuria. The routine side effects of hyperkalemia, anemia, and increased creatinine should be expected, and these drugs should not be used in patients with hyperkalemia, severe anemia, renal artery stenosis, or unstable renal function. Diltiazem and verapamil may increase calcineurin inhibitor blood levels. They have been used to lower the dosage of these agents by approximately 50%.

Cardiovascular Morbidity

Cardiovascular morbidity post-KT can be attributed to modifiable and nonmodifiable risk factors. The nonmodifiable risk factors can be used to identify high-risk population who can be targeted for screening purposes and possible intervention. The risk factors are: pre-KT cardiovascular disease, diabetes, smoking, hyperlipidemia (mostly high LDL), hypertension, platelet and coagulation abnormalities, allograft dysfunction or rejection, low albumin, erythrocytosis, presence of oxygen free radicals, infectious complications like CMV, and increased homocysteine.

The following are the American Heart Association (AHA) and American College of Cardiology (ACC) recommendations for primary prevention of coronary heart disease: cessation of smoking, blood pressure control (<130/80 mmHg), dietary reduction of trans-fats and saturated fats, low dose aspirin, increase physical activity (30 min per day for at least 5 days/week), weight management (BMI goal of 18.5–24.9 kg/m^2), maintenance of waist circumference (<35 inches in women and <40 inches in men), blood sugar control (HbA1c <7%), lipid management (LDL-C < 100 mg/dl; secondary goal, if triglyceride ≥200 mg/dl, HDL ≤40 mg/dl), and maintenance on ACE-I and beta blockers indefinitely for all post-MI patients.

Hyperlipidemia

High level of LDL and low level of HDL contribute to high cardiovascular disease risk in post-transplantation patients. Hypertriglyceridemia as a risk factor is less convincing in posttransplantation patients. The main reason to reduce triglycerides is to reduce incidence of pancreatitis. Most important cause of hyperlipidemia posttransplantation is immunosuppressive medications like rapamycin, cyclosporine, and tacrolimus (in order of severity). Other causes are steroid dose, diet, genetic predisposition, proteinuria, and possibly decreased renal function. Transplant patients with LDL >130 mg/dl should be considered for pharmacologic treatment, especially if they have preexisting cardiovascular disease, diabetes, or other risk factors. Recognizing patients with metabolic syndrome is important early after transplantation so that patients can be targeted for lifestyle modifications and drug therapy. Reduction in urine protein excretion with an ACE-I or ARB may help to reduce lipid levels for patients with nephrotic range proteinuria. Diet modification and physical activity can help reduce lipid levels.

Studies have shown that HMG-CoA reductase inhibitors (statins) are safe and effective in lowering LDL cholesterol after renal transplantation. In the ALERT (Assessment of Lescol in Renal Transplantation) trial, fluvastatin lowered LDL levels by 32%, and although there was no significant reduction in rate of coronary intervention or mortality, the incidence of cardiac deaths and nonfatal myocardial infraction appeared to be reduced (Fellstrom et al. 2004; Jardine et al. 2004). However, another study showed that HMG-CoA reductase inhibitors in KT recipients, who are on maintenance tacrolimus, were not associated with improvement in graft or patient survival. Another study analyzing the effects of statins in KT recipients reported a 24%

improvement in survival in KT recipients on statins (Cosio et al. 2002).

Plasma level of HMG-CoA reductase inhibitors is increased in cyclosporine-treated renal transplant recipients, and therefore, it is generally prudent to use half of the prescribed dose. KT recipients on statins should have lipid panel at baseline, 2–3 months after a change in treatment dose, and at least annually, thereafter.

Patients who would require LDL-C lowering agent may be treated with atorvastatin or simvastatin. Patients with low HDL-C levels may benefit from simvastatin use, while patients with elevated TGL may benefit from high dose atorvastatin. In patients with high TGL-C secondary to rapamycin, gemfibrozil may be the drug of choice and is better tolerated than nicotinic acid. Bile acid sequestrants may alter the bioavailability of immunosuppressive medications and may also increase TGL levels. Statins and fibrates interact with calcineurin inhibitors and may result in hepatitis, myositis, and rhabdomyolysis.

Reproduction and Pregnancy

By the end of the first year after a successful transplantation, fertility may be restored rapidly, menstrual function and ovulation typically return, and prolactin fall to normal levels in most women. Contraceptive counseling should begin immediately after transplantation because menstrual cycles may begin within 1–2 months of transplantation in women with well-functioning graft. It has been estimated that 2% of women of childbearing age can conceive after transplantation. The incidence of spontaneous abortion and ectopic pregnancy is reported to be 13% and 0.5%, respectively, which is similar to the general population. The criteria that should ideally be met before contraception (Danovitch, Handbook of transplantation 5th edition) are listed below:

Criteria for the reduction of posttransplantation pregnancy risk

1. At least 1 year after transplantation
2. Serum creatinine <2.0 mg/dL, preferably <1.5 mg/dL
3. No recent episodes of acute rejection
4. Normotensive or minimal antihypertensive regimen
5. Minimal or no proteinuria
6. Normal allograft ultrasound
7. Pregnancy safe drug regimen

Kidney Disease Improving Global Outcomes (KDIGO) recommendation is to wait for 1 year after transplantation when kidney function is stable with <1 gm/d proteinuria. It is recommended that mycophenolate mofetil (MMF) and enteric coated-mycophenolate sodium (EC-MPS) should be discontinued and/or replaced with azathioprine before pregnancy is attempted. Similar recommendations are for mammalian target of rapamycin inhibitors (mTOR-I) as well.

Male infertility may improve after kidney transplantation as well. Pregnancies fathered by a kidney transplant recipients appear to have no more complications than those in general population. Male kidney transplant recipient who wished to maintain fertility should consider avoiding mTOR inhibitors.

The Lisbon Conference reviewed the recommendations by the AST and KDIGO; the most important features are summarized in Table 4.

Infection

Infection is one of the most common and serious complications after transplantation. It is also the second most common cause of death in transplant recipients (Djamali et al. 2006; Danovitch, Handbook of transplantation 5th edition). Figure 1 illustrates timing of common infections (Abbud-Filho et al. 2007; Fishman and Rubin 1998). Patients who receive increased immunosuppression for acute rejection are more at risk for severe opportunistic infections like *Pneumocystis carinii*, *Listeria monocytogenes*, *Nocardia asteroids*, *Cryptococcus neoformans*, and *Aspergillus.*

Cytomegalovirus (CMV) is one of the most common infections after renal transplantation. CMV and Pneumocystis carinii pneumonia (PCP) prophylaxis with valganciclovir and sulfamethoxazole/trimethoprim, respectively, for 3–6 months is

Table 4 Recommended conditions before conception and appropriate prenatal care for pregnant women after renal transplantation

Parameter	Recommendation	
	AST 2005	KDIGO
Interval after transplantation and before pregnancy	1–2 years	1 year
Kidney function	Creatinine <133 μmol/L	Same
Proteinuria	None or minimal	<500 mg/day
Blood pressure	Normal	Normal
Allograft ultrasound only	N/A	N/A
Rejection history	None within first year	No recent rejections
Immunosuppression dosing	Stable	Stable
Care providers	High risk obstetrician and transplant physician	High risk obstetrician and transplant physician
Initial visit frequency	N/A	Every 4 weeks
Third trimester frequency	N/A	Every 1–2 weeks; weekly after 34 weeks
Postpartum frequency	N/A	To 3 months postdelivery
Laboratory frequency	N/A	Every 2–4 weeks
Blood pressure checks	N/A	At each visit
Blood pressure target	N/A	Not above baseline
Fetal monitoring	N/A	N/A

needed and is based on transplant center preference. BK virus is another emerging infection that can cause graft dysfunction and ultimately graft failure.

During the first month, bacterial infections such as wound infections and pneumonia are common. Fungal infections are frequent in programs using high-dose steroids but uncommon in steroid-free programs. Patients with preexisting viral hepatitis may develop increased viral replication and clinical liver disease. Immunization for viral hepatitis (hepatitis B) in nonimmunized patients is done at several transplant institutes prior to transplantation.

Epstein-Barr virus (EBV) may predate transplantation, or patients may acquire it as a primary infection from donor. It is associated with post-transplantation lympho-proliferative disease (PTLD). This usually develops in a setting of aggressive immunosuppression in patients at risk (new or preexisting exposure). Reduction of cessation in immunosuppression may be sufficient to cure many patients, although others may require chemotherapy. Patients with prior papillomavirus infection (HPV) may develop rapid growth in venereal warts or malignant cervical lesions. Herpes simplex virus (HSV) prophylaxis is also instituted at several transplantation centers.

Avoiding excessive immunosuppression can reduce the risk of serious posttransplantation infections. Prophylaxis and vaccination can prevent many infectious complications. Appropriate long-term tapering of immunosuppression and avoidance of repeated rejection treatment in poorly functioning grafts are important in reducing the risk of infectious complications. Periodontal infections are common in posttransplantation patients. These patients should maintain dental hygiene and have access to dental care.

Bone Disease

Clinically evident bone disease is a common complication after renal transplantation (Saifu et al. 2005). Maximum bone loss occurs within the first 3–6 months post-KT and continues at a slower rate in the long term.

Immunotherapy and secondary hyperparathyroidism are most important pathogenic factors leading to bone disease and fracture after transplantation. In addition to steroids, cyclosporine has been associated with decreased bone marrow density (BMD). Other implicated factors are

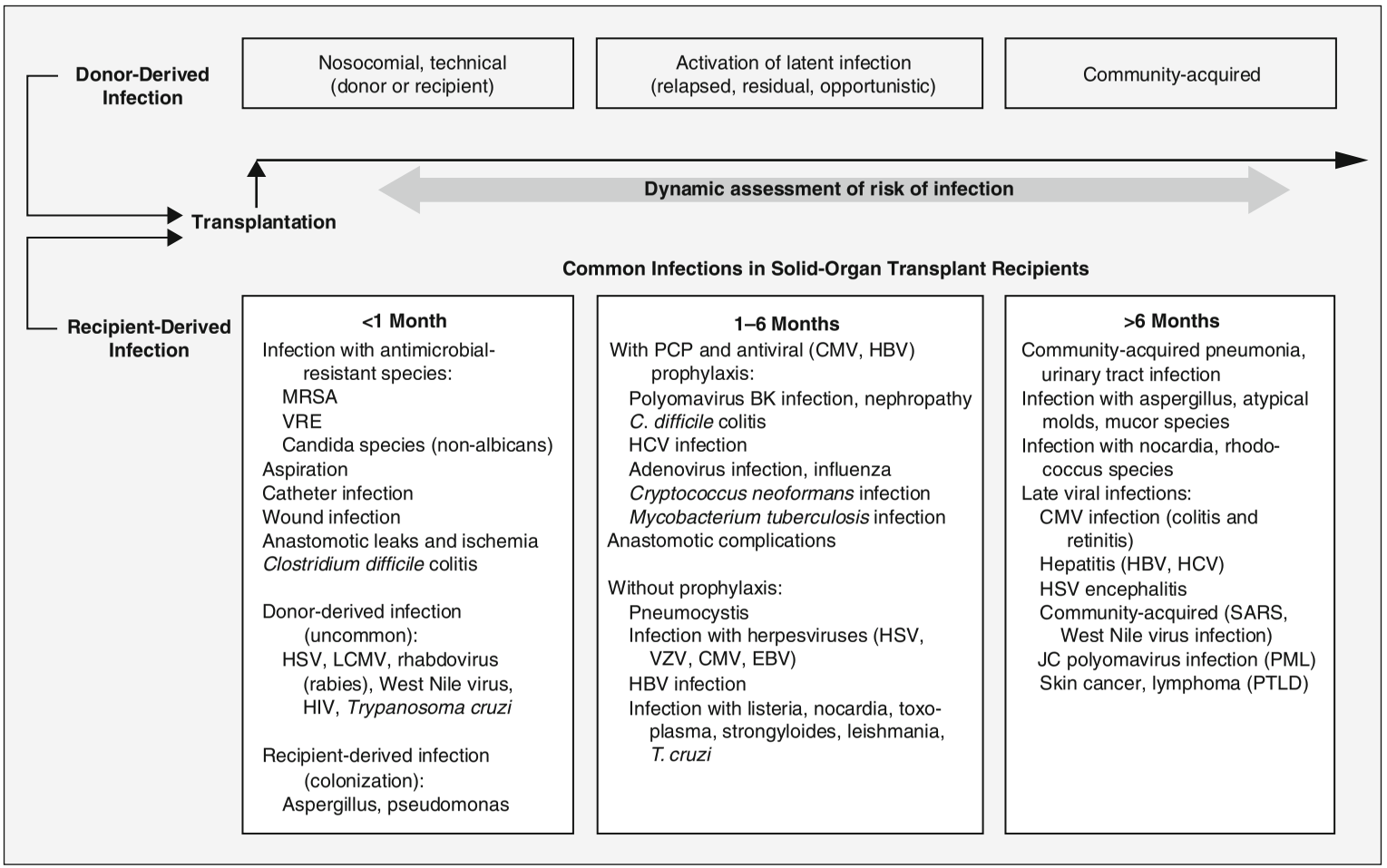

Fig. 1 Timeline of infection after organ transplantation (Fishman and Rubin 2007)

preexisting uremic osteodystrophy, metabolic acidosis, smoking, beta-2 microglobulin-associated amyloidosis, and diabetic osteodystrophy (Djamali et al. 2006; Heaf 2003; Rodino et al. 1998; NKF-K/DOQI 2003). Screening for decreased BMD with DEXA scan can be done at baseline, 6 months, and 12 months (if results of DEXA scan are abnormal) post-KT. Intact parathyroid hormone (iPTH) should be checked at 6 months and 12 months and then annually, at least during the first 3 years post-KT. Guidelines are based on extrapolation of CKD studies for iPTH goal. Patient with decreased BMD (>2.5 SD below adult mean value) may be candidate for oral calcium and vitamin-D supplementation. Management should begin with early ambulation, encouragement of physical exercise, and routine weight bearing exercise program. Phosphate binders, correction of metabolic acidosis, and/or Bisphosphonates have been used to manage these complications. But there are no data showing any benefit with the use of these agents in preventing fractures in KT patients. Bisphosphonate should be used with caution, as there is a risk for adynamic bone disease and should always be dose adjusted for impaired kidney function.

Corticosteroids cause bone disease by decreasing intestinal calcium absorption, increasing calcium excretion, decreasing production of insulin-like growth factor 1, suppressing gonadal hormone secretion, and inhibiting transformation of protoblasts to osteoblasts. They also cause avascular necrosis (AVN) or osteonecrosis, most commonly in the femoral head. The incidence of AVN is close to 1% per year in the 2nd and 3rd posttransplantation years, while the overall incidence is reported to be 5.5%.

Hypophosphatemia is common early after transplantation but less common in the late posttransplant period. It is usually caused by tertiary hyperparathyroidism that remains unresolved in late posttransplantation period. Hyperphosphatemia is encountered usually in transplant patient with renal insufficiency and can be managed with dietary restrictions and binders.

Persistent hyperparathyroidism is observed in approximately 50% of patients during the first year posttransplantation (Djamali et al. 2006). Patients may be treated with Cinacalcet (calcimimetics) with close monitoring of calcium and phosphorus levels. Parathyroidectomy may be required if calcium and PTH levels remain elevated. Bisphosphonates may be effective in reducing steroid-induced bone disease and bone fractures in kidney, liver, and lung transplants recipients. There is limited experience in the use of calcitonin in posttransplantation bone disease. Therefore, this should not be considered the first-line therapy in this setting.

Hypomagnesemia is seen in about 10% of KT recipients who are on maintenance CNI immunosuppressive medications. This is typically managed with oral magnesium replacement.

Posttransplantation Diabetes Mellitus (PTDM)

Posttransplant diabetes mellitus is diagnosed when plasma fasting glucose level is ≥126 mg/dl or the 2-hour plasma glucose level is ≥200 mg per/dl during an oral glucose tolerance test. About 20% of nondiabetic KT patients may develop hyperglycemia post-KT, of which approximately 5–10% would require oral hypoglycemic medications or insulin treatment. Immunosuppressive therapy with tacrolimus, older recipients, deceased donor status, hepatitis C seropositivity, acute rejection episodes, black race, and high body weight are independent risk factor for PTDM. Patients with strong family history of diabetes are also at increased risk for PTDM. The effect of PTDM in mortality and morbidity and graft survival is similar to pretransplantation diabetes. Steroids and CNI contribute in varying degrees to glucose intolerance and can significantly decrease patient and graft survival. Patients who develop PTDM should be referred to an endocrinologist for blood sugar monitoring and blood sugar control. It is also recommended to consider modifying immunosuppressive drug regimen to reverse progression of diabetes after weighing the risk for rejection and other potential adverse events.

Posttransplantation Anemia

It has been estimated that 25% of post-KT patients are anemic (defined as hemoglobin <13 g/dl for males and <12 g/dl for females), and 13% are iron deficient at 12 months post-KT. In the late post-transplantation period, anemia is most commonly caused by immunosuppression or decreased renal function. Immunosuppressive drugs, i.e., azathioprine, mycophenolate mofetil (MMF), and sirolimus, can cause anemia, thrombocytopenia, and leukopenia, which can be managed by dose reduction or discontinuation of these medications. ACE-Is and ARBs may also cause anemia. Parvovirus and CMV infection may cause refractory anemia for which treatment with intravenous immunoglobulin (IVIG) may be effective. Acute rejection, thrombotic microangiopathy anemia along with malignancies may also contribute to anemia. Comprehensive work-up to assess the etiology of anemia is warranted, and this should include the following: infectious work-up, monitoring iron stores, reticulocyte count, vitamin B12 and folate levels, and fecal occult blood. Appropriate therapy based on the work-up results should be instituted to manage anemia. When no underlying cause is found, erythrocyte stimulating agents may be indicated.

Posttransplantation Erythrocytosis (PTE)

Posttransplant erythrocytosis is seen in 20% of patients after transplantation and most commonly during the first 2 years post-KT. It is rarely seen in patients who have had a native nephrectomy. It is attributed to elevated levels of insulin-like growth factor 1 (IGF-1), which increases sensitivity of erythroid precursor to erythropoietin. Other conditions such as renal artery stenosis, malignancy, and obstructive sleep apnea should also be ruled out. Treatment of erythrocytosis should commence when hematocrit level reaches a level of >55%. Low-dose ACE-Is and ARBs are generally effective treatment for PTE. Phlebotomy may be indicated in refractory cases of PTE.

Posttransplantation Vaccination

All kidney transplant-approved patients should receive inactivated vaccines, according to recommended schedule for the general population, except for Hepatitis-B vaccination (HBV). KDIGO suggests HBV vaccination prior to transplantation. HBsAb titers should be checked 6–12 weeks after completing the vaccination series. Revaccination may be indicated if antibody titer falls below 10 mIU/mL. Live vaccines should be avoided in all KT recipients. Vaccinations should be avoided in the first 6 months following KT except influenza vaccination. KDIGO also suggests giving vaccination for rabies, tick borne meningoencephalitis, inactivated Japanese B encephalitis vaccine, meningococcus, pneumococcus, and *Salmonella typhi*-inactivated vaccination. This is because post-KT patients are at increased risk for these specific diseases, due to age, direct exposure, residency, or travel to endemic areas or other epidemiological risk factors.

Malignancies Posttransplantation

Age, smoking, immunosuppression, and chronic viral infections contribute to increased incidence of malignancies in the post-transplantation patient population. There is 2–3 fold increase in common malignancies such as lung, prostate, breast, colon, in situ carcinoma of uterine cervix, carcinomas of vulva and perineum, renal carcinomas, and sarcomas, and up to 100 fold increase for entity such as Kaposi sarcoma, posttransplantation lymphoproliferative disease (PTLD), and non-melanoma skin cancer (Kasiske et al. 2004; Morath et al. 2004). Nonmelanotic skin and lip cancers (basal or squamous cell) are the most common malignancies posttransplantation and develop more frequently in azathioprine-treated patients. After the first posttransplantation year, the KT recipient should undergo annual or biannual skin examination. Age-appropriate annual prostate-specific screening/measurements, fecal occult blood testing, digital rectal examination,

breast examination, mammography, and colonoscopy are indicated as in nontransplant patients. If the patient has a history of hepatitis B or Hepatitis C, hepatobiliary ultrasound examination and serum alpha-fetoprotein measurements are warranted. Patients with a history of cyclophosphamide use should undergo a cystoscopy to check for bladder malignancy. The use of sirolimus has been associated with decreased incidence of cancer, including skin cancer, in the first 2 years posttransplantation.

The reported incidence of PTLD in solid organ transplant recipients ranges between 0.8% and 15% depending on the type of transplantation, age, and immunosuppressive regimen. The incidence in the KT population is reported to be 1–2%. PTLD is 12-fold higher in the transplant compared to the nontransplant population. Most cases develop within 1 year of transplantation. Most cases are the non--Hodgkin's lymphoma type in age-matched control. They usually are of B cell origin and are CD20 positive. PTLD can be confused with acute rejection as they often present as graft dysfunction. There can be extra nodal involvement and multiple sites are often involved. Mortality is higher with PTLD compared to other lymphomas. Prolonged or repeated lymphocyte depleting agents and high risk for EBV (donor serology positive and recipient negative for EBV) are significant risk factors for development of PTLD. Although typically it is considered to be due to EBV infection of recipient B cells, PTLD may be of donor origin in some patients.

PTLD can be monomorphic/monoclonal or polyclonal B cell lesions. Polyclonal B cell lesions are likely to be benign and respond to withdrawal of immunosuppression and acyclovir, whereas monoclonal lesions are believed to be malignant. Polyclonal lesions might represent the early stages in the spectrum of disease progression.

The mainstay of treatment for PTLD is withdrawal or reduction of immunosuppression. Anti-CD20 monoclonal antibody (rituximab) with rapamycin has shown to be of benefit. Recently, a novel treatment has been reported using an infusion of EBV specific cytotoxic T cells.

Recurrent or De Novo Glomerular Renal Disease

The risk of recurrent disease varies by native disease. MPGN, oxalosis, and diabetic nephropathy have the highest risk of recurrence ranging from 80% to 100%. These are followed by focal segmental glomerulosclerosis, IgA nephropathy (by histology), HUS/TTP/TMA (recurrence rate of 30–70%), and membranous nephropathy (recurrence rate of 10–30%). Rare recurrent diseases post-KT include: ANCA vasculitis, Fabry disease, and lupus nephritis. In patients with little or no pre-ESRD care or follow-up, and who lack native kidney disease diagnostic biopsy, it is often difficult to assess whether the disease is recurrent or de novo. There is a significant increase in the incidence of graft failure among the recurrent and de novo disease groups (55%) when compared to others (25%, $p < 0.001$).

The true prevalence of recurrent glomerulonephritis also depends on counting both patients who have lost their allograft as a result of recurrence and those who have recurrence with a functioning graft. A retrospective analysis of the ANZDATA database revealed that 8.4% of patients lost their grafts as a result of recurrent glomerulonephritis by 10 years after transplantation. However, this analysis did not include those with a functioning graft. A more recent analysis of the ANZDATA database from 2001 through 2004, including those with a functioning graft, revealed recurrence in 93 (4.2%) of 3502 KT recipients (Table 5). The lower prevalence in the cohort of patients from 2001 through 2004 is possibly related to shorter duration of follow-up (Golgert et al. 2008; Danovitch, Handbook of transplantation).

Dense deposit disease recurs in 100% of patients and often leads to graft failure. Idiopathic MPGN recurs in 20–30% of patients and leads to graft failure in 50% of patients. Membranous nephropathy recurs in 5–10% of patients after KT, and about 25% of patients develop graft failure. Histologic recurrence is higher in IgA nephropathy and graft loss can be up to 25%. Antiglomerular basement membrane disease

Table 5 Epidemiology of recurrent glomerulonephritis reported through various registries

Registry	Prevalence of recurrent GN posttransplantation (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/ TTP (%)
NAPRTCS 2006	12.0	5.5	–	0.8	–	–	1.1
ANZDATA 1996–2005	4.0	–	–	–	–	–	–
RADR 1998–2001	2.9	1.0	0.1	0.1	0.1	0.1	0.2

NAPRTCS: North American pediatric renal trials and collaborative studies
ANZDATA: Australia and New Zealand dialysis and Transplantation registry
RADR: Renal allograft Disease Registry
GN glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *IgAN* immunoglobulin A nephropathy, *MPGN* membrano-proliferative glomerulonephritis, *MN* membranous nephropathy, *SLE* systemic lupus erythematosus, *HUS/ TTP* hemolytic uremic syndrome/thrombocytopenic thrombotic purpura

recurs in 10–25% of patients but rarely causes graft failure.

Chronic Kidney Dysfunction in Transplant

Although renal transplantation is a highly effective treatment for end stage renal disease, a few patients have normal renal function and should be classified as having chronic kidney disease (CKD), similar to patients before dialysis. Causes of CKD in transplant recipients include, among others, chronic allograft nephropathy, acute/subacute/chronic rejection, calcineurin nephrotoxicity, recurrent or de novo glomerular disease, polyoma (BK) nephropathy, and with aging donors, preexisting donor renal insufficiency or high KDPI organs.

All renal transplant recipients should have measures instituted aimed at delaying progression of renal disease regardless of stage (Table 6). These include excellent blood pressure control, minimization of nephrotoxic agents (including calcineurin inhibitors), and the use of ACE inhibitors (Abbud- Filho et al. 2007). Control of comorbid illnesses such as hyperlipidemia is particularly important in all stages. Avoiding nonadherence to medications is vital especially in young patients and in those with low socioeconomic status who may not be able to afford expensive immunosuppressive medications. Despite these measures, many patients progress to CKD stage 4 or 5. Such patients should be prepared for dialysis or preferably, re-transplantation (if deemed a candidate).

Table 6 Stages of chronic kidney disease and action plan in renal transplant recipients

Stage	Definition (eGFR in ml/min)	Clinical plan
1	≥90	Slow progression, treat comorbid illnesses
2	60–89	Above, and monitor progression
3	30–59	Above, and treat complication of CKD
4	15–29	Above, and prepare for dialysis and/or retransplantation
5	<15	Dialysis if uremic, retransplantation

The Failing Allograft

Once a patient has developed advanced chronic kidney disease posttransplantation (CKD-T) and returned to dialysis, immunosuppression should be reduced or discontinued. If the transplantation was performed within the previous year, most centers proceed to an allograft nephrectomy, because 50% of these patients will require nephrectomy due to rejection after weaning off immunosuppression.

Patients with longer surviving grafts can undergo slow weaning. Once patents have started dialysis, the general approach to weaning off

immunosuppression, includes the following: prednisone doses are slowly tapered by approximately 2.5–5 mg/month depending on starting dose; mycophenolic acid, rapamycin, and azathioprine can be stopped immediately; and calcineurin inhibitors are reduced by 50%. All agents should be progressively reduced so that most patients are off all immunosuppressive medications by 6–8 months. Patients losing their allograft to severe refractory rejection may benefit from nephrectomy regardless of the time posttransplantation.

Nephrectomy

Indications for allograft nephrectomy are listed in Table 7. Some patients develop graft intolerance syndrome and present with refractory anemia, pain over allograft, hematuria, fever, while being weaned off immunosuppression. Treatment usually involves a short course of steroids and nephrectomy, if steroid resistant.

Patients with recurrent severe nephrotic syndrome due to recurrence of glomerulonephritis may obtain pain relief from the symptoms of nephrotic syndrome after nephrectomy. Patients with persistent urinary tract infections involving the allograft should undergo nephrectomy, as should any other patients for whom rapid withdrawal of immunosuppression would be beneficial.

Table 7 Indications for allograft nephrectomy

Indication	Comments
Acute late rejection after withdrawal of immunosuppression/graft intolerance syndrome	Graft pain, fever, abdominal pain
Recurrent or de novo glomerulonephritis with severe nephrotic syndrome symptoms	Refractory to conservative management
Persistent urinary tract infection associated with calculi, pyelonephritis, hydronephrosis	Inability to produce sterile urine due to urological abnormalities
To allow rapid withdrawal of immunosuppression	Patients with nonrenal infection, cancer, or other reasons to avoid immunosuppression
Allograft renal artery stenosis	Persistent moderate to severe hypertension in dialysis patients in nonfunctioning graft

Conclusion

The incidence and prevalence of renal transplantation late complications depends on their long-term management and early recognition of modifiable risk factors. The vast majority of successful renal transplant recipients has CKD and should be managed similarly to patients who have CKD before progression to ESRD.

Avoiding excessive immunosuppression during the short- and long-term period can minimize complications. A great transplant team with multidisciplinary team approach can improve and target these risk factors and improve overall outcomes. Nonadherence with recommendations and medications, secondary to personal or social issues, remains a major barrier and needs to be identified early on.

Timely management of these late complications and management issues can significantly affect short- and long-term patient and graft survival outcomes.

Cross-References

- A History of Kidney Transplantation
- Infection in Kidney Transplantation
- Kidney Transplantation: Surgical Complications
- Pregnancy After Kidney Transplantation
- Psychosocial and Personal Financial Aspects of Transplantation
- Transplant Immunosuppression

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Immunology of Kidney Transplantation

John G. Lunz III

Contents

Abstract

The immunological response against an allograft kidney is a barrier to long-term graft survival. While the basic science of transplant immunology is well understood, the clinical application of this information is lagging. Histocompatibility testing has become the predominant immunological monitoring for allografts and largely focuses on assaying for donor-recipient human leukocyte antigen (HLA) compatibility and measuring circulating anti-HLA antibodies. The identification of HLA antigens and genes has permitted the accurate and comprehensive matching for donors and recipients.

Multiple histocompatibility methods have been developed to examine for the presence of anti-HLA antibodies and best determine donor-recipient suitability. Methods for antibody detection and crossmatching have become more sensitive with the introduction of fluorescent detection modalities compared to older cytotoxic methods. However, the functional characteristics of antibodies may be lost unless further assay enhancements are incorporated, such as complement-fixing antibody tests. Additionally, non-HLA antibodies are now being recognized as also contributing to the outcome of renal transplantation.

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Immunology · Histocompatibility · Human leukocyte antigen (HLA) · Antibody · Crossmatch · Luminex testing · Single antigen bead (SAB)

Introduction

The immunology of kidney transplantation is intertwined with renal transplant itself. The first long-term successful kidney allograft involving monozygotic twins effectively eliminated the genetic immunological differences between donor and recipient (Merrill et al. 1956). Many of the current practices in kidney transplantation revolve around controlling the immune system, including immunosuppression strategies, rejection treatment, and understanding tolerance. Volumes of work have been published on the immunology of transplantation, especially the basic science of transplant immunology. However, the application of these findings clinically has been slow.

Modern clinical transplant immunology predominantly revolves around testing the patient's humoral immunity, especially for antibodies against human leukocyte antigens (HLA) produced after exposure to nonself HLA antigens. Test to monitor cellular responses has historically lagged behind antibody analysis, with the gold standard test still being histopathological visualization of cellular infiltrates within a renal biopsy. Kidney transplantation has significantly evolved as the knowledge of histocompatibility has expanded and methods to test for HLA antigens and HLA antibodies have improved.

Basic Transplant Immunology

The underlying science of transplant immunology has been well described, and these studies have collectively helped further the understanding of how the immune system impacts nearly all facets of transplantation. It is well understood that host recognition of mismatched antigens in an allograft kidney can elicit rejection. Two major pathways of allo-recognition have been described, a direct and indirect pathway. In the direct pathway, donor antigen-presenting cells (APCs) present donor peptides to host T-cells. The indirect pathway involves the presentation of donor HLA peptides by recipient APC. A third, semi-direct pathway has also been identified, where an intact donor HLA molecule is acquired by a host APC by an exchange of the cell membrane. In all of these pathways, APC migrate from the donor organ and present donor antigen to T-cells in secondary lymphatic tissue leading to T-cell activation and potentially rejection (Lakkis et al. 2000). B-cells can act as both effector cells and APC. As APC, they can present donor peptides to T-cells resulting in activation. Antigen recognition by B-cell receptors causes B-cell activation, and the maturation into antibody-producing plasma cells is aided by interaction with T-cells and T-cell-produced cytokines.

While much has been published on the basic science of transplant immunology, by and large, the clinical use of this information has been lacking. This is especially true for monitoring the cellular response in human kidney allograft recipients. Currently, only a few non-invasive assays have been developed and validated to monitor cellular responses against the allograft kidney (Roedder et al. 2014; Modena et al. 2016), and the utility of these is still benchmarked against kidney biopsy results. Clinical tests to gauge the humoral response, especially antibodies against mismatched HLA, have been well described are widely adopted to monitor anti-donor reactivity and antibody-mediated rejection (Tait et al. 2013).

Histocompatibility

The study of immunological compatibility for organs and tissues before and after transplantation is referred to as histocompatibility. In modern transplantation, histocompatibility typically revolves around defining HLA antigens and

identifying anti-HLA antibodies. HLA proteins play a key immunological role in presenting foreign peptides to lymphocytes to initiate a cellular immune response. Moreover, HLA molecules were also identified as the target of antibodies in patients that had received multiple blood product transfusions (Dausset 1958a, b). Similar antibodies were also found in multiparous women (Payne and Rolfs 1958; Van Rood et al. 1958). The formation of these antibodies was driven by exposure to nonself HLA through transfusion or pregnancy. Subsequently, the HLA antigens were identified as the target of antibodies in transplantation, and defining HLA antigens in donors and recipients could be useful in matching organs.

Diagnostic Histocompatibility Testing and Renal Transplantation

Histocompatibility testing for renal transplantation involves three entities: (1) the identification of donor and recipient HLA antigens (HLA typing), (2) detecting HLA antibodies in the recipient, and (3) determining donor-recipient compatibility (crossmatching). In 1966, Kissmeyer-Nielsen and colleagues demonstrated that anti-donor antibodies could illicit hyperacute rejection in renal allografts (Kissmeyer-Nielsen et al. 1966). This was followed by Patel and Terasaki in 1969 demonstrating the association between kidney allograft hyperacute rejection and anti-donor HLA antibodies and the introduction of a diagnostic test, the lymphocytotoxic crossmatch, to predict immediate graft failure (Patel and Terasaki 1969). These studies established the need for two critical immunological tests for successful renal transplantation: prospective crossmatching to screen unacceptable donor-recipient pairings and identifying preformed anti-HLA antibodies in potential recipients.

The development of anti-HLA antibodies involves exposure to nonself HLA antigens. Three main routes of sensitization are generally accepted. During pregnancy, the paternal-derived HLA antigens of the developing fetus can be recognized as nonself, and a maternal response is the production of antibodies against these HLA antigens (Sanfilippo et al. 1982). A second path to sensitization is exposure to HLA antigens in blood products. As red blood cells do not express HLA antigens, exposure via red blood cell transfusion was historically thought to occur from leukocytes in the blood unit. As most red cell units are now leukoreduced, this is less of a problem, but increased HLA antibodies following transfusion are still observed. Platelets do express Class I HLA on their surface, and therefore platelet transfusions can also lead to sensitization. Third, allograft recipients can develop HLA antibodies to any mismatched HLA antigens. Other less frequent routes of sensitization include vaccination where the vaccine was prepared with human cell lines (Forney et al. 2008), human heart valve allografts (Kneib et al. 2012), and likely many more.

Human Leukocyte Antigen Genetics and HLA Typing

In the early days of histocompatibility, HLA antigens were defined by serological methods using HLA-specific anti-sera to assess antigens on isolated T- and B-cells. This method of HLA antigen typing lacked sensitivity and did not account for all HLA antigens. By serological methods, the extent of HLA antigens was quite limited defining only around 100 Class I and II HLA antigens. Molecular DNA techniques permitted a more precise identification of the genes encoding the HLA antigens. The HLA genes reside within the major histocompatibility complex (MHC), a cluster of genes on the short arm of chromosome 6 (6p21). The MHC region of the genome consists of over 200 genes with most categorized as having immunological functions, including the HLA gene family.

HLA genes are divided into two classes, each having a major and minor class of genes. For Class I, the major Class I genes are HLA-A, HLA-B, and HLA-C and the minor HLA-E,

HLA-F, and HLA-G. Class I antigens are single proteins stabilized by β2 microglobulin and expressed constitutively on cells throughout the body. The Class II major genes are HLA-DRA1, HLA-DRB1, HLA-DRB3/HLA-DRB4/HLA-DRB5, HLA-DQA1, HLA-DQB1, HLA-DPA1, and HLA-DPB1. The minor Class II genes are HLA-DM and HLA-DO, which are involved in the loading of peptides onto HLA molecules. Class II antigens are comprised of two HLA proteins, an alpha and beta chain, that combine to form a heterodimer mature protein. These are constitutively expressed by professional APC, but can be unregulated on all cells after exposure to pro-inflammatory cytokines. All Class II HLA genes have a high degree of polymorphism except HLA-DRA1, which only has a few defined variants and is functionally considered monomorphic.

HLA genes are highly polymorphic with over 14,000 alleles producing over 10,000 different protein sequences having been identified as of April 2016 (Robinson et al. 2015). The greatest diversity lies within the Class I genes, with HLA-B having the greatest number of alleles identified for a single locus. The selective forces behind HLA genetic diversity were driven by the immunological need to present foreign peptides to effector immune cells (Blackwell et al. 2009). As pathogens vary geographically, so do the diversity of the HLA genes (Sanchez-Mazas et al. 2012). And therefore it is not surprising that the diversity of HLA genes generally follows geographic and ethnic distribution of man. Additionally, the genetics of HLA also follow unique patterns of inheritance, as the Class I and II HLA genes are distributed to gametes as an entire haplotype rather than each gene following Mendelian inheritance.

HLA antigen typing for donors and recipients is essential for matching, understanding HLA antibody testing results, and determining donor-specific antibody (DSA) status. Current methods for defining HLA antigens involve DNA-based methods, including sequence-specific primer (SSP) method, sequence-specific oligonucleotide probe (SSOP) method, and sequence-based typing (SBT). Each of these methods can provide typing at both low and high resolution. Ultimately, the goal for renal transplant is generally to achieve a low-resolution molecular HLA typing that can be translated into a serological equivalent to be used in donor-recipient matching. Current UNOS OPTN requirements for HLA typing mandate that renal allograft donors be typed at HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/HLA-DRB4/HLA-DRB5, HLA-DQA1, HLA-DQB1, and HLA-DPB1. However, the matching algorithm for kidney allocation only considers the degree of HLA-A, HLA-B, and HLA-DRB1 similarity. Knowledge of the recipient's HLA typing is also often critical when analyzing single antigen bead HLA antibody testing as false positive reactions can be observed and discriminating self from nonself antigens is useful to accurately assign HLA antibodies. Higher resolution HLA typing is more frequently being required, especially when a patient may have allelic HLA antibodies, or for use in epitope-based donor-recipient matching.

HLA Antibody Testing

The basic tenet of HLA antibody testing, both historic and current, involves reacting a patient's serum with HLA antigens and measuring the amount of antibody binding. Methods for detecting HLA antibodies have continually sought to increase testing sensitivity while also trying to gain functional information about the antibodies with the hope of correlating results to clinical significance. Two general methods for detecting HLA antibodies have been developed, live cell-based assays and solid-phase assays using purified HLA antigens. Both techniques carry several advantages and disadvantages (Tait et al. 2013), but the solid-phase methods have become the mainstay of testing in histocompatibility laboratories.

The first generation of HLA antibody testing was performed by lymphocytotoxic methods. T-cells from multiple different individuals were isolated and reacted with patient sera, typically on microtiter plates, and the cell killing ability of antibodies in the sera was visualized using a vital cell dye. Initially, the cells used for this

antibody testing were obtained from volunteers within the local area of the transplanting hospital, as these cell donors would best represent the HLA diversity within the local organ donor population. And, therefore, this test would produce a panel reactive antibody (PRA) percentage for each patient, which would estimate the general compatibility they would have against a theoretical local donor. Subsequent generations of this test used commercially prepared cell panels representative of the donor population across the country.

Lymphocytotoxic testing relied on there being sufficient antibody present to activate the complement pathway ending in cell death. Even if the test was negative, this did not mean that the serum was completely free of HLA antibodies. These tests could, therefore, only identify patients with high titers of HLA antibodies sufficient to induce cytotoxicity. The method also lacked specificity. If cytotoxicity was observed across the panel of donor cells, it was difficult, if not impossible, to define the specific antigens that were targeted. Enhancements were introduced to improve the sensitivity including extending incubation times, adding an outside source of complement to ensure uniformity, and introducing antihuman globulin (AHG). When cell-based HLA antibody testing is performed using fluorescent detection and flow cytometry, the sensitivity is markedly increased, but the antibody cytotoxic potential cannot be gauged. However, commercial tests that use fluorescent detection are typically not available, and therefore this technique is not routinely performed.

Antibody screening by cytotoxicity remains limited, as it is typically restricted to using T-cells and therefore can only test for Class I HLA antibodies. Additionally, both cytotoxicity and flow cytometry cellular assays need live cells, which may not be available or require strict storage requirement to maintain viability. Finally, as cell-based assays are typically only performed on T-cells, antibodies against Class II antigens are not detected. Live cell-based HLA antibody testing does, however, have a significant benefit in that the HLA antigens expressed are identical in conformation and the level of protein expression is similar to that of an organ donor.

The identification of the HLA genes and development of recombinant DNA techniques have enabled the production of purified HLA proteins that could be isolated and affixed to a solid substrate. These so-called solid-phase HLA antibody assays utilize purified HLA proteins that are produced with the precise knowledge of the allele-level gene resolution. The first generation of solid-phase HLA antibody tests were colorimetric ELISA assays that achieved a much greater level of sensitivity compared to lymphocytotoxic assays and had the added benefit of detecting Class II HLA antibodies (Zachary et al. 2001).

The greatest enhancement to date in HLA antibody detection was the incorporation of fluorescent detection modalities into solid-phase assays. HLA proteins conjugated to microsphere beads can be assayed using a flow cytometer or Luminex instrument to detect HLA antibodies with tremendous sensitivity (Pei et al. 1999, 2003). The most popular tests used today are the Luminex-based assays. Luminex beads are polystyrene microspheres that can be coated with a variety of molecules, including HLA antigens (Fuggle and Martin 2008). There are typically up to 100 Luminex beads, each impregnated with different concentrations of red and infrared dyes, which allows for the unique identification of each bead on a two-laser Luminex analyzer instrument.

Various forms of HLA antigens can be adhered to Luminex beads, including multiple pooled HLA antigens for general screening, a specific Class I or II HLA phenotype for PRA analysis, and single HLA antigens (Tait et al. 2013). Typically, HLA antibodies are detected using a phycoerythrin-labeled antihuman IgG antibody. Of all the available Luminex test variants, single HLA antigen beads (SAB) have become the mainstay for specific detection of HLA antibodies. The HLA antigens on SAB are precisely defined, such that antibodies directed toward individual HLA alleles can be identified. SAB testing is used pretransplant to define unacceptable antigens and posttransplant to determine if DSA are present.

HLA antibody strength can be measured by Luminex-based methods; however the commercially available tests are not licensed to be quantitative, only qualitative. The output from the

Luminex instrument is mean fluorescent intensity (MFI), which measures the amount of fluorescence from the detection antibody. Most labs assign MFI cutoffs to call an antibody present or absent. Additionally, the relative strength (i.e., strong, moderate, weak) of an antibody might be assigned. These strength categories are usually correlated with the ability of an antibody to show reactivity on another assay, such as crossmatch (Batal et al. 2010). An antibody that may be observed below the cutoff does not, however, mean that it is completely absent. A clearly defined HLA antibody pattern of reactivity that is below a lab's positive threshold may be apparent when visualizing the raw data. Thus, Luminex-based HLA antibody results need to be carefully interpreted. Even these very weak (low MFI) antibodies can rapidly increase in strength during a memory response. MFI values also can vary from lab to lab due to differences in testing practices (Reed et al. 2013) and are also influenced by serum factors such as endogenous complement (Schnaidt et al. 2011), medications including IVIg (Badders et al. 2010) and antithymocyte antibody treatment (Gloor et al. 2007), and antibodies against denatured HLA antigens (Pereira et al. 2011; Poli et al. 2011).

The flexibility of Luminex-based testing platform has yielded several SAB assay modifications developed to help augment the assay sensitivity by providing functional characteristics of the HLA antibodies. These include commercial assays to determine complement-fixing ability detecting C1q or C3d (Chen et al. 2011; Sicard et al. 2015). Studies that have examined the presence of complement fixing DSA using these assays have shown that kidney allograft survival is markedly decreased compared to recipients with non-complement fixing DSA (Loupy et al. 2013; Sicard et al. 2015).

Crossmatching

The final pretransplant assessment of donor-recipient immunological compatibility is determined by performing a crossmatch. Serum from a potential recipient is mixed with donor cells, and the amount of cell death or antibody binding is measured. The importance of performing a prospective crossmatch was demonstrated in the seminal manuscript by Patel and Terasaki where a positive cytotoxic crossmatch was strongly associated with hyperacute rejection (Patel and Terasaki 1969). This fundamental study established the donor-recipient crossmatch as the essential compatibility test necessary to be performed immediately prior to transplantation to prevent hyperacute rejection. And since then, the histocompatibility laboratory has become a central resource in facilitating successful transplantation.

Two principal crossmatching methods have been developed: lymphocytotoxicity and flow cytometry. Both examine the antibody reactivity against donor T- and B-cells. Lymphocytotoxic methods assess the ability of circulating anti-donor antibodies to kill donor cells. The technique is facilitated by the addition of exogenous complement, typically from rabbit, to ensure cell killing should sufficient anti-donor antibody be present. Thus, the technique is also referred to as complement-dependent cytotoxicity or CDC crossmatching. In general, the cytotoxic methods are less sensitive than flow cytometric methods. However, this method does provide functional information about the anti-donor antibodies, specifically if they can elicit a cytotoxic response. Therefore, a positive cytotoxic crossmatch result is strongly correlated with the incidence of hyperacute rejection (Patel and Terasaki 1969). Since the inception of cytotoxic crossmatching methods, several modifications have been developed to increase the sensitivity (Gebel et al. 2003). These include extended incubations, increased number of washes, and the addition of antihuman globulin (AHG). CDC crossmatching is also typically performed with serum treated with dithiothreitol (DTT) a chemical agent that reduces disulfide bonds. In this assay, DTT is used to eliminate IgM antibodies leaving only serum with IgG reactivity. In general, anti-donor IgG DSA are considered to elicit a greater pathology than IgM DSA (ten Hoor et al. 1993; Chapman et al. 1986; Taylor et al. 1989), although studies showing reduced graft survival with IgM DSA have been reported.

The enhancements to the CDC crossmatch increased the assay sensitivity, but it is still inferior to the level achieved by analyzing anti-donor antibody binding by fluorescent flow cytometric methods. The fluorescent antibody detection using flow cytometry yields a significantly greater ability to identify anti-donor antibodies (Bray et al. 1989). A typical three-color flow cytometric crossmatch involves incubating donor cells with recipient serum followed by the addition of antibodies against T-cells (CD3), B-cells (CD19), and antihuman IgG to identify anti-donor antibodies bound to the lymphocytes. Although flow cytometry crossmatching is much more sensitive, it does not identify if anti-donor antibodies can bind complement, which might signify a greater immunological risk. And the significance of weakly positive flow crossmatch results is unclear, especially in the absence of Luminex-defined HLA DSA (Couzi et al. 2011). Regardless, flow cytometry crossmatching has become the principal method for crossmatching. Enhancements to flow cytometry crossmatching have been performed, especially treatment of donor cells with a proteolytic enzyme, pronase, to help cleave B-cell Fc receptors and increase specificity (Vaidya et al. 2001). However, this cell treatment can lead to false positive reactivity, especially in patients with underlying conditions, such as HIV infection (Szewczyk et al. 2016).

Recently, a third crossmatch method has been introduced, virtual crossmatch. This technique utilizes the information gathered from solid-phase HLA antibody testing and compares these results to the HLA typing for a potential donor. This crossmatch method has been used to screen potential donors for suitability prior to performing an actual crossmatch. However, it has also been successfully implemented in place of a physical crossmatch (Johnson et al. 2016). When virtual crossmatch is used as the final crossmatch, having accurate and recent HLA antibody and donor HLA typing information is of utmost importance. This has placed a tremendous importance on both precise HLA antibody analysis and HLA typing and a close interaction between the laboratory and the transplant team. With the national sharing of kidneys in the United States, virtual crossmatching has been successfully used to minimize cold ischemic time by bypassing the physical crossmatch.

Non-HLA Antibodies

HLA antibodies have been the principal target when diagnosing allograft dysfunction or the root of crossmatch positivity. However, antibodies against non-HLA antigens have also been identified as potential causes of allograft injury, although the absence of commercial testing kits for many non-HLA antibodies has hindered the widespread monitoring of these antibodies. One of the first non-HLA antibodies demonstrated to have deleterious effects on renal allografts was directed against major histocompatibility complex class I-related chain A (MICA) antigens. The MICA antigens are encoded by a series of polymorphic genes within the MHC and thus can differ between recipients and donors leading to allo-recognition. Exposure to nonself MICA antigens can stimulate an antibody response, and the presence of MICA antibodies was associated with increased rejection and decreased graft survival in a large study of renal allograft recipients (Zou et al. 2007). MICA proteins are not expressed on lymphocytes and thus would not be detected by traditional cytotoxic or flow cytometric crossmatch methods.

Antibodies against angiotensin II type 1 receptor (AT1R) have been correlated with poorer graft function and rejection (Philogene et al. 2016; Dragun et al. 2005). AT1R antibodies are considered autoantibodies and are seen in patients with malignant hypertension and preeclampsia. However, in the initial study identifying AT1R antibodies hypertension was not directly associated with rejection (Dragun et al. 2005). Interestingly, drugs targeting the angiotensin system may be effective in treating rejection due to AT1R, as some can block the binding site of the AT1R antibody to the AT1R protein. The incidence of pretransplant AT1R antibodies was recently correlated to posttransplant rejection (Lee et al. 2015; Giral et al. 2013) and may also contribute to recurrent focal segmental glomerular sclerosis in the allograft kidney (Mujtaba et al. 2015).

Detection of a general class of non-HLA antibody, anti-endothelial cell antibodies (AECA), has been facilitated by the development of an endothelial cell specific crossmatch (Jackson et al. 2013). The presence of anti-donor AECA has been correlated with elevated serum creatinine and cellular rejection (Jackson et al. 2011) and has been suggested to contribute to hyperacute rejection in the absence of HLA antibodies (Jackson et al. 2012). Identifying AECA is more difficult as it requires the availability of donor blood to isolate endothelial cell precursors to use in an endothelial cell crossmatch. Donor blood may be readily available from living donors and deceased donors prior to transplant. However, if donor blood is unavailable after the transplant, as it likely would not be for deceased donors, serial monitoring posttransplant cannot be performed.

Multiple other non-HLA antibodies have been described to have a negative impact on allograft function. Most of these can be classified as antibodies against autoantigens including vimentin, tubulin, myosin, and collagen (Besarani et al. 2014; Dragun 2008; Tait et al. 2013). Antibodies targeting these self-proteins may be generated against epitopes that ectopically expressed during allograft rejection, as the appearance of these antibodies typically is seen along with HLA antibodies during rejection episodes (Reinsmoen et al. 2014). As more commercially available testing resources become available to assay for non-HLA antibodies, the significance of these in kidney transplantation will become more apparent.

Conclusion

Safe and successful renal transplantation is heavily dependent on interactions with the histocompatibility laboratory to understand the donor-recipient immunological compatibility. Immunological testing is more common for the humoral response as many commercial tests are available. However, due to the lack of standard non-invasive assays, monitoring the anti-donor cellular immunity is not routinely performed. Histocompatibility testing has continued to improve over time, with the increased sensitivity of fluorescent detection of antibodies. Much needed assays to determine cellular responses in allograft kidneys are being developed, but further correlation with biopsy and graft outcome is needed for these to be used as standalone tests.

Cross-References

- Donor Selection: Deceased Donor
- Organ Procurement Organization and New Kidney Allocation
- Pathology of Kidney Transplantation
- Recipient Selection for Kidney Transplantation

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Pathology of Kidney Transplantation

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Abstract

Kidney transplantation has been effectively used as therapy for end-stage kidney disease, thanks to advances in the surgical, immunologic, and therapeutic realms. Decreased mortality and improved quality of life are cited among reasons to continue to pursue transplantation in the growing number of patients with chronic kidney disease (Tonelli et al. Am J Transplant 11(10):2093–2109, 2011). Unfortunately, however, renal allografts are subject to a variety of injuries, including physical, ischemic, immunologic, infectious, therapy-induced, and neoplastic, in addition to the ever-present threat of recurrent and de novo disease. Renal biopsy remains a mainstay in diagnosing and categorizing the type of injury present, so as to best inform the clinical approach (Williams et al. Nat Rev Nephrol 8(2):110–121, 2012). Timely and accurate representation of the histopathologic features present in a representative sample of renal allograft tissue, combined with appropriate ancillary testing, such as immunohistochemical (IHC) stains and molecular-based tests, are necessary to facilitate the best clinical approach to an individual patient and support optimal survival of the graft. This chapter highlights key pathologic features of the common and significant types of injury to which renal allografts are subject, and discusses key diagnostic features of each.

Keywords

Renal allograft · Renal injury · Antibody-mediated rejection · Cell-mediated rejection · Renal infection · Drug-induced renal injury · Ischemic renal injury · Recurrent renal disease · De novo renal disease

Introduction

Renal allografts are vulnerable to a variety of injuries, beginning with the initial surgical procurement of the organ from the donor and continuing through transport and surgical implantation into the recipient. Moreover, once successfully implanted, the allograft, having been introduced into the foreign milieu of the recipient, is subject to further potential insults, including ischemic, immunologic, infectious, therapy-induced and neoplastic, as well as recurrent and de novo disease. Serum and urine laboratory evaluation are typically used to monitor for any hint of compromised renal function, since azotemia or abnormal urinalysis findings are often key indicators of such.

Whether used as part of a protocol, or when clinical suspicion warrants, renal biopsy with thorough and timely pathologic evaluation is key to categorizing the type of injury that may be present at a given time within a renal allograft. Furthermore, the use of ancillary studies on the allograft tissue specimen, including immunohistochemical stains, molecular-based tests, immunofluorescence stains, and electron microscopy can further amplify the information available through a single biopsy specimen. By promptly addressing the histopathologic findings with appropriate therapeutic intervention, a clinician can, in many circumstances, positively impact patient quality of life and graft survival.

This chapter discusses and illustrates key histopathologic findings of the most common and significant injuries encountered in renal allografts, so as to provide a succinct, comprehensive, and up-to-date review of renal transplant pathology. The role of the pathologist as a member of the patient care team is emphasized. Where

appropriate, discussions about ancillary tests are included to promote the best use of the renal biopsy in positively effecting clinical outcomes for patients.

Renal Biopsy: Pathologic Approach

Samples of renal tissue are routinely obtained, processed, and evaluated by a general surgical or renal pathologist in the setting of renal transplantation. A brief overview of the pathologic approach and intent of evaluation follows in this section.

Utility and Approach of Donor Kidney Biopsy

In some circumstances, prior to implantation of a harvested donor kidney, a transplant surgeon obtains a small wedge-shaped, capsular-based sample of the donor kidney and sends it to the pathology laboratory for urgent, on-site evaluation. A general surgical pathologist or renal pathologist can appropriately review the donor kidney sample in this context. In many pathology laboratories, this testing is achieved by means of performing an urgent frozen section of the renal tissue, with rapid, routine hematoxylin and eosin staining and light microscopic evaluation.

The primary intent of this on-site evaluation is to provide verification that the donor kidney is histologically viable and has no significant histopathologic findings that might preclude implantation into the recipient or significantly impact graft survival (Cockfield et al. 2010). Examples of such findings include a heavy burden of chronic damage (as manifest by high numbers of globally sclerosed or diseased glomeruli, significant tubular atrophy, or significant interstitial fibrosis), chronic vascular damage (such as severe arteriolar hyalinosis), heavy acute inflammation (that might suggest infection), nonviable parenchyma (necrosis), or unsuspected neoplasm, among others. The pathologist generally calls the surgeon in the surgical suite within minutes of reviewing the specimen, and reports on the viability of the renal tissue, as well as the status of glomeruli, tubules, interstitium, and blood vessels. Based upon the pathologist's report, the surgeon may either proceed with implanting the kidney or refuse to implant the organ, given a significant short- or long-term risk to the patient. It is worth noting that performance of on-site evaluation of donor samples varies across the globe, and a recent systematic literature review has called for a reexamination of this practice in the context of appropriate patient care (Wang et al. 2015).

Utility and Approach of Allograft Kidney Biopsy

Once a kidney is implanted into the recipient, allograft renal biopsy specimens may be obtained at regular intervals (protocol biopsies), or on an as-needed basis, depending on systemic findings, renal-specific signs and symptoms, or serum or urine laboratory test results. The specimens may be procured in the days immediately following transplantation, or in the months and years thereafter. The biopsy specimens may be procured by the transplant surgeon, a (transplant) nephrologist, or an interventional radiologist with on-site specimen adequacy evaluation performed by a pathologist or technician. Once obtained, renal tissue is often reserved for immunofluorescence and electron microscopic studies, if needed, and the majority of the sample is processed for light microscopic evaluation via paraffin-embedded sections, supplemented by special and immunohistochemial (IHC) stains (see below) (Walker et al. 2004). The primary intent of obtaining samples from the grafted kidney is to determine whether or not there is histopathologic evidence of injury, and if so, to determine the extent of the damage and most likely pathophysiologic mechanism for the injury.

Once obtained, allograft renal biopsy specimens are usually processed on an urgent basis, with the goal of evaluating the sample and determining the presence and extent of injury within hours. In many laboratories, stat processing is employed, with stained microscopic slides available for review within 4–6 hours. Most renal

pathologists advocate for obtaining multiple sections and stains of the specimen, to include a minimum of two hematoxylin and eosin (H&E), two periodic acid-Schiff (PAS), two Masson's trichrome (trichrome), and two Jones methenamine silver (silver) stains. The stains are typically used in a complementary fashion, with H&E stains providing a general overview of all structures, cytoplasmic and nuclear features, PAS stains serving to highlight tubular and glomerular basement membranes, trichrome stains accentuating fibrous tissue and fibrin, if present, and silver stains highlighting the glomerular and tubular basement membranes, as also sclerosis. An immunohistochemical or immunofluorescence stain for C4d is also routinely employed to evaluate for antibody-mediated rejection. Light microscopic review employing all stains is performed and results are typically reported directly by the pathologist to the surgeon or nephrologist.

Discussion with the clinician regarding the presence or absence of specific findings in the allograft may inform additional sections, stains, and ancillary studies, or prompt additional laboratory evaluation. As an example, in the absence of features of rejection, pursuit of immunofluorescence studies and/or electron microscopic studies may be warranted, so as to elucidate the cause of glomerular dysfunction, particularly if the suspicion of recurrent or de novo glomerular disease is high.

Physical Injury and Ischemia

Direct physical injury may occur during implantation of the renal allograft. The surgeon is likely immediately aware of the injury, and will repair the injury at that time (such as direct capsular injury, direct vascular injury). In these circumstances, the injurious effects may or may not have an impact on functioning of the graft postoperatively. If lingering effects of operative injury are suspected or if there is delayed allograft function, an allograft biopsy may be performed. Depending upon the nature of the injury, histopathologic findings may include fibroblastic capsular proliferation with acute inflammation, edema and/or hemorrhage, indicating previous capsular injury with subsequent repair.

Ischemic changes, such as those caused by direct vascular injury or ischemic reperfusion injury, may be manifest in the hours and days following transplantation. If an allograft renal biopsy is performed, the histopathologic changes may be subtle or profound. Subtle changes may include tubular epithelial cell blebbing, vacuolization, or epithelial cell attenuation. Accompanying interstitial edema may be seen. More profound changes may be manifest as overt acute tubular injury or necrosis (ATN). Tubular epithelial cell sloughing with necrotic and apoptotic cells filling or distending the tubular lumina may be present (Salvadori et al. 2015), and manifest in urine sediment as renal tubular epithelial (RTE) cell casts or individual RTEs. If significant vascular injury has occurred, changes may also be seen within the renal cortex proper, including overt necrosis of glomeruli. In some instances, depending upon the timing of the originating vascular insult, significant neutrophilic infiltration of the renal parenchyma can be seen, raising concern for acute bacterial infection. Correlation with urine microscopy and/or culture may be important in such cases to exclude acute pyelonephritis.

Rejection

Acute rejection, both cellular and antibody-mediated, has been shown to be a significant factor in diminished renal allograft survival in a number of studies (El Ters et al. 2013). Many risk factors for developing acute rejection, both cellular and antibody-mediated, have been evaluated, and efforts to identify those recipients of "high immunological risk" continue. In a recent study of multivariate analyses, Lebranchu et al. evaluated a number of recipient clinical and immunological characteristics as well as donor clinical characteristics and transplant-related factors in an attempt to definitively determine the relative contribution of these factors to development of acute rejection. Those risk factors with good quality of evidence and strong impact for developing acute rejection

included younger recipient age, HLA mismatch, presence of anti-HLA antibodies, presence of pre-transplant donor-specific antibodies (DSA), and delayed graft function (Lebranchu et al. 2013). Awareness of the characteristics of antibody-mediated and cellular rejection, as well as their clinical and histopathologic commonalities, is important to providing optimal care of the renal transplant patient.

Antibody-Mediated Rejection (ABMR)

Antibody-mediated rejection (ABMR) remains one of the key effectors of long-term adverse outcomes in kidney transplants (Sellarés et al. 2012; Wiebe et al. 2012). ABMR has been traditionally classified into hyperacute, acute, and chronic ABMR types.

Hyperacute Rejection

Hyperacute rejection, characterized by rejection within minutes to hours, caused by preexisting antibodies with a histopathologic picture of diffuse vascular thrombosis, hemorrhage and ischemic necrosis, and positive C4d staining in peritubular capillaries has become rare due to improved matching strategies (Colvin and Mauiyyedi 2008).

Acute and Chronic ABMR

Acute and chronic ABMR, however, have remained both a diagnostic and therapeutic challenge. Acute and chronic ABMR is initiated by B cell and plasma cell activation that generate donor-specific antibodies binding to HLA and other non-H antigens on the endothelium, initiating a cascade of complement dependent and independent pathways that eventually contribute to capillaritis (Farkash and Colvin 2012). Initial definitions of acute ABMR included neutrophils in peritubular capillaries (PTCs), de novo anti-donor HLA class I antibodies, and C4d endocapillary positivity as key markers. C4d detection can be performed on both fixed and frozen tissue using immunohistochemistry with peroxidase or fluorescent conjugated antibodies. The sensitivity of these tests is low and highly dependent on the density of PTCs in the biopsy, leading to the concept of C4d-negative acute and chronic ABMR. The 2013 Banff criteria acknowledge these limitations with the inclusion of modified diagnostic criteria for ABMR. These include (1) histologic evidence of acute tissue injury, (2) evidence of antibody interaction with vascular endothelium (may or may not have positive C4d staining), and (3) serologic evidence of donor-specific antibodies (Haas et al. 2014) (see Table 1). The threshold for C4d positivity was lowered with a score of greater than 0% staining noted to be positive by IHC (see Fig. 1). The current Banff scheme also standardizes definitions of capillaritis. Absence of peritubular capillaritis or PTC0 is defined as less than three luminal inflammatory cells in 10% or less of cortical PTC, PTC1 is defined as greater than 10% of cortical PTCs involved with 3–4 luminal inflammatory cells, PTC2 is defined as greater than 10% of PTCs with 5–10 luminal inflammatory cells, and PTC3 is defined as greater than 10% of cortical PTCs with greater than 10 inflammatory cells. The cellular

Table 1 Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

Acute/active ABMR; all three features must be present
1. Histologic evidence of acute tissue injury, including one or more of:
a. Microvascular inflammation, in the form of glomerulitis or peritubularcapillaritis
b. Intimal or transmural arteritis
c. Acute thrombotic microangiopathy (without other etiology)
d. Acute tubular injury (without other etiology)
2. Evidence of recent or ongoing antibody interaction with endothelium, including one or more of:
a. Linear C4d staining in peritubular capillaries
b. Moderate microvascular inflammation (at least)
c. Increased expression of gene transcripts supporting endothelial injury
3. Serologic evidence of donor-specific antibodies (DSAs)

Reference: Haas et al. (2014), p. 277

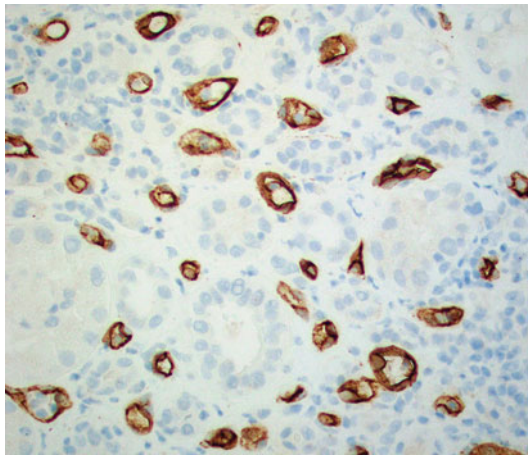

Fig. 1 C4d positive staining in setting of acute antibody-mediated rejection (*AMR*). Peritubular capillaries demonstrate intense positive staining with C4d by immunohistochemical staining (C4d immunostain x400)

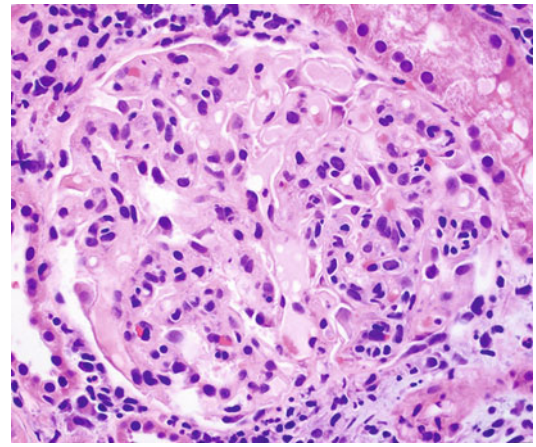

Fig. 2 Thrombotic microangiopathy. The glomerulus demonstrates neutrophilic and lymphocytic inflammation, as also a fibrin thrombus. In such cases, ABMR and acute TCMR may be concurrent (H&E x400)

composition with subsets of mononuclear cells versus polymorphonuclear cell components may also be important, as high monocyte to T cell ratios may be observed with C4d-negative ABMR. The minimum number of inflammatory cells within the glomerulus for a diagnosis of glomerulitis has not been similarly defined, though five or more mononuclear cells/glomerulus are considered to be adequate. Immunohistochemical stains for CD68 may be employed to highlight infiltrating glomerular macrophages.

Chronic stage thrombotic microangiopathy (TMA) is not specific to the ABMR process. The differential diagnosis includes TMA secondary to calcineurin inhibitors or viral infections and can be diagnostically challenging (Nadasdy 2014). Chronic stage TMA and transplant glomerulopathy share morphologic similarities, including light microscopic features of thickened glomerular capillaries with double contours, widening of the subendothelial space, endothelial cell vacuolation and thickening (see Fig. 2). Thickened glomerular capillaries and double contours are typically highlighted on silver stains and electron microscopy. Banff 2013 definitions include cg1 with mild remodeling of the glomerular tufts in 10–25% of glomerular capillaries, cg2 to 25–50% of glomerular capillaries, and cg3 greater than 50% of glomerular capillaries. Of interest is the concept of subclinical ABMR which can also be C4d positive or negative and is defined by the identification of peritubular capillaritis and glomerulitis greater than 0. Identification of subclinical rejection is strongly associated with subsequent interstitial fibrosis, tubular atrophy, and chronic allograft nephropathy (Moreso et al. 2006). Additionally, a recent study has shown that patients with subclinical ABMR experience long-term effects distinct from those patients with subclinical TCMR (Loupy et al. 2015). Banff 2013 guidelines include molecular tests for antibody interaction with vascular endothelium such as measuring of endothelial activation and injury transcripts (ENDATs). In addition, the noninvasive blood test "diagnosing acute rejection in kidney transplant recipients" (DART) prospective multisite study examining the levels of donor-derived cell-free DNA levels using a commercial test (AlloSure) (Bloom et al. 2017) has recently shown that elevation of cell-free DNA levels greater than 1% was associated with acute and chronic ABMR. However, two cases of BK virus injury were also associated with elevated cell-free DNA, indicating that elevated levels may still need to be explored using traditional biopsies.

T Cell-Mediated Rejection (TCMR)

Acute T Cell-Mediated Rejection (TCMR)

Acute T cell-mediated rejection (TCMR) is a relatively common cause of renal allograft dysfunction, particularly in the days to months following transplantation. While less common, acute TCMR can be seen years following transplantation (Rao et al. 1989).

Clinically, acute TCMR may manifest as fatigue, fever, weight gain, or swelling, with accompanying decreased urine output and graft tenderness. Patients may experience an elevation in serum creatinine to varying degrees (Nankivell and Alexander 2010). Accompanying urinalysis findings are usually subtle to nonexistent, but may include hematuria, proteinuria, or inflammation. Sometimes, subclinical acute TCMR may be present, and only is discovered upon a routine allograft biopsy for other reasons or as part of a protocol (Nankivell and Alexander 2010). In many cases, the transplant nephrologist or surgeon will perform an allograft renal biopsy and serologic evaluation for donor-specific antibodies (DSAs) simultaneously. In this way, histopathologic findings in the allograft biopsy specimen can be interpreted in the context of new serologic findings, if any (Haas et al. 2014).

Molecular Diagnostics of Rejection

Given concerns with intraobserver agreement on histopathologic diagnoses for renal allograft biopsy specimens using rejection classification schema (Joh et al. 2006), molecular diagnostic tests may prove beneficial in the near future, offering more specific and sensitive markers for acute TCMR. As molecular diagnostics and mRNA microarray data are gathered, increasing evidence is mounting to support a specific signature or molecular phenotype in the setting of acute TCMR. Further, combining clinical, histopathologic, and molecular-based diagnostic tests may serve to additionally increase the diagnostic power in settings of acute TCMR (Reeve et al. 2009, 2013).

Gross Features of Acute TCMR

Gross changes may be seen within the kidney in acute TCMR some of which may be visualized with appropriate radiologic evaluation (O'Neill and Baumgarten 2002; O'Neill 2014). In cases of severe disease, renal function may be significantly impaired to the point of necessitating graft removal. In such cases, gross findings of organ swelling, significant parenchymal hemorrhage and segmental necrosis consistent with cortical and sometimes medullary infarcts may be seen in the resected graft. In cases of severe vascular injury (such as fibrinoid necrosis) imparted by T cell infiltration, or if accompanying antibody-mediated rejection (ABMR) is present, grossly visible intravascular thrombi may also be noted upon sectioning of the resected organ (Nickeleit et al. 2015).

Light Microscopic Features of Acute TCMR

In acute TCMR, activated T cells infiltrate various renal structures, thereby negatively impacting overall renal function. The degree of cellular infiltration and the structures affected ultimately determine the grade or degree of acute cellular rejection (Solez et al. 2008) (see Table 2). While activated T cells are typically the predominant infiltrating inflammatory cells, accompanying macrophages, neutrophils, plasma cells, and even B cells and eosinophils may be seen. As expected, with cytokine generation, vascular dilation with endothelial cell prominence and interstitial edema are seen, particularly in more severe cases. Careful

Table 2 Banff 97 diagnostic categories for T cell-mediated rejection (TCMR) – Banff'07 update

Type/ grade	Criteria
IA	Significant interstitial inflammation (i2 or i3) and foci of moderate tubulitis (t2)
IB	Significant interstitial inflammation (i2 or i3) and foci of severe tubulitis (t3)
IIA	Mild to moderate intimal arteritis (v1)
IIB	Severe intimal arteritis (v2)
III	Transmural arteritis with or without fibrinoid change and necrosis (v3)

Reference: (Solez et al. 2008), p. 758

evaluation of multiple tissue sections and special stains is warranted, since acute TCMR may be focal. If necessary, immunohistochemical stains such as CD3 for T cells and CD68 for macrophages can be employed to distinctly determine the origin of a specific infiltrating mononuclear cell.

Tubular and Interstitial Changes

Most commonly in acute TCMR, T cells infiltrate cortical tubules, often with associated reactive tubular epithelial and interstitial changes. In some cases, tubulitis may be widespread within a renal allograft sample and easily detected on H&E stains (see Fig. 3a). In other cases, tubulitis may be more difficult to ascertain. PAS stains can be used to highlight tubular basement membranes, thereby accentuating and delineating the location of inflammatory cells (either within tubules or the interstitium) (see Fig. 3b). As mentioned, an immunohistochemical stain for CD3 will also highlight tubulitis (see Fig. 3c).

Determination of the number of infiltrating lymphocytes per tubule cross section is key to classifying the degree of tubulitis as nonexistent (t0, no lymphocytes present), mild (t1, 1–4 cells per tubule cross section), moderate (t2, 5–10 cells per tubule cross section), or severe (t3, greater than 10 cells per tubule cross section) (Racusen et al. 1999). Associated tubular epithelial changes

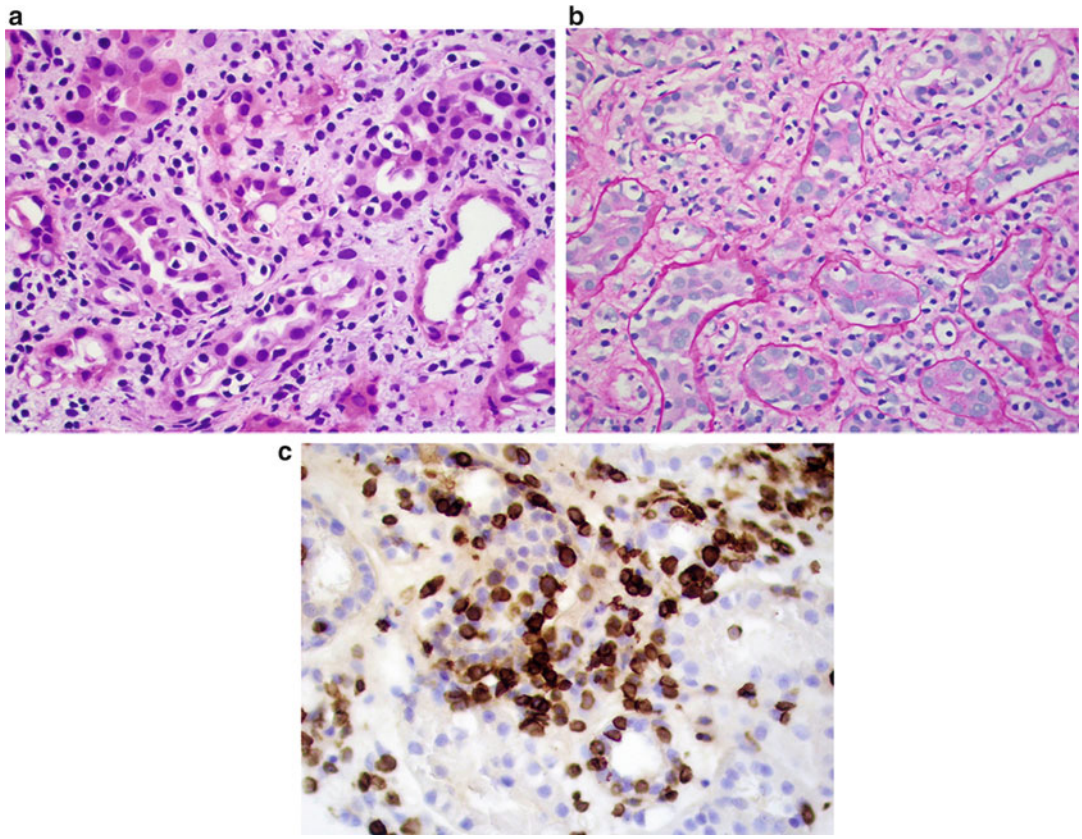

Fig. 3 (**a**) Acute cellular rejection, tubulitis. Cortical parenchyma demonstrates interstitial lymphocytic inflammation and lymphocytes infiltrating tubules, consistent with tubulitis. Note the halos surrounding infiltrating lymphocytes (H&E x400). (**b**) Acute cellular rejection, tubulitis, PAS stain. Use of PAS stain highlights basement membranes, which allows for detection of lymphocytes infiltrating tubules (PAS x400). (**c**) Acute cellular rejection, tubulitis, CD3 stain. Use of immunohistochemical stain for CD3 highlights T cells infiltrating tubules (CD3 immunostain x400)

may include nuclear enlargement, presence of visible nucleoli, and tubular epithelial cell mitoses. In severe cases, overt tubular epithelial cell necrosis may be present. Of note, there is some debate regarding whether a diagnosis of tubulitis should be rendered if inflammation is seen only within atrophic tubules. At this time, most renal pathologists score tubulitis within nonatrophic tubules (Mannon et al. 2010). Detailed review of multiple tissue sections is necessary, given the focal nature of tubulitis that is seen in some cases.

Accompanying interstitial inflammation plays a role in grading rejection, depending upon the percentage of sampled parenchyma that is involved. If less than 10% of the parenchyma is occupied by inflammation, the case is scored as i0; if 10–25% of the parenchyma is involved, a score of i1 is rendered; if from 26–50% of the parenchyma is inflamed, a score of i2 is given, and inflammation occupying greater than 50% of the tissue is scored as i3 (Racusen et al. 1999). In severe cases of acute TCMR, aggregates of interstitial inflammatory cells are typically easy to detect on low-power microscopic evaluation of the renal allograft biopsy specimen.

If accompanying neutrophils demonstrate margination along the endothelium, particularly of peritubular capillaries, acute antibody-mediated rejection or pyelonephritis should be suspected (Solez et al. 2008). Acute TCMR and ABMR or pyelonephritis can be present in the same specimen and may be difficult to delineate.

Glomerular Changes

While not frequent, some cases of acute TCMR may demonstrate mononuclear inflammatory cell infiltration of glomeruli, consistent with glomerulitis. In such instances, reactive glomerular changes, including endothelial cell swelling and occlusion of glomerular capillaries, may be seen (see Fig. 4a). These findings are often segmental but may be global in nature. Use of immunohistochemical stains to delineate glomerular infiltrating CD3-positive T cells can be employed to highlight acute TCMR (see Fig. 4b). Immunohistochemical stains for CD68 may also be used to highlight accompanying infiltrating macrophages.

Less often, infiltrating glomerular neutrophils may be present. If significant numbers of neutrophils are noted, accompanied by intraluminal thrombi or fibrinoid necrosis, ABMR should be considered, and a careful search for arteritis should be undertaken. Additionally, infiltrating glomerular neutrophils may be a manifestation of thrombotic microangiopathy (Racusen et al. 1999). As with tubulitis and interstitial

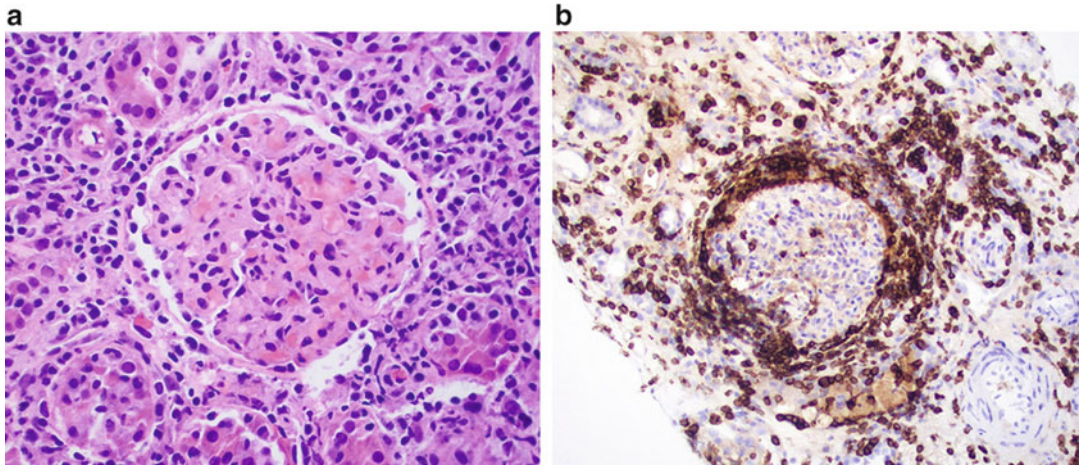

Fig. 4 (**a**) Acute cellular rejection, glomerulitis. Cortical tissue shows a relatively dense lymphocytic inflammatory infiltrate with focal infiltration of a congested glomerulus by mononuclear cells (H&E x400). (**b**) Acute cellular rejection, glomerulitis, CD3 stain. An immunohistochemical stain for CD3 shows T cells surrounding and focally infiltrating a glomerulus with focal infiltration of adjacent tubules as well (CD3 immunostain x200)

inflammation, the degree of glomerulitis should be appropriately documented, and is graded based upon the percentage of glomeruli involved by the inflammatory process (Racusen et al. 1999).

Vascular Changes

Infiltration of arteries by T cells, as demonstrated by histopathologic evaluation, should trigger a diagnosis of at least grade II cellular rejection by the Banff criteria. Such inflammatory cell infiltration is usually accompanied by endothelial cell changes, including swelling and apparent activation. Detection of focal arteritis may be challenging, and as with tubulitis, requires careful review of multiple sections with the aid of special stains. Grading of arteritis is dependent upon a determination of how much luminal area is involved by inflammation in a given artery. For a designation of v1, mild to moderate intimal arteritis must be present in at least a cross section of one artery. A designation of v2 requires inflammation involving at least 25% of the luminal area of one arterial cross section. Changes such as significant transmural inflammation, necrosis of the media, or fibrinoid change warrant a diagnosis of a higher grade of arteritis (v3) and thus, of acute TCMR. Similarly, such changes may also raise suspicion of synchronous ABMR. Notably, in cases of at least moderate acute TCMR with arteritis, associated tubulitis and significant interstitial inflammation will be present. However, some cases may manifest at least mild arteritis (v1), with only minimal to mild tubulitis (t0 or t1) and mild interstitial inflammation (i1) (Racusen et al. 1999; Solez et al. 2008). Changes of acute TCMR may also be present in a background of chronic rejection (see Fig. 5a, b).

Grading of Acute TCMR

Currently, for acute TCMR, the 2007 update to the Banff 97 classification is used by pathologists, nephrologists, and transplant surgeons (Solez et al. 2008). Utilizing a common language for the findings in renal allograft biopsy specimens allows for effective communication and optimal patient care. Additional studies to evaluate criteria for inclusion in the Banff classification are ongoing, with published updates occurring on a relatively regular basis (Haas et al. 2014).

Acute TCMR may occur synchronously with antibody-mediated rejection (ABMR) and with chronic changes in the renal allograft (Racusen et al. 2003). Careful determination of the presence and degree of tubulitis, interstitial inflammation,

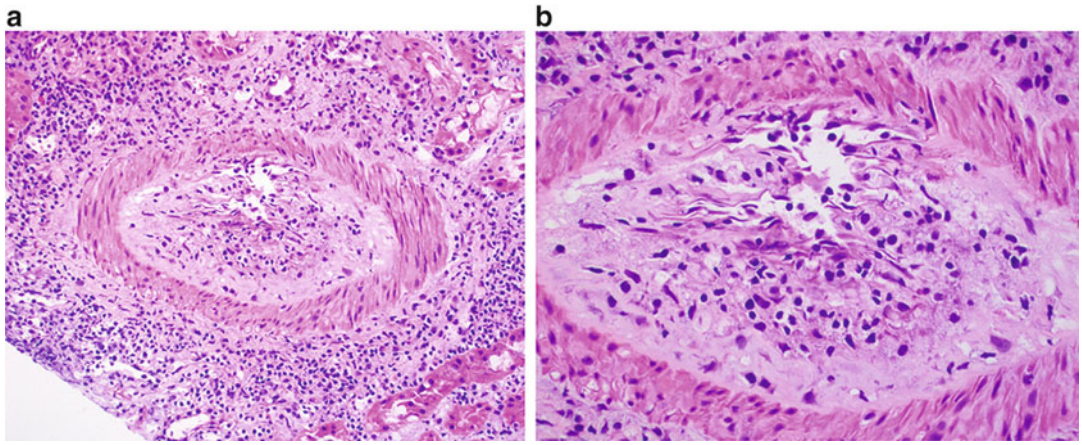

Fig. 5 (**a**) Acute cellular rejection in setting of chronic rejection. This muscular artery shows infiltration of the wall by mononuclear cells, consistent with cellular rejection, as well as significant intimal thickening and marked luminal narrowing, consistent with chronic rejection (H&E x200). (**b**) Acute cellular rejection in setting of chronic rejection, high power. This muscular artery shows infiltration of the wall by mononuclear cells, consistent with cellular rejection, as well as significant intimal thickening and marked luminal narrowing, consistent with chronic rejection (H&E x400)

and arteritis are all essential to determining the overall category or grade of acute TCMR. Allograft biopsy specimens that are categorized as borderline or "suspicious" may demonstrate tubulitis with only minor interstitial inflammation or significant interstitial inflammation with only mild tubulitis and no evidence of arteritis (Solez et al. 2008). In such cases, additional sampling may reveal diagnostic findings that are more definitive for acute TCMR, suggest resolving injury, or indicate sampling errors (Solez et al. 1993). For acute TCMR, cases are graded from I to III, with types I and II being subdivided into A and B subtypes (see Table 2). As mentioned, if at least some degree of arteritis is present, then a diagnosis of at least type II acute TCMR is warranted. A diagnosis of type III acute TCMR rejection is reserved for cases with severe transmural arteritis with or without fibrinoid change and necrosis of the arterial smooth muscle cells (Racusen et al. 2003; Solez et al. 2008). As noted previously, these changes can occur in concert with features of chronic rejection and ABMR.

Immunofluorescence Studies

Immunofluorescence (IF) microscopy utilizing antibodies against immunoglobulin components, light chains, complement components, and fibrinogen can be employed on fresh renal allograft biopsy tissue. If the light microscopic features are diagnostic for acute TCMR, IF may not be performed. However, if IF is pursued in cases of acute TCMR (or even ABMR), fibrinogen may be deposited within blood vessels, particularly if significant vascular injury is present. In the setting of thrombotic microangiopathy, fibrin thrombi can also be easily highlighted. If light microscopic findings are not definitive for acute TCMR or ABMR, immunofluorescence studies can be used to help evaluate for the presence of a recurrent or de novo glomerular disorder, which may be immune complex-mediated (Walker et al. 2004). As noted previously, some institutions perform an immunofluorescence stain for C4d as an alternative to traditional immunohistochemistry to support a diagnosis of ABMR (Solez et al. 2008; Haas et al. 2014).

Electron Microscopy

Electron microscopic (EM) evaluation of glutaraldehyde-preserved renal allograft biopsy tissue may be performed in some cases. If the light microscopic features are diagnostic for acute TCMR or other acute injury, EM may not be performed. Typically, if EM is done in the setting of acute TCMR, glomerular inflammatory cell infiltration (glomerulitis) may be demonstrated, along with interstitial inflammation, tubulitis, and arteritis. Previously suspected or unsuspected chronic changes, such as allograft glomerulopathy and multilayering of the peritubular capillary basement membranes, may be found, as well as evidence of an immune complex-mediated disorder with deposition of characteristic electron dense deposits (Racusen et al. 1999; Haas et al. 2014).

Chronic T Cell-Mediated Rejection (TCMR)

Some features of chronic TCMR may be difficult to distinguish histologically from other forms of allograft injury, such as chronic ABMR, hypertension, and therapy-related injury (Racusen et al. 1999). Changes of chronic TCMR and declining graft function may be expected if the patient has experienced any type of TCMR, particularly if late, or if the episodes of acute TCMR have been more severe with vasculitis (v) with or without accompanying ABMR (Wu et al. 2014). Light microscopic features are used to determine the presence and extent of chronic allograft injury, with the aid of special stains.

Vascular Changes

As might be predicted, vascular changes are a prominent histopathologic feature of chronic TCMR. Significant intimal fibrosis usually associated with varying degrees of luminal compromise and neo-intima formation (chronic allograft arteriopathy) is often seen. Such arterial lesions often show disruption of elastic lamina. Associated foam cells may be present along the intima beneath endothelial cells. Also, mononuclear cells may be seen within the wall,

particularly along the internal elastic lamina (Racusen et al. 1999; Solez et al. 2007).

Glomerular Changes

Glomerular changes of chronic TCMR may not be easy to distinguish from those seen in chronic ABMR, since these injurious mechanisms may occur concurrently in the same allograft. Transplant glomerulopathy is more often associated with chronic ABMR, and is manifest by reduplication of glomerular basement membranes and proliferative changes, often with a membranoproliferative pattern. Glomerular mononuclear cell infiltration may also be seen. These changes may be difficult to distinguish from chronic thrombotic microangiopathy. Glomerular basement membrane reduplication is most easily highlighted with PAS or silver stains (see Fig. 6). Confirmation of characteristic circumferential reduplication of glomerular basement membranes around glomerular capillary loops can be easily detected by electron microscopy (Solez et al. 2008; Haas et al. 2014).

Tubulointerstitial Changes

Chronic TCMR may result in tubular atrophy and interstitial fibrosis, although these findings are not specific. Tubular atrophy is highlighted with PAS stains, and interstitial fibrosis is accentuated with trichrome stains. Accompanying mononuclear cells, including lymphocytes and plasma cells, may also be present within the interstitium, along with mast cells.

Over the years, Banff classifications have relied on estimates of the percentage of parenchyma occupied by interstitial fibrosis and tubular atrophy. Grade I implies that less than 25% of the sampled cortex is involved; grade II is diagnosed when 26–50% of the cortex is involved; and grade III is diagnosed when greater than 50% of the cortical area is involved with interstitial fibrosis and tubular atrophy. Furthermore, these designations are ascribed only when no other etiology for the chronic features is determined (Solez et al. 2007). A recent study attempted to delineate a standardized method for evaluating chronic tubulointerstitial changes, given the interobserver variability in visually assessing tubular atrophy and interstitial fibrosis. Computer-assisted determination of collagen III staining by immunohistochemistry did show promise in this study (Farris et al. 2014). Of note, when evaluating the tubulointerstitial compartment, if significant numbers or clusters of plasma cells are seen, then acute ABMR should also be considered in the differential diagnosis, along with BK virus infection.

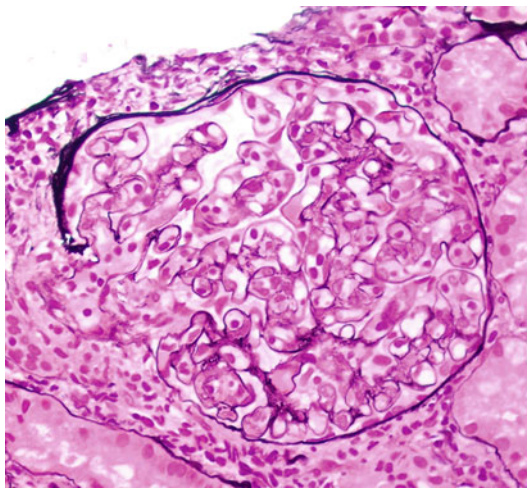

Fig. 6 Chronic transplant glomerulopathy. Focal splitting of the glomerular basement membranes is highlighted on this silver stain (PAM x400)

Infections

Immunosuppressed renal transplant patients are susceptible to both systemic and organ-limited infections of viral, bacterial, or fungal etiology. Viral pathogens, including polyoma virus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), can cause renal dysfunctions as also graft failure. Virus-induced allograft nephropathy and cellular, as also ABMR, rejection can coexist, giving rise to not only diagnostic, but also therapeutic challenges (Nickeleit and Mihatsch 2004; Celik et al. 2003).

Polyoma virus nephropathy (PVAN), a mainly iatrogenic complication resulting from use of high-dose immunosuppressive drugs, has seen a reduction in incidence from 10.5% to 2.5% with low-dose maintenance immunosuppression

(Cosio et al. 2007). Polyoma BK and JC viruses are associated with transplant nephropathy, with BK virus being the predominant virus. Morphological changes caused by these viruses include nuclear changes with inclusion bodies, cell injury, and rare granulomatous inflammation, commonly affecting ductal and tubular epithelium as also glomerular endothelial cells (see Fig. 7). The viral changes can be noted in both the cortex and medulla, but may be focal and missed on small biopsies. Diagnosis can be established by the presence of characteristic morphologic features or by using ancillary tests including immunohistochemistry, in situ hybridization, or polymerase chain reaction (PCR) (see Fig. 8). The BIFQUIT (Banff Initiative for Quality Assurance in Transplantation) multicentric trial evaluated the reproducibility of BK immunohistochemistry (IHC) at 60 institutions using central review adjudication as well as real-time BK virus PCR estimated loads as standards. Though PCR demonstrated superior sensitivity to IHC as expected, increasing concentrations of viral nucleic acid correlated well with staining intensity in the study, suggesting that BK virus IHC using heat retrieval, citrate or EDTA buffers, and monoclonal PAb416 antibody from Calbiochem (San Diego, CA) at a dilution of less than 1:100 for 25–35 min is a reproducible method for BK virus identification. Accurate viral load estimation in differentiation between BK and JC virus may still need additional PCR analysis (Adam et al. 2014).

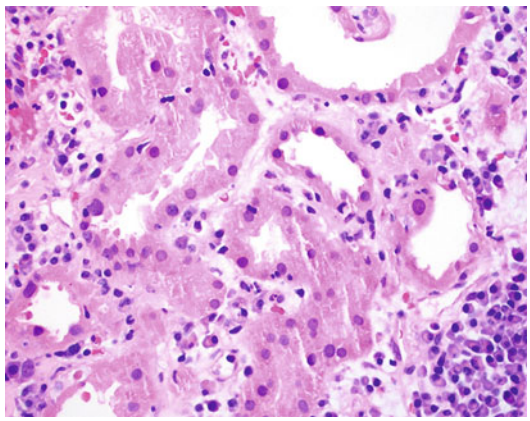

Fig. 7 Polyoma virus (BK) effect. Tubular epithelial cells demonstrate focal nuclear enlargement and atypia. The interstitium is occupied by a focally dense plasma cell infiltrate (H&E x400)

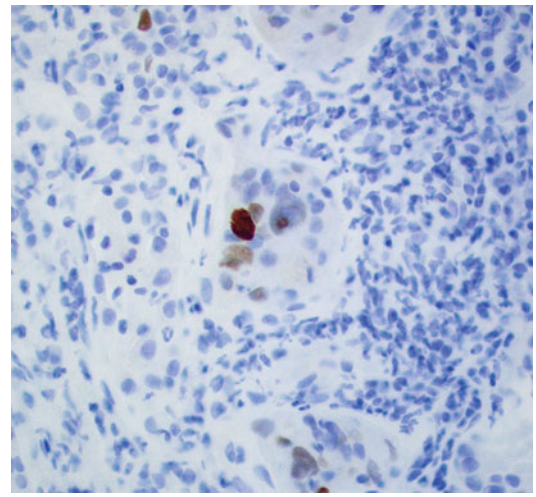

Fig. 8 Immunohistochemistry for SV40T antigen. Immunohistochemical stain for SV40T antigen shows strong nuclear staining within some tubular epithelial cell nuclei, consistent with BK virus infection (SV40T immunostain x400)

Cytomegalovirus (CMV) and adenovirus can cause symptomatic renal infections with defined pathologic features, including characteristic inclusions. CMV is more prevalent and pathological changes include cytopathic effects in nuclei and cytoplasm of tubular epithelial cells, endothelial cells, and also inflammatory cells. CMV-infected cells have a characteristic “owl’s eye” nuclear appearance, with occasional cytoplasmic inclusions identified as well. Techniques including IHC, in situ hybridization, and PCR can be used to detect CMV.

EBV is most commonly associated with post-transplant lymphoproliferative disorders (PTLD) in renal transplants. EBV-associated PTLD is commonly seen in patients on high-dose immunosuppression and in recipients with EBV seronegative status (Allen et al. 2013). The spectrum of PTLD can range from early reactive lymphocytic hyperplasia to monoclonal populations, eventually transforming into lymphomas of B cell, T cell, or Hodgkin’s type. Characteristic expansile infiltrates of activated lymphocytes can occasionally be mistaken for acute rejection.

However, PTLD infiltrates have a monotonous appearance with a paucity of other inflammatory cell types and may involve the capsule or perirenal tissue. IHC for B cell lineage and lack of CD3 and/or CD68 cells can help differentiate this infiltrate from that of rejection. ISH for EBV-encoded small nuclear RNA (EBER) is diagnostic on tissue biopsy sections (Allen et al. 2013).

Invasive fungal infections account for 5% of all infections in renal transplant patients and infections with *Aspergillus* species, *Mucorales* species, *Candida* species, and *Cryptococcus neoformans* are reported to cause most infections (Badiee and Alborzi 2011). Though these are usually systemic diseases, fungal or mycobacterial infection should be ruled out when granulomas are identified in renal allograft tissue.

Therapy-Induced Injury

As with native kidneys, renal allografts are susceptible to drug-induced injury. Injury due to immunosuppressive therapy is common and well-documented in the literature, although injury due to drugs, such as antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDS), is also encountered in renal transplant recipients.

Calcineurin Inhibitor (CNI) Toxicity

Use of calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, has afforded significant benefits to patients by impacting overall renal allograft survival. CNIs are used widely throughout the United States to suppress the immune response to renal allografts and reduce the number of episodes of acute rejection that patients experience. These immunosuppressive agents are not without toxic effects that can impact graft function and structure in significant ways. The most common pathologic manifestations of such toxicity are seen within the blood vessels, including glomeruli, and the tubulointerstitial compartment, and may be acute or chronic (Naesens et al. 2009).

Vascular Changes of CNI Toxicity

Vascular changes of CNI toxicity may be minor or clinically significant, and CNIs may impart acute or chronic effects. Subtle endothelial injury can be a minor acute vascular effect, while overt thrombotic microangiopathic injury with glomerular capillary and arteriolar fibrin deposition may be significant. In cases of severe acute vascular injury due to CNIs, histopathologic changes may be indistinguishable from other thrombotic microangiopathies and even ABMR (Williams et al. 2012). These vascular changes may have significant consequences to glomeruli, including membranoproliferative changes and necrosis (in the setting of thrombotic microangiopathy), capsular fibrosis, as well as segmental or global sclerosis. Significant chronic vascular changes may include hyaline deposition within arteriolar walls (hyalinosis), which often appears nodular, and can cause significant luminal narrowing (Naesens et al. 2009). Such arteriolar changes are easily highlighted on PAS stains (see Fig. 9).

Tubulointerstitial Changes of CNI Toxicity

As with vascular changes, tubular and interstitial changes due to CNIs may be acute or chronic. In the acute setting, isometric vacuoles can be seen within tubular epithelial cell cytoplasm (see Fig. 10). These represent dilated endoplasmic reticulum as viewed by electron microscopy. Typically, the proximal tubular epithelial cell brush borders remain intact, as highlighted on PAS stain. Occasionally, microcalcifications may be seen within tubule lumens in cases of longstanding CNI use, but this is not a specific finding. Within the interstitium, chronic changes are typically not specific either, but are an expected consequence of chronic vascular injury due to CNIs. Interstitial (striped) fibrosis is commonly seen, highlighted with trichrome stains. This name has been coined since the fibrosis is zonal, with more normal-appearing tubules alternating with fibrotic zones (Naesens et al. 2009).

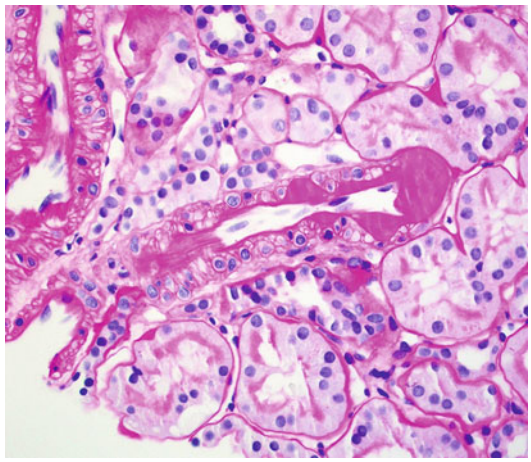

Fig. 9 Calcineurin inhibitor toxicity in arteriole. A PAS stain highlights the nodular aggregates of hyaline material within the wall of an arteriole, causing some luminal compromise (PAS x400)

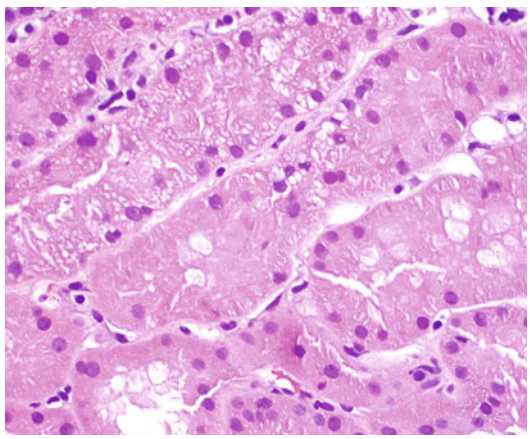

Fig. 10 Calcineurin inhibitor toxicity in tubules. Isometric vacuoles can be seen within tubules, consistent with calcineurin inhibitor toxicity. Note the prominent vacuoles in the *upper left hand corner* of the figure (H&E x400)

Other Therapy-Induced Injury

As with native kidneys, renal allografts are susceptible to acute interstitial nephritis induced by agents such as NSAIDS and antibiotics. In such cases, findings similar to those seen in native renal specimens can be seen, including lymphocytic and plasma cell interstitial infiltrates accompanied by eosinophils and neutrophils. However, these histopathologic findings may overlap with those seen in acute TCMR and ABMR. For that reason, careful histologic evaluation of the allograft specimen and appropriate clinical correlation are required, so as not to overlook acute rejection. The finding of non-necrotizing granulomas may be a clue that favors a diagnosis of drug-associated injury over acute TCMR, but associated infection should also be excluded (Hotta et al. 2012).

Neoplasia

Renal allograft recipients are at risk for developing malignancies at a rate higher than that of the general population, and this can be associated with increased morbidity and mortality. Means whereby these malignancies develop include those that are present in the recipient prior to organ transplantation, those that are donor-derived and are transplanted into the patient, and those malignancies that develop de novo in the recipient after transplantation (Stallone et al. 2015). A recent study by Farrugia et al. in England found that the most common cancer deaths in kidney transplant patients were attributable to lymphoproliferative disease, lung cancers, and kidney cancers, although a significant number of cancer deaths (18.6%) were due to unspecified malignancies. More studies are needed to determine the most appropriate immunosuppressive regimens that might ameliorate the risk of malignancy in renal transplant patients. Targeted surveillance for malignancies by transplant nephrologists and surgeons is strongly recommended (Farrugia et al. 2014).

As mentioned above, cases of PTLD include EBV-associated B cell (or less often T cell) proliferations, which may contain polyclonal or monoclonal lymphocytic populations. Common sites of PTLD in renal transplant patients include abdominal and pelvic lymph nodes, the renal allograft itself, and lymph nodes in the chest, as also the gastrointestinal tract and retroperitoneum. Clinical symptoms vary and PTLD can be difficult to diagnose. Histopathologic features, immunohistochemistry, flow cytometric studies, and molecular tests, as noted above, remain essential

to the diagnosis, and in differentiating neoplasia from acute TCMR (Morgans et al. 2010).

Recurrent and De Novo Disease

In addition to ischemic, immune, infectious, and therapy-associated insults, renal allografts are subject to both recurrent and de novo disease, both primarily affecting glomeruli. Recurrent and de novo disease may be seen simultaneously with any number of the aforementioned renal insults. For both recurrent and de novo disease, retransplantation may or may not be pursued, depending upon the disorder present (Ponticelli et al. 2014).

Recurrent Disease

Recurrent disease represents a significant number of graft failures over time, which might be expected, given the nature of many glomerular disorders and the fact that renal allograft transplantation replaces the target but does not impact the cause of many glomerular disorders. It seems obvious, but recurrent disease can only be recognized when the original disorder causing renal failure was diagnosed and characterized prior to renal transplantation. Furthermore, documentation of recurrence in the renal allograft typically requires thorough investigation with the aid of special stains, immunofluorescence and electron microscopy, and differentiation from other injuries suffered by the graft (Marinaki et al. 2013).

Common recurring disorders in renal allografts include focal and segmental glomerulosclerosis (FSGS), C3 nephropathies (including dense deposit disease/membranoproliferative glomerulonephritis (MPGN)), IgA nephropathy, and idiopathic membranous nephropathy, although other primary glomerular disorders can also recur, such as antiglomerular basement membrane (GBM) glomerulonephritis, antineutrophil cytoplasmic antibody (ANCA)-mediated disease, lupus nephritis, and diabetic nephropathy. Depending upon the disorder, recurrence may occur soon after transplantation or late (Marinaki et al. 2013). When recurrent, these disorders demonstrate histopathologic features very similar to those seen in the original manifestation of the disease. However, the course of the recurrent disorder may be altered, due to the use of immunosuppression in renal allograft recipients.

De Novo Disease

Any number of glomerular disorders can occur de novo within the renal allograft, and diagnosis thereof relies on evaluation of the renal allograft biopsy specimen with appropriate studies. More frequent de novo glomerular disorders encountered include minimal change disease, FSGS, membranous nephropathy, MPGN, and IgA nephropathy. De novo focal and segmental glomerular sclerosis (FSGS) may occur as a result of hyperfiltration injury or hypoperfusion, resulting in secondary type glomerular scarring. Interestingly, patients with de novo membranous nephropathy often lack autoantibodies to phospholipase A2 receptor (PLA2R), which is in contrast to patients with primary membranous nephropathy. Other de novo disorders might be expected to occur in specific patient populations, given the pathogenesis of the disorder. For example, patients with Alport syndrome, given their lack of specific α chains in type IV collagen, may manifest autoantibodies against the glomerular basement membrane, which can prompt antiglomerular basement membrane antibody-mediated disease. De novo diabetic nephropathy has been documented to occur in patients who develop diabetes mellitus after renal allograft transplantation. Other de novo disease of most types has been reported in the literature (Ponticelli et al. 2014).

Conclusion

Significant clinical improvements in the outcome of patients with chronic kidney disease have been made with the advent of renal allograft transplantation. Such allografts may experience a variety of insults, which may have

inconsequential or significant impact on graft function and patient morbidity and mortality. These insults range from ischemia to immunologic, infectious, therapy-induced, and neoplastic, and include recurrent and de novo disease. Patients must be closely monitored clinically, with the aid of laboratory evaluation, so as to detect even slight changes in allograft function. When warranted, procurement and appropriate interpretation of a renal allograft biopsy specimen can yield very helpful insights into the pathophysiologic mechanisms underlying allograft dysfunction. Use of special studies in the pathology laboratory can further augment histopathologic findings and direct the most appropriate therapeutic interventions, in efforts to assure optimal graft survival.

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Cross-References

- Immunology of Kidney Transplantation
- Infection in Kidney Transplantation
- Medical Complications After Kidney Transplantation: Early
- Medical Complications After Kidney Transplantation: Late
- Transplant Immunosuppression

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Radiology of Kidney Transplantation

Christopher G. Roth, Daniel J. Mizrahi, and Laurence Needleman

Contents

Abstract

Radiologic imaging procedures include a wide array of modalities and many are indicated in the diagnosis and treatment of renal transplant recipients and donors. In the renal donor candidate, CT is the optimal imaging modality for anatomic assessment and MRI is a potential alternative. CT is also utilized for the vascular evaluation of recipients at risk for peripheral vascular disease. Imaging modalities are central to the diagnosis and treatment of renal transplantation complications. Ultrasound (US) is the first-line imaging modality to evaluate allograft dysfunction with utility for identifying parenchymal and vascular complications, fluid collections, and urinary complications. While renal scintigraphy provides an alternative to US in assessing graft dysfunction and detecting these complications, CT and MRI serve an ancillary role. Interventional radiology procedures in the posttransplant setting include a variety of diagnostic and therapeutic procedures. Arteriography confirms arterial disease and precedes angioplasty/stenting for renal artery stenosis and

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embolization for arteriovenous fistula and pseudoaneurysm. Urologic complications are treated with procedures such as percutaneous nephrostomy, urinary stent placement, or stricture angioplasty. Image-guided fluid collection drainage is usually accomplished with ultrasound, reserving CT for cases in which a poor acoustic window limits US.

Keywords
Radiology · Ultrasound · Computed tomography · Magnetic resonance imaging · Nuclear scintigraphy · PET/CT · Interventional radiology · Renal transplantation

Introduction

Imaging figures prominently throughout the renal transplantation life cycle from donor and recipient workup to posttransplant surveillance and management. The noninvasive nature of most diagnostic procedures and minimally invasive nature of interventional procedures make radiologic techniques central to patient care.

Imaging utilization incurs cost and potential complications, depending on the modality, which do factor into the management approach (Fig. 1). X-ray plays an ancillary role in renal transplantation imaging – as a quick survey to identify or exclude gross complications. Computed tomography (CT) and ultrasound (US) constitute the core diagnostic imaging modalities in managing renal transplantation. CT employs an X-ray tube rotating within a gantry as a means to obtain a volume of image data reconstructed into axial images by convention, but easily reformatted into sagittal, coronal, or any oblique plane desired. Unenhanced CT images portray anatomy clearly, but lack contrast between visceral organs and other soft tissue densities. Tissue contrast is magnified with the administration of intravenous iodinated contrast material because normal and abnormal tissues exhibit different enhancement patterns (Fig. 2). Oral contrast, in the form of either barium or iodine suspension, is administered to isolate bowel from surrounding normal structures and fluid collections, abscesses, etc. The low risk, convenience, and speed of CT tend to preempt consideration of the potential downsides – ionizing radiation, cost and potential nephrotoxicity, and allergic reactions related to iodinated contrast media. However, nephrotoxicity risk only mounts with advanced renal dysfunction and only relevant with an estimated glomerular filtration rate (eGFR) of less than 30–45 mL/min/1.73 m^2 (Davenport et al. 2013).

US has no adverse side effects at a lower cost. Additionally, the native and transplant kidneys – in addition to other visceral organs – are well-imaged sonographically. The major caveat is the operator-

Modality	Cost	Radiation	Nephrotoxicity	Other Side Effects	Imaging Medium
X-Ray	+	+	None	None	Ionizing radiation
Ultrasound	++	-	None	None	Sound waves
CT	+++	+++	+ (eGFR >/= 40-45 poses minimal risk)	Contrast allergy	Ionizing radiation
MRI	++++	-	None	Interaction with implanted devices and ferromagnetic objects; NSF in ESRD; contrast allergy	Radiofrequency waves in a strong magnetic field
NM	+++	+++	None	None	Gamma rays
IR	+++++	+++	+	Bleeding, organ injury, infection (depending on the procedure); contrast allergy	Ionizing radiation and/or sound waves

Fig. 1 Imaging modalities in renal transplantation

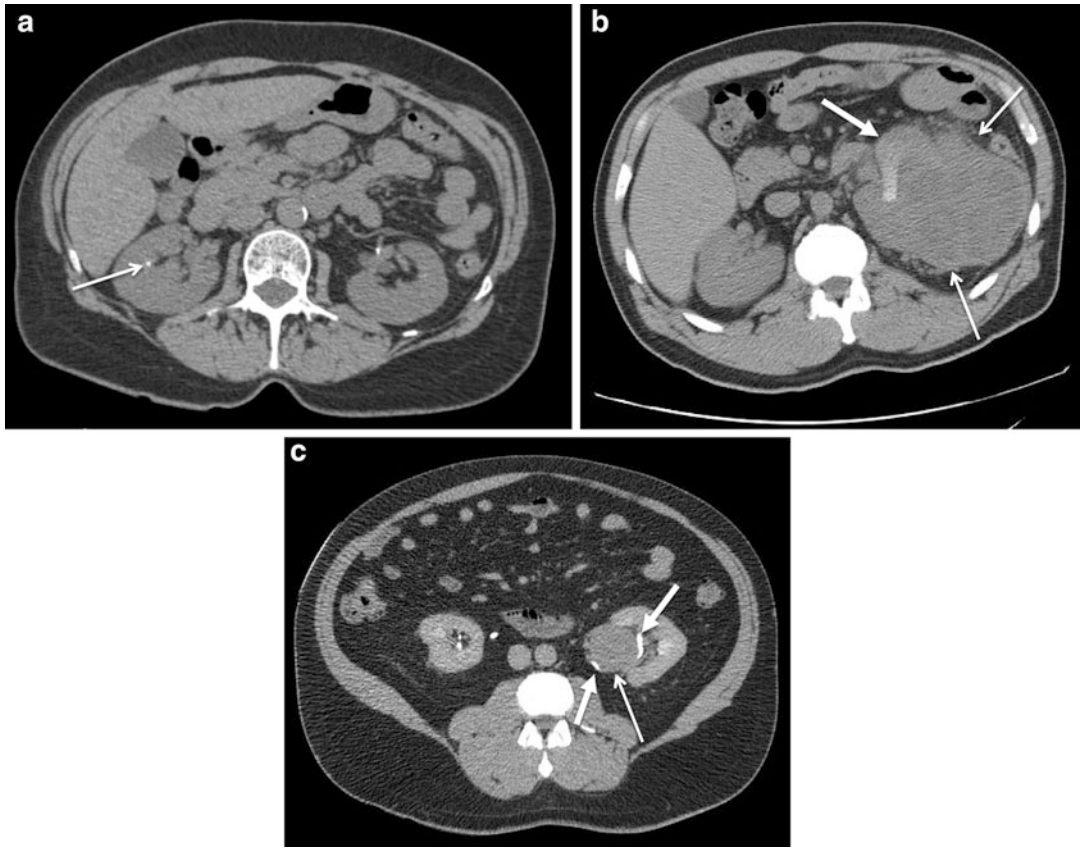


Fig. 2 Examples of CT images. (**a**) An axial image from a CT of the abdomen and pelvis without either oral or intravenous contrast shows a punctate, nonobstructing right renal calculus (*arrow*). (**b**) Another unenhanced CT image in a different patient with a chromophobe-type RCC demonstrates a large, heterogeneous mass (*arrows*) replacing the left kidney; hyperdense material in the left renal collecting system (*thick arrow*) represents excreted gadolinium from a preceding MRI. (**c**) The axial post-contrast pyelographic phase image in a another patient with a chromophobe-type RCC shows a small, exophytic mass (*arrow*) extending into the renal hilum displacing the renal collecting system (*thick arrows*)

dependency of US; obtaining diagnostic US images requires mastery of the modality and of the relevant anatomy. Also, generating diagnostic US studies is fairly time-consuming (exam duration ranges from 15 or 20 min to 45 min, depending on the type of study) and requires careful attention to technique. US technical considerations include optimal position and machine settings, understanding when and how to use Doppler US including how to sample vessels and measure various parameters correctly (e.g., velocity, resistive index, acceleration, etc.). Nonetheless, US is the first-line imaging modality for most indications.

While ultrasound is the first-line modality to evaluate renal allograft failure, renal scintigraphy is a potentially useful alternative posing no threat to the allograft. Renal scintigraphy involves the intravenous administration of a radioisotope, which emits gamma rays detected with a gamma camera, yielding images that illustrate the distribution of the radioactive agent. Serial images are obtained over the course of approximately 30 min and used to assess arterial perfusion, followed by parenchymal uptake and excretion.

Magnetic resonance imaging (MRI) plays an ancillary role in the setting of renal transplant imaging, although it offers advantages by avoiding ionizing radiation and nephrotoxicity. Its relatively high cost and the availability and diagnostic accuracy of other modalities generally relegate MRI to the role

of problem-solving. While gadolinium contrast agents pose no risk of nephrotoxicity, in the setting of end-stage renal disease (ESRD) and acute renal injury, gadolinium contrast agents potentially risk nephrogenic systemic fibrosis (NSF). However, the greater stability of modern gadolinium agents mitigates this risk. Virtually all reported cases of NSF were associated with older contrast agents (Thomsen et al. 2013; Morcos 2014; Yang et al. 2012). Notwithstanding, ESRD with eGFR below 30 constitutes a relative contraindication to gadolinium administration. Most NSF cases have occurred with eGFR levels below 15 (ACR 2013).

Interventional radiology (IR) provides a wide array of procedures for diagnostic and therapeutic management of renal transplantation (Fig. 3). These procedures are generally performed with image guidance – either ultrasound, CT, or fluoroscopy (and many modern IR suites also feature rotational angiography, or cone beam CT, which generates 3D CT-like images). Diagnostic IR procedures include renal biopsy, percutaneous nephrostography (to identify the site of a urinary leak), percutaneous catheter-directed angiography to identify and characterize vascular complications, and percutaneous fluid collection aspiration. Many of these procedures offer concurrent treatment strategies: drainage of fluid collections, diversion of flow in urinary leaks, transcatheter embolization of vascular injuries, and angioplasty of renal artery stenosis (RAS).

Renal Donor Imaging

While renal transplant recipients have many imaging needs, imaging plays a crucial role in the preoperative management of the renal transplant donor. Anatomic characterization is the chief imaging objective in the donor to determine the kidney more safely transplanted. Vascular anatomic considerations figure prominently in the surgical approach and the Organ Procurement and Transplantation Network (OPTN) sanctions the use of CT, MRI, or angiography for the anatomic donor workup (OPTN 2016). Both CT and MRI accurately depict arterial and venous anatomy. The occasional missed small accessory renal artery is less common with newer technology (Rankin et al. 2001; Kawamoto et al. 2003). The superior spatial resolution of CT explains its wider acceptance for preoperative renal donor assessment (Singh and Sahani 2008). The CT protocol involves several series before and after intravenous contrast administration in order to assess the parenchyma, vascular structures, collecting systems and ureters, and other relevant factors (i.e., stones and extraurinary findings). Noncontrast scan of the abdomen and pelvis is followed by an acquisition obtained during arterial enhancement and a third minutes later during the excretory phase. The precontrast phase image set detects renal calculi and serves as a reference standard to determine the degree of enhancement of renal tissue and unexpected lesions. The arterial-phase image set

Procedure	Objective
Arteriography	Renal/iliac artery stenosis: diagnosis and treatment (angioplasty and stenting)
	Pseudoaneurysm and AVF: diagnosis and treatment (superselective embolization)
Percutaneous nephrostomy	Urinary obstruction: diagnosis, drainage and treatment (angioplasty)
	Urinary leak: diagnosis, urinary diversion and treatment (nephroureteral stent)
Image-guided percutaneous biopsy (usually US)	Diagnosis of graft failure
Image-guided drainage of fluid collections	Diagnosis and treatment

Fig. 3 Interventional radiologic procedures in renal transplantation

demonstrates arterial anatomy and renal tissue enhancement and the delayed-phase image set highlights the renal collecting system, ureters, and bladder. Venous anatomy is depicted on all images sets (some favor adding an acquisition between the arterial- and delayed-phases at the cost of adding ionizing radiation exposure). Vascular and urographic anatomy is optimally displayed with the benefit of image postprocessing in the forms of 3D volume-rendered angiographic, maximal intensity projectional (MIP), and curved planar reformatted images (Fig. 4).

CT imaging provides information regarding various potential donor contraindications and considerations regarding the surgical approach (Fig. 5). Parenchymal features excluding donation include: unilateral agenesis, horseshoe kidney (Fig. 6), cortical atrophy, polycystic disease, medullary sponge kidney, and papillary necrosis (Sebastià et al. 2010). Other features inform presurgical planning, such as relative kidney size (discussed further in the volumetry section), renal ectopia, and ureteropelvic junction (UPJ) stenosis. Renal arterial anatomy and anatomic variations influence the surgical approach and require image postprocessing software to characterize and illustrate to guide surgery. While 71% of kidneys have single renal artery supply, 24% have dual supply, and the remaining 5% with more than two renal arteries are not suitable for transplantation, except when one of three arteries is a small superior polar artery less than 2 mm in diameter (because only a small segment of tissue is sacrificed). Lower polar vessels often supply the

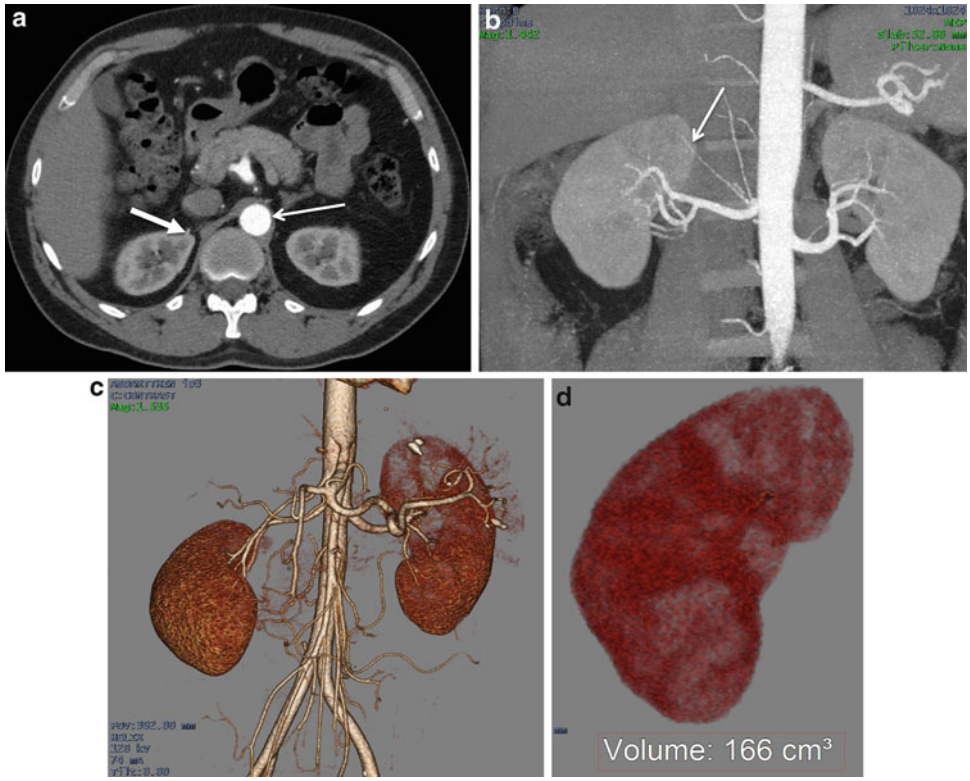


Fig. 4 CT images in preoperative renal donor transplantation. (**a**) The axial image from a CTA in a renal transplant donor candidate shows avid aortic enhancement (*arrow*) and a small transcortical penetrating arterial branch to the right renal upper pole (*thick arrow*). (**b**) The corresponding maximal intensity image demonstrates the course of the small right upper polar branch to better advantage (*arrow*). (**c**) A 3D volume-rendered postprocessed image in a different patient provides an overview of the arterial and renal anatomy. (**d**) From the CTA image dataset, using dedicated software, the kidneys are extracted and renal volumes are calculated

Absolute Contraindications	Surgical Considerations
Significant unilateral atrophy	Renal location and size
Horseshoe kidney	Number of renal arteries and veins
Solitary kidney	Types of accessory arteries
Polycystic disease	First arterial segmentary bifurcation
Significant atherosclerotic disease	Renal venous anatomy/anomalies
Fibromuscular dysplasia	Presence of arterial disease
Renal tumors	Number/location/size of renal cysts and angiomyolipomas
Extensive nephrolithiasis	Number/location/size of renal calculi
Active infection	Number/location/size/stage of renal tumors
More than 2 or 3 renal arteries	Upper urinary tract evaluation

Fig. 5 Imaging objectives in the renal transplant donor workup

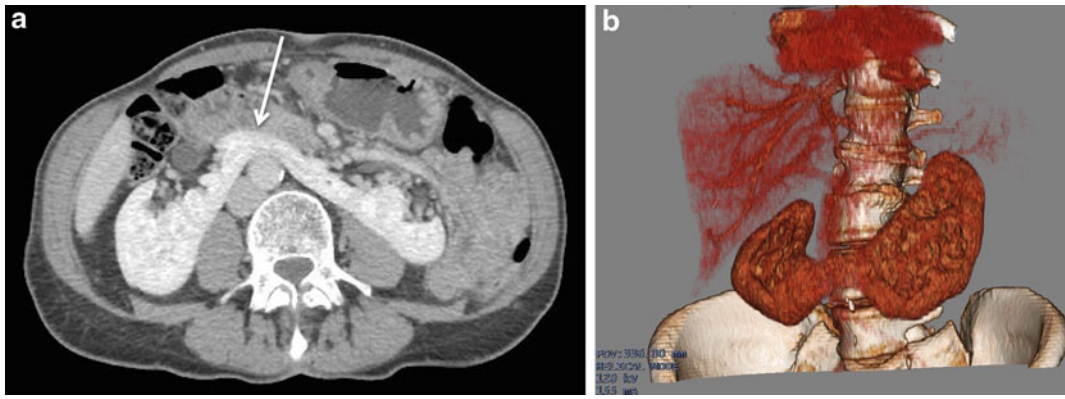


Fig. 6 Horseshoe kidney. (**a**) Axial postcontrast CT image shows a horseshoe kidney with enhancing renal tissue (*arrow*) interconnecting the two moieties anterior to the aorta and IVC. (**b**) 3D volume-rendered postprocessed image provides an anatomic overview of the horseshoe kidney and surrounding anatomy

upper urinary tract (Uflacker 2006). With multiple renal arteries, the largest caliber is the main renal artery and the other(s) is/are accessory arteries (Türkvatan et al. 2009). With dual arterial supply, the ostial-bifurcation segment length of each vessel factors into the decision to favor end-to-end or side-to-side anastomosis over double arterial anastomosis to the recipient iliac artery. Arteries less than 3 mm in diameter are technically challenging and experience worse outcomes post-anastomosis with a higher incidence of thrombosis. Segmentary bifurcation anatomy has surgical implications and three measurements on CT images help to inform the surgical approach:

1. Right renal artery origin to first segmentary bifurcation
2. Right lateral inferior vena cava (IVC) margin to first segmentary bifurcation
3. Left renal artery origin to first segmentary bifurcation

Retrocaval right segmentary anatomy – with a prevalence of 10–12% (Kawamoto et al. 2004) – complicates the surgical approach because of the threat of vascular injury. For this reason, early, retrocaval right renal artery bifurcation is tantamount to dual artery supply, from a surgical standpoint; the same is true of the left renal artery

with bifurcation within 1–1.5 cm of the origin (Fig. 7).

Another renal artery anatomical characteristic to consider is the entry point, either: (1) hilar (most common), (2) polar, or (3) capsular, surrounding the kidney (Fig. 8). Small upper polar arteries below the size threshold (2 mm) for successful anastomosis are safely sacrificed because of the small volume of infarcted tissue – less than 10% (Satyapal et al. 2001). However, sacrificing lower polar arteries is contraindicated by the fact that they often provide supply to the upper collecting system, threatening pyeloureteral necrosis when ligated or thrombosed. Capsular

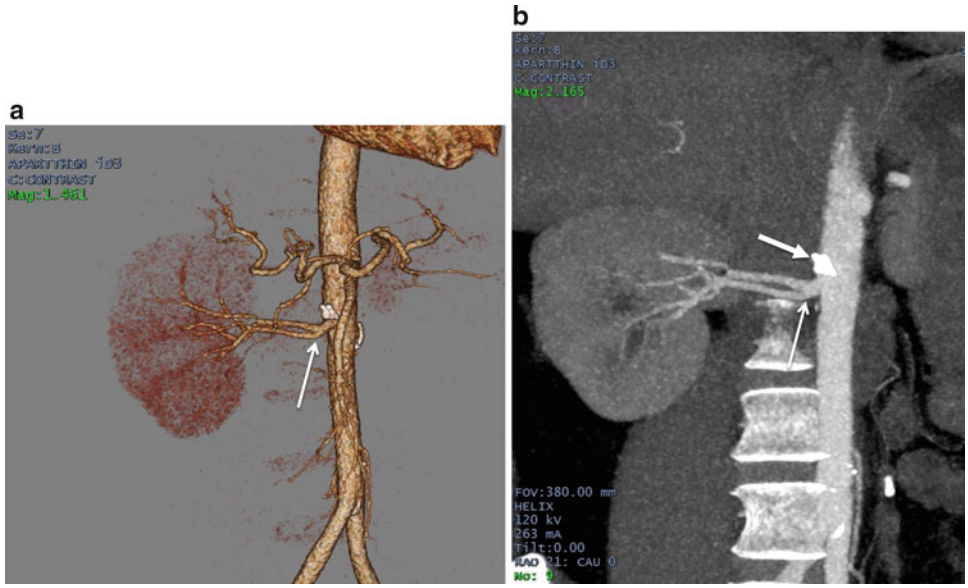
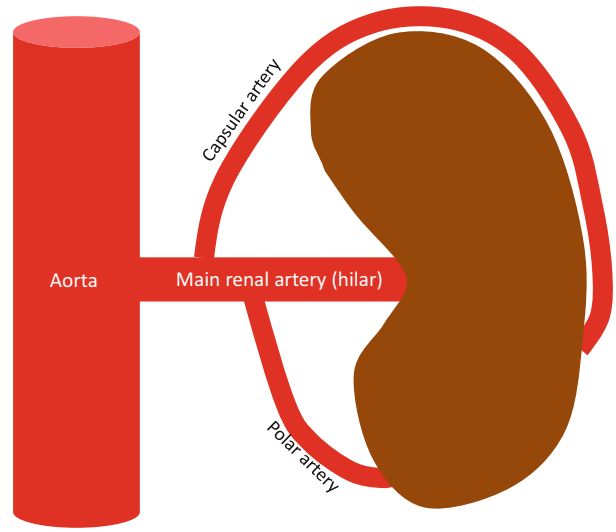


Fig. 7 Early renal artery branching. (**a**) 3D volume-rendered image from a CTA in a patient post left nephrectomy demonstrates a single right renal artery with an early bifurcation (*arrow*) just beyond the ostium. (**b**) The corresponding maximal intensity projection image from the same CTA in a similar projection shows the early bifurcation (*arrow*) and adjacent surgical clips (*thick arrow*)

Fig. 8 Renal artery types



arteries perfusing the renal capsule are generally even smaller than polar arteries and course tangentially around, rather than into, the renal parenchyma. Capsular arteries generally perfuse little to no parenchyma and are ligated without consequence (Pozniak et al. 1998).

Intrinsic renal artery diseases affect the approach to renal donor harvesting. Atherosclerotic disease usually afflicts the origin and/or proximal segment of the main renal artery. Detecting significant atherosclerotic disease preoperatively may lead to intraoperative endarterectomy. Additionally, heavily calcified renal artery or aortic plaque threatens intimal laceration and life-threatening bleeding when clamped. Fibromuscular dysplasia (FMD) – a potentially stenosing arteriopathy – involves the mid and more distal renal arteries with a prevalence of 3.5–6% in living-renal donors (Edwards et al. 1992; Linder et al. 1989; Spring et al. 1979; Andreoni et al. 2002). CTA and MRA achieve sensitivity for FMD approaching 100% by demonstrating the "string-of-pearls" appearance, which refers to the alternating dilated and stenotic segments, along with focal stenoses and aneurysms involving the mid and/or distal renal artery and segmental arteries (Fig. 9). DSA secures the diagnosis in equivocal cases. Bilateral FMD contraindicates transplantation – unilateral FMD deserves circumspection and potentially venous grafting or other arterial reconstructive techniques (Balzer et al. 2007; Pfeiffer et al. 2002; Blondin et al. 2010).

Renal venous anatomy also plays into renal donor surgical planning, and CT and MRI demonstrate renal venous anatomy accurately. Renal venous anatomic variation occurs much more commonly than arterial variation (Pérez et al. 2013). The renal cortex drains successively into stellate, arcuate then interlobar veins, which anastomose, usually forming the superior and inferior venous trunks, which merge draining into the main renal vein, usually situated anterior to the artery at the renal hilum (Fig. 10). Multiplicity is more common in the right renal vein, present in 15–30% of the population (Harrison et al. 1978; Abrams 1983). However, the left renal vein often receives multiple tributaries along its longer course to the IVC. A circumaortic configuration is the most common left-sided variant with a prevalence of 17% (Fig. 11) (Urban et al. 2001). The pre- and retroaortic limbs either arise from separate hilar veins or from a single hilar vein that splits before encircling the aorta. The left-sided retroaortic variant occurs in 3% of the population and usually courses caudally, draining into the lumbar IVC and less commonly the iliac vein (Kahn 1973; Chai et al. 2008; Kawamoto and Fishman 2006).

Renal venous measurements relevant to surgical planning include:

1. Right renal venous segmentary confluence to the IVC
2. Left renal venous segmentary confluence to the IVC
3. Left renal venous confluence to the left aortic margin

The lengths of the left and right renal veins average 8.5 cm and 2–2.5 cm, respectively (Cuttino and Clark 1990). The left kidney is favored because of the longer course of the left renal vein and, unlike the difficulty with the retrocaval arterial approach, transecting the left renal vein in front of the aorta is not problematic. However, unlike the right renal vein, the left renal vein receives numerous tributaries, including the adrenal, gonadal, hemiazygous, ascending lumbar, and lumbar veins. Large tributary veins (>5 mm) often require modifications to the standard surgical approach (Türkvatan et al. 2009).

Another reason to favor CT over MRI in the transplant donor workup is the superior sensitivity of CT for stones, which is virtually 100% (Smith et al. 1996; Fowler et al. 2002). MRI demonstrates the secondary findings of perinephric edema and periureteral edema vividly in the setting of obstructive urolithiasis, the sensitivity to non-obstructing renal stones is mediocre and much lower than CT (Sudah et al. 2001; Lipkin and Preminger 2013; Regan et al. 2005). The utility of CT lies in the fact that virtually all renal calculi attenuate X-rays much more than the surrounding renal parenchyma and all other tissues, with the exception of the skeleton (Figs. 2 and 12) (Saw

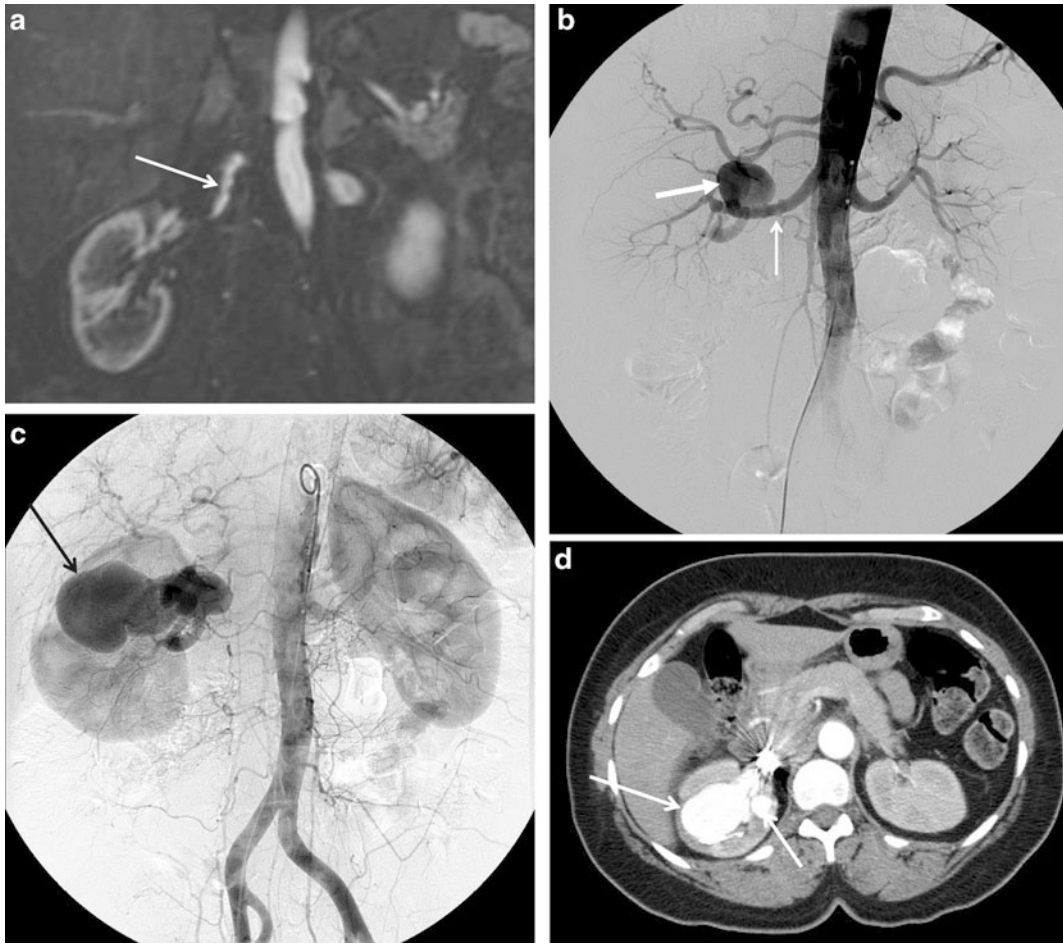


Fig. 9 CTA and MRA of fibromuscular dysplasia. (**a**) The T1-weighted, fat-suppressed postcontrast MRA image shows beaded irregularity of the right renal artery (*arrow*). (**b**) The image from an catheter-directed arteriogram also reveals the beaded appearance of the right renal artery (*arrow*) and an aneurysm arising from the right renal artery (*thick arrow*). (**c**) A more delayed image from the arteriogram reveals another larger renal artery aneurysm (*arrow*). (**d**) The CTA image shows the renal artery aneurysms (*arrows*) demonstrating enhancement equivalent to the aorta

et al. 2000). Kidneys with small asymptomatic renal calculi (<4 mm) are safely harvested, while larger and symptomatic calculi require treatment (Martin et al. 2007).

CT and MRI detect renal masses with high sensitivity and relatively high specificity. Renal cysts are encountered very frequently and pose no barrier to transplantation (Grotemeyer et al. 2009). Cysts appear hypodense compared with normal renal parenchyma and exhibit no enhancement or complexity (i.e., mural nodularity or septation) (Fig. 13). While the appearance is unmistakable in larger lesions, with small size (<15 mm), distinguishing cystic versus solid composition on CT is challenging because of "pseudoenhancement," where an increase in lesion density following contrast administration is induced by artifactual phenomena, rather than true enhancement (Maki et al. 1999; Wang et al. 2008). Correlation with either US or MRI is useful because both modalities characterize small renal lesions accurately (Lingard and Lawson 1979; Einstein et al. 1995; Zagoria 2000; Ho and Choyke 2004; Nikken and Krestin 2007). Sonographically, simple cysts conform to spherical, uniformly anechoic (dark) lesions with

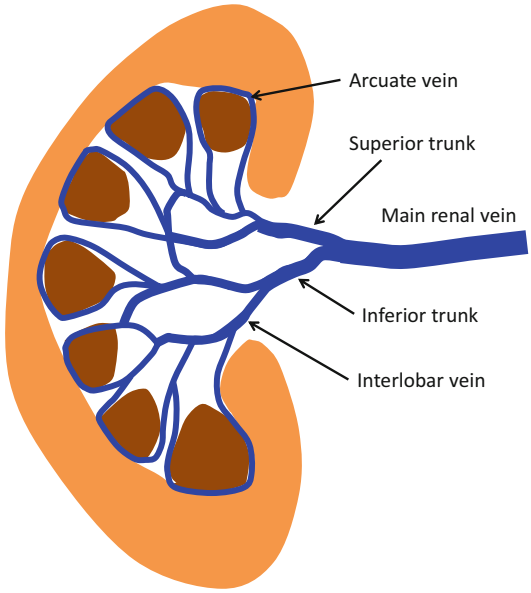


Fig. 10 Renal venous anatomy

acoustic enhancement (increased transmission of sound waves distally, which brightens tissues deep to the cyst) and a thin, barely perceptible wall. Simple cysts demonstrate marked hyperintensity matching other fluid-filled structures (i.e., gallbladder, thecal sac) on T2-weighted MRI images with corresponding T1-hypointensity and lack of enhancement (Fig. 13). When simple cysts are complicated by hemorrhage, infection, or inflammation, the imaging appearance changes. However, the common denominator of simple and complicated cysts is lack of vascular flow and enhancement. Sonographically, complicated cysts contents are hypoechoic (as opposed to anechoic) and/or septated, potentially with a thickened wall. Septation is also an occasional complicated cyst feature on CT and MR images and hemorrhagic or proteinaceous contents appear relatively CT hyperdense. Hemorrhage and protein convert

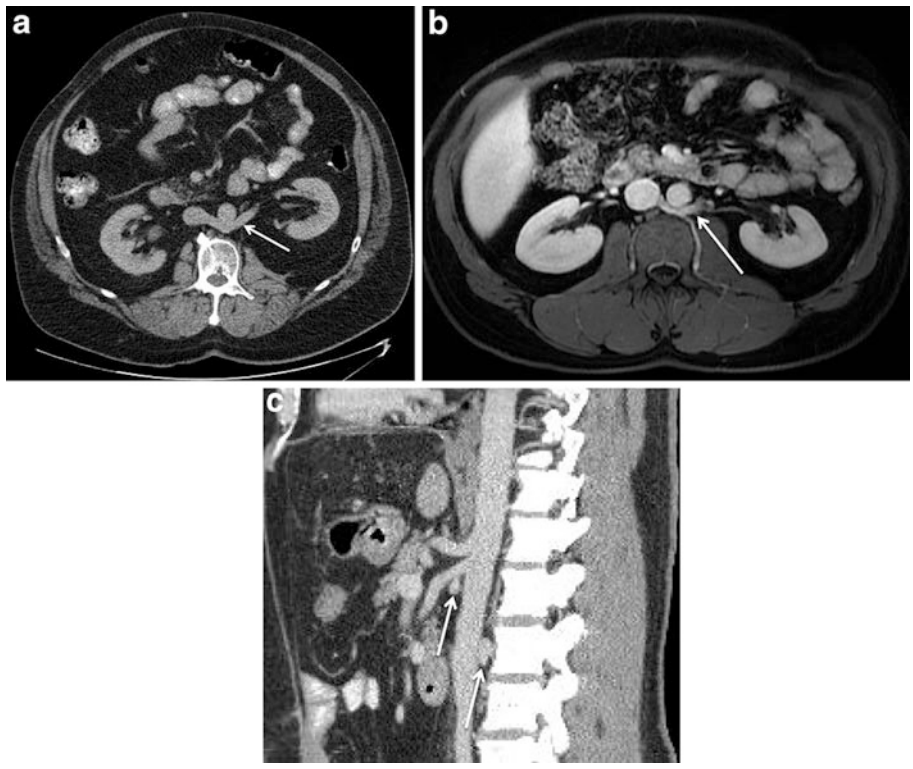


Fig. 11 Renal venous anomalies. (**a**) Axial postcontrast CT image shows a retroaortic left renal vein (*arrow*). (**b**) In a different patient, the T1-weighted, fat-suppressed postcontrast MR image shows a retroaortic limb (*arrow*) of a circumaortic vein. (**c**) The sagittally reformatted image shows both limbs of the circumaortic left renal vein (*arrows*) surrounding the aorta

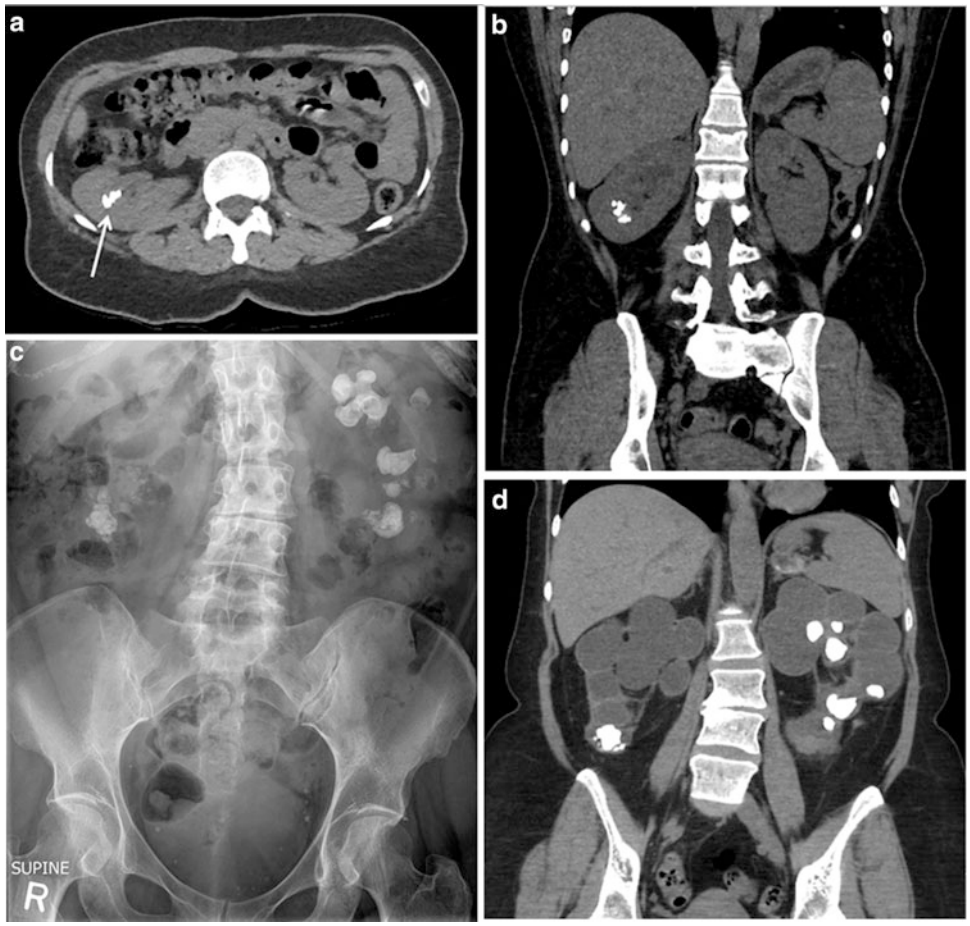


Fig. 12 CT of renal calculi. (**a**) Axial unenhanced CT image shows multiple calcified stones in the right renal collecting system (*arrow*) with no stones in the left kidney. (**b**) The coronally reformatted CT image shows the stones in the right renal lower polar collecting system and right renal hydronephrosis. (**c**) Supine X-ray in a different patient reveals multiple large calcifications projected over the renal shadows bilaterally. (**d**) The corresponding coronally reformatted CT image shows the value of tomographic imaging by revealing the underlying polycystic renal disease, in addition to the renal calculi

simple fluid MR signal characteristics from T1-hypo- and T2-hyperintense to the opposite pattern – T1-hyper- and T2-hypointense with or without a fluid-fluid level (Fig. 13).

Neoplastic cysts must be differentiated from complicated nonneoplastic cysts because of the prognostic and management implications. Luckily, only a small minority of renal neoplasms appears truly cystic on imaging studies – approximately 10–15% (Koga et al. 2000; Harisinghani et al. 2003). The Bosniak renal cyst CT classification system was devised in an effort to standardize and stratify management based on the likelihood of malignancy (Fig. 14) (Bosniak 1986; Curry et al. 2000; Siegel et al. 1997; Koga et al. 2000). The Bosniak classification system classifies renal cystic lesions from I to IV based on the degree of complexity. With increasing complexity – thicker septations, wall thickening, wall and/or septal enhancement – the risk of malignancy increases. With increasing malignancy risk, management escalates from none to imaging surveillance to ablative or surgical treatment.

The clear cell renal cell carcinoma (RCC) histologic subtype accounts for most renal cystic neoplasms, and 10–15% of RCCs are cystic

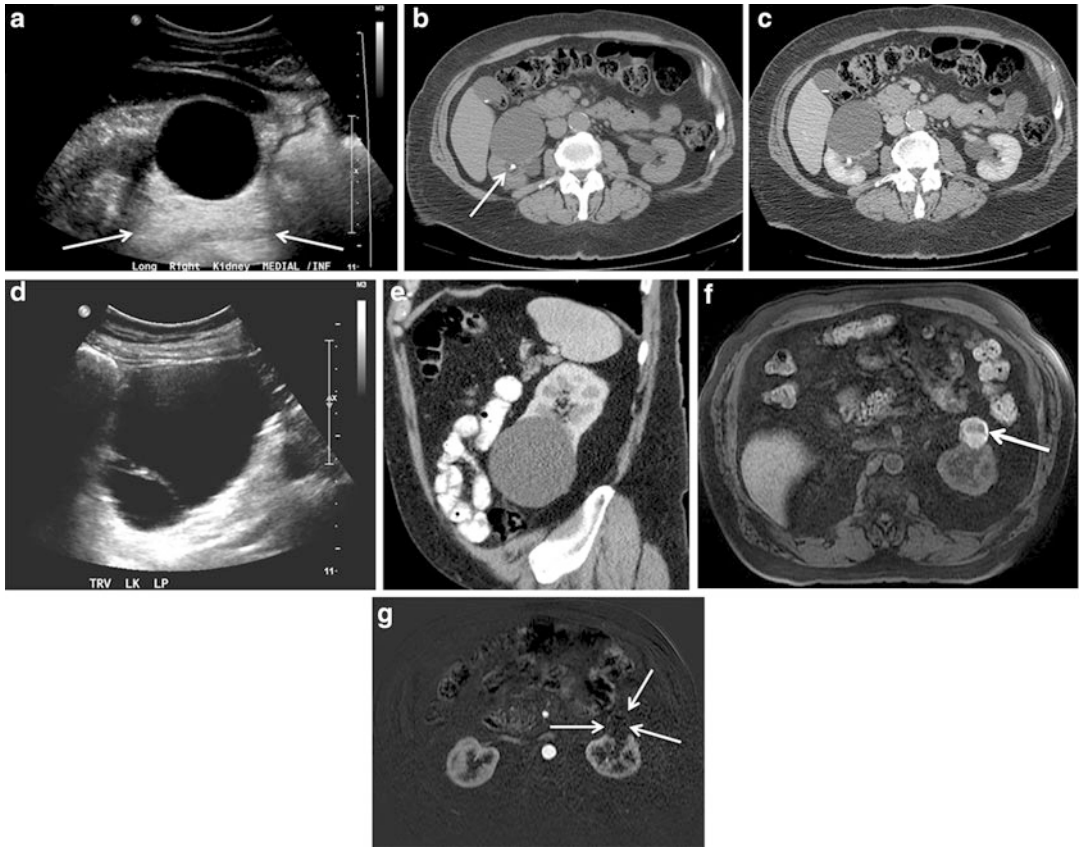


Fig. 13 Imaging of simple and complicated renal cysts. (**a**) Longitudinal sonographic image of the left kidney reveals a simple, unilocular, exophytic, uniformly anechoic cyst with acoustic enhancement (*arrows*) and an imperceptible wall. (**b**) The unenhanced CT image shows uniform fluid hypodensity within the cyst with an adjacent nonobstructing calculus (*arrow*). (**c**) The postcontrast CT image demonstrates absent enhancement within the cyst. (**d**) Transverse sonographic image in a different patient shows a large left renal cystic lesion with an irregular thickened septation. (**e**) The corresponding sagittally reformatted postcontrast CT image demonstrates lack of enhancement, which relegates this cystic lesion to Bosniak Category IIF. (**f**) Axial T1-weighted, fat-suppressed MR image in a different patient reveals an exophytic lesion (*arrow*) arising from the left kidney with hyperintensity that indicates hemorrhage. (**g**) The postcontrast subtracted image reveals no enhancement within the lesion (*arrows*) confirming the cystic and nonneoplastic nature of the lesion

(Sun et al. 2009; Prasad et al. 2006). When even mostly cystic, cystic RCCs generally harbor perceptible enhancing nodules or septa or wall thickening and enhancement. The rare multilocular cystic RCC is the only consistently cystic RCC histologic subtype with a typical multilocular appearance with asymmetry of the intervening septa, simulating the multilocular cystic nephroma (MLCN). However, the demographic patterns diverge with the multilocular cystic RCC favoring males with a mean age of 51 and MLCN demonstrating a bimodal distribution – males aged 3 months to 4 years and females in the 5th to 6th decades (Chowdhury et al. 2013; Freire and Remer 2009). Herniation into the renal pelvis is a distinctive feature of MLCN (Kettritz et al. 1996).

While cystic lesions only occasionally imply malignancy, solid lesions detected radiographically are generally malignant RCC (Silverman et al. 2008). The prevalence of solid benign lesions identified radiographically is fairly low – 12.8% in a series of 2770 cases –and oncocytomas and angiomyolipomas (AMLs) constitute most of the benign lesions. With smaller size, benignity

Category	Description	Imaging Features	Malignancy Risk	Management
I	Simple cyst	Imperceptible wall with fluid contents	0%	None
II	Minimally complicated cyst	Minimal septations without enhancement; thin calcifications	0%	None
IIF	Mildly complicated cyst	Mildly thickened septations; thickened or nodular calcifications	5%	Imaging surveillance
III	Complex cyst	Thickened or nodular septa or wall	55%	Ablation or partial nephrectomy
IV	Cyst with solid components	Enhancing soft tissue components	100%	Ablation or partial or total nephrectomy

Fig. 14 Bosniak classification of renal cystic lesions

becomes more likely: 25% <3 cm, 30% <2 cm, and 44% <1 cm (Frank et al. 2003). Small size also confers a relatively good prognosis for malignant lesions, especially when less than 3 cm (Rendon et al. 2000; Remzi et al. 2006). The only benign lesion diagnosed reliably on imaging studies is the AML due to its fat content. The AML typically appears hyperechoic sonographically because of its fat content and also hemorrhage and heterogeneous architecture (Raghavendra et al. 1983; Scheible et al. 1978; Lee et al. 1978; Bosniak 1981). While this appearance is suggestive, small RCCs often demonstrate increased echogenicity, which often prompts further evaluation with CT or MRI. CT and MRI demonstrate fat easily, as CT hypodensity less than water/fluid and MRI T1 and T2-hyperintensity suppressing with fat saturation (Fig. 15). The exception is the rare lipid-poor AML (representing 5% of cases), which simulates RCC (Yang et al. 2013; Sant et al. 1984; Jinzaki et al. 1997).

The appearances of other solid renal neoplasms generally overlap too frequently to confidently differentiate between them. As such, curative treatment –surgery or ablative techniques – is the standard for solid renal neoplasms detected radiographically. However, because with small size the frequency of benign neoplasms increases and the aggressiveness of RCCs decreases, conservative management with imaging surveillance becomes more justifiable. Management strategies provide for imaging follow-up for lesions ranging from 1 to 3 cm. While RCC historically contraindicated transplantation, recent experience following partial nephrectomy offers promise (Ali et al. 2012; Meyyappan et al. 2012; Zhang et al. 2014). While lesion imaging patterns often differ, the features lack adequate specificity and enhancement on CT or MRI is the common denominator. Once a solid, enhancing renal lesion is identified, the next step in the imaging evaluation involves staging – assessing the renal veins and IVC for vascular invasion, the retroperitoneum for lymphadenopathy (lymph nodes greater than 1 cm in short axis diameter), and surrounding organs for metastatic spread.

Urinary tract disorders deserve attention because some contraindicate transplantation and others affect surgical planning. For example, hydronephrosis, papillary necrosis, medullary sponge kidney, and urothelial neoplasms contraindicate transplantation. Complete and partial ureteral duplication and ureteropelvic junction (UPJ) obstruction are important to detect and characterize presurgical planning. While ultrasound depicts pyelocalyceal distention in the setting of obstruction, identification, and characterization of other collecting system and ureteral disorders are better demonstrated on CT and MRI. Excreted contrast during the pyelographic phase after intravenous contrast administration (on both CT and MR

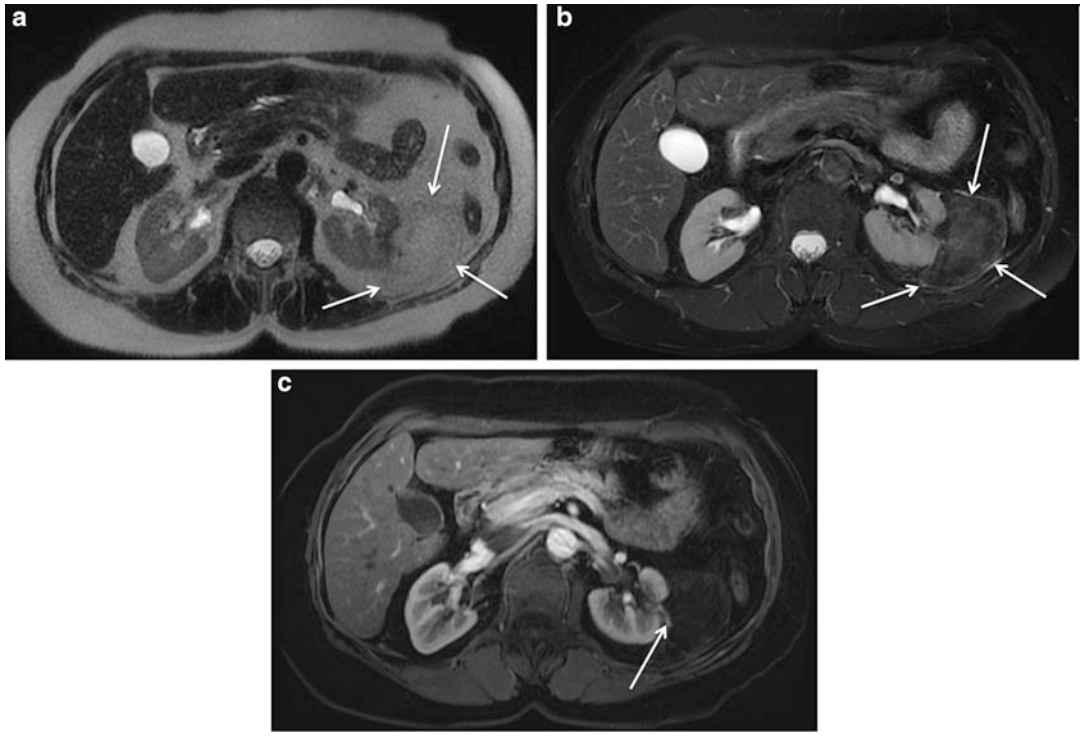


Fig. 15 Angiomyolipoma. (**a**) The axial T2-weighted image shows an exophytic lesion arising from the lateral aspect of the left kidney (*arrows*) with signal intensity matching retroperitoneal and subcutaneous fat. (**b**) The fat-suppressed T2-weighted image demonstrates virtual complete elimination of signal from the lesion (*arrows*) confirming fat content and the etiology of angiomyolipoma. (**c**) The fat-suppressed, T1-weighted, arterial phase postcontrast image also reveals hypointensity equal to fat with a prominent, dysplastic arterial structure at the margin of the mass (*arrow*)

images) maximizes tissue contrast and offers the opportunity to postprocess image data and display the collecting system and ureteral anatomy with exquisite detail (Fig. 16). T2-weighed MR images also maximize collecting system and ureteral urine contrast and clearly demonstrate these conditions.

Renal Recipient Imaging

The indications for renal transplant recipient imaging are for: pretransplant screening and posttransplant complications. During the pretransplantation evaluation, the only routine imaging studies performed include a chest X-ray and screening mammography (within 12 months of transplant in women over 50 years of age). However, certain risk factors prompt a focused imaging workup, specifically peripheral vascular disease (PVD) and cardiovascular disease (CVD). PVD – obviously common in this population – potentially complicates surgical technique because calcified plaque limits the ability to adequately clamp the vessel and threatens intimal laceration. Imaging screening options include either CT of the abdomen and pelvis without intravenous contrast to identify and quantify atherosclerotic calcification (especially of the iliac arteries) and CTA runoff to provide an assessment of the entire arterial system, depending on clinical findings (Fig. 17). Since cardiac disease is the leading cause of death following transplantation, CVD screening provides a means to improve posttransplant outcomes. Imaging screening is typically performed with either nuclear scintigraphy or echocardiography using either exercise or pharamacologic agents (if physical limitations preclude exercise).

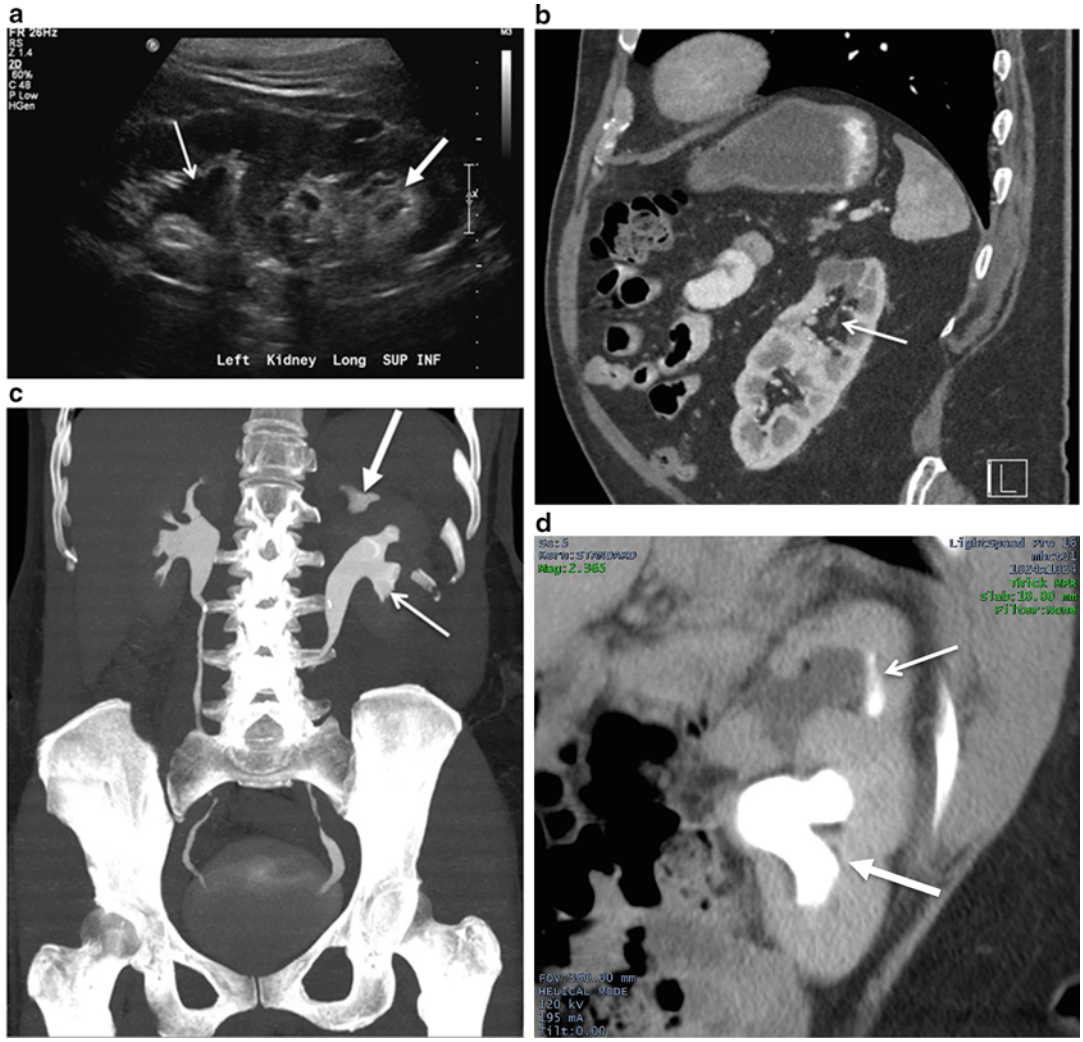


Fig. 16 Collecting system duplication during the pyelographic phase. (**a**) Longitudinal sonographic image of the left kidney shows duplication of the collecting system with mild upper polar moiety hydronephrosis (*arrow*) and normal lower polar moiety collecting system (*thick arrow*). (**b**) The corresponding sagittally reformatted postcontrast CT image shows resolution of the upper polar moiety hydronephrosis (*arrow*) with normal appearance of the lower polar moiety. (**c**) Thick coronally reformatted CT image in the pyelographic phase postcontrast in a different patient reveals a normal right renal collecting system and ureter and mild dilatation of the left lower polar moiety collecting system (*arrow*) with a small amount of contrast in the upper polar moiety collecting system (*thick arrow*). (**d**) The sagitally reformatted CT image through the left kidney shows layering excreted contrast in the upper polar moiety collecting system (*arrow*) and the distended lower polar moiety collecting system (*thick arrow*)

While renal transplant recipients undergo an extensive routine surveillance regimen, mammography and bone densitometry constitute the only surveillance imaging studies (Hariharan 2006). Screening mammography in these patients conforms to the standard annual recommendation for all patients. Bone densitometry is recommended at the time of transplantation, at 6 months and annually if previous results are abnormal, otherwise every other year to monitor for the effects of steroid-induced bone loss (Fig. 18). Bone densitometry, or dual energy X-ray absorptiometry (DXA), estimates bone density by calculating the area density based on the X-ray attenuation

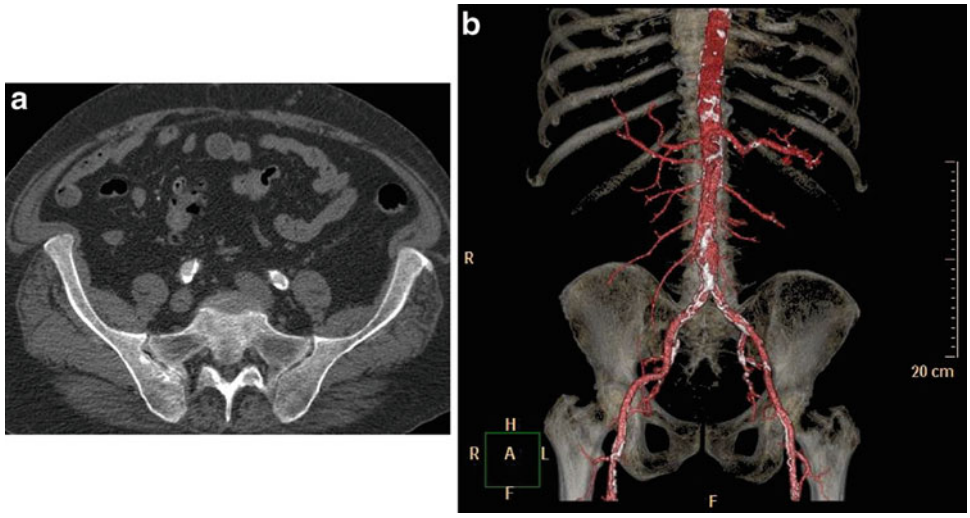


Fig. 17 CT and CTA in transplant recipient candidates. (**a**) The axial image from a CTA shows heavy atherosclerotic calcification of the common iliac arteries (*arrows*). (**b**) The 3D volume-rendered image from the CTA shows the extent and distribution of atherosclerotic calcifications to better advantage

information obtained from two X-ray beams at different energies. The result is a calculated bone density in gm/cm^2 of regions-of-interest (ROIs) – typically the lumbar spine and proximal femurs and the distal radius is an alternative when other body parts are precluded by prior surgery or other condition. This number is compared to two cohorts – young adults and age-matched peers – to yield a T-score and Z-score, respectively, in standard deviation (SD) units. T-score value cut-offs for normal, osteopenia, and osteoporosis are: (1) −1.0 and higher = normal, (2) <−1.0 to −2.4 = osteopenia, and (3) </= −2.5 = osteoporosis. The FRAX® tool, developed by the World Health Organization (WHO), predicts the fracture risk integrating femoral bone density and clinical parameters, such as alcohol consumption, steroid use, history of fractures, tobacco use, etc., and is typically reported in terms of the 10-year probability of a major osteoporotic or hip fracture (Kanis 2016).

In the setting of graft dysfunction, imaging is generally implicated to help diagnose the etiology and to identify other potential complications. The long list of transplant complications stratifies according to postoperative time course, which limits the differential diagnosis considerably (Fig. 19). (Sharfuddin 2014) US, CT, MRI, and nuclear medicine are the modalities generally implicated to evaluate graft dysfunction (Fig. 20).

Ultrasound

Ultrasound (US) usually is the initial imaging test (Fig. 20) because it is available, portable, able to provide anatomic and physiologic information, noninvasive, and avoids contrast material and ionizing radiation. It has no contraindications but may be technically difficult because of overlying bandages or surgery. Additionally, the superficial location of the graft allows higher frequency transducers and greater spatial resolution, which improve image quality.

The techniques used to evaluate renal transplants are grayscale (B-mode) ultrasound, as well as color Doppler and spectral Doppler. Grayscale ultrasound creates images from reflected sound waves and shows returning echoes as white or shades of gray. This method allows for evaluation of renal size and volume, renal parenchyma echogenicity, hydronephrosis, and peritransplant collections. The normal renal cortex is normally less or equally echogenic compared with the liver. The renal sinus is hyperechoic and the medullary pyramids mildly hypoechoic relative to

the renal cortex (Fig. 21). The shape of the allograft should be ellipsoid and the width should be greater than the anteroposterior dimension. Renal allograft hypertrophy is a ubiquitous finding that can be seen normally 6 months after transplantation, but is also present in acute rejection, pregnancy, or early diabetes mellitus (Absy et al. 1987).

Doppler ultrasound uses color encoding or spectral Doppler waveforms to display information about blood flow in the graft. Color flow shows direction and a gross estimate of vascularity (Fig. 22). Sensitive machines can show the main renal arteries (anterior and posterior divisions), segmental arteries, and some smaller arteries as well as their corresponding veins. Power Doppler is another mode where any blood flow is colorized but where arterial and venous flow are combined. This leads to better color filling in the parenchyma. Spectral Doppler graphically displays flow and velocities accurately but from a small volume of tissue. The information is displayed as a spectral display with velocity in the y axis, time in the x axis, and amount of signal (roughly the number of red cells detected) as shades of white and gray. A useful parameter extrapolated from the spectral Doppler tracing is the arterial resistive index (RI). This is calculated by subtracting the end diastolic velocity (D) from the peak systolic velocity (S), that quantity divided by the peak systolic velocity (S) - [(S-D)/S]. A normal resistive index = 0.7–0.8; a resistive index greater than 0.75–0.8 is a nonspecific indicator of transplant dysfunction (Rifkin et al. 1987). Resistive indices may be elevated in many processes, especially rejection, ATN, extrinsic compression from collections, and hydronephrosis.

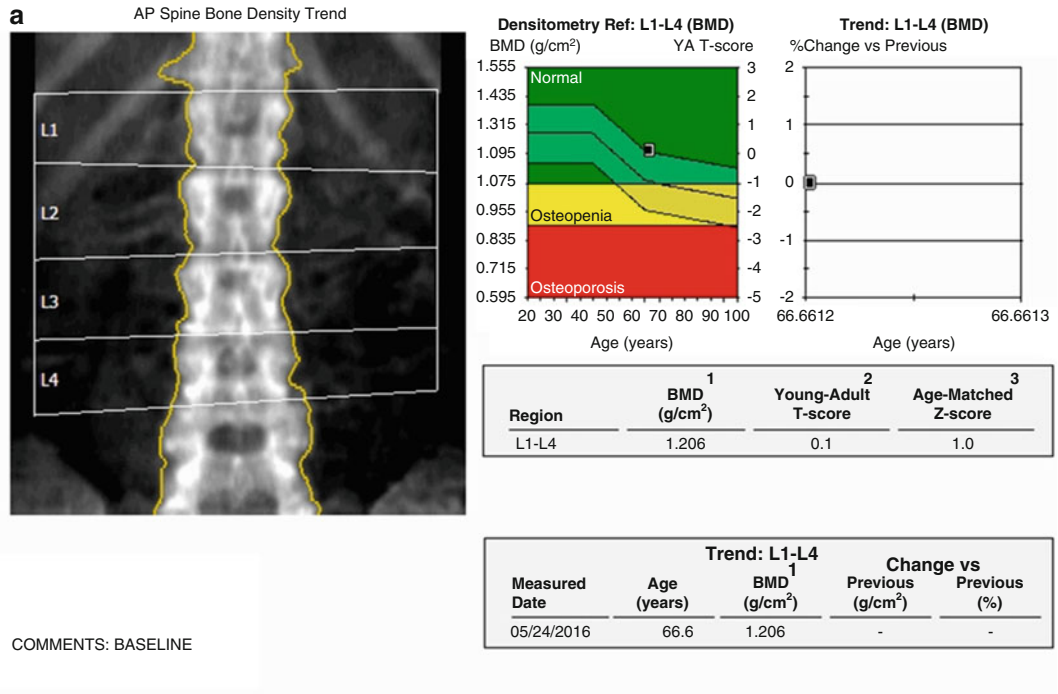


Fig. 18 (continued)

The interpretation of the renal ultrasound should be made along with clinical, blood, and urinary findings. Interpretation also is affected by the time after transplantation, i.e., immediate (first week), early (one to 4 weeks), or late (after 4 weeks).

Immediate evaluation of graft function after transplantation is standard of care and correlates with shorter hospital stays and improved short-term and long-term survival (Ferguson and Henry 1993). Critical immediate complications are frequently vascular and can be diagnosed via duplex ultrasound. Arterial occlusion typically occurs at the arterial anastomosis and there will be absence of arterial flow on Doppler. If equivocal or technically challenging, angiography, CT or MR, may be confirmatory. On gray scale, ultrasound findings of renal vein thrombosis are graft hypertrophy yielding an overall hypoechoic appearance and rarely a hyperechoic thrombus in the main renal vein. On Doppler, there is a characteristic reversal of diastolic flow on arterial spectral tracings (Fig. 23). The main renal vein is not seen if renal vein thrombosis is complete but can have an attenuated signal if part of the obstructed venous system remains open.

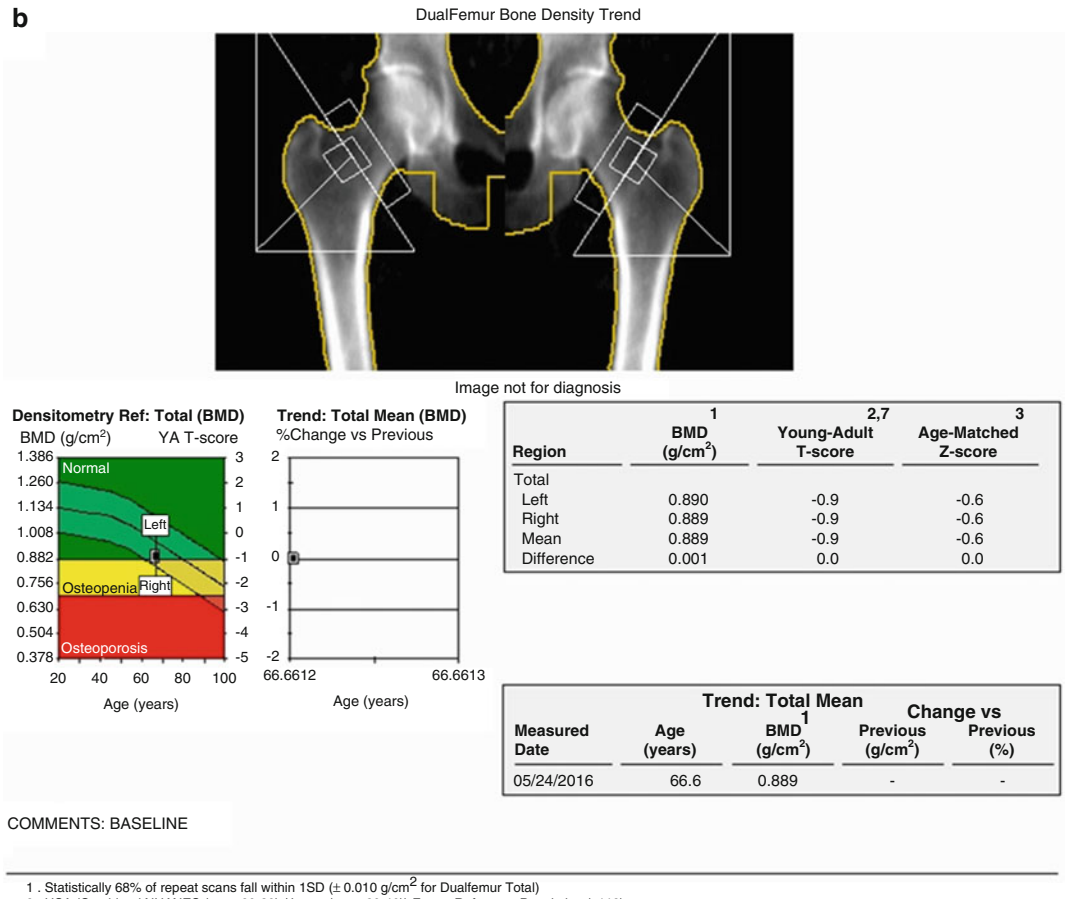


Fig. 18 (continued)

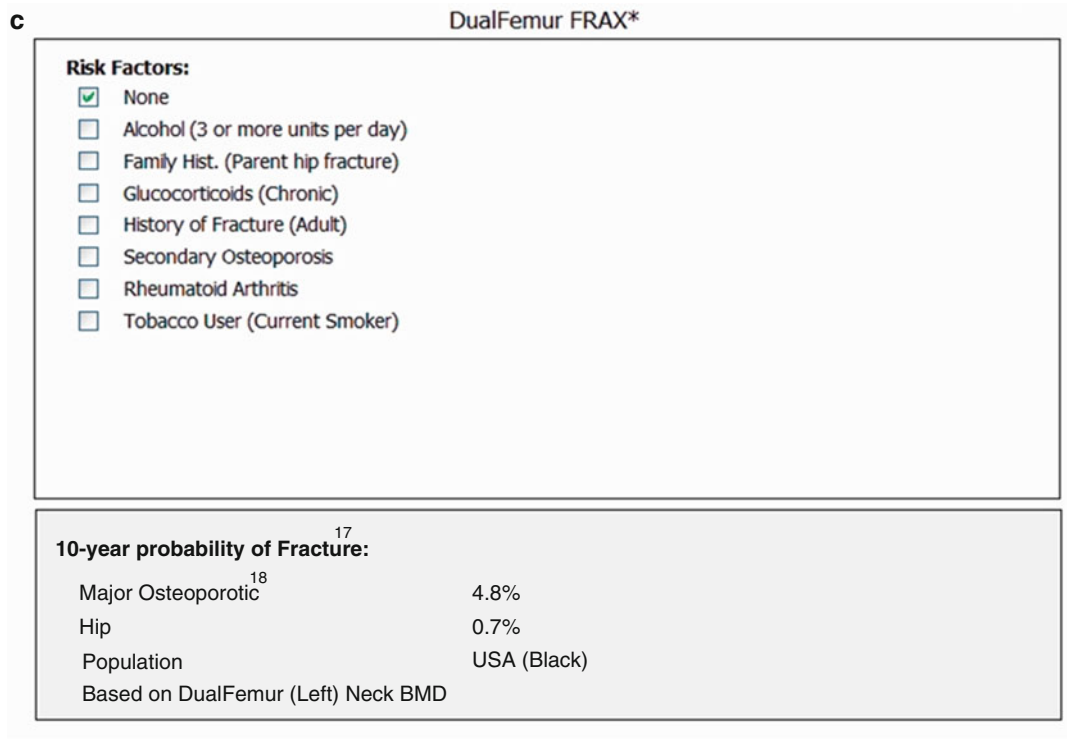


Fig. 18 Bone densitometry. (**a**) Dual-energy image of the lumbar spine is obtained, and ROIs are manually generated to isolate L1–L4 vertebral bodies and individual vertebral body bone densities are generated from which a composite bone density in grams per centimeter squared is calculated, which corresponds to a T-score. The T-score represents bone density compared with the normal young adult bone density in standard deviations (−1.0 and above = normal, −1.1 to −2.4 = osteopenia, </=2.5 = osteoporosis). (**b**) Bilateral proximal femoral bone density is also measured with T-scores generated in the same fashion. (**c**) The fracture assessment tool (FRAX) uses bilateral femoral bone densities in conjunction with clinical parameters to predict the risk of osteoporotic fracture

Diagnosing acute tubular necrosis can be difficult and often has overlapping findings with accelerated acute rejection and acute rejection. Furthermore, the grafts can appear normal on ultrasound in biopsy proven disease. Potential findings include hypertrophy with a generalized hypoechoic appearance and loss of normal cortical and medullary differentiation. The resistive index may be elevated in acute tubular necrosis or can be normal.

The sonographic appearance of accelerated acute rejection is hypertrophy from edema, hypoechoic cortex, swelling of the medullary pyramids, loss of corticomedullary differentiation, and edema in the renal sinus fat. In severe cases Doppler can show reversed diastolic flow and elevation in the resistive index. These findings are identical to acute tubular necrosis and acute rejection as mentioned previously.

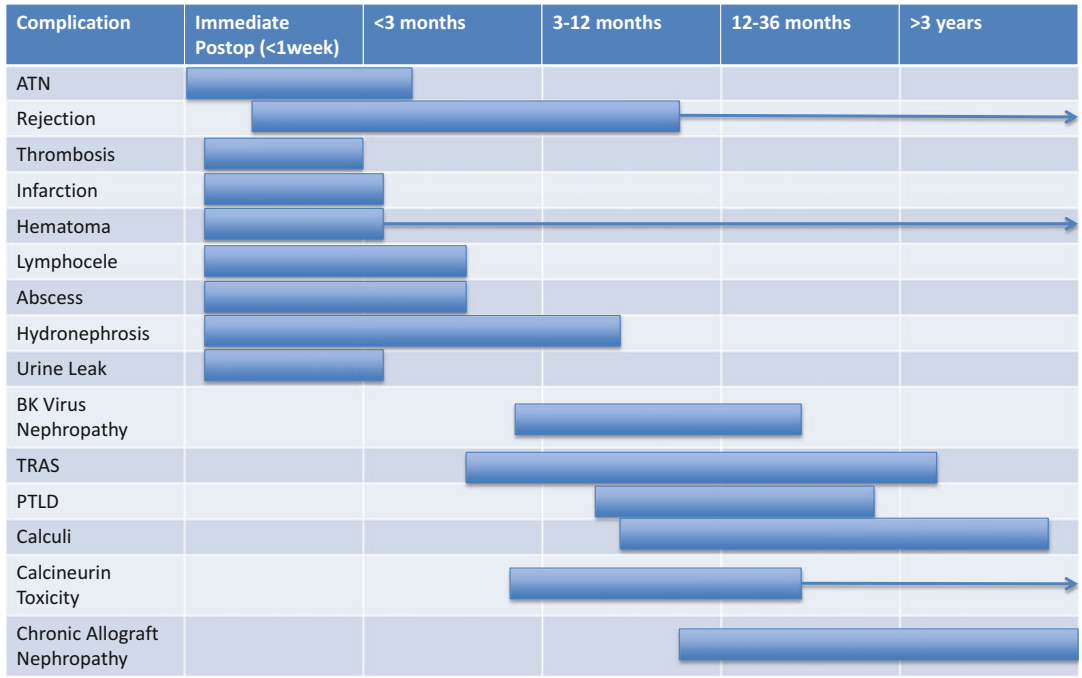


Fig. 19 Postoperative renal transplantation complications

Complication	US	CT	MRI	NM	DSA
Early postoperative dysfunction/ATN	1st-line; operator-dependent; detects hydronephrosis and collections	NA	NA	2nd-line; not readily available; time-consuming	NA
Urinary tract obstruction	1st-line; follow serially for improvement	2nd-line; sensitive for calculi and other potential obstructing lesions	NA	2nd-line; differentiate functional from chronic obstruction	NA
Renal artery stenosis	1st-line; operator-dependent	Theoretically high accuracy; risk of nephrotoxicity	2nd-line; confirmatory after US; gadolinium contraindicated with eGFR <30	NA	2nd-line; confirmatory; simultaneous intervention; risk of nephrotoxicity and procedure complications
Fluid collections	1st-line; follow serially; option for simultaneous drainage	2nd-line; anatomic depiction; surgical planning	3rd-line; problem-solve equivocal cases	Only useful for possible urine leak	NA
PTLD	2nd-line	1st-line; sensitive; nonspecific	1st-line; sensitive; nonspecific	NA	NA
Nephrolithiasis	2nd-line; follow serially	1st-line; sensitive and specific	NA	NA	NA
Biopsy complications	1st-line	2nd-line	NA	NA	2nd-line; sensitive and specific; simultaneous intervention; risk of nephrotoxicity and procedure complications

Fig. 20 Imaging modalities and transplant complications

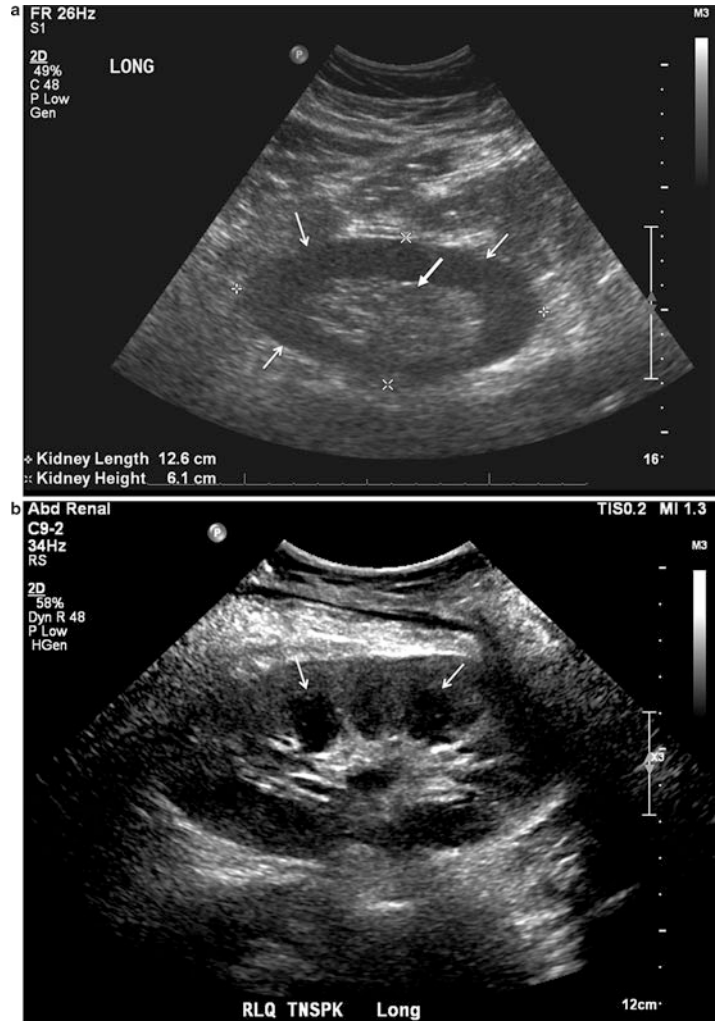


Fig. 21 Ultrasound image of normal renal transplant. (**a**) The longitudinal gray-scale ultrasound image of the renal allograft in the left iliac fossa demonstrates the normal hypoechoic appearance of the renal cortex (*arrows*) compared with the echogenic renal sinus (*thick arrow*). (**b**) The longitudinal gray-scale ultrasound image of renal allograft a few days after transplant shows the hypoechoic medullary pyramids to better advantage (*arrows*)

Other complications that can occur in the immediate posttransplantation period are acute tubular necrosis (ATN) and accelerated acute rejection. ATN gray scale findings are usually absent but may demonstrate hypertrophy with a generalized hypoechoic appearance and loss of normal cortical medullary differentiation. Arterial RIs may be normal or elevated.

The sonographic appearance of acute rejection is enlargement of the transplant especially anterior-posterior with respect to width giving a round cross-sectional shape. Hypertrophy from edema, hypoechoic cortex, swelling of the medullary pyramids, loss of corticomedullary differentiation, and edema in the renal sinus fat may be found. In severe cases Doppler can show elevation in the resistive index or even absent or reversed diastolic flow. These findings may be identical to acute tubular necrosis; acute rejection may require biopsy, response to therapy, or progression or regression over time to distinguish between the two.

Hematomas can be a normal posttransplant finding following surgery and typically appear as fluid collections, sometimes with complex internal architecture and septations (Fig. 24). Hematomas are frequently anechoic immediately and after the liquefaction. More commonly, the fluid has some or many internal echoes, sometimes with septations. Abscesses are rare but demonstrate fluid with echoes. If characterization of peri-transplant fluid is required, ultrasound-guided aspiration is usually easy due to the superficial position

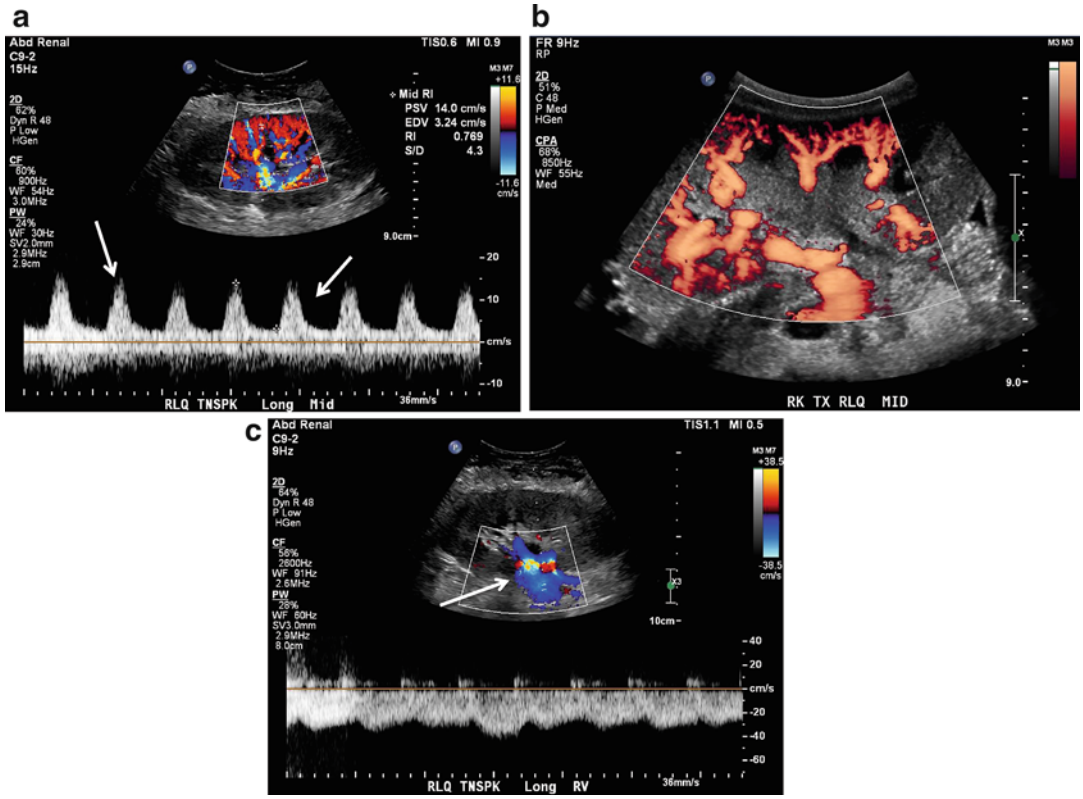


Fig. 22 Normal color and spectral Doppler images in renal transplantation. (**a**) Color Doppler image shows how blood flow is color-encoded depending on whether flow is toward (*red*) or away from (*blue*) the ultrasound probe. Additionally, a spectral Doppler tracing (*arrows*) can be obtained from a selected vessel in order to assess hemodynamics, such as the resistive index (*asterisk*), which in this case is normal. (**b**) The power Doppler image demonstrates the magnitude of flow without the directionality. (**c**) Color Doppler is also used to demonstrate the patency and flow characteristic of the major renal vessels, and this example shows the normal renal vein with blood flow directed away from the allograft (*arrow*) with the spectral waveform showing normal velocity

of the graft. Fluid collections such as hematomas rarely cause sufficient mass effect to alter hemodynamics. Ascites adjacent to the graft does not have the well-defined wall fluid collections do.

Early complications (occurring at 1–4 weeks) are acute rejection, urinary fistula, and ureteral obstruction. Acute rejection was originally described with typical gray-scale findings. These are frequently minimal or absent as treatment for rejection has improved so dramatically. Enlargement rounding and equalization of the anteroposterior dimension and width, hypoechoic cortex, swelling of the medullary pyramids, loss of corticomedullary differentiation, thick uroepithelium, and diminished echogenicity in the renal sinus fat have been described.

Hydronephrosis usually indicated ureteral obstruction. Attention to the ureterovesical anastomosis on ultrasound is important as this is the most common site of obstruction, urinary leak, or narrowing. Intrinsic narrowing can be caused by fibrosis, ischemia, blood clots, or rejection. Ultrasound of the ureter may show internal echogenic contents or diminished caliber of the ureter. Examples of extrinsic secondary causes of obstruction are fluid collections. Ureteral reflux can cause hydronephrosis but is uncommon compared with obstruction.

Large urinary fistulas or leaks commonly occur at the ureterovesical junction and present with urinomas and/or urinary ascites. Urinomas appear as hypoechoic fluid collections, internal

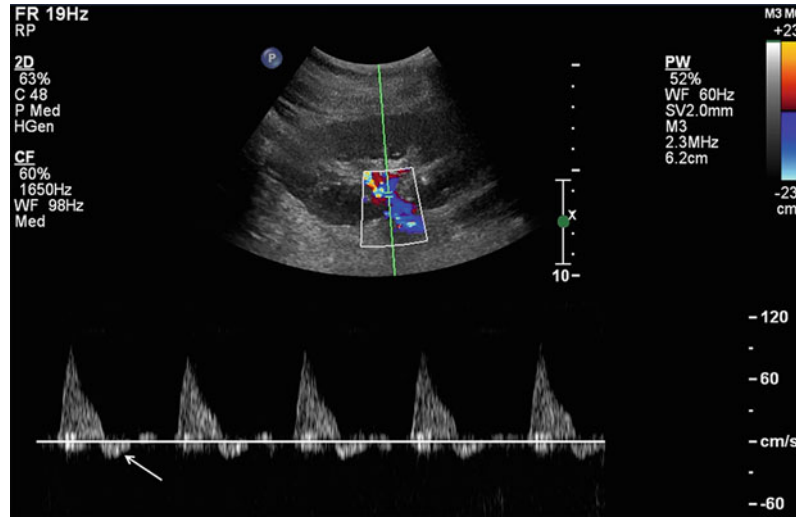


Fig. 23 Renal vein thrombosis. The renal arterial spectral Doppler tracing shows transient diastolic flow reversal (*arrow*), which is a nonspecific finding of graft dysfunction

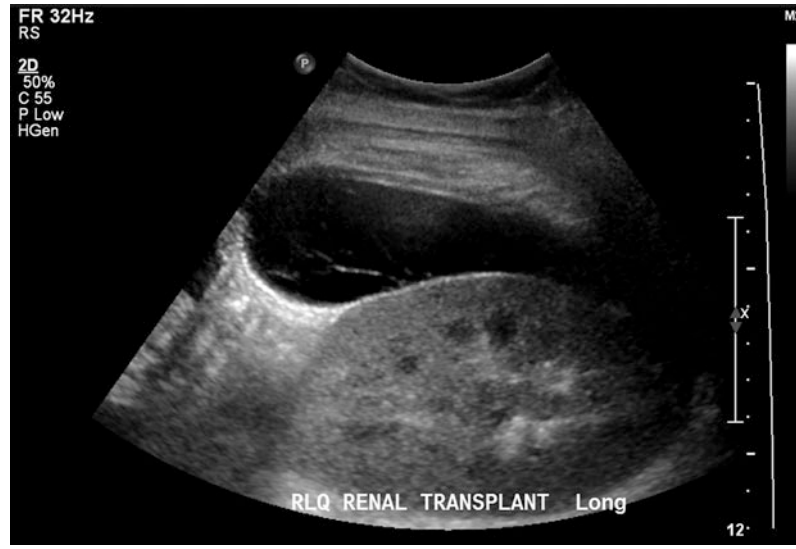


Fig. 24 Posttransplant hematoma. Hypoechoic collection superficial to the kidney containing internal septations

septations are less often seen compared with hematoma so (Fig. 24). Diagnosis can be confirmed with ultrasound guided percutaneous needle sampling of the fluid or opacification of the collection after contrast administration.

Late complications after transplantation include chronic rejection, collections and infections, vascular processes, and posttransplant lymphoproliferative disorder (PTLD). PTLD can appear as focal hypoechoic solid masses in or around the renal parenchyma.

Chronic rejection is seen as atrophy and thinning of the renal cortex. Other potential findings include increased echogenicity (Fig. 25) and a decreased number of intrarenal vessels (Bin et al. 2007). On spectral Doppler, the RI is normal to slightly elevated.

Lymphoceles are collections of lymphatic fluid that appear as round fluid collections, the fluid lacking internal echoes. The kidney with pyelonephritis may appear normal or enlarged. There may be focal hypoechoic regions. Color may show reduced cortical vascularity. There may be echogenic debris in the collecting system and/or thickening of the uroepithelium. Abscesses are fluid collection in or around the

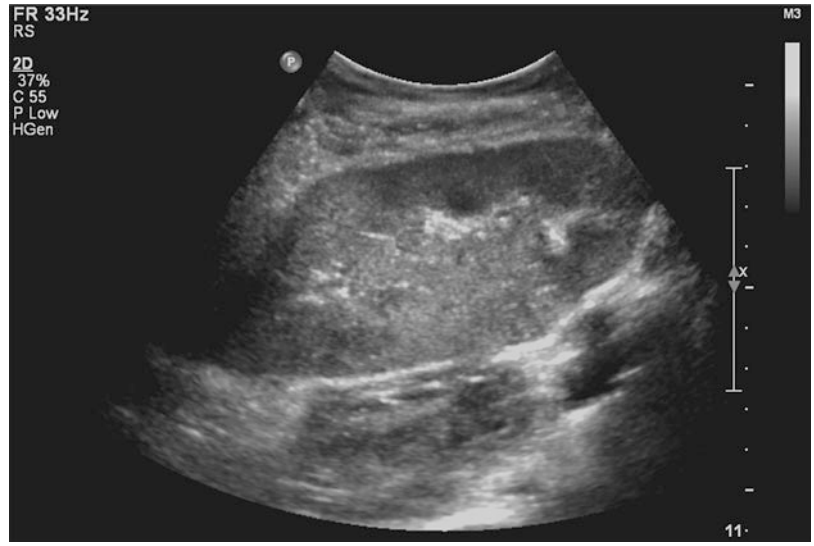


Fig. 25 Chronic rejection. Longitudinal gray-scale US of a renal allograft placed years earlier shows increased cortical echogenicity in the setting of histopathologic findings of chronic rejection

transplant, the fluid usually has low level echoes.

Renal artery stenosis commonly occurs at the anastomosis. Doppler ultrasound will show high velocity at the site of narrowing. Downstream turbulence is detected beyond the high velocity jet. Diminished RI and/or accelerations in the parenchymal vessels are also specific findings but are less sensitive than the direct evaluation of the transplant artery itself. Doppler criteria for renal artery stenosis are an elevated renal artery peak systolic and/or an elevated ratio of blood velocities in the stenotic renal artery divided by the iliac artery. Intrarenal waveforms are frequently blunted. An iliac inflow stenosis can create similar pathophysiology with blunted intrarenal waveforms without the elevated velocities in the main artery.

Arteriovenous fistulas (AVFs) can result from biopsy or rarely from surgical technique. Asymmetrically enlarged arteries and draining veins are often seen with larger AVFs on color. The turbulence that AVFs create are common and produce false color in the parenchyma ("color bruit artifact") and heralds an underlying vascular process (Fig. 26). Arterial feeders show increased arterial systolic and diastolic velocities and the draining vein can show pulsatile ("arterialized") flow.

Pseudoaneurysms may form as a result of biopsy, rarely from surgical technique or infection. Pseudoaneurysms appear as round hypoechoic areas with internal color flow. All "cysts" in the transplant should be evaluated with color since pseudoaneurysms may mimic masses or cysts. Doppler is used to diagnose pseudoaneurysms. In additional to the color flow in the collection, the pseudoaneurysm neck can be identified and typical spectral Doppler "to-and-fro" flow into and out of the pseudoaneurysm sac are definitive.

Hydronephrosis can be detected at any time frame from transplantation but is not always significant obstruction (Fig. 27). A dilated collecting system can occur due to reflux across an incompetent ureteroneocystostomy or a denervated flaccid collecting system. These can often be distinguished from obstructive hydronephrosis by having the patient void (Koga et al. 1996; Platt et al. 1989; Platt et al. 1991).

CT

CT plays a secondary role in imaging post-transplant complications. While providing a useful anatomic overview – albeit somewhat limited by the avoidance of iodinated contrast material in the setting of renal graft dysfunction – CT images lack the physiologic information that Doppler US provides. The normal CT appearance of the transplanted renal graft in the iliac fossa simulates the

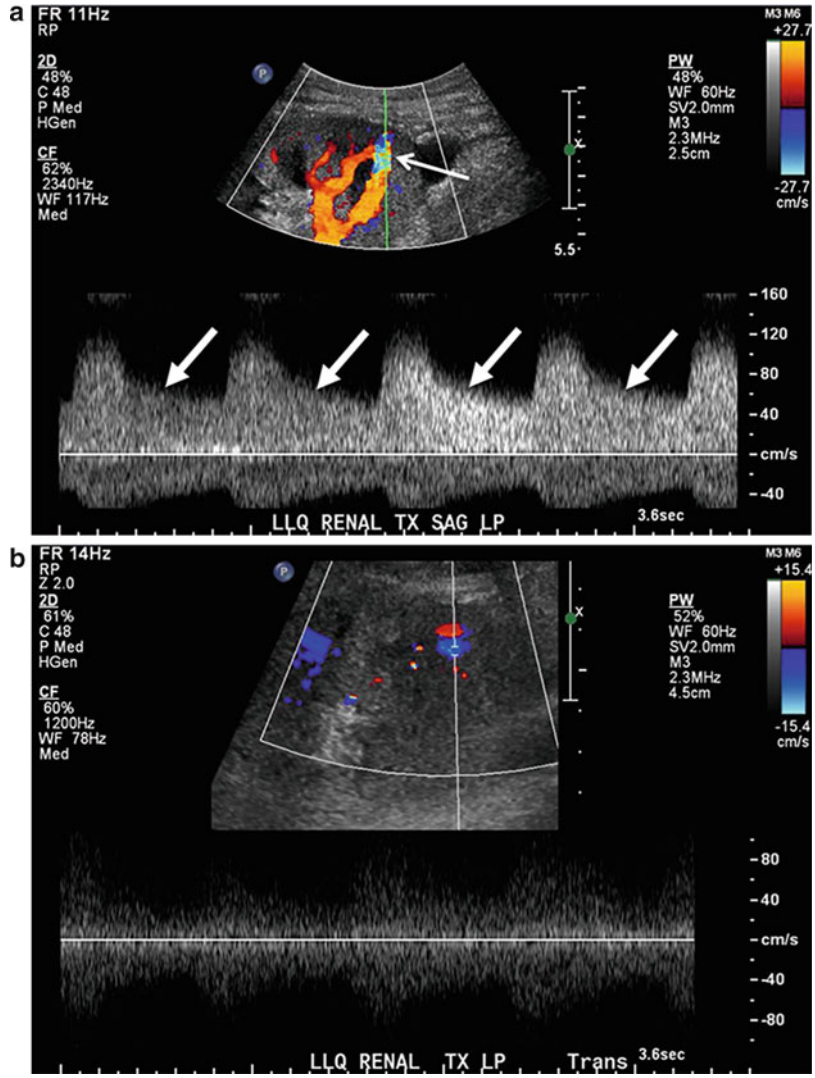


Fig. 26 Arteriovenous fistula in the lower pole of the renal allograft in the left iliac fossa. (**b**) The spectral Doppler tracing of a prominent vessel at the lower pole of the renal allograft (*arrow*) demonstrates relatively elevated diastolic flow velocities (*thick arrows*) indicating low resistance in the setting of a direct arterial-venous communication. (**b**) The corresponding venous waveform reveals pulsatile flow

appearance of native kidneys, except for mild collecting system dilatation due to ureteral anastomotic edema (Muglia et al. 2013). In the immediate posttransplant setting, changes in the fat surrounding the renal transplant are inevitably present, including small fluid collections, which often appear heterogeneously dense because of blood content (Fig. 28). Unless associated with mass effect on adjacent structures, signs of infection, or urinary complications, fluid collections in the immediate postoperative period are considered incidental and typically followed with US. One notable exception is a hematoma in the setting of potential graft rupture or vascular pedicle injury (Sebastià et al. 2001). However, hematomas generally do not signify catastrophic complications and appear relatively hyperdense compared with simple fluid in the acute phase and undergo a progressive decline in density with evolution of blood products and gradually decrease in size.

CTA serves an ancillary role in assessing posttransplant vasculature due to the need for iodinated contrast and its potential nephrotoxicity. While US is the first-line diagnostic test, CT plays a problem-solving role when MRI is precluded by susceptibility artifact (signal void obscuring regional structures) arising from

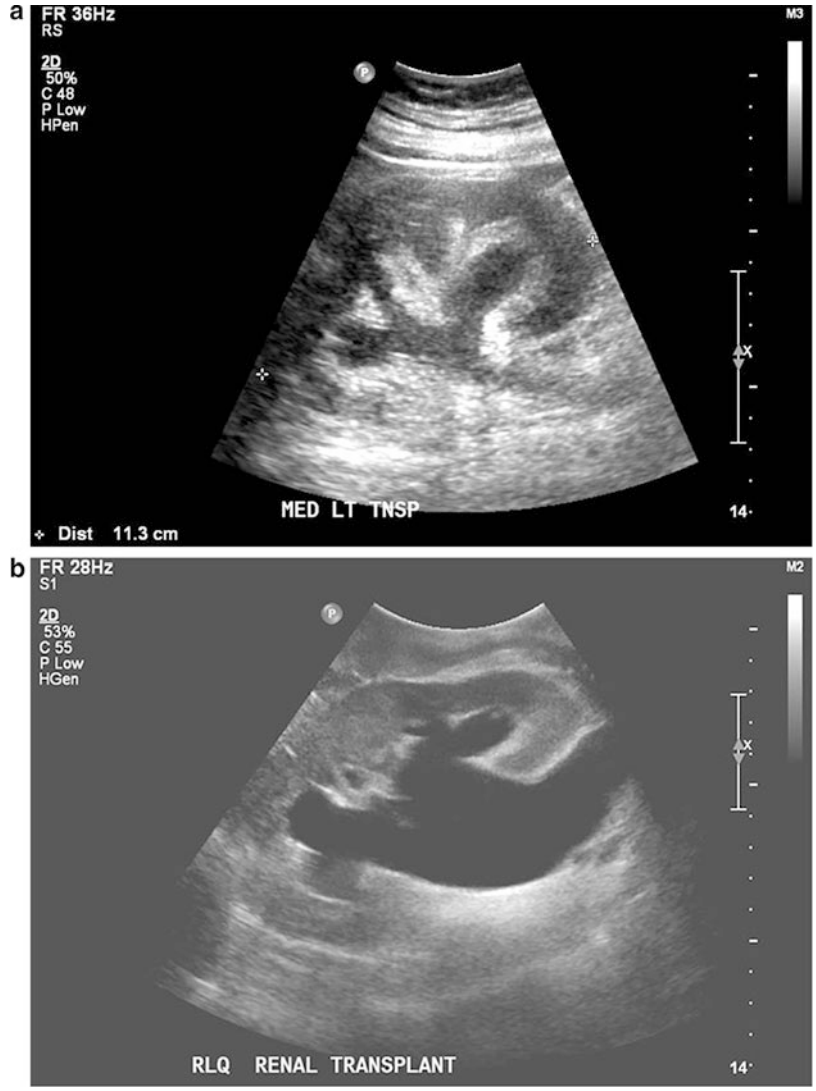


Fig. 27 Hydronephrosis in transplanted renal allografts. (**a**) Longitudinal gray-scale US image of a renal allograft in the left iliac fossa shows a branching anechoic, fluid-filled structure corresponding to mild hydronephrosis. (**b**) Longitudinal gray-scale US image in a different patient with a right iliac fossa renal allograft shows a greater degree of collecting system, pelvic, and proximal ureteral distention connoting moderate hydronephrosis

surgical clips or other foreign bodies or implanted devices (Hofmann et al. 1999). Renal artery stenosis, the most common vascular complication, usually occurs near or at the anastomosis and appears as a narrow waist measuring less than 50% of the caliber of the prestenotic normal vessel (Eriksson et al. 2010).

CT also identifies other vascular complications, including renal artery thrombosis, iliac artery stenosis, arteriovenous fistula (AVF), pseudoaneurysm, and renal vein thrombosis and stenosis. Renal artery thrombosis occurs in the immediate transplant period and CTA demonstrates absent arterial enhancement and lack of renal parenchymal enhancement (Fig. 29). AVFs and pseudoaneurysms usually arise following percutaneous biopsy and often resolve spontaneously. Both lesions usually appear as round arterially enhancing lesions with AVFs demonstrating early venous drainage. Renal vein thrombosis also requires intravenous contrast administration, but with a longer delay to opacify systemic veins. Findings range from a discrete hypodense filling defect against enhancing normal venous lumen to complete lack of enhancement. Venous stenosis is seen on CT images as a significant caliber luminal caliber change usually in the perianastomotic region.

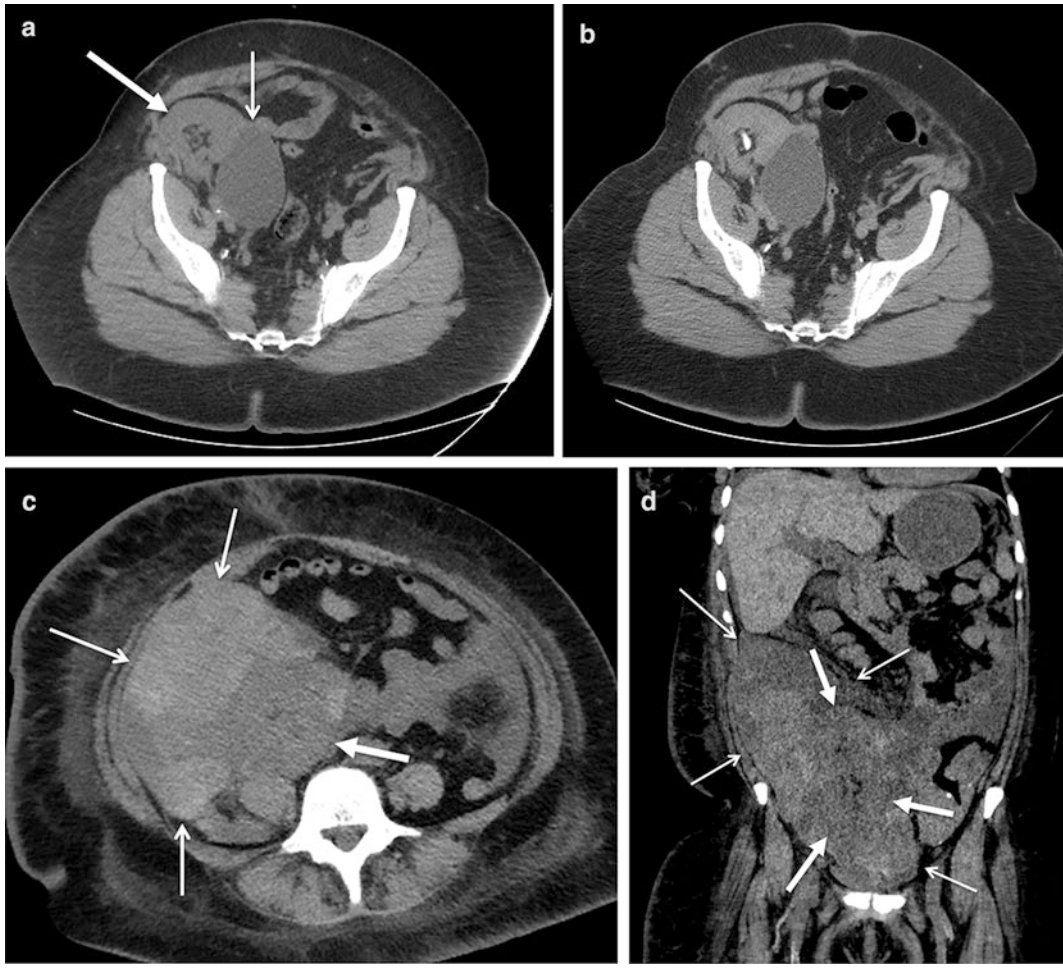


Fig. 28 CT of posttransplant fluid collections. (**a**) The precontrast image shows an ovoid fluid collection (*arrow*) medial to the renal allograft in the right iliac fossa (*thick arrow*). (**b**) The corresponding postcontrast image demonstrates absent enhancement, confirming the absence of solid tissue and the cystic nature of this lymphocele. (**c**) An axial unenhanced image in a different patient reveals a large, heterogeneous collection (*arrows*) surrounding a renal allograft in the right iliac fossa (*thick arrow*). (**d**) The corresponding coronally reformatted image shows the extent of the large hematoma (*arrows*) surrounding the renal allograft (*thick arrows*)

Posttransplant urologic complications include urinoma and ureteral obstruction. The CT appearance of a urinoma is a nonspecific, hypodense fluid collection interchangeable with the appearances of seromas, lymphoceles, and chronic hematomas after the lysis of hyperdense blood products. The definitive CT diagnosis of a urinoma requires the intravenous administration of iodinated contrast material to confirm the communication from renal collecting system or ureter to the collection. Ureteral obstruction is easily identified as collecting system dilatation.

Immunocompromised-related posttransplant malignancies include skin, cervical, and rectal malignancies and Kaposi's sarcoma and lymphoma (Kyllönen et al. 2000). While PTLD frequently manifests with lymphadenopathy, PTLD potentially involves any organ, yet has a predilection for the transplanted renal graft (Lopez-Ben et al. 2000). Contrast-enhanced CT is generally the first-line imaging modality for PTLD because of its availability and diagnostic utility. Nodal disease involves any lymph node station and manifests as either: (1) a discrete, enlarged lymph

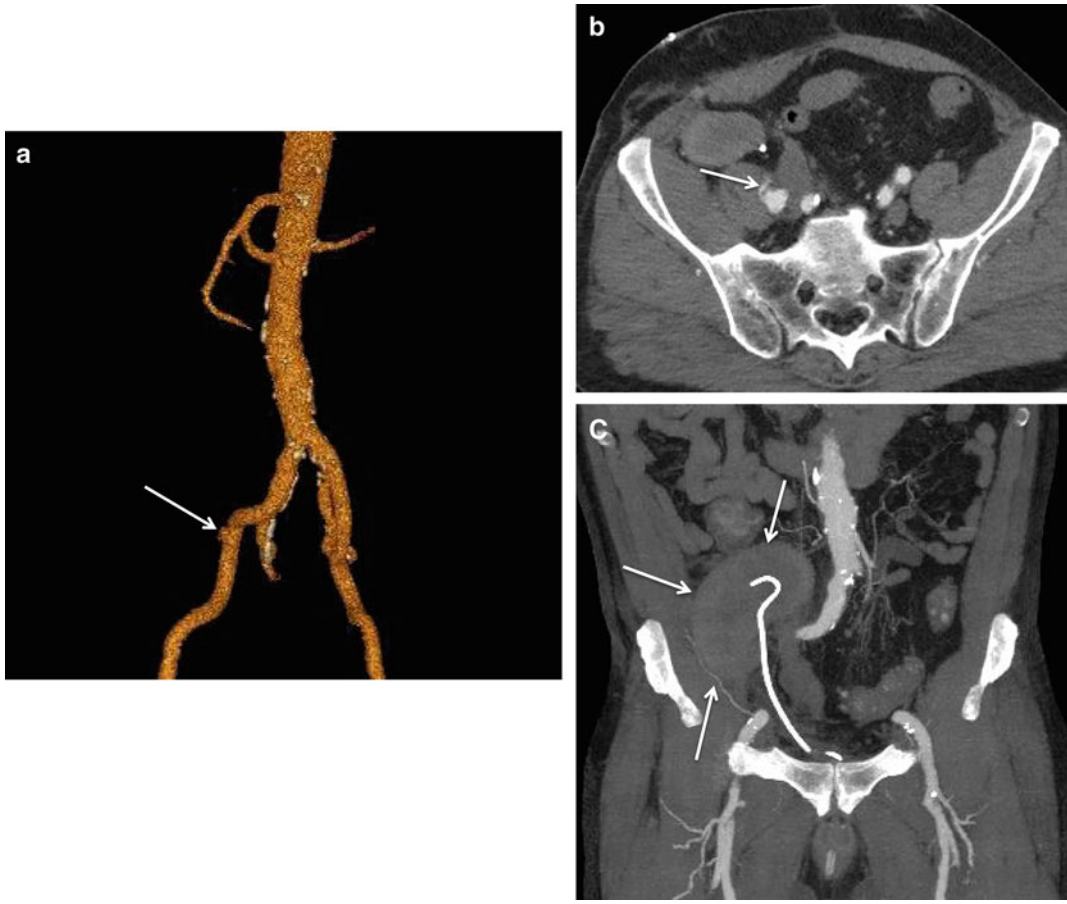


Fig. 29 Renal artery thrombosis. (**a**) Volume-rendered image from a CTA shows absence of the renal artery supplying the right renal allograft – only irregularity at the ostium is apparent (*arrow*). (**b**) Axial image from the CTA shows an attenuated stump on the origin of the renal artery (*arrow*). (**c**) Coronal maximal intensity projection from the CTA shows minimal enhancement of the renal allograft (*arrows*)

node, (2) a cluster of enlarged lymph nodes, or (3) a bulky soft tissue with or without central necrosis (Fig. 30) (Borhani et al. 2009). PTLD involving the renal allograft generally conforms to either a homogeneous hilar mass or multifocal parenchymal masses exhibiting relatively mild enhancement.

Positron emission tomography (PET)/CT combines the sensitivity for hypermetabolism characteristic of neoplastic tissue with the anatomic detail provided by CT. PET detects the radiation emitted by the decay of the glucose metabolism radiotracer 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG). The PET/CT sensitivity and specificity for PTLD is greater than CT alone (Fig. 31) (Borhani et al. 2009; Bakker et al. 2006; Bakker et al. 2007; Bianchi et al. 2008; McCormack et al. 2006). In addition to increasing the sensitivity for neoplastic lesions, PET/CT also adds utility in evaluating the response to therapy by demonstrating the posttreatment impact on metabolic activity, in addition to demonstrating size changes (von Schulthess et al. 2006).

MRI

MRI also plays an ancillary role in the post-transplant setting. However, MRI poses no risk to the allograft, involves no ionizing radiation,

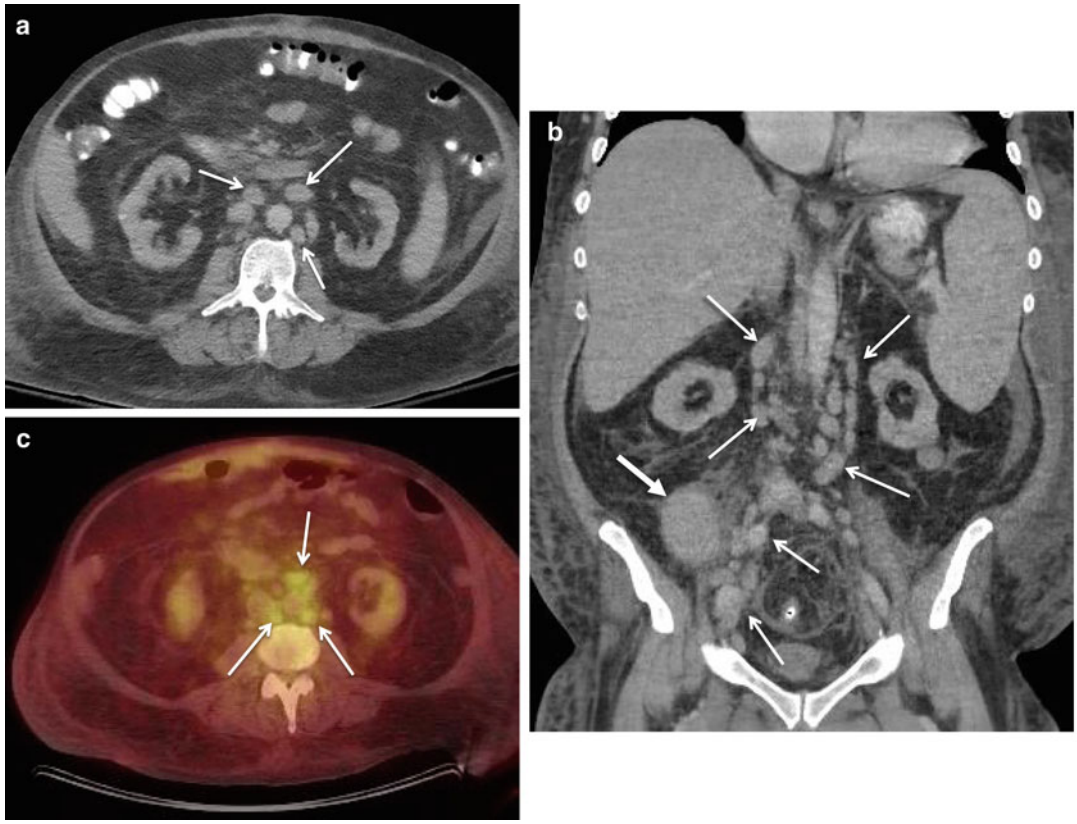


Fig. 30 CT of PTLD manifesting as lymphadenopathy. (**a**) Axial postcontrast CT image reveals multiple mildly enlarged retroperitoneal lymph nodes (*arrows*) in a patient with PTLD. (**b**) The corresponding coronally reformatted image shows the retroperitoneal lymphadenopathy, pelvic lymphadenopathy (*arrows*), and a portion of the transplanted kidney in the right iliac fossa (*thick arrow*). (**c**) The PET/CT image shows hypermetabolic activity in the retroperitoneal lymph nodes (*arrows*)

and features much greater tissue contrast than CT. For example, posttransplant fluid collections are much more conspicuous through fat suppression and the extreme T2-hyperintensity of fluid compared with surrounding tissues and often better differentiated through MR imaging because of the unique T1 hyperintensity of the methemoglobin breakdown product in hemorrhage, the ability to visualize septation, and the higher conspicuity of the urinary excretion of contrast. Hematomas demonstrate hyperintensity on both T1- and T2-weighted images, whereas all other fluid collections are generally T1-hypointense and T2-hyperintense. Lymphoceles feature no specific MR findings, although occasional thin septa discriminate them from seromas and urinomas (Letourneau et al. 1987). Following intravenous gadolinium administration, the accumulation of excreted contrast within the collection establishes the diagnosis of urinoma. Urinary obstruction is also better evaluated with MRI compared with CT. By acquiring MR urographic images using two techniques – extremely T2-weighted and delayed T1-weighted postcontrast images – the renal allograft collecting system, ureter, and point and etiology of obstruction are vividly portrayed (Fig. 32). However, renal calculi are less conspicuous on MR images compared with CT.

Regarding vascular complications, MR provides an alternative to CT in cases where iodinated contrast is contraindicated. MR angiography combines unenhanced and postcontrast techniques to evaluate the renal artery and vein, supplemented

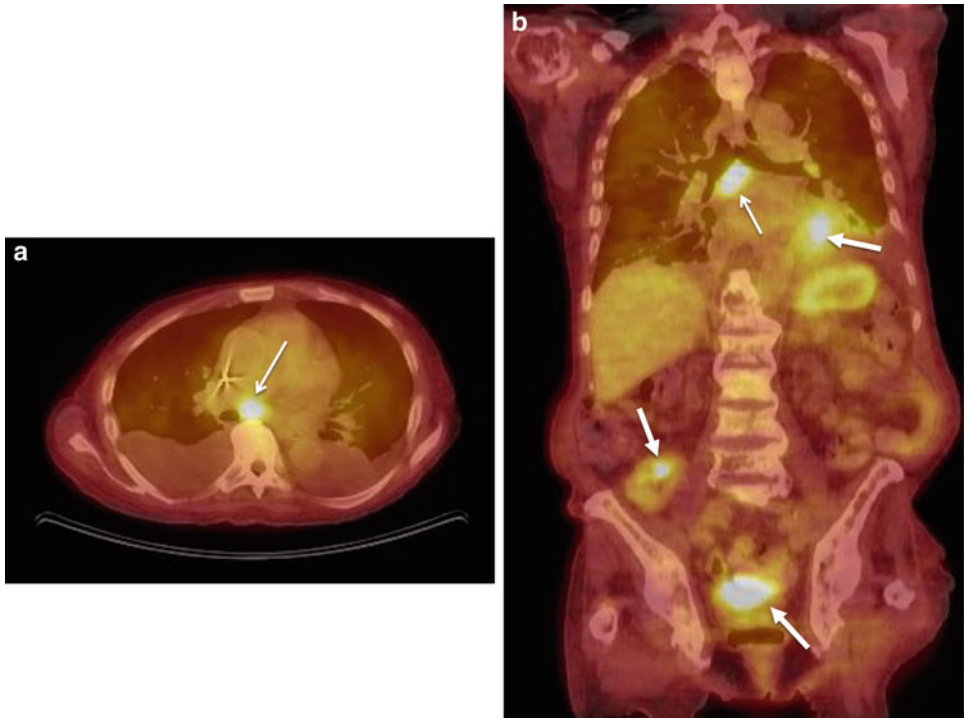


Fig. 31 PET/CT in PTLD. (**a**) The fused PET/CT axial image shows a hypermetabolic subcarinal lymph node (*arrow*) in a patient with PTLD following renal transplantation. (**b**) The corresponding coronal fused image shows the subcarinal lymph node (*arrow*) with normal activity in the myocardium, renal collecting system and bladder (*thick arrows*)

by nonangiographic pulse sequences demonstrating parenchymal changes associated with vascular complications (such as segmental infarction, for example). The renal artery and vein are hyperintense on both unenhanced and enhanced MRA images with conspicuity maximized by fat suppression. The primary MR findings in renal artery stenosis and thrombosis are the same as seen on CT – (usually anastomotic) narrowing and absent enhancement or flow-related signal (in the case of unenhanced MRA), respectively. The iliac arteries are also included and reliably evaluated with MRA (Fig. 33). Associated renal infarcts are T2-hyperintense, nonenhancing, subcapsular, usually wedge-shaped foci, which help confirm the diagnosis of vascular insufficiency. The MR findings of renal venous stenosis and thrombosis also mirror the CT findings – (usually anastomotic) narrowing and lack of enhancement or flow-related signal, respectively. Additionally, in renal vein thrombosis, the renal allograft enlarges with absent enhancement and relatively edematous T2-hyperintensity; subscapsular hemorrhage is also occasionally observed (Neimatallah et al. 1999).

MRI plays an ancillary role to CT and PET/CT regarding posttransplant malignancies, at least partly because of the greater challenge in covering the entire torso or body. Nonetheless, neoplastic tissue is generally more conspicuous on MRI compared with CT. Because of the relatively greater density of cells in malignant tumors, the diffusivity of water is restricted, reflected by hyperintensity on diffusion-weighted MR images with corresponding hypointensity on ADC map images. Diffusion restriction is especially prominent in lymphoma and PTLD. Additional MR features include T1-hypo- and T2-hyperintensity and mild homogeneous enhancement. Renal hilar involvement is notable for the lack of mass effect on vascular and collecting system structures disproportionate to size and central location.

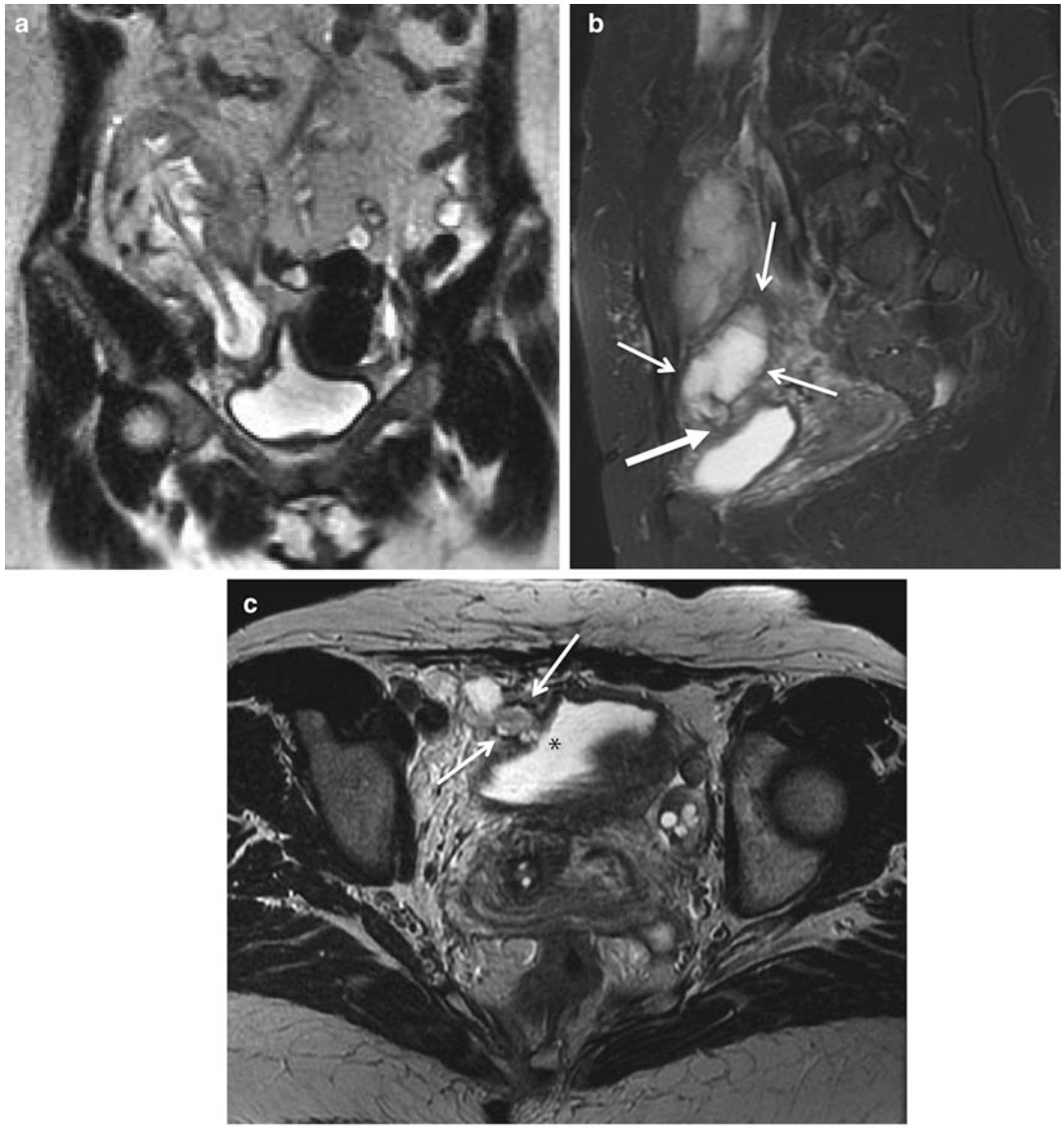


Fig. 32 MR urographic imaging demonstrating urinary obstruction. (**a**) Coronal T2-weighed image shows hydronephroureter involving the renal allograft in the right iliac fossa with a nephroureteral stent in place. (**b**) The sagittal T2-weighted, fat-suppressed image shows a portion of the dilated ureter (*arrows*) proximal to a hypointense, fibrotic distal ureteral stricture (*thick arrow*). (**c**) Axial T2-weighted image shows the distal ureteral stricture (*arrow*) just proximal to the ureterovesical junction (*asterisk*, bladder)

Renal Scintigraphy

While ultrasound is the first-line modality to evaluate renal allograft failure, renal scintigraphy is a potentially useful alternative posing no threat to the allograft. Renal scintigraphy involves the intravenous administration of a radioisotope, which emits gamma rays detected with a gamma camera, yielding images that illustrate the distribution of the radioactive agent. Regarding the radioisotope, technetium-labeled mercaptoacetyltriglycine (Tc-99 m MAG3) is favored over technetium-labeled diethylenetriamine pentaacetic acid (Tc-99 m DTPA) because of its higher

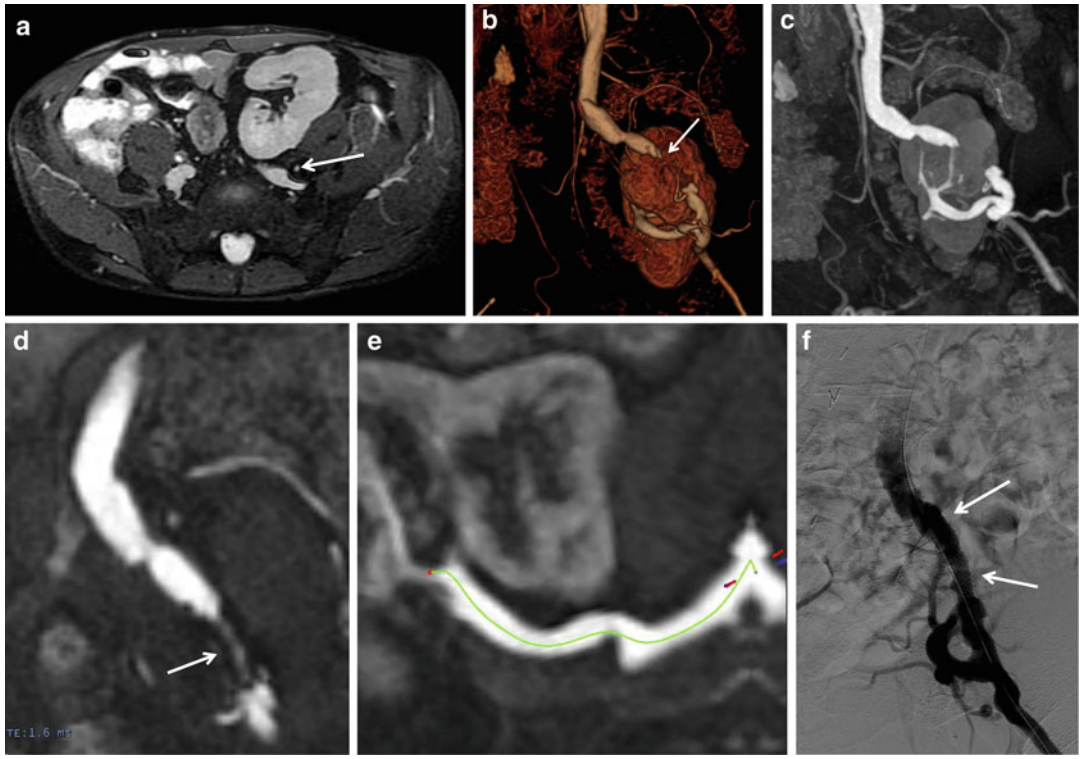


Fig. 33 MR findings in iliac artery stenosis. (**a**) Axial unenhanced MRA image shows virtual occlusion of the left external iliac artery (LEIA) with a minimal residual lumen (*arrow*). (**b**) The volume-rendered image from the contrast-enhanced MRA exaggerates the findings, giving the appearance of LEIA occlusion (*arrow*), but the renal artery appears relatively normal (*thick arrow*). (**c**) The maximal intensity projection image from the contrast-enhanced MRA mirrors the findings on the volume-rendered image. (**d**) The obliquely coronally reformatted image from the contrast-enhanced MRA shows the critical LEIA stenosis (*arrow*) to better advantage. (**e**) The curved planar reformatted image of the renal artery from the contrast-enhanced MRA excludes high-grade stenosis. (**f**) Image from left iliac arteriography following LEIA stent placement (*arrows*) shows restoration of normal arterial caliber

extraction efficiency and greater utility in depressed renal function. Immediately following the injection of the radiopharmaceutical, serial images are acquired initially in 3 s frames for 1 min to assess arterial perfusion and then 15 s frames for approximately 30 min to evaluate radiotracer uptake and clearance. Planar images are obtained and semiquantitative analysis is performed by generating a time-activity curve of the renal allograft region-of-interest. The chief indications for renal transplant scintigraphy include:

Evaluation of renal perfusion (vascular occlusion)
Evaluation of graft dysfunction (acute tubular necrosis, rejection, etc.)
Evaluation of peritransplant fluid collections
Evaluation of urologic complications (leak and vesicoureteral reflux)

Renal artery thrombosis manifests scintigraphically as nonvisualization of the allograft. Renal artery stenosis results in diminished radiopharmaceutical uptake with normal parenchymal transit and without radiotracer retention. Acute tubular necrosis (ATN) classically demonstrates normal or near-normal perfusion with delayed radiopharmaceutical uptake and excretion and progressive cortical accumulation (Fig. 34) (Aktas 2014). However, in severe ATN, perfusion declines and the pattern overlaps with the appearance of rejection. Rejection typically exhibits

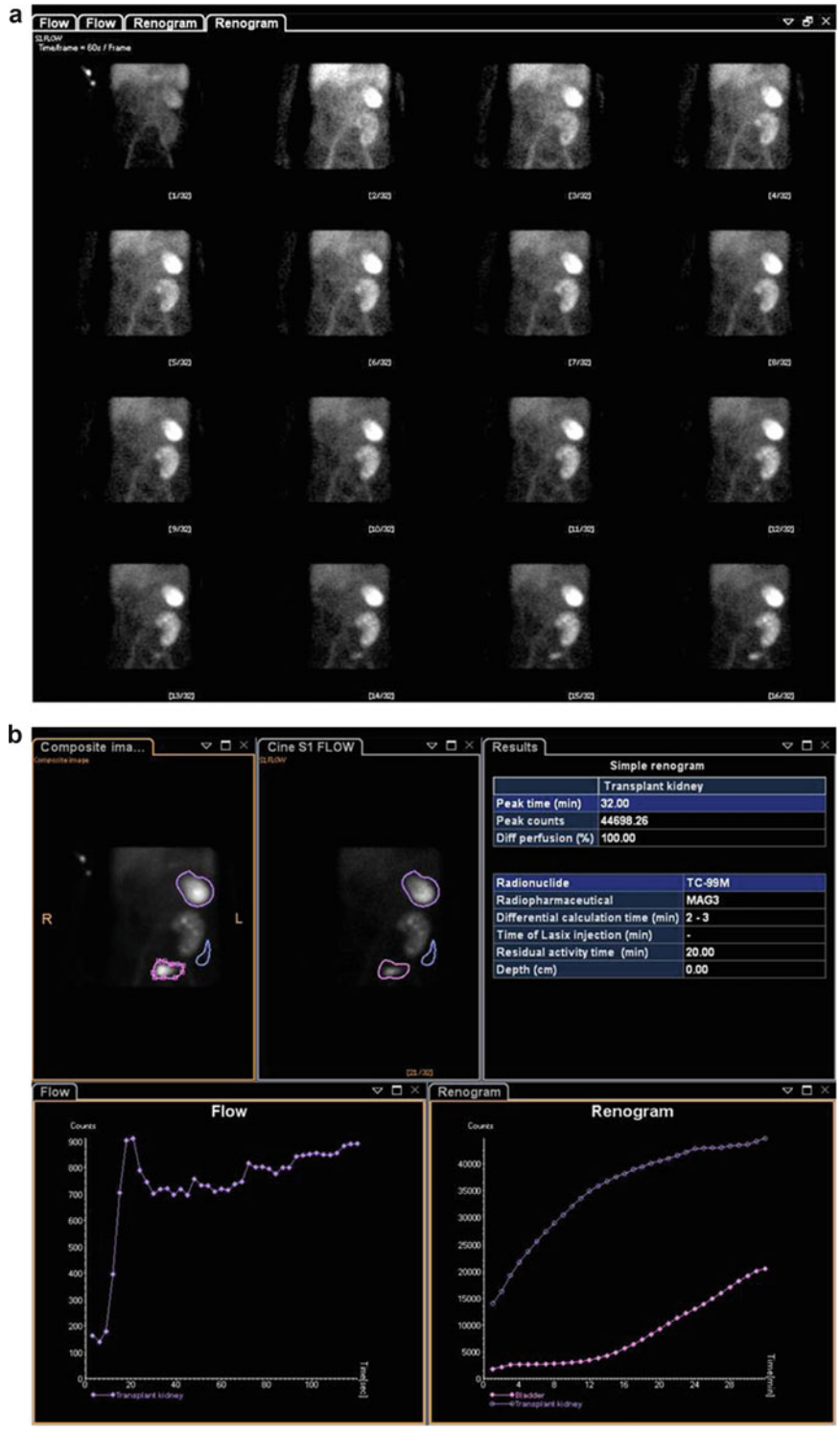


Fig. 34 Renal scintigraphy in acute tubular necrosis. (**a**) Serial images obtained during the renographic phase show progressive cortical radiotracer uptake without excretion. (**b**) The time-activity curves (at the *bottom*) show normal flow (*bottom left*) and progressive cortical uptake (*bottom right*) of radiotracer

decreased perfusion, diminished uptake, and delayed excretion. Drug (cyclosporine) toxicity simulates rejection and potentially ATN scintigraphically with normal-to-depressed perfusion and parenchymal retention (Boubaker et al. 2006; Dubovsky et al. 1999). While considerable overlap in the scintigraphic appearances of etiologies of graft dysfunction limits definitive diagnosis, renal scintigraphy is useful to exclude other etiologies, such as urine leak or urinary obstruction (Sharfuddin 2011).

The scintigraphic evaluation of urinary obstruction is usually prompted by hydronephrosis detected sonographically. Renal scintigraphy adds diagnostic information by determining patency of the urinary tract in the setting of pelvicalyceal distention in terms of whether excreted radiotracer reaches the bladder. Scintigraphy detects posttransplant fluid collections as a peritransplant photopenic area, which gradually accumulates excreted radiotracer only when the etiology is urinary leak forming a urinoma (Fig. 35).

Vesicoureteral reflux (VUR) afflicts as many as 50–86% of patients following renal transplantation and is a consequence of ureteroneocystostomy (Ostrowski et al. 1999; Mastrosimone et al. 1993). The chief consequence of VUR is urinary tract infection and grading the degree of VUR with scintigraphy helps guide management, including open reimplantation or ureteroureterostomy to the native ureter when

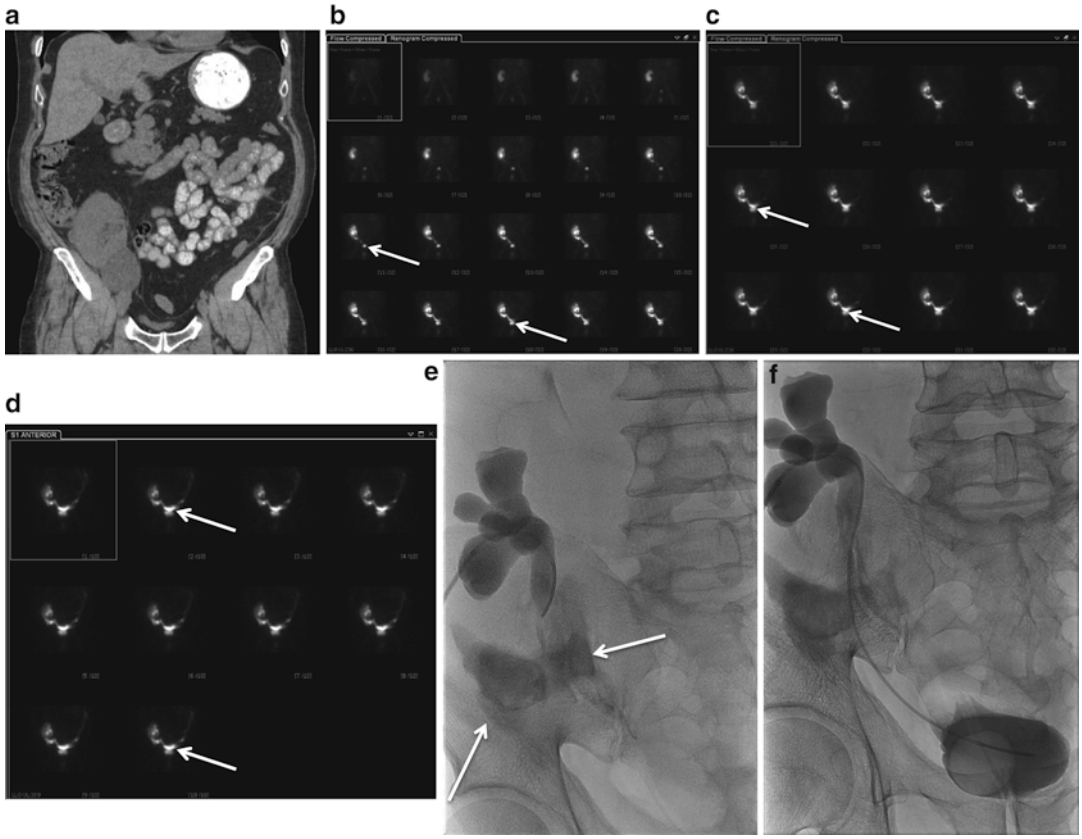


Fig. 35 Renal scintigraphy in urinary leak. (**a**) Coronally reformatted unenhanced CT image shows a fluid collection (*arrow*) abutting the lower pole of the allograft in the right iliac fossa. (**b**–**d**) Serial renographic images from renal scintigraphy reveals progressive accumulation of radiotracer outside the confines of the renal collecting system, ureter, and bladder (*arrows*). (**e**) Image from a percutaneous nephrostomy shows extravasation of contrast (*arrows*) from the ureter. (**f**) Subsequent image shows placement of an antegrade nephroureteral catheter prior to stent placement

severe (Duty et al. 2013). VUR manifests scintigraphically with a "double peak" on the time-activity curve with the second peak reflecting refluxed radiotracer into the renal collecting system.

Interventional Radiology

With the rise of diagnostic imaging modalities, interventional procedures are generally reserved for the treatment of transplant complications. Image-guided procedures potentially address vascular and urinary complications and peritransplant fluid collections, as well as providing the means of obtaining histologic diagnosis when necessary for graft dysfunction. Renal allograft biopsy is usually undertaken under ultrasound guidance with real-time guidance optimizing targeting of glomeruli and preventing inadvertent injury to renal vascular structures. The complication rate varies from 0.06% to 13% (Ahmad 2004) with major complications leading to allograft failure exceedingly rare (Huraib et al. 1989; Bach et al. 1999).

Vascular disorders related to surgical technique and procedural complications amenable to interventional management include renal artery stenosis (RAS) and thrombosis and arteriovenous malformations and pseudoaneurysms. Although catheter-directed arteriography serves as the diagnostic gold standard for posttransplant RAS, the definition of hemodynamically significant transplant RAS has not been standardized. Stenoses starting at 50 up to 80% have been identified as significant (Lo et al. 1996; Krishnamoorthy et al. 2009). Transplant RAS usually presents to arteriography with refractory hypertension. With renal insufficiency, carbon dioxide may serve as an alternative contrast agent to iodinated contrast.

Arterial access is ideally achieved through the common femoral artery, although the brachial or axillary arteries serve as possible alternatives under certain circumstances. While most stenoses occur at the anastomosis, an inflow/preanatomotic stenosis potentially mimics transplant RAS clinically, which necessitates nonselective aorto-iliac arteriography (Fig. 33). Thereafter, anteroposterior and oblique projects of the iliac arteries are obtained to localize the renal artery and identify and quantify the degree of stenosis (Fig. 36). At this point, percutaneous angioplasty and stenting can be performed. Postprocedural arteriography confirms resolution of the stenosis and stent location.

In the cases of (symptomatic) AVFs and (enlarging) pseudoaneurysms, transcatheter embolization is the treatment of choice. To minimize the loss of functioning allograft tissue, these lesions are approached with superselective embolization with metal coils (Kobayashi et al. 2007).

While graft thrombosis generally requires surgical thrombectomy, successful catheter-directed thrombolysis has been reported. However, it is contraindicated in the early postoperative period (within 2 weeks) because of the risk of sutural leakage at the immature anastomosis (Melamed et al. 2005; Rouviere et al. 2002).

Urologic complications amenable to IR management include ureteral obstruction and urinary leak. While noninvasive modalities generally secure the diagnosis of urinary obstruction, percutaneous nephrostomy provides a drainage pathway for recovery of renal function and a portal to subsequent percutaneous intervention. Additionally, the site and nature of the obstruction is demonstrated through antegrade nephrostography; the terminal ureter is often the culprit because of its vulnerability to ischemia as a consequence of its location far from the renal artery supplying the ureteral branch (Sandhu and Patel 2002). For high-grade perianastomotic strictures, balloon angioplasty post reasonably high success rates in the early posttransplantation period, ranging from 73% to 100% (Swierzewski et al. 1993; Bhagat et al. 1998; Bennett et al. 1986; Lojanapiwat et al. 1994; Fontaine et al. 1997). However, obstructions at other sites usually respond poorly to percutaneous treatment.

Urinary leaks usually occur at the distal ureter either related to ischemia or rejection or at the ureteroneocystostomy site. Once the diagnosis is established through either percutaneous aspiration of extravasated fluid or through scintigraphy, antegrade nephrostography accurately demonstrates the leakage site and percutaneous nephrostomy provides a diversionary pathway

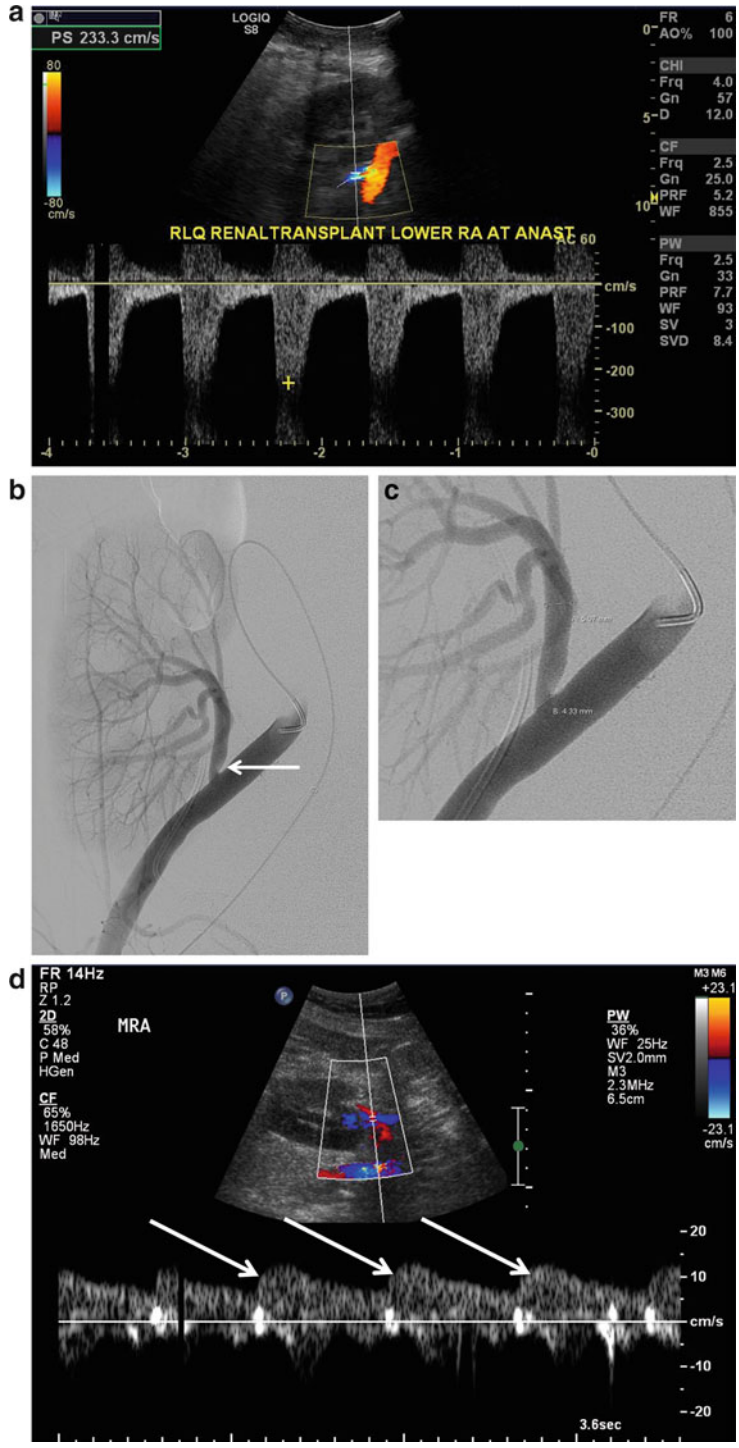


Fig. 36 (continued)

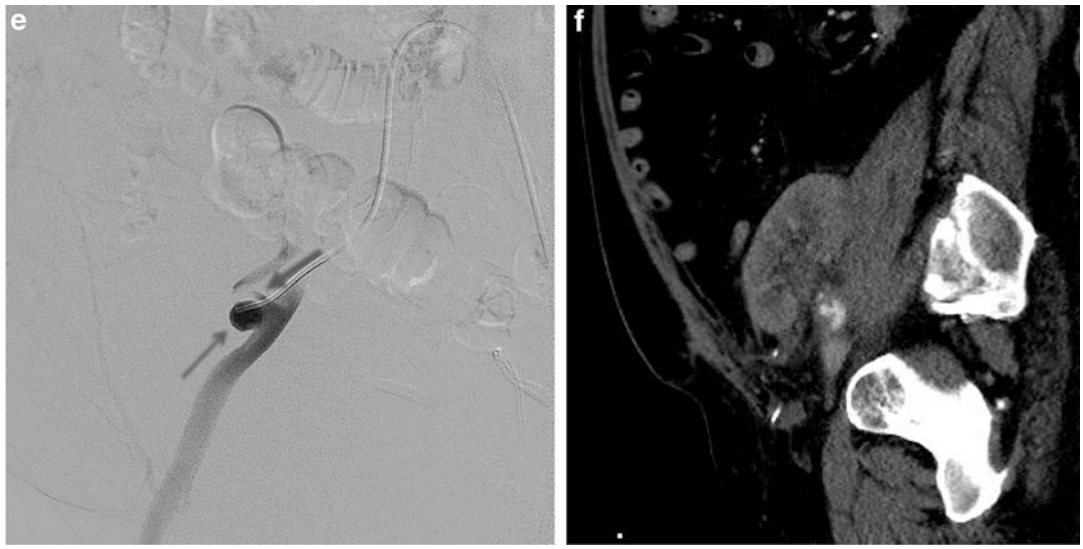


Fig. 36 Arteriography in renal transplant artery stenosis. (**a**) The spectral Doppler tracing of the proximal, post-anastomotic renal artery reveals elevated peak systolic velocity (233 cm/s), which is more than double the velocity in the external iliac artery (not shown). (**b**) Oblique projection from a catheter-directed arteriogram shows narrowing in the proximal renal artery (*arrow*). (**c**) Magnified view in the oblique projection with superimposed luminal diameter measurements shows the relatively mild degree of stenosis comparing the stenotic diameter (4.33 mm) to the normal downstream diameter (5.07 mm). (**d**) Spectral Doppler tracing of the transplanted renal artery shows blunted waveform with a slow systolic upstroke (*arrows*). (**e**) Oblique projection from a right external iliac arteriogram reveals a pseudoaneurysm (*arrow*) at the anastomosis with an adjacent high-grade stenosis of the proximal renal artery (*thick arrow*). (**f**) Sagittal reformatted image from a CTA through the anastomosis shows the pseudoaneurysm (*arrow*)

for urinary flow, promoting ureteral healing (Fig. 35). Subsequent nephroureteral stent placement across the injured ureter with external nephrostomy drainage is a treatment option, although success rates vary widely and surgical revision is occasionally necessary.

Peritransplant fluid collections often require drainage for either diagnostic and/or treatment purposes. With graft dysfunction or symptoms arising from mass effect, percutaneous fluid collection aspiration is generally necessary. Seromas and hematomas undergo drainage only when large enough to exert mass effect and elicit symptoms or with superinfection (Fig. 37). Simple drainage of lymphoceles is associated with an 80–90% recurrence rate (Brockis et al. 1978) and indwelling catheter drainage combined with sclerotherapy posts a higher success rate (Johnson and Berry 2001). Urinomas are drained to alleviate mass effect and to preempt infection. Abscesses demand early percutaneous drainage.

Conclusion

Radiology factors into the preoperative planning and the postoperative management of renal transplantation. Choosing the most appropriate imaging modality requires an understanding of the properties and relative utility of each. Regarding donors in the preoperative planning setting, the primary objective of imaging is anatomic characterization and CT is the mainstay with its high spatial resolution to portray vascular anatomy and its ability to demonstrate parenchymal lesions, calculi, and collecting system anatomy. CTA imaging depicts small-caliber arteries, which affect the surgical approach, and delayed CT images demonstrate venous anatomy to help identify the more suitable donor venous drainage. The relatively high sensitivity for intrinsic vascular diseases, solid and cystic lesions, and collecting system anomalies and diseases also recommends

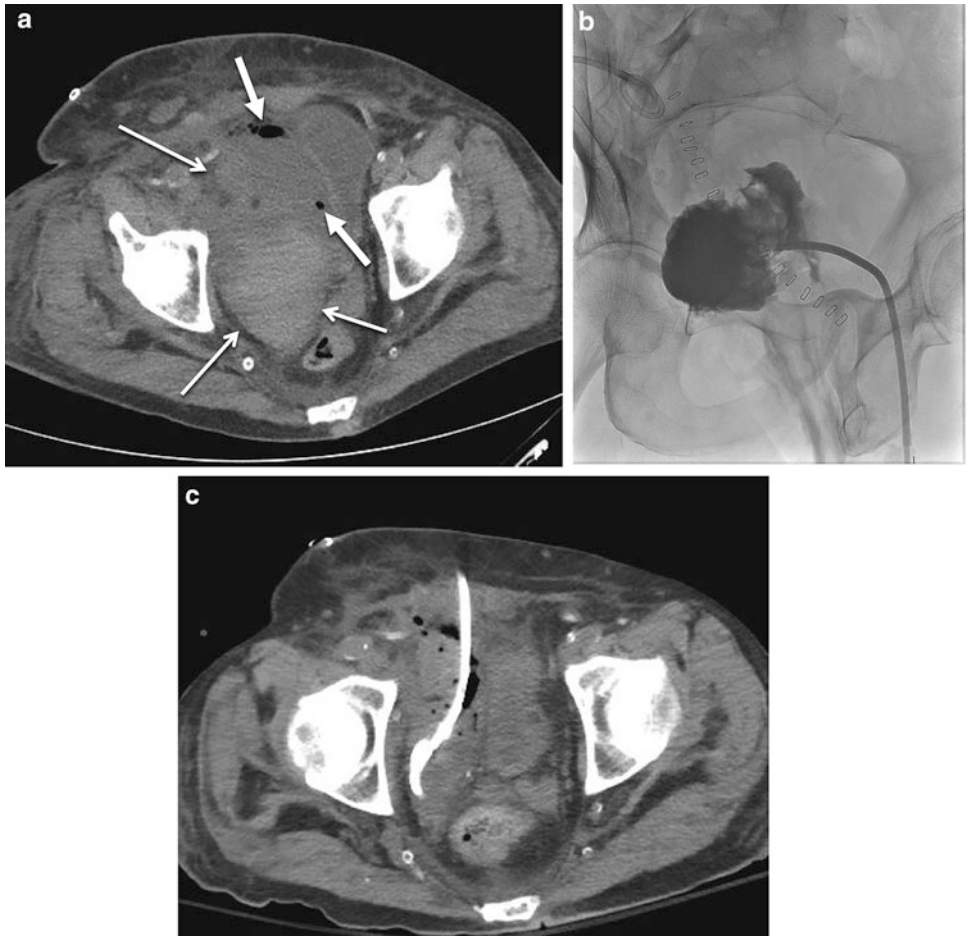


Fig. 37 Infected hematoma. (**a**) Axial unenhanced CT image shows a heterogeneous fluid collection (*arrows*) with layering dense material typical of a hematoma with punctate foci of gas (*thick arrows*) indicating infection displacing the bladder laterally (*asterisk*). (**b**) Fluoroscopic image obtained following ultrasound-guided drainage catheter placement with contrast injection to confirm successful placement outlines the confines of the collection. (**c**) Axial unenhanced CT image following drainage catheter placement shows decreased size of the collection and mass effect on the adjacent bladder

CT and MRI generally serves as a reasonable alternative, with a limited sensitivity for nephrolithiasis.

Preoperative imaging of renal transplant recipients, aside from a chest X-ray and screening mammography, is generally limited to patients with peripheral and cardiovascular risk factors. In these patients, unenhanced CT versus CTA is used to assess the burden of atherosclerotic calcification and/or provide an overall assessment of the relevant arterial system, respectively. Cardiovascular disease screening is achieved with either nuclear scintigraphy or echocardiography including either physical exercise or pharmacologic stress.

Routine posttransplant surveillance includes bone densitometry to assess the effects of long-term steroid administration. In the setting of graft dysfunction, imaging plays a major role and ultrasound is the most important imaging modality because of its noninvasiveness, availability, suitability of the relatively superficial renal allograft, and the ability to demonstrate anatomic and physiologic information. As such, US detects fluid collections, hydronephrosis and vascular complications, such as arterial occlusion or stenosis and

venous thrombosis, and guides most percutaneous treatments. Other complications, such as rejection and ATN, manifest with a nonspecific combination of parenchymal changes and elevation of the resistive index, prompting further workup to identify the etiology. CT plays an ancillary role in managing posttransplant complications, but provides greater anatomic coverage than US. While CTA provides confirmatory information regarding vascular complications, iodinated contrast is often avoided in the early posttransplant setting. However, CT is the first-line modality for PTLD, which generally manifests with either lymphadenopathy or allograft involvement in the form of a hilar mass or multifocal parenchymal lesions. PET/CT combines the sensitivity of hypermetabolism with the anatomic information provided by CT.

MRI also serves an ancillary role to assess posttransplant complications. Because of its exquisite tissue contrast, fluid collections are more accurately characterized compared with other imaging modalities. Obstructive uropathy is also vividly portrayed along with the etiology of obstruction, except in the case of calculi. Vascular complications are also well demonstrated with MRI, even without intravenous contrast, when contraindicated by renal insufficiency or contrast. Renal scintigraphy is a useful alternative to US in evaluating allograft dysfunction. By obtaining serial images for approximately 30 min after injecting a radioisotope (usually Tc-99 m MAG3), information regarding arterial perfusion and radiotracer uptake and clearance are obtained. This provides diagnostic information regarding possible vascular complications, graft dysfunction by generating time-activity curves, fluid collections (corresponding to photopenic regions), and urologic complications by demonstrating abnormal accumulation of radiotracer in a dilated collecting system in the case of obstructive uropathy or outside the collecting system in the case of extravasation.

Interventional radiology includes an array of procedures managing vascular and urologic complications and fluid collections. After confirmatory diagnostic arteriography, renal artery stenosis can be treated with angioplasty and stenting. AVFs and pseudoaneurysms are treated with superselective transcatheter embolization. Urologic complications rely on percutaneous nephrostomy to establish an alternative urinary drainage pathway and access point for possible ureteral stent placement and for diagnostic antegrade nephrostography and potentially ureteral stricture angioplasty. Fluid collections requiring drainage are performed with imaging guidance – ultrasound is the modality of choice and CT provides an alternative in the setting of a poor acoustic window.

Radiology fulfills many roles in the life cycle of renal transplantation from donor screening, recipient anatomic assessment to diagnosing and treating posttransplant complications. Each modality has unique utility and understanding the respective properties and limitations of each is necessary to optimize patient care in the transplant setting.

Cross-References

- ▶ Kidney Transplantation: Surgical Complications
- ▶ Living Donor Evaluation and Selection
- ▶ Medical Complications After Kidney Transplantation: Early
- ▶ Medical Complications After Kidney Transplantation: Late

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Transplant Immunosuppression

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Contents

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Abstract

Advances in our understanding on the mechanisms of the immune response have led to the development of a wide array of drugs that are commonly used for the treatment of autoimmune diseases, cancer, and organ transplantation. Our knowledge of the immune system has also helped to refine target selectivity which has decreased drug side effects. Since the introduction of calcineurin inhibitors, patient and allograft outcomes in the short term are excellent, but despite the increase in the repertoire of drugs, we have not been able to improve long-term outcomes. Goals for the new drugs that are getting developed are not only to maintain the same excellent short-term outcomes, but also to improve the side effect profile, be easy to use and tolerate, and to improve long-term outcomes. This review will present the main pharmacological agents that are currently used in solid organ transplantation, some of the agents that are in the pipeline, and some of the agents that have been left aside despite potential benefits in transplantation.

Keywords

Immunosuppression · Lymphocytes · Complement · Cytokines · Antibodies

Introduction

The first transplant performed in the United States happened in Boston in 1954 between identical twins. The transplant lasted for almost 10 years and demonstrated that transplantation was a feasible option for treatment of end stage renal disease. In the early stages of transplantation, immunosuppression consisted in total body irradiation and corticosteroids and resulted in dismal allograft longevity. In 1960, transplant protocols included azathioprine and steroids, and in 1970 anti-thymocyte globulin and anti-lymphocyte globulin were introduced with change in overall prognosis, but with a patient and allograft survival that would be considered unacceptable for our current standards. The biggest advancement in transplantation up to date was the discovery of cyclosporine in 1980 by Jean Borel. After cyclosporine, graft and patient survival increased dramatically and have continued to improve with the discovery of many other drugs including muromonab or OKT3 in 1985; tacrolimus, mycophenolate, basiliximab, and daclizumab in the 1990s; sirolimus in 1999; belatacept in 2011; and currently the long-acting tacrolimus: Astagraft (FDA approved 2013) and Envarsus (FDA approved 2015). Despite the steady state of drug development in kidney transplantation, as outcomes are much improved, it is more challenging to come up with agents that are both safe and superior to current therapies. Also due to the limited number of transplant complications, it is also unlikely the drugs will be tested in big multicenter trials, and many times transplant physicians will be left with off-label use of drugs that are approved by the FDA for oncology or autoimmune indications. This review will summarize the most common used therapies after kidney transplantation and also will give a brief look at drugs in the development pipeline that are promising.

Classification

Transplant immunosuppression can be classified depending on the cellular target, the phase of the immunological response that they affect, or type of pharmacological agents. The immune response

Table 1 T cell activation signaling

Signal 1	Binding T cell receptor (CD3) to an antigen in the surface of an antigen-presenting cell
Signal 2	Binding of T cell CD28 to CD80/86 in antigen-presenting cell or costimulation signaling
Signal 3	IL2 binding to IL2 receptor in the surface of T cells causing downstream activation of mammalian target of rapamycin (mTOR) pathway, phosphoinositide-3-kinase (PI3K) pathway, and Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT)
Signal 4	Nucleotide synthesis

to an allograft involves not only T cell activation but also B cell activation, and complement activation, and there is a wide array of drugs that act at different levels. The majority of the drugs that are utilized in transplantation block T cell activation and division, a process that involves four major immunological signaling pathways (Table 1). For the purpose of this chapter, immunosuppression agents will be organized as:

1. T cell-directed therapy including agents that target signal 1, signal 2 (costimulation blockage), signal 3 (IL2 inhibition and mTOR inhibitors)
2. Inhibitors of purine or pyrimidine synthesis (antimetabolites)
3. Agents that target cytokines
4. B cell-directed therapy including complement inhibition
5. Agents with multiple cellular targets

T Cell-Directed Therapies that Target Signal 1

Signal 1 in the T cell activation includes the interaction of the T cell receptor (TCR) to the MHC complex in the antigen presenting cells. Anti-TCR therapies include the murine monoclonal antibody muromomab-CD3 also commonly called OKT3 that target specifically the CD3 subunit of the TCR (Ortho Multicenter Transplant Study Group 1985). It was used as a lymphocyte depleting agent for induction but is no longer used.

After the interaction between TCR and MHC, the calcineurin pathway gets activated to enhance T cell transcription of cytokines including IL2 that will promote further T cell activation and division. Cyclosporine (CYA), the first calcineurin inhibitor that was approved in the early 1980s, is a fungal polypeptide composed of 11 amino acids from *Tolypocladium inflatum*. CYA binds to cyclophilin in the cytoplasm and the complex of CYA-cyclophilin inhibits calcineurin, a phosphatase necessary for dephosphorylation of nuclear factor of activated T cells (NFATc). NFATc is a transcription factor required for the synthesis of critical cytokine genes including IL2. CYA when given orally is slowly and incompletely absorbed as it has poor solubility in water and is largely lipophilic. CYA is highly dependent on bile solubility. It was initially marketed as Sandimmune which is an oil-based formulation that was replaced by a micro-emulsion formulation called Neoral. The bioavailability of Neoral was much improved compared to Sandimmune and currently there are multiple generic formulations. There are also intravenous (IV) preparations of CYA that are normally used in a 3:1 ratio when converted from the oral formulation. Calcineurin inhibitors (CNI) have a narrow therapeutic window, and therapeutic drug monitoring (TDM) has been widely embraced with the use of trough levels used as good representation of systemic exposure. Initial doses will depend on the formulation used but recommended through levels during the first 3 months are 200–300 ng/mL and after 3 months 100–200 ng/mL or lower if clinically indicated. CYA is associated with significant side effects that are dose dependent which again makes a case for TDM. CYA has been associated with nephrotoxicity from renal vasoconstriction and upregulation of fibrotic pathways. Nephrotoxicity due to renal vasoconstriction can present acutely and be easily reversible with a dose decrease or more chronically due to progressive interstitial fibrosis and tubular atrophy. CYA also is associated with neurotoxicity including tremors, headache, insomnia, hypertension from impaired Na excretion, hyperuricemia, hyperkalemia from type IV renal tubular acidosis, hypomagnesemia due to downregulation of

magnesium transport proteins, post-transplant diabetes due to beta cell toxicity, gum hyperplasia, hirsutism, and hyperlipidemia. Calcineurin inhibitor use has also been associated with development of thrombotic microangiopathy, and, in many cases, the endothelial damage is just limited to the renal vessels without thrombocytopenia or peripheral schistocytes (Schwimmer et al. 2003).

CYA is metabolized by CYT-P450 system (CYP3A4) and as such it has multiple interactions with drugs that impact the cytochrome activity. Common CYP3A4 inhibitors that will cause a significant increase in CYA drug levels and potentiate toxicity include antibiotics such as clarithromycin, antifungals such as fluconazole, antihypertensive medications such as diltiazem, protease inhibitors such as boceprevir, telaprevir, or ritonavir, and amiodarone. Grapefruit juice is also a potent CYP3A4 inhibitor. On the other hand, CYP3A4 inducers will cause a significant decrease in CYA levels with an increase in rejection risk. CYP3A4 inducers include rifampin and rifabutin, carbamazepine, phenytoin, phenobarbital, efavirenz, and modafinil.

CYA is rarely used in transplantation currently as it has been substituted by tacrolimus. Tacrolimus is a fungal macrolide antibiotic that is chemically not related to cyclosporine, although both drugs have similar mechanism of action. The internal receptor for tacrolimus is the immunophilin FK-binding protein (FK-BP), and the tacrolimus-FKBP complex inhibits calcineurin similarly to CYA. Tacrolimus (FK) is also available in oral and IV formulations with a 3:1 conversion when switched from oral to IV. Immediately post-transplant, FK is dosed at 0.1 mg/kg/day in two divided doses given every 12 h. The goal trough level for the first 3 months is normally 8–12 ng/ml and can be maintained between 5 and 7 ng/ml thereafter. It is also poorly absorbed if given orally and it is mainly excreted in the bile with minimal excretion in the urine. Prograf is the main brand name for tacrolimus although there are currently several generic formulations available. The side effect profile is a little different than CYA. FK still has significant nephrotoxicity similar to CYA but has more pronounced neurological side effects including posterior reversible encephalopathy syndrome. In contrast to CYA, FK is associated with hair loss but no gum hyperplasia. FK is associated with higher rates of post-transplant diabetes than CYA (Johnston et al. 2008). FK is also metabolized by the CYP3A4 with the same drug interactions as CYA.

Voclosporin is a new calcineurin inhibitor that resulted from the addition of an extra carbon molecule at the first amino acid residue of CYA. Voclosporin studies showed more consistent pharmacokinetic and pharmacodynamic responses to the drug than CYA, more potent cyclophilin binding, and faster elimination of metabolites. The pharmacological profile suggests voclosporin can be more potent and less toxic than CYA. Phase II studies in kidney transplantation have shown safety and tolerability as well as efficacy (noninferior to CYA in preventing acute rejection compared to FK with potentially lower incidence of post-transplant diabetes) but there are not currently any phase III trials underway for its use in transplantation (Busque et al. 2011).

Extended Released Tacrolimus Formulations: Recently, extended release formulations of tacrolimus have been approved by the FDA. Astagraf XL, a daily tacrolimus drug, was approved in 2013 followed by Envarsus XR in 2015. The once a day formulation has been touted to facilitate patient adherence, to achieve a more consistent drug exposure, and to improve patient and graft long-term outcomes. There is also a budget-impact model analysis from the United Kingdom that shows significant cost savings over 5 years with conversion to Astagraf from bid dosing (Muduma et al. 2014a, b). Unfortunately, the UK data will be hard to generalize to the USA. The once a day formulations are only currently approved for use in kidney transplantation and there is only minimal data in other organ transplants. Astagraf is not indicated for liver transplant due to data showing increased mortality in female recipients in post-hoc analysis (Astagraf 2015). The package insert of both extended release formulations emphasizes that the medications are not interchangeable or substitutable with the immediate release formulation. Astagraf was studied as de novo immunosuppression (Silva et al. 2007, 2014; Kramer et al. 2010) and conversion (Alloway et al. 2005) from twice

daily formulations. Current recommendations are to convert twice daily tacrolimus dosing to extended release Astagraf in a 1:1 total daily dose base but consider a 20% increase during the first week post-transplantation (Van Hooff et al. 2012).

Phase II and III clinical trials with Envarsus demonstrated 15–30% lower dose requirements than with twice daily dosing in general, and a 15% lower dose in African Americans. Envarsus has 50% more bioavailability than bid tacrolimus so for conversions of twice daily tacrolimus to Envarsus, the twice daily tacrolimus dose should be reduced by 20% (Bunnapradist et al. 2013; Rostaing et al. 2016). The flatter pharmacokinetics seen with Envarsus with lower peak-trough fluctuations is probably the cause of lesser peak-related side effects like tremors, insomnia, and fatigue. Due to the decreased dose requirement, Envarsus presents a more favorable PK profile for patients with CYP3A5.1 considered rapid metabolizers of tacrolimus and highly prevalent in African Americans.

T Cell-Directed Therapies that Target Signal 2: Costimulation Blockade

Belatacept

The interaction between the antigen presenting cell surface molecule CD80/86 and CD28 from T cells is necessary for effective T cell activation and it is referred as costimulation. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) is a cell surface molecule that is expressed in T cells. Its function is to bind CD80/86 competitively and downregulate the T cell response. Abatacept was the first-generation costimulation blocker composed of Fc fragment of a human IgG1 fused to the extracellular domain of CTLA4. Abatacept is approved for treatment of autoimmune disorders such as adult rheumatoid arthritis and juvenile idiopathic arthritis but it is also used off label for renal disorders such as focal segmental glomerulosclerosis. Abatacept was not effective in preclinical studies of organ transplantation so a second-generation costimulation blocker was then developed for use in transplantation. Belatacept was approved by the FDA in 2011 after 3-year data outcomes were obtained by two phase 3 clinical trials in both standard criteria (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial or BENEFIT trial (Vincenti et al. 2010, 2012a)) and expanded criteria kidney recipients (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial–Extended Criteria Donors or BENEFIT-EXT trial (Durrbach et al. 2010; Pestana et al. 2012)) that used low intensity and high intensity belatacept arm versus CYA maintenance. Belatacept is not approved for liver or any other organ transplant except kidney. The population included in the BENEFIT trial was mainly Caucasian with a really low representation of African Americans/Blacks, and less than $<15\%$ of patients in every arm had PRA $>20\%$, so we can conclude it was mainly a low immunological risk population. The BENEFIT trial that included standard criteria deceased donors and living donors demonstrated lower rates of graft loss and death in the low-intensity belatacept group compared to cyclosporine (CYA) despite higher rates of rejection even after extended follow-up (up to 7 years now (Vincenti et al. 2016)). Belatacept was used in combination with basiliximab induction, mycophenolate mofetil, and glucocorticoids for maintenance immunosuppression. Belatacept use was associated with higher rates of post-transplant lymphoproliferative disorder (PTLD) especially in Epstein Barr virus (EBV) naïve patients or patients that used lymphocyte depletion agents for induction, and its current indication is restricted to EBV positive patients. The BENEFIT-EXT trial that included extended criteria deceased donors showed similar patient and graft survival between the belatacept and CYA arms but lower measured glomerular filtration rates. There were also similar rates of rejection, infections, and malignancies between the treatment groups and again higher rates of PTLD in EBV naïve patients. Currently the bigger barriers for belatacept use are its increased cost, the need for IV infusion, and the lack of comparison trials with tacrolimus. A recent retrospective trial that used registry

data compared 1 year clinical data between kidney recipients treated with tacrolimus alone, belatacept alone, and tacrolimus plus belatacept at discharge from kidney transplantation (Wen et al. 2016). The rates of 1-year patient and graft loss in the two belatacept regimens were not different from those in the tacrolimus-alone group with significantly higher rejection rates in any of the belatacept groups compared to tacrolimus group. Rejection rates were higher in patients with high PRA that did not receive lymphocyte depleting agents for induction. Also recipients that would have been eligible for BENEFIT-EXT had higher renal function at 1 year in the belatacept arms. More studies that compare tacrolimus with belatacept protocols are needed but it will be reasonable to consider regimens that use belatacept and low dose tacrolimus with lymphocyte depletion agents in patients with high immunological risk. Currently, there are more than 40 clinical trials in renal transplantation that are using belatecept in different regimens that will help to shed light on how to combine this drug for different recipient needs.

Anti-CD40 (ASKP1240)

The interaction between CD40L (CD154) in activated T cells to CD40 in antigen presenting cells is a key stage in costimulation blockage as it upregulates CD80/86 in the antigen presenting cells. ASKP1240 is a fully human monoclonal IgG4 antibody to CD40 that is currently under development for use in kidney transplantation in either a CNI free-regimen or a CNI minimization regimen (Okimura et al. 2014; Harland et al. 2015).

T Cell-Directed Therapies that Target Signal 3, IL-2, and mTOR Pathway

After activation of signal 1 and 2, IL2 and other cytokines are released from the T lymphocyte. IL2 binds to IL2R or CD25 in the T cell causing downstream activation of phosphoinositide-3-kinase (PI3K) pathway and Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT) and eventually activate the mammalian target of rapamycin (mTOR) pathway. Upregulation of these pathways will allow the T cell to proliferate and expand peptide-specific effector T cells.

IL-2 Receptor Antagonists (Basiliximab)

Basiliximab is a humanized antibody towards CD25 (α-subunit chain of IL-2 receptor on activated lymphocytes). The term humanized means that Basiliximab is a chimeric human-mouse IgG with 25% of the IgG molecule being from murine origin and 75% from human origin. Basiliximab blocks IL-2 stimulated T cell replication. It is used intravenously in two divided doses (intraoperative and day 4 post-transplantation) to prevent transplant rejection as part of induction protocols in low immunological risk patients. In general, it is well tolerated with mainly GI side effects.

Sirolimus and Everolimus

Sirolimus is macrolide antibiotic from *S. hygroscopicus* from Easter Island. It binds to FKBP and the formed complex binds to mTOR (mammalian target of rapamycin). The mTOR pathway leads to cell cycle progression from G1 to S phase and proliferation in response to cytokine stimulation, including but not limited to IL-2. Sirolimus was approved for its use in kidney transplantation in 1999 with the hope that it would improve long-term transplant outcomes due to the lack of nephrotoxicity. Everolimus is a metabolite of sirolimus with shorter half-life than the parent compound. De novo use of sirolimus was found to be difficult due to the increased rates of wound dehiscence, urinomas and seromas, as well as prolonged delayed graft function and increased rejection. Further systematic reviews also showed increased mortality (Knoll et al. 2014). Sirolimus then was used concomitantly following conversion from CYA. Initial studies showed a significantly higher eGFR in the sirolimus group at 12 months post-transplant

(Budde et al. 2011) but the same data were not reproduced in later studies (Weir et al. 2011; Flechner et al. 2011). Also when the conversion from a CNI to sirolimus was done more than 6 months post-transplant, only patients with higher GFRs and that did not have proteinuria benefitted in the long run (Schena et al. 2009).

Besides the limited efficacy, mTOR inhibitors are associated with significant toxicity which limits further its widespread use. Hyperlipidemia, proteinuria, mouth ulcers, pneumonitis, interstitial lung disease, sodium retention, thrombocytopenia, and an increased renal toxicity with calcineurin inhibitors when used concomitantly are some of the main side effects observed besides the well-known wound healing, and delayed graft function issues. Sirolimus has also been associated with cases of thrombotic microangiopathy and post-transplant diabetes. Despite the significant side effects, sirolimus has been associated with decreased risk of skin cancers (Euvrard et al. 2012), and it is possible that sirolimus has antitumor effects in other cancers.

Currently the use of sirolimus is mainly in patients with CNI toxicity, in patients with malignancies and with PTLD.

Janus Kinase Inhibition (Tofacitinib)

Tofacitinib (tositinib, CP-690,550) is a Janus associated kinases inhibitor (JAK3 and JAK2), which inhibits cytokine signaling through the IL-2Rγ chain. It has been used in different trials in kidney transplantation as an alternative to CNI. Initial enthusiasm with this small molecule (phase IIb trial showed similar rates of acute rejection when compared to cyclosporine, with better renal function and chronic allograft changes at 12 months) has been tainted by an increased rate of infections in patients treated with tofacitinib, specifically cytomegalovirus, BK virus, and also increased rates of PTLD (Vincenti et al. 2012b). Currently, the pursuit of the transplantation indication has been abandoned by the pharmaceutical company as tofacitinib has been successful for the treatment of rheumatoid arthritis and the company is focused on other autoimmune disease indications.

Inhibitors of Purine or Pyrimidine Synthesis (Antimetabolites)

Azathioprine (AZA)

AZA is a derivative of mercaptopurine. It was the first immunosuppressant used in transplantation in conjunction with steroids. Initially AZA gets metabolized in the liver to 6-mercaptopurine (6-MP) and thanks to hypoxanthine-guanine phosphoribosyltransferase (HGPRT) 6-mercaptopurine is converted to 6-mercaptopurine nucleotide, and ultimately to thioinosinic acid, a nucleotide analog. The metabolites incorporate into replicating DNA, halting replication, as well as blocking the pathway for purine synthesis. AZA strongly affects proliferating cells, such as the T cells and B cells of the immune system. 6-MP can also be inactivated by two enzymes, thiopurine s-methyltransferase (TPMT) and xanthine oxidase (XO), to nontoxic metabolites. Allopurinol inhibits xanthine oxidase, thus promoting AZA toxicity by increasing its bioavailability fivefold. There are also different polymorphisms of the TPMT gene that will result in different enzyme activity. Up to 10% of the general population may present with reduced TMPT activity with 0.3% of the population presenting a real enzyme deficiency (Mcleod and Siva 2002). There are more than 25 variant alleles described with different clinical relevance. Four variant alleles account for >95% of reduced TPMT activity: TPMT*2 (238G>C), TPMT*3A (460G>A and 719A>G), TPMT*3B (460G>A), and TPMT*3C (719A>G). Wild type TPMT1* homozygotes have normal enzyme activity. Patients with TPMT deficiency treated with standard doses of AZA or 6-MP are at significantly increased risk of side effects. TPMT genotyping can identify patients who are at an increased risk for developing AZA toxicity and is easily available in commercial labs. AZA can be used either orally or IV with a 1:1 conversion. AZA is widely distributed but does not cross the blood brain barrier and is excreted primarily in urine. Usual maintenance doses range from 1–3 mg/kg in one or two divided doses.

The main side effects of AZA are leukopenia, bone marrow depression, macrocytosis,

gastrointestinal toxicity and less likely, liver toxicity. Blood counts should be monitored during AZA treatment.

Mycophenolate Mofetil (MMF)

MMF is a semisynthetic derivative of mycophenolic acid (MPA) from penicillium molds. MMF blocks the proliferation of T and B cells by inhibiting inosine monophosphate dehydrogenase (IMP), an enzyme that is crucial for purine synthesis. MMF was approved in the 1990s for use in kidney transplantation after three large randomized studies showed its improved efficacy over AZA in combination with CYA and steroids (European Mycophenolate Mofetil Cooperative Study Group 1995; The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group 1996; Sollinger 1995).

MMF can be given orally and IV with a 1:1 conversion rate. MMF is converted to the active form MPA by esterases in the stomach, small intestine, and other tissue including the liver. MPA is extensively bound to plasma proteins and is metabolized in the liver by glucuronidation, and excreted in urine as glucuronide conjugate (MPAG). Some MPAG gets deconjugated in the gut and enters the enterohepatic circulation adding to the active drug pool.

MMF absorption is reduced by CYA as CYA inhibits the biliary secretion of MPA glucuronide (MPAG) through multidrug resistance protein 2 transporter, resulting in decreased MPA reabsorption during enterohepatic recirculation. Dose of MMF should be adjusted accordingly when patients are switched from tacrolimus to CYA. Usual doses range from 1500 mg to 2000 mg divided in two daily doses.

MPA main toxicity is gastrointestinal including nausea, vomiting, and diarrhea, in up to 10% of the patients. Abdominal pain, leukopenia, and neutropenia are also common. An enteric-coated formulation of mycophenolate sodium or myfortic was developed to decrease the upper gastrointestinal side effects (nausea and vomiting). Enteric-coated formulations have similar efficacy than MMF with some studies showing marked decrease in gastrointestinal side effects (Salvadori et al. 2004; Bolin et al. 2007; Chan et al. 2006). For conversion of MMF to enteric-coated formulations, 250 mg of MMF are considered equivalent to 180 mg of the enteric-coated formulation.

MPA is contraindicated during pregnancy as it is associated with increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, including external ear and facial abnormalities including cleft lip and palate. MMF has also been associated with anomalies of the distal limbs, heart, esophagus, kidney, and nervous system.

Therapeutic drug monitoring is not widely used for MMF as trough levels do not correlate well with total exposure of the drug and AUC measurements are cumbersome to do. Also studies that looked at fixed and concentration controlled doses of MMF have not consistently shown improved outcomes in the therapeutic drug monitoring groups (Gaston et al. 2009).

Agents that Target Cytokines

Corticosteroids

Steroids have always been part of the backbone for immunosuppression for renal transplantation. Steroids affect the immune system through several mechanisms but mainly by decreasing the production of cytokines (IL-1, IL-2, interferon, TNFα). Inhibition of cytokines then suppresses T-cell helper function, decreases T lymphocyte proliferation (IL-2), facilitates eosinophil apoptosis (IL-5), and inhibits antigen processing by macrophages (IL-1 and TNFα). Steroids have little effect on neutrophil function or beta cell function.

Corticosteroids are potent immunosuppressive and anti-inflammatory agents but are associated with a myriad of metabolic side effects including adrenal suppression, osteoporosis, hypercholesterolemia, hyperglycemia, hypertension, and cataracts.

Corticosteroid withdrawal protocols have been studied in randomized controlled trials and discontinuation of steroids 7 days post-transplantation has not been associated with detrimental

outcomes at 12 months post-transplantation when used in conjunction with thymoglobulin induction and tacrolimus and MMF maintenance (Woodle et al. 2010).

Tocilizumab

Tocilizumab is a first-in-class humanized monoclonal antibody with specificity for IL-6R. Tocilizumab binds to both soluble and membrane-bound forms of IL6 receptor. It is approved by the FDA for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. IL6 contributes to CD8 T cell and B cell differentiation. Recently, a phase I/II trial of tocilizumab as a desensitization agent has been published. The trial included highly sensitized patients who failed desensitization with intravenous immunoglobulin and rituximab (ClinicalTrials.gov identifier NCT01594424) (Vo et al. 2015). This first study of tocilizumab in human kidney transplants demonstrates that the drug has a good safety profile and encouraging efficacy. Larger trials will be necessary to assess efficacy end points.

B Cell-Directed Therapy

Rituximab

Rituximab is a chimeric monoclonal antibody againts CD20 (70% human and 30% murine). Rituximab binds to CD20 on B cells and mediates B-cell lysis through multiple mechanisms, including complement-dependent cytotoxicity, growth arrest, and apoptosis. Rituximab causes a profound and long-lasting B cell depletion that can be maintained up to 6–9 months. Rituximab use in kidney transplantation has been focused in the treatment of antibody mediated rejection (Sautenet et al. 2016), induction therapy (Macklin et al. 2015; Cheungpasitporn et al. 2015), and for desensitization protocols (Vo et al. 2008; Kahwaji et al. 2016). No randomized trials have been published that support efficacy of rituximab in any of its current off-label uses. Side effects are mainly related to infusion reactions (fever, chills, rash, urticaria, hypotension, bronchospasm, acute respiratory distress syndrome) and also infection reactivations such as hepatitis B and C and progressive multifocal leukoencephalopathy due to reactivation of JC virus.

Anti CD20 therapies that are more humanized (ocrelizumab) or fully humanized (ofatumumab) have been developed but its use in transplantation has not been studied.

Bortezomib

Bortezomib is a proteasome inhibitor that was approved in 2003 by the FDA for treatment of multiple myeloma. Proteasome inhibition causes inhibition of the cell cycle and apoptosis in plasma cells. In renal transplantation it has been mainly used to treat antibody mediated rejection (Cicora et al. 2013; Gupta et al. 2014) and also as part of desensitization protocols (Shah et al. 2015). The studies where bortezomib has been used have been small and with conflicting results, but bortezomib may have some role in the treatment in early antibody mediated rejection (Walsh et al. 2012). The role in desensitization protocols is still unclear. Recent data has shown that bortezomib is able to decrease HLA antibodies for up to 10 months (Woodle et al. 2015), although other cohorts were only able to show a modest reduction of HLA antibodies after an intensive course of treatment and with more side effects (Moreno Gonzales et al. 2016). The main side effect of bortezomib is peripheral neuropathy, although gastrointestinal side effects and cytopenias are also common. In general, bortezomib is well tolerated.

Complement Inhibition: Eculizumab

Eculizumab is a humanized monoclonal antibody to C5 that effectively inhibits its cleavage to C5a and C5b. Because C5a is a neutrophil chemoattractant and because C5b is required to form the C5b-9 membrane attack complex, inhibition of this enzymatic step results in blockade of pro-inflammatory, pro-thrombotic, and lytic functions of complement. Approved for its use in paroxysmal nocturnal hemoglobinuria, and atypical

hemolytic-uremic syndrome (HUS), its use in renal transplantation has been in the setting of antibody mediated rejection (Stegall et al. 2011) and in desensitization protocols. The main risk of eculizumab is infection from encapsulated organisms, and vaccination to Neisseria, Pneumococcus, and Haemophilus is required before its use.

Immunosuppressive Agents with Multiple Cellular Targets

Polyclonal Antithymocyte Globulin (ATG)

Antibody to lymphocyte antigens have been created in different ways. Immunization of rabbits (Thymoglobulin) or horses (Atgam) to human thymocytes or immunization of rabbits to lymphocytes from a Jurkat T cell leukemia line (Fresenius antithymocyte globulin) results in polyclonal antibodies after purification of IgG fraction from the serum. These polyclonal antibodies are directed to multiple T cell epitopes and bind to the surface of circulating T lymphocytes making them susceptible to phagocytosis in the liver and spleen, to complement-derived cytolysis, and to apoptosis. The result is profound lymphopenia and impaired T-cell responses and cellular immunity. Even though thymocytes were used as the main antigenic stimulus, many other cells of the immune system will share same epitopes and that is why ATG will also have some effects in B cells, neutrophils, and monocytes. They are used mainly as IV preparations for transplant induction and to treat allograft rejection and the dose is usually 5 mg/kg divided over 4–5 days. Side effects include cytokine release syndrome or serum sickness reactions (including fever, chills, flu-like syndrome, hypotension, pulmonary edema), and anaphylaxis. They are also associated occasionally with significant thrombocytopenia.

Panlymphocyte Depleting Agents

Alemtuzumab is a humanized monoclonal antibody that targets CD52, present in T and B cells, most monocytes, macrophages, and natural killer cells, causing cell lysis and prolonged cell depletion (up to 6–12 months). Alemtuzumab has been used mainly as an induction agent. Since 2012 alemtuzumab is not available commercially as the manufacturer removed the drug from the market in preparation for relabeling change for its use in multiple sclerosis. Consequently, its use is currently greatly diminished. Its main side effect is profound and prolonged lymphopenia with increased risk for infection including CMV and PTLD. Alemtuzumab is a humanized antibody and infusion reactions are also possible.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is a pool of immunoglobulins purified from multiple donors that contains unselected IgG antibodies with the same subclass distribution as the normal serum. It was initially developed for use in humoral immune-deficiencies as a monthly infusion but has been used widely in other autoimmune and inflammatory diseases. The mechanism of action of pooled immunoglobulins includes modulation of B and T cell responses as well as anti-inflammatory and inhibition of cell growth. IVIG can be used in low doses (100 mg/kg) in acute antibody rejection protocols in combination with plasmapheresis, or at high doses up to 2 g/kg for a maximum of 140 g in a single administration in transplant desensitization protocols (Jordan et al. 2011). The main side effects of IVIG include infusion reactions with fever, chills, nausea, vomiting, hypotension, flushing, and the older formulation were also associated with acute kidney injury secondary to osmotic injury. There is also the possibility of anaphylactic reactions in patients with IgA deficiency that can produce anti-IgA antibodies. In general IVIG is considered more as an immunemodulator agent versus immunosuppressant agent.

Other Agents in the Pipeline

IdeS is an enzyme purified from *Streptococcus pyogenes* that degrades immunoglobulin G

(IgG). It cleaves all the IgG human subclasses preventing IgG-mediated antibody-dependent cellular cytotoxicity and complement-mediated injury. Recent data showed good safety in normal human subjects (Winstedt et al. 2015). This finding could be very important in the prevention and treatment of antibody-mediated rejection. Studies of this agent are now underway in Sweden and the United States (ClinicalTrials.gov identifier NCT02426684).

The success with belatacept has shown that blockage of the costimulation signal is an effective target for transplant immunosuppression giving grounds to the development anti-CD28 antibodies. Selective blockade of CD28 allows CTLA4 and PD-L1 to bind to CD80/CD86 and activate the inhibitory pathways resulting in added immunosuppression effects on T cells. In contrast to CTLA4 Ig or belatacept, anti-CD28 antibodies may have less of an adverse effect on T regulatory cells that require signaling through CTLA4 for optimal function (Vanhove et al. 2003). There are currently two anti-CD28 antibodies in preclinical development (FR104 from Effimune (Poirier et al. 2015) and BMS-931699 from Bristol Myers Squibb).

Conclusion

Multiple new agents have emerged in the past 10 years that are still under investigation in different combinations and compared with the cornerstone of maintenance immunosuppression treatment that is based in tacrolimus and mycophenolate mofetil. Immunosuppression for solid organ transplants will likely continue to expand in the incoming years as drug development within the oncology and autoimmune disease arena can frequently be extrapolated to the transplant population. Short-term and long-term transplant outcomes have to be weighed against the risk of infection and malignancy. The main future challenge will be to demonstrate that the new drugs are superior to tacrolimus and mycophenolate mofetil combinations which would allow CNI substitution and the possibility of better long-term outcomes.

Cross-References

- ▶ Immunology of Kidney Transplantation
- ▶ Medical Complications After Kidney Transplantation: Early
- ▶ Medical Complications After Kidney Transplantation: Late

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Infection in Kidney Transplantation

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Abstract

Infection is an important cause of morbidity and mortality after kidney transplantation. It has been estimated that 70% of kidney transplant recipients will experience an infection episode within the first 3 years after transplantation (Dharnidharka et al. 2007). After cardiovascular disease, infection is the second leading cause of death in recipients with allograft function (Snyder et al. 2009). The immunosuppressive therapy required to prevent organ rejection places the kidney transplant recipient at increased risk for donor-derived, nosocomial, and community-acquired infections as well as reactivation of latent pathogens. Pretransplant screening, immunizations, and optimal antibacterial and antiviral prophylaxis can help to reduce the impact of infection. Awareness of the approach to infection in the transplant recipient including diagnostic and management strategies is essential to optimizing outcomes.

Keywords

Renal transplant · Solid organ transplant · Immunocompromised host · Viral · Bacterial · Fungal · Atypical infections

Introduction

A total of 17,600 kidney transplants were performed in the United States in 2013. As the incidence of acute rejection has declined, the probability of graft and patient survival continues to improve (USRDS 2015). Infection, however, remains an important cause of morbidity and mortality after kidney transplantation. It has been estimated that 70% of kidney transplant recipients will experience an infection episode within the first 3 years after transplantation (Dharnidharka et al. 2007). After cardiovascular disease, infection is the second leading cause of death in recipients with allograft function (Snyder et al. 2009). The immunosuppressive therapy required to prevent organ rejection places the kidney transplant recipient at increased risk for donor-derived, nosocomial, and community-acquired infections as well as reactivation of latent pathogens.

Infection Timeline

The kidney transplant recipient's net state of immune suppression and epidemiologic exposures determine the risk for infection at a given time. A traditional timeline has been used to predict patterns of infection after organ transplantation. This timeline has been altered in recent years with changes in immunosuppressive therapy and the routine use of antibacterial and antiviral prophylaxis. Treatment for acute rejection and coinfection with viruses such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may also alter predictable patterns of infection (Fishman 2007).

The basic concepts of the traditional timeline, however, are still used to establish a differential diagnosis for infection at varied intervals post-transplantation (Fig. 1). Within the first month, infections are noted to include those related to surgical complications, nosocomial exposures, and donor-derived pathogens. Multidrug-resistant organisms including Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), and Carbapenem-resistant enterobacteriaceae (CRE) are important considerations, as is *Clostridium Difficile*. Urinary tract

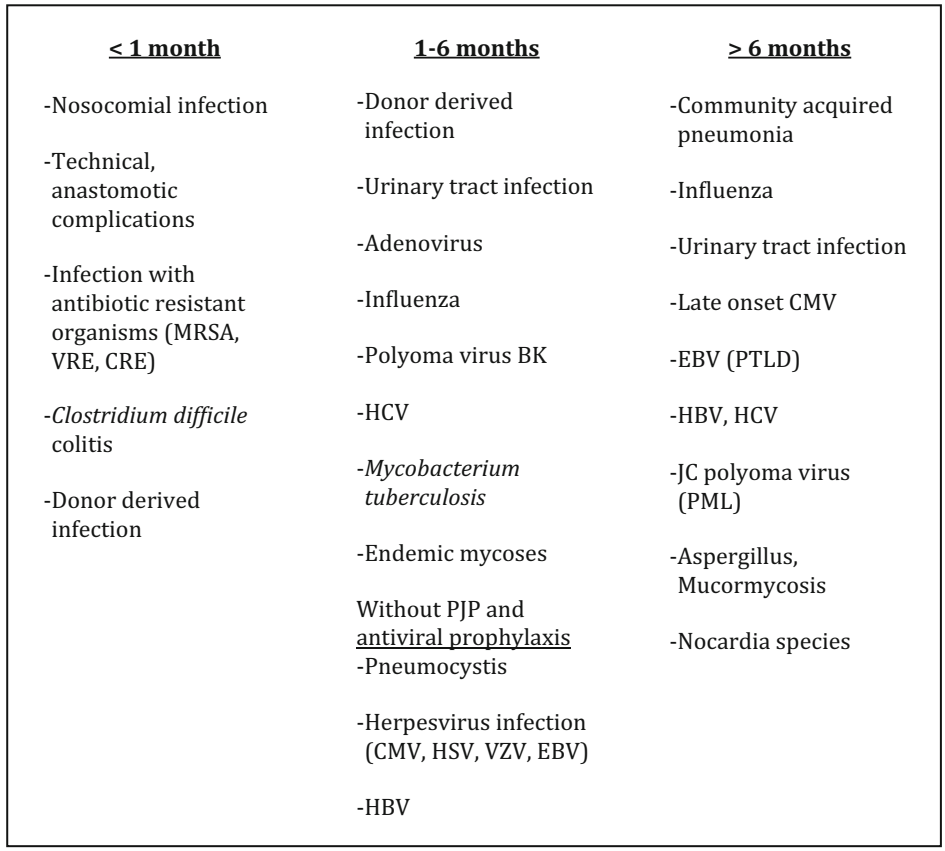

Fig. 1 Timeline of infection after kidney transplantation

infections are common within the first 6 months. Opportunistic infections are more likely to occur 1–6 months after transplantation, reflecting the greater impact of immune suppression during this time. Reactivation of latent pathogens such as polyoma virus BK, hepatitis C virus (HCV), and mycobacterium tuberculosis may also occur. Prophylaxis for *Pneumocystis jiroveci,* herpes viruses including CMV, and hepatitis B virus (HBV) makes these infections less common during this time period. Beyond 6 months, the degree of immune suppression for most patients decreases. Risk remains, however, for community-acquired infection, environmental exposures, recurrent infection, and the late presentation of viral infection, in particular CMV, once prophylaxis has been discontinued (Fishman 2007; Karuthu and Blumberg 2012).

Pretransplant Screening

Interventions can be undertaken to reduce the impact of infection after kidney transplantation. Pretransplant screening of donors and recipients for infection that can be transmitted with organ donation or reactivated in an immune suppressed recipient is essential for optimizing transplant outcomes. Guidelines for pretransplant screening are available from the American Society for Transplantation (Fischer et al. 2013), Kidney Disease: Improving Global Outcomes (KDIGO 2009) and the US Public Health Service (Seem et al. 2013). Recommended screening tests for donors and recipients are listed in Table 1.

Screening of living donors is performed prior to transplantation with varied timing. If there is a

Table 1 Pretransplant screening

Pathogen and test	Donor status	Recipient status	Recommendation
HIV: Anti-HIV ½ or HIV Ag/Ab combination assay and HIV NAT	HIV(+)	HIV(−)	Reject
	HIV(−)	HIV(+)	Consider if HIV is well controlled
	HIV(+)	HIV(+)	Consider if HIV is well controlled
HCV: Anti-HCV and HCV NAT	HCV(+)	HCV(−)	Reject, may be a consideration in the future
	HCV(−)	HCV(+)	Consider, HCV(+) candidates should have a liver biopsy, improved outcomes if HCV is treated pretransplant
	HCV(+)	HCV(+)	Consider (as for D−/R+)
HBV: HBsAg, HBsAb and HBcAb (IgM/IgG); HBV NAT (center dependent)	sAg(−), cAb(−)	sAg(−), cAb(+), sAb(+/−)	Accept, vaccinate sAb(−) candidates
	sAg(+/−), cAb(+/−)	sAg(+), cAb (+)	Consider, with prophylaxis posttransplant
	sAg(−), cAb(+)	sAg(−), cAb (+/−), sAb (+/−)	Accept if donor is cIgM(−) and vaccinate sAb(−) candidates, offer prophylaxis posttransplant if sAb(−) or lost; reject if donor is cIgM(+)
	sAg(+), cAb(+)	sAg(−), cAb (+/−), sAb (+/−)	Reject
CMV IgG	CMV(+) or (−)	CMV(+)	Accept; will need posttransplant prophylaxis or preemptive therapy
	CMV(+)	CMV(−)	Accept; high risk for CMV infection, will need posttransplant prophylaxis
EBV IgG	EBV(+) or (−)	EBV(+)	Accept
	EBV(+)	EBV(−)	Accept; at risk for primary EBV and PTLD, monitor posttransplant
HSV 1/2 IgG	HSV(+)	HSV(+) or (−)	Accept; Acyclovir prophylaxis used for CMV D−/R−
HTLV 1/2 antibody (optional)	HTLV ½(+)	HTLV ½(−)	Reject if HTLV 1+; need Western blot testing or NAT to distinguish HTLV 1 from 2
VZV antibody	NA	VZV−	Vaccinate prior to transplant
RPR, VDRL	RPR or VDRL(+)	RPR or VDRL(+/−)	Accept; recipient will need treatment with penicillin if donor or recipient tests positive and is confirmed with a treponemal-specific test and not treated
Toxoplasma gondii IgG	Toxoplasma(+/−)	Toxoplasma (+)	Accept; TMP/SMX prophylaxis posttransplant
	Toxoplasma(+)	Toxoplasma (−)	Accept; TMP/SMX prophylaxis posttransplant
Tetanus, diphtheria and acellular pertussis	NA	Confirm vaccination history	Vaccinate candidates if not vaccinated as adult
Streptococcus pneumoniae	NA	Confirm vaccination history	Vaccinate candidates prior to transplant

(*continued*)

Table 1 (continued)

Pathogen and test	Donor status	Recipient status	Recommendation
Measles, mumps and rubella	NA	MMR titer	Vaccinate candidates if titer(−) (not to be given posttransplant)
Influenza	NA	Confirm vaccination history	Vaccinate candidates annually
Mycobacterium tuberculosis: PPD or interferon-gamma release assay	Screen *live* donor PPD or interferon-gamma release assay(+)	PPD or interferon-gamma release assay(+)	Evaluate for active TB in any (+) live donor or candidate; delay transplant until active TB is treated; recipient can complete treatment for latent TB after transplant
CNS viral pathogens (e.g. LCMV, rabies, WNV)	Clinical suspicion	NA	Reject
Strongyloides stercoralis IgG (based on exposure, prevalence of infection in region)	Screen *live* donor Strongyloides(+)	Strongyloides (+/−)	Treat (+) donor or recipient with Ivermectin prior to transplant
West Nile virus NAT (based on exposure, prevalence of infection in region)	Screen *live* donor: WNV NAT(+)	NA	Reject
	Screen *deceased* donor: Unexplained febrile or neurologic illness(+)	NA	Reject
Zika virus, also consider dengue virus and chikungunya virus (based on history of exposure, prevalence of infection in region)	Zika infection(+)	NA	Defer transplant
	Travel to Zika area in past 28 days(+)	NA	Defer transplant The risk of Zika transmission should be balanced with the benefit of the transplant
Endemic mycoses *Coccidioides* IgM/IgG, *Histoplasma* Ab (based on exposure, prevalence of infection in region)	Screen *live* donor *Coccidioides* or *Histoplasma*(+)	*Coccidioides* or *Histoplasma* (+)	Treat donor or recipient with active infection prior to transplant. Consider prophylaxis posttransplant if donor or recipient has latent infection

significant delay (more than 28 days) between screening and the time of transplant, living donors should be re-evaluated to rule-out recently acquired infection. The CDC recommends that all living donors be rescreened for human immunodeficiency virus (HIV) prior to donation to exclude recent infection (CDC 2011). Repeat screening for HCV and HBV may also be indicated if risk factors for infection are identified (Fischer et al. 2013).

Deceased donor screening, in contrast, is under time constraints and is usually performed within hours of transplantation in coordination with organ procurement organizations. Infection with HIV, HBV, and HCV may not be detected in the early stages of infection. Many transplant centers now perform more sensitive rapid molecular testing on potential organ donors including nucleic acid amplification (NAT) testing for HIV, HBV, and HCV. A comprehensive medical and social history on potential organ donors is required in order to identify risk factors for blood borne pathogens. In efforts to expand the pool of available organs, recipients may consent to receipt of a kidney from a NAT negative donor who is deemed "high risk" for blood borne infection based on identified risk factors. Recipients of such organs are monitored posttransplantation with testing for HIV, HBV, and HCV between 1 and 3 months and for HBV again at 12 months (Fischer et al. 2013; Seem et al. 2013; Kovacs et al. 2014; Len et al. 2014). Use of HCV- and HBV-positive organs can be considered in respective positive recipients. Furthermore, in 2013 the HIV Organ Policy Equity

Act lifted a long-standing ban on allowing HIV-positive organs to be donated to HIV-positive recipients (Mgbako et al. 2013; Muller et al. 2015).

Donors who have active bacterial infection at the time of kidney procurement may transmit infection to the recipient. Screening for bacterial infection in kidney donors includes assessing for urinary tract infection and bacteremia. Urine and blood culture data are reviewed. If a kidney donor is known to have a urinary tract or systemic infection with a virulent organism such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Candida* species, the organ recipient is usually treated with a 10–14 day course of targeted antimicrobial therapy since these bacteria can compromise vascular and urinary anastomoses leading to mycotic aneurysms, anastomotic, and organ failure (Fischer et al. 2013). Allograft contamination can occur during organ procurement or processing. Interpretation of organ preservation fluid cultures is challenging. The risk of transmission of infection to the organ recipient from contaminated preservation fluid, however, is low (Fischer et al. 2013; Len et al. 2014).

Vaccinations

Candidates for kidney transplantation should have their vaccine status reviewed and updated in accordance with recommendations issued by the Advisory Committee on Immunization Practices with the Centers for Disease Control and Prevention (CDC 2012). While vaccinations in end stage renal disease patients may be less effective and durable than in healthy patients, a better response can be anticipated prior to transplantation than after (Janus et al. 2008; Kausz and Pahari 2004).

Special consideration should be given to vaccination for pneumococcus, influenza, and HBV. Two pneumococcal vaccines are currently licensed for use in the United States: the 13-valent pneumococcal conjugate vaccine (PCV 13, Prevnar 13) and the 23-valent-pneumococcal-polysaccharide vaccine (PPSV 23, Pneumovax 23). Current guidelines recommend that unvaccinated patients with chronic renal failure receive PCV 13 followed at least 8 weeks later by PPSV 23 (Kobayashi et al. 2015). A second dose of PPSV 23 is recommended 5 years after the first dose (CDC 2012). Influenza vaccination should be administered annually. There are a number of influenza vaccine formulations available. Live attenuated influenza vaccination (FluMist) is not recommended in chronic kidney disease patients. An inactivated vaccine option should be used (CDC 2012). A high dose inactivated influenza vaccine is now available and was shown to induce a higher antibody response than traditional vaccines in adults over the age of 65 (Diaz-Granados et al. 2014). The use of this vaccine in transplant candidates and recipients is currently under investigation. Transplant candidates not immune to HBV should receive high dose HBV vaccination (40 micrograms antigen per dose) due to decreased response rates with standard dosing (Huprikar et al. 2015).

Viral Infections

Cytomegalovirus Infection

Human cytomegalovirus-human herpes 5 (CMV), a member of the family Herpesviridae, is an opportunistic pathogen occurring in 20–60% of solid organ transplant recipients (Brennan 2001). CMV is a cause of significant morbidity and mortality in this population (Mwintshi and Brennan 2007). The incidence of CMV in the renal transplant population is estimated to be between 8% and 32% (Patel and Paya 1997). Renal transplant patients are at lower risk for primary CMV compared with other organ transplant recipients owing to a lower burden of latent virus in renal allograft tissue.

The risk factors for development of CMV disease include donor seropositivity/recipient seronegativity(D+/R−), use of induction immunosuppression (antilymphocyte antibodies), donor age >60 years, simultaneous kidney-pancreas transplantation, treatment for acute rejection, impaired transplant function, and concurrent infection from other viruses (like EBV and HHV-6 and 7) (De Keyzer et al. 2011). CMV-seronegative recipients of CMV-seropositive donors (D^+/R^-) are at the highest risk, whereas D^+/R^+ or D^-/R^+ transplantations are

considered to be moderate risk with D^-/R^- being lowest risk, with an incidence of CMV disease <5% (De Keyzer et al. 2011). Immunosuppressive drugs also influence the incidence and severity of CMV disease. For instance, cyclosporine increases the risk of CMV disease, whereas use of sirolimus seems to have a protective effect (San Juan et al. 2008) The use of antilymphocyte antibody (antithymocyte globulin or muromonab-CD3) is associated with a two to fivefold increase in the rate of CMV, but basiliximab and daclizumab do not seem to increase its incidence (De Keyzer et al. 2011).

CMV infection may occur in solid organ transplantation recipients as primary infection when a CMV seronegative individual receives cells latently infected with CMV from a seropositive donor, donor-derived reinfection, or reactivation of latent recipient infection (Patel and Paya 1997). The following definitions are commonly used in the transplant literature to differentiate CMV infection from CMV disease. CMV infection is evidence of CMV replication regardless of symptoms, and CMV disease is evidence of CMV infection with symptoms, such as viral syndrome, leukopenia, thrombocytopenia, or invasive tissue disease (e.g., pneumonitis, hepatitis, retinitis, gastrointestinal disease) (Humar and Snydman 2009). CMV disease and even asymptomatic CMV infection have been shown to be independent risk factors for reduced graft survival and overall mortality beyond 100 days post-transplantation (Sagedal et al. 2004). Infection with CMV has been implicated in acute allograft dysfunction and chronic allograft nephropathy (McLaughlin et al. 2002; Tong et al. 2002). CMV disease is also associated with posttransplant lymphoproliferative disorder (PTLD), post-transplant diabetes mellitus, and transplant artery stenosis (Pouria et al. 1998; Hjelmesaeth et al. 2004; Manez et al. 1997).

CMV infection can occur as acute infection between the first and 6 months following transplant, when immunosuppression is at its maximum or as delayed infection from reactivation of latent virus after antiviral prophylaxis has completed, later in the first year. Given the significant effect of CMV on patient outcomes, prevention plays an important role. Serologic screening for CMV should be performed on both donor and recipient prior to transplant to categorize high risk patients. Several CMV vaccine candidates are under investigation although none are currently available. Universal prophylaxis involves giving antivirals to those recipients at risk post-transplant before the onset of infection, whereas in preemptive therapy patients are monitored at regular intervals and started on antivirals when there is early evidence of replication prior to onset of clinical disease. Chemoprophylaxis in high risk patients (D+/R−) has shown to reduce the incidence of CMV disease by 60% and has decreased CMV associated mortality and opportunistic infection (Hodson et al. 2005). Preemptive therapy in high risk patients based on CMV viral load monitoring has not shown reduction in acute rejection or all-cause mortality (Strippoli et al. 2006). A randomized controlled trial by Kliem et al. in 2008 comparing oral ganciclovir chemoprophylaxis with viral load monitoring revealed improved graft survival in those who received ganciclovir chemoprophylaxis (Kliem et al. 2008). A recent Cochrane review from 2013 concluded that the efficacy of preemptive therapy compared with prophylaxis to prevent CMV disease remains unclear due to significant heterogeneity between studies and that additional head-to-head studies are required to determine the relative benefits and harms of preemptive therapy and prophylaxis to prevent CMV disease in solid organ transplant recipients (Owers et al. 2013).

Standard prophylactic guidelines recommend therapy in D+/R−, D+/R+, and D−/R+ using oral ganciclovir or valganciclovir for a minimum of 3 months posttransplant and 1–3 months after treatment of rejection with antilymphocyte therapy (Humar and Snydman 2009; Kotton et al. 2013). Valganciclovir has replaced ganciclovir because of better bioavailability, lower pill burden, and reduced availability of oral ganciclovir (Paya et al. 2004). The optimal length of prophylaxis is unknown, but recent trials have shown that 6 months of prophylaxis is more effective in decreasing the incidence of CMV disease in D+/R− kidney transplant recipients (Humar et al. 2010; Doyle et al. 2006). Current guidelines recommend dosing valganciclovir at 900 mg daily

(adjusted for renal dysfunction) if tolerated in D+/R− recipients. Some centers have successfully treated patients with half of this dose (450 mg daily) with less drug toxicity. However, D+/R− recipients may be at higher risk of breakthrough infection and the development of resistance with this lower dosing strategy (Kotton et al. 2013).

The diagnosis of CMV disease can be made by several techniques including CMV antigenemia assay, nucleic acid testing (NAT), serology, antibody testing, viral culture, and histopathology. NAT is generally more sensitive than antibody testing or culture. Higher values by NAT are suggestive of CMV disease and weekly viremia testing can be used to monitor response to therapy. The interlaboratory variability of NAT is expected to be reduced with the recent establishment of international standards, intended to be used in the standardization of nucleic acid amplification technique (NAT)-based assays for HCMV (Karuthu and Blumberg 2012). Patients with gastrointestinal and neurologic CMV disease often fail to exhibit CMV viremia and histopathology is necessary to establish diagnosis in these instances.

Treatment of active CMV disease requires a combination of immunomodulation, antiviral therapy with or without adjuvant therapy and if possible, reduction of immunosuppression (Kotton et al. 2013; Green et al. 2004). The mainstay of therapy is intravenous ganciclovir. The VICTOR trial (Valcyte in CMV Disease Treatment of Solid Organ Recipients) demonstrated oral valganciclovir was not inferior to intravenous ganciclovir in mild to moderate CMV disease in solid organ transplant recipients (Asberg et al. 2009). The current guidelines recommend renally adjusted intravenous ganciclovir 5 mg/kg twice daily or oral valganciclovir, 900 mg twice daily for mild CMV disease (Kotton et al. 2013). In severe CMV disease, intravenous ganciclovir is preferred with reduction of immunosupression despite the increased risk of rejection (De Keyzer et al. 2011). The use of adjuvant therapy with CMV-specific hyperimmune globulin or standard intravenous immunoglobulin may be considered in individuals with hypogammaglobulinemia, severe systemic infection, or in failure to respond to standard therapy (Humar et al. 2010).

CMV resistance to ganciclovir has been noted in renal transplant recipients due to mutations in UL 97, the gene responsible for the first phosphorylation step in ganciclovir activation and UL 54, the gene responsible for DNA polymerase (Limaye et al. 2000). CMV resistance should be considered when patients have worsening disease or persistent, unchanged viremia at 2 weeks of therapy and in such cases, genotype testing for mutations of the genes encoding UL 97 and UL 54 should be performed (Weikert and Blumberg 2008). Treatment options for drug resistant CMV include the use of high dose ganciclovir, foscarnet, and cidofovir; however, no clinical trial data are available regarding optimal therapy options for resistant CMV. The use of novel agents including leflunomide and artesunate has been attempted as salvage therapy with varying success. Several new antiviral treatment options are currently under investigation including maribavir and brincidofovir (an oral prodrug of cidofovir with less nephrotoxicity) for use in the treatment of drug resistant CMV (Limaye et al. 2000).

Epstein Barr Virus Infection

Epstein Barr Virus – Human herpesvirus 4 (EBV) is a ubiquitous gamma herpes virus that remains latent in lymphocytes following primary infection. It is responsible for posttransplant lymphoproliferative disorder (PTLD) which increases morbidity and mortality in the transplant population. Approximately 62–79% of PTLD cases have been associated with EBV (Karuthu and Blumberg 2012). PTLD most commonly occurs in the first year posttransplant (Cockfield et al. 1993). The risk factors for PTLD include EBV naïve recipients who receive EBV seropositive organs, active primary EBV infection, younger recipient, coinfection by CMV and other viruses, prior splenectomy, second transplant, acute or chronic graft versus host disease, immunosuppressive drug regimen (OKT3 or polyclonal antilymphocyte antibody), and the type of organ transplanted. Kidney transplant recipients are at lower risk compared with other types of transplants and have an incidence

of approximately 1–3% (Gulley and Tang 2010; Allen et al. 2009; Taylor et al. 2005).

The majority of symptomatic EBV infections in renal transplant recipients are primary infection likely related to transmission of donor virus. EBV disease can be asymptomatic or presents with a nonspecific febrile syndrome, lymphadenopathy, hepatosplenomegaly, atypical+ lymphocytosis, hematologic disorders including anemia, leukopenia, thrombocytopenia, and organ-specific diseases like gastroenteritis, hepatitis, or pneumonitis (Allen et al. 2009). PTLD typically follows primary infection and frequently presents as a rapidly enlarging mass in the grafted organ, lymph nodes, bone marrow, or extranodal sites (Manez et al. 1997). PTLD is divided into four major histopathologic subtypes as per the World Health Organization (WHO): early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma type PTLD.

Definitive diagnosis of PTLD requires histopathologic confirmation by tissue excision biopsy with immunologic cell typing, cytogenetics, immunoglobulin gene rearrangements, and EBV-specific staining (Allen et al. 2009). Staging is performed by histologic types (monoclonal versus polyclonal, T cell versus B cell) and location (allograft, other organs, metastasis) (Weikert and Blumberg 2008). Clinical management of PTLD typically involves reduction of immunosuppression which can lead to remission in 23–86% of the patients (Weikert and Blumberg 2008). Antiviral therapy with acyclovir or ganciclovir is controversial and no evidence supports its efficacy (Taylor et al. 2005). Rituximab (monoclonal antibody to CD20) is commonly used for treatment of PTLD in recipients who failed reduction of immunosuppression alone (Allen et al. 2009). In isolated graft PTLD, surgical resection is an option (Weikert and Blumberg 2008). In patients that fail the above strategies, IFN and IVIG have been used with varying success and cytotoxic chemotherapy with radiation remains salvage therapy (Green et al. 2004).

There is no standardized therapy to prevent PTLD. KDIGO guidelines recommend monitoring EBV viral load in high risk renal transplant patients within the first week after transplant, then at least monthly for 3–6 months and then every 3 months for the rest of the first posttransplant year. Additional viral load monitoring is recommended after treatment for acute rejection in high risk groups (children, EBV D+/R−). Outcomes with PTLD in renal transplant patients vary according to the site involved. Patients with isolated graft involvement have a 5-year survival of 68% compared with those patients with PTLD extending beyond the allograft whose survival varied between 36% and 38% (Weikert and Blumberg 2008).

Herpes Simplex Virus and Varicella Zoster Virus Infection

Human herpesvirus 1 – herpes simplex virus types 1 and 2 (HSV) – and Human herpesvirus 3 – varicella zoster virus (VZV) – are alpha herpes viruses. HSV 1 has a seroprevalence of 60% in the adult population, while HSV 2 has a seroprevalence of 15% and VZV rates can be as high as 90% (Green et al. 2004). The incidence of HSV disease in renal transplant recipients is approximately 53% and VZV 4–12% (Patel and Paya 1997).

HSV may cause primary infection following which the virus remains latent in the sensory nerve ganglia or more commonly causes reactivation infection. HSV may be seen as early as in the first posttransplant month in the absence of prophylaxis. HSV infection usually presents with oral or genital mucocutaneous lesions, occasionally pneumonitis, tracheobronchitis, esophagitis, hepatitis, encephalitis, or disseminated infection (Green et al. 2004). VZV causes localized dermatomal or multidermatomal or disseminated zoster with or without visceral involvement (pneumonitis, hepatitis, pancreatitis, encephalitis).

Pretransplant screening for prior VZV infection should be performed, and naïve patients should be vaccinated with live attenuated varicella vaccine before transplant whenever possible in order to avoid primary VZV infection posttransplantation (Fehr et al. 2002). Since VZV is a live vaccine, it should not be given if transplant is expected within 4–6 weeks in order to avoid active shedding of virus at the time of transplant. Posttransplant prophylaxis is recommended with acyclovir, valacyclovir, or ganciclovir (in those

who need CMV prophylaxis) for approximately 1–3 months posttransplant in order to avoid HSV and VZV reactivation (Green et al. 2004).

Diagnosis of HSV and VZV infection can be made with PCR or direct fluorescence antibody for HSV from vesicular lesions, CSF, or visceral tissue samples. Serologies are rarely helpful in active infection owing to high seroprevalence. KDIGO guidelines recommend that renal transplant recipients who develop less severe HSV or VZV infections can be treated with an appropriate oral antiviral agent (e.g., acyclovir, valacyclovir, or famciclovir), and those with systemic infection should be treated with intravenous acyclovir and a reduction in immunosuppressive medication and subsequently switched to an appropriate oral antiviral agent (Green et al. 2004). The use of foscarnet, cidofovir, or topical trifluridine may be considered in patients with acyclovir resistant virus with careful monitoring of renal functions (Kotton and Fishman 2005; Tan and Goh 2006).

Human Herpesvirus 6, Human Herpesvirus 7, and Human Herpesvirus 8 Infection

Human herpesvirus 6 and human herpesvirus 7 (HHV 6 and HHV 7) are ubiquitous with high seroprevalence in adults. These viruses are common causes of fever in children and remain latent in lymphocytes following primary infection. HHV 6 uses the CD46 molecule as its receptor but may also infect other cell types, such as monocytes, and epithelial and endothelial cells. HHV 7 uses the CD4 molecule as its receptor and is more strictly lymphotropic. Infection occurs as a result of reactivation in the first 4 weeks following transplant often in recipients not on CMV prophylaxis (Singh and Carrigan 1996). Clinical manifestations include fever, rash, hepatitis, interstitial pneumonitis, encephalitis, leukopenia, and myelosuppression. Owing to its immunomodulatory effects, it is hypothesized that HHV 7 may act as a cofactor for HHV 6 and CMV reactivation, while both HHV 6 and HHV 7 may act as cofactors in the pathogenesis of CMV disease and acute rejection (Kidd et al. 2000; Chapenko et al. 2000; Dockell and Paya 2001). The diagnosis of HHV 6 and HHV 7 is made by tissue immunohistochemistry or NAT testing of peripheral blood lymphocytes. Treatment includes reduction in immunosuppression and ganciclovir, but cidofovir and foscarnet have also been utilized (Green et al. 2004; Kotton and Fishman 2005; Dockell and Paya 2001).

HHV 8 is associated with primary effusion lymphoma, Kaposi's sarcoma, and multicentric castleman's disease. Infection can be acquired as primary through the allograft or through reactivation of latent virus (Diociaiuti et al. 2000; Regamy et al. 1998). HHV 8 causes Kaposi's sarcoma, the most common presentation in renal transplant recipients, through upregulation of vascular endothelial growth factor (VEGF) receptor F1 K1/KDR in endothelial cells (Stallone et al. 2005). Treatment includes reduction in immunosuppression and cytotoxic chemotherapy. Sirolimus, an immunosuppressive drug used in renal transplant patients is thought to inhibit not only the production of VEGF but also dampens its effect on endothelial cells (Stallone et al. 2005).

BK and JC Virus Infection

BK polyomavirus (BKV) and JC polyomavirus (JCV) belong to the family Polyomaviridae. BKV is responsible for causing polyomavirus associated nephropathy (PVAN) in 95% of cases and JCV in less than 5% of the cases. PVAN occurs in 1–10% of patients with renal transplantation and causes renal allograft loss in 10–80% of cases (Drachenberg et al. 2005; Dadhania et al. 2008).

The risk factors for BKV associated PVAN include the use of potent immunosuppressive regimens, Caucasian race, older age, diabetes mellitus, cadaveric renal transplant, and combined kidney and pancreas transplant (Hirsch et al. 2005; Trofe et al. 2003). BKV is known to cause interstitial nephritis, ureteral stenosis, and ureteral stricture of the allograft kidney most commonly occurring within the first 3–4 months after renal transplant patients when immunosuppression is at

its highest (Randhawa and Brennan 2006). JCV less commonly causes PVAN and is more frequently associated with Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disorder of the white matter presenting as neurologic impairment and dementia (Phillips et al. 2004).

Diagnosis of BKV includes the use of viral load assays (blood, urine), detection of viral cytopathic effect (decoy cells), NAT, BKV-specific antibody, or histopathology (Hariharan 2006). KDIGO guidelines recommend screening all renal transplant recipients for BKV with quantitative plasma NAT at least monthly for the first 3–6 months after transplantation, then every 3 months until the end of the first posttransplant year, whenever there is an unexplained rise in serum creatinine, and after treatment for acute rejection. The guidelines suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10,000 copies/ml (107 copies/l) (KDIGO 2009). Sustained high BK viremia in spite of reduction in immunosuppression may need additional antiviral therapy, although data regarding optimal treatment options are unknown. There are limited data regarding the effectiveness of leflunomide and/or cidofovir or the use of fluoroquinolones or IVIG for treatment of BKV infection (Randhawa and Brennan 2006; Josephson et al. 2006). To date there is no effective treatment for PML. Patients with allograft loss due to PVAN have undergone successful retransplantation (Hariharan 2006).

Hepatitis B and C Virus Infections

Patients with chronic renal failure, in particular those receiving hemodialysis, are at increased risk for contracting hepatitis B virus (HBV). The prevalence of hepatitis B surface antigen (HBsAg)-positive patients has declined because of HBV vaccination, strict segregation of HBsAg-positive patients in dialysis units, improved screening of blood products, and the use of erythropoiesis stimulating agents (Karuthu and Blumberg 2012). Approximately 2–10% of patients with a history of HBV prior to transplant will reactivate posttransplant (Weikert and Blumberg 2008). Serial monitoring of HBV DNA every 3–6 months is required after transplantation as liver enzyme levels do not reflect infection status and elevated viral loads suggest resistance to therapy (Levitsky et al. 2013). In a meta-analysis conducted by Fabrizi and his colleagues, HBsAg seropositivity was an independent risk factor for allograft loss and posttransplant death (Fabrizi et al. 2005). The treatment options currently approved for chronic HBV include: IFN alpha, pegylated IFN, lamivudine, entecavir, telbivudine, tenofovir, and adefovir (Fabrizi et al. 2005; Chan et al. 2002; Chang et al. 2010). KDIGO recommends that interferon treatment generally be avoided because of the high associated incidence of rejection. Tenofovir or entecavir are preferable to lamivudine, to minimize the development of drug resistance, unless medication cost requires that lamivudine be used. During therapy with antivirals, HBV DNA and ALT levels should be measured every 3 months to monitor efficacy and to detect drug resistance. All HBsAg-positive renal transplant recipients should receive prophylaxis with tenofovir, entecavir, or lamivudine. HBsAg-positive patients with cirrhosis should be screened for hepatocellular carcinoma every 12 months with liver ultrasound and alpha feto-protein. Patients who are negative for HBsAg and have HBsAb titer <10 mIU/ml should receive booster vaccination to raise the titer to >100 mIU/ml (KDIGO 2009).

Hepatitis C virus (HCV) infection has been increasingly recognized in end stage renal disease patients (ESRD). Donor-derived HCV may uncommonly occur after transplantation. Screening of patients with ESRD and testing renal transplant patients for newly acquired HCV should include NAT (Levitsky et al. 2013). HCV-positive donors can be considered for HCV-positive recipients and possibly will be considered for HCV-negative recipients in the future given improved treatment options for cure of HCV that could be administered post transplant. HCV-infected renal transplant recipients have decreased survival and increased complication rates. Posttransplant complications include glomerulonephritis (GN), posttransplant diabetes mellitus, and accelerated progression to cirrhosis with fibrosing cholestatic hepatitis (Morales et al.

2010). Liver biopsy within 6–12 months of transplantation and subsequent biopsies are required for evaluation of liver disease posttransplant as 20–51% of patients may have normal liver enzyme levels with abnormal histologic features (Ashry Ahmed Gheith 2011). HCV-infected recipients should be tested for proteinuria every 3–6 months, and patients with new onset proteinuria should undergo allograft biopsy (KDIGO 2009).

The effect of immunosuppression on the progression of HCV-related liver injury and the management of immunosuppression in the HCV-infected renal transplant recipient remain uncertain. Thus, it is preferable to treat HCV in transplant candidates prior to transplantation given the potential for improved outcomes with successful HCV treatment and the complications associated with treatment posttransplant. Patients with a sustained virologic response to pretransplant treatment have a reduced risk for HCV recurrence and decreased posttransplant GN (Domınguez-Gil and Morales 2009). Options for treatment include interferon/peginterferon alone or in combination with ribavirin. The risk of toxicity with the addition of ribavirin has limited the use of combination therapy in chronic kidney disease (CKD) patients. The availability of direct acting HCV protease and polymerase inhibitors has sparked new enthusiasm for treating HCV-infected CKD patients and studies are ongoing evaluating the use of these agents in CKD. If treatment cannot be given prior to transplant, KDIGO recommends monotherapy with standard interferon for HCV-infected renal transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (KDIGO 2009). The use of direct acting HCV antivirals posttransplantation can also be considered and will likely be preferred in the future given improved tolerance and efficacy with these agents with an understanding that drug interactions with calcineurin inhibitors may occur.A study looking at 20 HCV-positive kidney transplant recipients (60% treated pre-transplant with interferon unsuccessfully) treated with direct acting antivirals posttransplant found that 100% cleared the virus and had a sustained virologic response at 12 weeks. The most common agents used were sofosbuvir and simeprevir (Sawinski et al. 2016).

Human Immunodeficiency Virus Infection

Human immunodeficiency virus (HIV) belongs to the family of Retroviridae. With the introduction of antiretroviral therapy (ART) in the mid-1990s, the incidence of HIV related deaths has been reduced. Renal diseases related to HIV infection include HIV associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy (Frassetto et al. 2009). A total of 10% of patients with HIV develop HIVAN and it remains an important complication of HIV infection, progressing rapidly to end stage renal disease (ESRD) (Shahinian et al. 2000).

A large prospective clinical trial examining outcomes among 150 HIV^+ kidney transplant recipients reported 3-year patient and graft survival rates of 88.2% and 73.7%, respectively, which were similar to survival rates among a cohort of unmatched elderly (>65 years) HIV-negative (HIV^-) kidney recipients (Stock et al. 2010). The candidates for transplantation include those with well-controlled HIV infection with undetectable viral loads, CD4 >200 cells per microliter, and absence of untreatable infections or malignancies (Blumberg et al. 2009). The most significant complications in this patient population posttransplant include increased rejection rates (up to 25%), managing drug interactions between ART and immunosuppressive therapy and complications related to cardiovascular risk factors and hepatitis coinfection (Blumberg et al. 2009). The choice of ART should be based on susceptibility results and if possible, the use of protease inhibitors should be avoided owing to significant drug interactions with this class of ART. With regards to immunosuppressive therapy, the use of thymoglobulin may result in prolonged depression of CD4 counts, whereas monocloncal anti-IL2 receptor antibodies, such as basiliximab/daclizumab, have been shown to increase CD4 cell counts (Ciuffreda et al. 2007; Carter et al. 2006). The risks of antilymphocyte therapy should be balanced with the risks of rejection in HIV-infected recipients. Of note, HIV-positive donors can now be considered in HIV-positive recipients.

Respiratory Virus Infections

The various respiratory viruses that cause infection affecting the renal transplant patient population include adenovirus, respiratory syncytial virus (RSV), influenza, parainfluenza, human metapneumovirus, rhinovirus, and coronavirus (Green et al. 2004). Clinical manifestations include upper respiratory tract infection, bronchitis, and pneumonia. In addition to respiratory illness, adenovirus is known to cause gastroenteritis, hemorrhagic cystitis, pancreatitis, meningoencephalitis, necrotizing hepatitis, and nephritis/renal dysfunction in renal transplant recipients (Pham et al. 2003; Alsaad et al. 2007). Infection with these viruses may also be associated with rejection (Weikert and Blumberg 2008). Prevention involves hand hygiene and the use of droplet precautions for those suspected of having infection. Influenza vaccination is recommended prior to transplant and yearly following transplant. Treatment of respiratory viral infection involves supportive care and antiviral medications. Influenza can be treated with oseltamivir or zanamavir. Ribavirin is approved for the treatment of RSV. Adenovirus infection is treated with reduction of immunosuppression with consideration of cidofovir (Ison 2006).

Emerging Viral Infections

Emerging viral pathogens include newly recognized viruses or previously known viruses that are either increasing or threatening to increase in incidence. Some of the emerging viruses causing infections in renal transplant population include Human T-cell Leukemia Virus Type 1 (HTLV-1), Hepatitis E virus (HEV), Measles virus, Rabies virus, Lymphocytic Choriomeningitis virus (LCMV), Dengue virus (DENV), West Nile virus, and Zika virus. Case reports of adult T-cell leukemia (ATL) following renal transplantation in HTLV-1-positive patients have been documented, though in a case series of renal transplant recipients with long-term follow-up, no cases of ATL or HTLV-1-associated myelopathy (HAM) developed (Nakamura et al. 2005; Tanabe et al. 1998). HEV may induce kidney injury with significant reduction in glomerular filtration rate. Glomerular injuries such as membranoproliferative glomerulonephritis have been described in kidney transplant patients with acute and chronic HEV infections (Kamar et al. 2012). The incidence of measles in transplant recipients is unclear. Cases of subacute measles encephalitis (SME) have developed in renal transplant recipients. The clinical course is one of deteriorating mental status and treatment refractory seizures (Waggoner and Deresinski 2013). Worldwide, vector-borne viral disease is increasing in incidence and can be transmitted with blood products and organ transplantation. Fatal cases of dengue have been reported within the first month following renal transplant (Waggoner and Deresinski 2013). West Nile virus has also been reported in transplant recipients with a high incidence of neuroinvasive disease and poor outcomes. ZIka virus is also now a concern. Cases of donor-derived rabies in the SOT population have been reported. Patients typically developed encephalitis between 1 and 2 months posttransplant, and all symptomatic reported patients died (Srinivasan et al. 2005). Cases of LCMV causing severe disease in organ transplant patients have been documented. The 4 clusters of LCMV infection occurred in the United States and involved kidney, liver, and lung transplants; symptoms included fever, abdominal pain, nausea, diarrhea, and altered mental status (Srinivasan et al. 2005; Barry et al. 2008; Fischer et al. 2006). Two renal transplant recipients survived LCMV infection. Ribavirin has been employed in some cases, though the benefits remain unclear (Waggoner and Deresinski 2013). Data regarding the incidence, screening and treatment options of the above-mentioned emerging viruses are limited. Given the risk of donor-derived viral transmission, organs should not be accepted from donors with unexplained febrile or neurologic illness. In unclear cases, the risk of donor-derived infection should be balanced with the benefit of the transplant.

Bacterial Infections

Bacterial infections after renal transplantation can be due to surgical complications at the time of transplantation, nosocomial infection, immunosuppression, or community-acquired infection. Donor-derived bacterial infections from the transplanted kidney or blood stream can occur as well. About 47% of kidney transplant recipients develop bacterial infections (Patel and Paya 1997). Occurring any time posttransplantation, urinary tract infections account for the overwhelming majority of these infections and are the most common bacterial infections prolonging or leading to re-hospitalization (Wyner 1994). Enterococci, staphylococci, enteric gram-negative organisms, and *P. aeruginosa* are the most common bacteria isolated (Wyner 1994). Bacterial pneumonia, postoperative wound infections, and bacteremia or sepsis, although less common, also prolong or lead to re-hospitalizations after transplantation (Karuthu and Blumberg 2012). Common bacterial pathogens for these infections are gram-negative organisms, including multidrug resistant bacteria; gram positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *entercococci* (VRE), as well as organisms more typically seen in immunocompromised patients such as Listeria. Months after the operation, bacterial pathogens include *Streptococcus* species, *Mycoplasma*, *Legionella, Listeria, Salmonella*, and *Nocardia*. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has been shown to reduce the incidence of some of these infections. Increased antimicrobial resistance, urgency of treatment, drug interactions, and toxicities, as well as the risk for *Clostridium difficile* colitis all contribute to the complex decision making required for antimicrobial management.

Urinary Tract Infection (UTI)

Risk factors for urinary tract infection after transplantation are a prolonged period of hemodialysis before transplant, prolonged bladder catheterization, female sex, deceased donor transplant, kidney-pancreas transplant with bladder drainage, uretero-vesical stents, and an increased immunosuppressed state (Karuthu and Blumberg 2012; Lapchik et al. 1992). Prophylaxis to lower the risk of infection after transplant with trimethoprim-sulfamethoxazole is routine (Karuthu and Blumberg 2012). Controversy regarding the exact dosing and duration of prophylaxis exists. Typically it is given at a dose of 160 mg trimethoprim and 800 mg of sulfamethoxazole daily for 6–12 months (KDIGO 2009). Trimethoprim-sulfamethoxazole reduces the risk of UTI and bacteremia (Karuthu and Blumberg 2012; Patel and Paya 1997).

Symptoms of UTI include frequency, urgency, and dysuria as well as nausea and vague abdominal complaints. Some patients are asymptomatic. *Escherichia coli* is the most common pathogen and an increasing number of pathogens are multidrug resistant. Sensitivity testing is required. Treatment of asymptomatic bacteriuria in the renal transplant recipient is controversial and is not routinely recommended (Coussement and Abramowicz 2013). Although not well studied, since UTIs in renal transplant patients are complicated, 7–14 days of antibiotics is a typical duration. Removal of stents and catheters as well as drainage of abscesses are frequently required to prevent relapse and for cure.

Surgical Wound Infections

Surgical wound infections, occurring at a rate of 3–4%, usually present within the first 4 weeks after transplant (Ramos et al. 2008). Obesity, urine leaks, re-operation through the original incision, diabetes, high creatinine levels in plasma, and prolonged bladder catheterization are risk factors for wound infections (Humar et al. 2001; Khoury and Brennan 2005). Improved organ procurement, preservation, and surgical techniques along with preoperative antibiotics all reduce the risk of subsequent postoperative wound infection. Bacterial organisms causing these types of infections may be nosocomial and multidrug-resistant making antibiotic treatment difficult due to limited options or toxicities. Source control with good wound care is critical in the management of these types of infections.

Bacterial Pneumonia

Although pneumonia is the most common bacterial infection in all solid organ transplant recipients, its incidence is lowest in those who have received a kidney (Khoury and Brennan 2005). Occurring early in the posttransplant period, CMV infection and rejection treatment with antilymphocyte preparations increase the pneumonia risk. Hospital-acquired pneumonia due to resistant pathogens, such as MRSA, and extended spectrum beta lactamase (ESBL) or carbapenem-resistant (CRE) gram-negative organisms are increasing in incidence and sometimes require nephrotoxic agents for treatment. Community-acquired pneumonia can occur any time after transplantation and the incidence of community-acquired pneumonia specifically due to *Streptococcus pneumoniae* can be lowered with vaccination.

Bacteremia

Bacteremia and sepsis are most commonly due to a urinary source, followed by lung, wound, and abdomen (Khoury and Brennan 2005). Intravenous catheters also play a role. Diabetes mellitus and posttransplant dialysis increase the incidence of sepsis which decreases the survival rate in these patients (Abbott et al. 2001). Prompt treatment with broad spectrum antibiotics followed by rapid de-escalation to pathogen-specific therapy based on sensitivities is required. Removal of foreign bodies such as intravenous catheters and stents is also necessary for cure.

Nocardia Species

Nocardia is a rare infection seen in the renal transplant recipient occurring in less than 4% of patients (Wilson et al. 1989). Trimethoprim-sulfamethoxazole prophylaxis used after transplant to prevent *pneumocystis jiroveci* pneumonia (PCP) likely prevents Nocardia infection as well. *Nocardia asteroides* is the most common species and causes pulmonary infections, including cavitary lesions and pleural effusions (Patel and Paya 1997). Other common sites of infection, due to dissemination, are central nervous system (CNS) and cutaneous. All patients with Nocardia should be evaluated for CNS disease. Allograft rejection, high-dose prednisone, azathioprine, instead of cyclosporine based immunosuppression, and neutropenia are risk factors for this infection (Patel and Paya 1997). Diagnosis is made by the identification of branching and beading rods on gram and modified acid fast staining and cultures of infected sites. Antimicrobial susceptibility testing should be performed on all isolates. High dose trimethoprim-sulfamethoxazole sometimes in combination with amikacin is the treatment of choice, but allergic reactions and other side effects sometimes limit their use. Alternatives include imipenem, minocycline, and ceftriaxone, but choices should be based on susceptibilities and site of infection (Spelman 2016). Nocardia infections can relapse and prolonged therapy up to a year is recommended followed by chronic suppressive therapy (Spelman 2016; Arduino et al. 1993).

Listeria

Listeria monocytogenes is a bacterial organism that is transmitted most commonly during summer and early fall to humans via the gastrointestinal tract from contaminated dairy products, raw vegetables, and meat. Although more common during the first 2 months after transplantation, infection may occur at any point, and risk is increased with rejection therapy (Patel and Paya 1997). Infections involving the central nervous system, such as meningitis and meningoencephalitis, are most common and present with headaches, fever, meningismus, altered mental status, and possibly focal neurologic deficits including cranial nerve palsies and seizures (Patel and Paya 1997). Cerebrospinal fluid examination typically reveals a pleocytosis, mostly polymorphonuclear leukocytes, decreased glucose, and elevated protein, but as the name implies, a mononuclear predominance may occur instead. Gram staining has a low sensitivity and may be negative or reveal gram positive bacilli which may be

confused with diphtheroids. Other sites of infection include bacteremia, pneumonia, endophthalmitis, and septic arthritis. While trimethoprim-sulfamethoxazole, used for P. carinii prophylaxis, may also prevent infection with Listeria, the treatment of choice is intravenous ampicillin and gentamicin for up to 8 weeks in those with CNS infections to prevent relapses. Gentamicin is usually continued for a shorter duration, about 2 weeks if kidney function is stable. (Gelfand 2016). Trimethoprim-sulfamethoxazole is an alternative treatment for those who are allergic to penicillin. Decreasing immunosuppressive agents is sometimes, but not always necessary.

Legionella

Legionella infections in renal transplant recipients most commonly occur early in the post-transplantation period, but can be seen any time, especially during episodes of rejection. *Legionella pneumophila* is the most common species to infect humans, and although more commonly community-acquired, nosocomial transmission occurs (Patel and Paya 1997). Most infections are pulmonary including pneumonia, and abscess with cavitation. Symptoms are typical of lung infections but also may include headache and diarrhea. A legionella urinary antigen test and culture of lower respiratory secretions on selective media are used for diagnosis. Empiric treatment for Legionella is appropriate while waiting for results. Quinolone antibiotics, such as levofloxacin, are preferred over macrolides in renal transplant patients because of drug interactions between macrolides and immunosuppressive medications. Initially given intravenously, quinolone antibiotics can be quickly deescalated to oral treatment when the patient has defervesced. Renal transplant patients, especially those who are severely ill at presentation, should receive 21 days of treatment (Yu 2016). Along with PCP and *Listeria*, as noted above, prophylaxis with trimethoprim-sulfamethoxazole may also prevent Legionella infection.

Mycobacterium tuberculosis

Immunosuppression increases the risk of developing Mycobacterium tuberculosis (TB) disease. Although the majority of tuberculosis infections in renal transplant recipients occur in the first 18 months, TB can occur any time after transplantation (Khoury and Brennan 2005). Its overall incidence is lower in the United States when compared to the rest of the world, and foreign-born recipients are at greatest risk. Having a high index of suspicion is important in renal transplant patients because presentation can be atypical and pretransplant screening with tuberculin skin tests or IFN-gamma release assays are unreliable in chronic kidney disease patients due to anergy. Extra-pulmonary sites of infection and disseminated disease occur in about a third of cases (Karuthu and Blumberg 2012). Laryngeal, meningeal, skeletal, cutaneous, intestinal, and renal infections are examples of extra-pulmonary disease. Fevers are common, but sweats and weight loss may be absent (Patel and Paya 1997).

Screening prior to transplant should include a history regarding prior exposures, and treatment for TB, as well as a chest x-ray and urine AFB culture. Prophylaxis with isoniazid or rifampin should be offered to patients prior to transplantation with a history of inadequately treated TB, an abnormal chest x-ray suggestive of prior TB exposure, a positive PPD or IFN gamma assay, contact with someone with active TB, or a kidney from a PPD-positive donor in order to minimize reactivation disease after transplantation (Khoury and Brennan 2005). Patients receiving treatment for latent TB may undergo renal transplantation and complete their defined course afterwards with special attention to potential drug interactions and toxicities (Karuthu and Blumberg 2012).

Diagnosis of TB after renal transplantation often requires a biopsy of the infected site with stains for acid fast bacilli and cultures for sensitivity testing. Treatment of active disease after transplantation requires multiple drugs and should follow the American Thoracic Society, Center for Disease Control, and Infectious Disease Society of America Guidelines (MMWR 2003). Special attention to drug toxicities and interactions with

immunosuppressive agents is required. Rifampin, in particular, decreases cyclosporine levels and increases the risk for rejection.

Fungal Infections

Fungal infections in kidney transplant recipients occur less frequently than in other solid organ transplant recipients. Most present within the first 6 months after transplantation (Hagerty et al. 2003) and can represent primary, reactivated, or donor-derived infection. Those associated with geographic and environmental exposures include histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis. Others are considered opportunistic and include infections such as *Candida, Aspergillus*, and *Cryptococcus* (Karuthu and Blumberg 2012). Broad spectrum antibiotics, corticosteroids, diabetes mellitus, rejection therapy, CMV infection, and duration of pretransplant dialysis are risk factors (Khoury and Brennan 2005). Esophageal candidiasis, urogenital candidiasis, and pneumonia are the three most common sites of fungal infections in these patients (Abbott et al. 2001). Clinical presentation may be nonspecific and diagnosis difficult due to testing limitations. Positive cultures may represent colonization rather than infection with pathogens such as *Candida* and *Aspergillus.* Cultures, antigen assays, serum galactomannan assays, and radiography may be helpful, but are not always diagnostic. Subsequently, biopsy with pathology and cultures is considered the gold standard for diagnosing fungal infections (Karuthu and Blumberg 2012). Drug interactions and toxicities as well as immune reconstitution, due to lowering of immunosuppressive medications, further complicate the management of fungal disease in these patients and require expert advice (Karuthu and Blumberg 2012).

Pneumocystis jiroveci

Pneumocystis jiroveci (formerly *Pneumocystis carinii* (PCP), protozoa) is a pathogen currently considered a fungus based on nucleic acid and biochemical analysis. Presenting as pneumonia with interstitial infiltrates on chest x-ray within the first year after transplantation in those not receiving prophylaxis, mortality may be high. Nonproductive cough and shortness of breath with rapid progression to hypoxia is a classic presentation. Diagnosis is based on silver staining of deep respiratory specimens from induced sputum, bronchoalveolar lavage, or transbronchial biopsy (Martin and Fishman 2013). The treatment of choice is high dose trimethoprim-sulfamethoxazole for 21 days with corticosteroids in hypoxic patients (partial pressure of oxygen of <70 mmHg on room air) tapered over 14 days. Atovaquone or clindamycin plus pyrimethamine are alternative agents (Martin and Fishman 2013). Trimethoprim-sulfamethoxazole prophylaxis for 6–12 months after transplantation is highly effective in preventing this infection and should be administered to all renal transplant patients if tolerated. Frequently used alternatives for prophylaxis in allergic patients include dapsone (if glucose-6 phosphate dehydrogenase levels are normal) and atovaquone.

Conclusion

Infection remains an important concern in patients undergoing kidney transplantation. Attention to pretransplant screening of the potential organ donor and recipient is essential to optimizing transplant outcomes. Advances in the management of transplant-related infections include the increasing use of rapid molecular diagnostic testing as well as improvements in the approach to prophylaxis and treatment. Ongoing challenges include the need for prolonged immunosuppression to prevent organ rejection, drug-drug interactions, and the management of resistant and emerging pathogens. Continued awareness of the risks, timing, and presentation of infection posttransplant and strategies to reduce its impact will contribute further to progress in the field of kidney transplantation.

Cross-References

- Donor Selection: Deceased Donor
- Ethical Issues in Organ Transplantation
- Living Donor Evaluation and Selection
- Necessary Components of a Living Donor Team
- Recipient Selection for Kidney Transplantation
- Transplant Immunosuppression

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The Regulatory and Legal Environment of a Contemporary Kidney Transplant Program

Maria McCall and Linda S. Wright

Contents

Abstract

Organ transplantation is one of the most complex sectors of healthcare available in only approximately 4% of hospitals nationwide. It is a high-risk and high-skill program utilizing scarce resources. As such, it is highly regulated with a number of different federal agencies enforcing regulations, policies, and bylaws. The Organ Procurement and Transplantation Network (OPTN) managed by contract agency the United Network for Organ Sharing (UNOS) enforces these rules concurrently with the Centers for Medicare and Medicaid Services (CMS) among other agencies. The governing rules are dynamic, layered, often repetitive, and sometimes open for interpretation by Transplant Centers putting the issue of compliance at the forefront of all decision-making at all levels. The OPTN's primary focus has been the fair and equitable distribution of organs with focus on patient and donor safety, whereas CMS's primary focus has been patient health and safety with a focus on nondiscrimination in practices. Given this complexity, Transplant Centers put forth a tremendous amount of resources ensuring compliance and often routinely employ Compliance Specialists/Managers. A number of resources are available to Transplant Centers to be informed about regulatory oversight and requirements.

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Keywords
Transplant regulation · Transplant legal oversight · OPTN · UNOS · Transplant compliance

Introduction

In the past 10 years, organ transplantation has evolved to be one of the most highly regulated segments of health care. The National Organ Transplant Act (NOTA) of 1984 was the first step in true regulatory oversight of organ transplantation. The purpose of NOTA, however, was to address the national organ shortage; therefore, it was a number of years before the gaps in oversight were brought to the forefront and addressed through further legislation (Transplant Act. 42 USC 201 1984). NOTA called for the development of the Organ Procurement and Transplantation Network (OPTN) and awarded the first contract for oversight of the OPTN to the United Network for Organ Sharing (UNOS) in 1986 (Linden 2009).

OPTN Oversight

The first layer of regulation for transplant programs is that of meeting criteria for institutional membership through the OPTN. Transplanting hospitals, Organ Procurement Organizations, and tissue typing laboratories, known as Human Leukocyte Antigen (HLA) Labs, are among those granted institutional membership based on specifically defined criteria. For Transplanting Hospitals, these criteria include facility specifications related to care areas and operating rooms as well as demonstrated hospital commitment through business planning for growth and program development and significant ancillary support through pharmacy and laboratory. The most complex and specific of the institutional membership requirements for transplanting hospitals are those of the rules describing criteria for a designated primary physician and primary surgeon. Membership is not granted until each of those roles completes fulfillment of criteria. These criteria include training and education, defined volumes of experience related to managing patients, performing procedures, observing organ recoveries, specified written recommendations from program directors, and a written commitment to the program as the primary person in the role. Once all criteria are met, through an application process, institutional membership is granted, and these criteria are monitored on an ongoing basis via member attestation of any significant changes as well as check-in at routine onsite surveys by UNOS personnel (Brown et al. 2008).

The second layer of oversight for transplant programs is that of the OPTN policies governing the fair and equitable distribution of organs nationally. Predominantly, these policies define how organs are allocated and the waitlist patient criteria for the complicated algorithms that make up the allocation rules. Policies are developed via wide collaboration of representative OPTN committees, public comment, and board of director approval. Once policies are effectuated, it is the responsibility of the institutional member to comply. Policies are validated for compliance via data reviews, audits, and onsite surveys conducted by UNOS personnel (Brown et al. 2008).

OPTN Survey Process

Transplant programs are routinely surveyed for compliance with all applicable policies on a 3-year recurrent cycle. This includes an onsite visit from UNOS personnel, follow-up desk audits when necessary, and further follow-up when programs are found to not meet policies and guidelines.

In order to assist transplant programs in maintaining compliance with the OPTN policies, UNOS has developed a comprehensive Evaluation Plan. This document, available to the public, defines how each policy will be evaluated and at which interval. For example, Chapter 14 of the OPTN policies is dedicated to Living Donation. Within this Chapter is a policy describing requirements for determining the blood type of living donors. The

policy introduction is as follows: *"Recovery hospitals must develop and comply with a written protocol for blood type determination and reporting that includes all of the requirements below. 14.5.A Living Donor Blood Type Determination The recovery hospital must ensure that each living donor's blood type is determined by testing at least two donor blood samples prior to generation of the living donor ID. The recovery hospital must develop and comply with a written protocol to resolve conflicting primary blood type results:* (OPTN.transplant.hrsa.gov/policies)*."* There are further explanatory subsections for this policy following the main policy header. The OPTN Evaluation Plan assists transplant programs in ensuring they meet this policy by providing detailed guidance on how this will be evaluated for compliance. Below you will find an excerpt from the OPTN Evaluation Plan specific to this policy example. It demonstrates how compliance will be evaluated by UNOS onsite and chart audit.

OPTN Evaluation Plan Excerpt: Living Donor Blood Type Determination
Policy 14.5.A: Living Donor Blood Type Determination
Effective Date: 6/23/2016

At Living Donor recovery hospitals, site surveyors will review a sample of living donor medical records, and any material incorporated into the medical record by reference, for documentation that:

- Tests were completed on two separate blood samples.
- The draw times for the samples used for the two tests are at different times.
- The two tests returned identical results before the donor ID was generated.

Recovery hospitals will provide the requested sample of living donor records.

In addition to the survey process, OPTN requirements for outcomes and volumes are monitored remotely by UNOS staff, and transplant programs are made aware of noncompliance and required follow-up. Steps often include explanatory conference call and data presentation with the OPTN Committee for Membership and Professional Standards and formal presentation to this Committee. Programs may lose their good standing as members and in egregious situations of volume or outcome deficiencies without a practical resolution, may lose their membership in the OPTN.

CMS Oversight

In response to high-profile quality of care and staffing concerns in transplant programs, in 2005 the Centers for Medicare and Medicaid Services (CMS) released a proposed rule for Conditions of Participation, which were a sweeping paradigm shift of regulatory oversight in organ transplant and attempt to fill the gaps in oversight not covered by the OPTN rules and UNOS oversight (Hamilton 2008). As the majority of transplant programs seek Medicare reimbursement, and private payors often require certification, CMS approval is rarely optional. On June 28, 2007, after a public comment period, CMS published the rule in final in the Code of Federal regulations. The newly established Conditions of Participation had some duplication with the existing OPTN policies in terms of outcomes measurement, but the majority of the rule was new and a culture change for transplant programs nationally. The Conditions were published in the format of structural standards, process standards, and outcomes and volume standards. As is typical with federal Conditions of Participation, an Interpretive Guideline for State Agency Surveyors was also released and available to the public. In order to evaluate compliance with the Conditions, CMS tasked the State Survey Agencies with onsite surveys for assessment. In descending order, the most commonly cited deficiencies within the first 100 surveys included noncompliance with the new rules for verification of blood type at the time of transplant, informed consent, patient/living donor care, multidisciplinary planning, and quality assurance and

performance improvement (Hamilton 2009). With 54% of all transplant programs surveyed having one or more of these deficiencies in combination, CMS took the position that the Conditions of Participation were effective in detecting issues despite the early criticism from the transplant community that the risk-adjustment related to the outcomes requirements is hampering innovate practice (Hamilton 2009).

The CMS Survey Process

The onsite survey process, which is more similar in nature to that of the Joint Commission and other CMS hospital inspections, is in stark contrast to the chart review conducted by UNOS staff during their onsite visit. Also, unlike OPTN surveys, CMS surveys are unannounced and therefore making survey planning a routine duty. Surveys may occur as a new program requests initial certification, as part of a routine recertification occurring every 3 years, a result of a complaint occurring at any time, and as part of a federal Quality Assurance and Performance Improvement (f-QAPI) focused survey. The f-QAPI survey is a focused onsite visit strictly set up for the purpose of reviewing the complex Condition of Participation for QAPI. It may be triggered with lower than expected outcomes or higher than expected outcomes and is an unprecedented change to how quality assurance programs are reviewed nationally in healthcare (CMS 2013). Surveyors for CMS conditions not only review a sample of medical records based on phases of transplantation, but the patients are not chosen in advance and all patient medical records must be survey-ready. Also, unlike UNOS onsite surveys, members of all of the multidisciplinary team may be interviewed for understanding of their role in the phases of transplantation, the entirety of policy manuals are reviewed for completeness and consistently with practice, job descriptions, training and education, and staffing competencies are reviewed for all members of the multidisciplinary team and not just primary surgeons and physicians.

Conclusion

Transplant programs are under intense scrutiny from regulatory agencies for all aspects of clinical care, staffing, and patient safety. Regulatory oversight has grown to the extent that over 65% of programs nationally have staff dedicated to compliance and quality assurance (UNOS Transplant Administrators Staffing Survey 2016). This role is typically responsible for ensuring that updates to policies and bylaws are not only distributed to all team members, but Transplant Center policies and practices are updated to reflect new policies. It has become a critical role in the day-to-day operational monitoring to avoid a situation of noncompliance and help programs ensure patient safety. To avoid noncompliance, transplant program medical and surgical leadership, administrative leadership, and compliance management should have ongoing and open communication with UNOS, be active in UNOS sponsored meetings and activities, and should have a mechanism to remain abreast of all current information being released by CMS.

Cross-References

- A History of Kidney Transplantation
- Organ Procurement Organization and New Kidney Allocation
- Quality Measurement of a Contemporary Kidney Transplant Program
- The Finance of Kidney Transplantation

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Epidemiology of End-Stage Renal Disease and Kidney Transplantation

Maria P. Martinez Cantarin and Jerry McCauley

Contents

Abstract

Chronic kidney disease (CKD) affects a large proportion of the population and is associated with increased morbidity, mortality, disability, and healthcare expenditure. CKD frequently progresses to end-stage renal disease (ESRD) that requires renal replacement therapy including renal transplantation. The prevalence of ESRD continues to grow despite a recent decrease in the incidence of CKD, which is most likely secondary to improvements in the care of patients with ESRD. Kidney transplantation is associated with much better long-term outcomes than any other modality of renal replacement and should be the goal for the majority of patients with ESRD. Despite this, the growth of kidney transplantation has not kept up with the growth in the ESRD population. Living donation still represents a small proportion of the overall kidney transplantation in the USA regardless of the growth of the pair exchanged program. The main challenge for the future will be to increase the numbers of kidney transplants and specifically the promotion of living donation.

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Keywords
Prevalence of ESRD and transplant · Incidence of ESRD · Outcomes of kidney transplant · Morbidity of kidney transplant · Mortality of kidney transplant

Introduction

The availability of dialysis and kidney transplantation for the care of patient with end-stage renal disease (ESRD) changed the therapeutic landscape of patients with chronic kidney disease. Before 1970, treatment options for ESRD were very limited as dialysis was only offered to the healthiest and fittest patients and kidney transplantation was rarely performed and not an appealing option due to its dismal short-term outcomes. So for many patients at that point, a diagnosis of chronic kidney disease (CKD) was felt to be similar to receiving a death sentence. Current advancements in dialysis techniques and excellent outcomes post kidney transplantation have greatly improved survival with reduced morbidity in our ESRD population. The growing population of patients with CKD poses big societal challenges, due to the enormous economic costs of these treatments. Many low to middle income countries do not provide social safety net care for maintenance dialysis or kidney transplantation. In such countries, the economic burden is entirely carried out by the patients and in many instances patients will not have the economic means to access treatment. In the USA, since 1972 Medicare has paid for maintenance dialysis and kidney transplantation. But even in industrialized and higher income countries, to continue to care for a growing population of patients with ESRD is perceived as a challenge due to rising costs. Different nationwide programs for health promotion and disease prevention have incorporated goals specifically related to CKD after recognizing that ESRD is just the tip of the iceberg, and that CKD is a progressive disease that affects a much bigger population. As an example, the Healthy People 2020 initiative of the U.S. Department of Health and Human Services has targeted a 10% reduction of CKD in the US population (Centers for Disease 2016) which contrasts with the 2010 recommendations that focused exclusively on ESRD. This chapter will review epidemiologic data from the ESRD and transplant registries to understand current trends in ESRD and transplant populations.

Global Epidemiology of CKD

Chronic kidney disease (CKD) continues to be a major public health problem worldwide. It is estimated that 200 million people suffer from CKD (Ojo 2014). CKD prevalence in the USA has not changed much for the past 15 years. Data from the NHANES participants aged 20 and older since 1999 shows that the overall prevalence of CKD has varied between 13.9% and 14.8% of the population. In absolute numbers, that represents more than 20 million people only in the USA (Healthy People 2020 2016). Chronic kidney disease is more common in people over 60 years old, diabetics, hypertensive population, and people with cardiovascular disease. From the latest NHANES survey around 40% of all CKD patients suffer from diabetes, 32% from hypertension, and 42% cardiovascular disease. BMI >30 was present in 18% of the CKD patients from the same survey. Also, African Americans in the USA have a fourfold excess risk of developing kidney disease. Genetic background explains some of this higher likelihood of developing CKD and progression to ESRD in African Americans. Polymorphisms in the apolipoprotein L1 (*APOL1*) gene increase the risk of early onset CKD, more rapid decline of eGFR, and progression to ESRD (Parsa et al. 2013). *APOL1* mutations are only described in African American backgrounds and they are believed to confer resistance towards trypanosomal infections (Genovese et al. 2010).

According to the Global Burden of Disease project, total mortality from CKD rose from 2005–2015 by 31.7% representing an increase of more than 1 million deaths a year. Furthermore, there was also almost 40% increase in mortality in patients with CKD due to diabetes from 2005, with a total of 418,000 deaths (Mortality and Causes of Death C 2016). Chronic kidney disease not only contributes to mortality but also to morbidity that result in disability. In the 1990s, chronic kidney

disease was the 28th out of the 30 leading causes of years lived with disability (YLD). Its importance has been growing and in 2005 it represented the 25th and in 2015 the 24th leading cause of YLD (Disease et al. 2016). Chronic kidney disease burden will most likely grow in the years to come due to aging of the general population and also the increased rates of diabetes mellitus.

Global Epidemiology of ESRD

CKD may be classified in five stages. Stage 1 patients have normal glomerular filtration rates (GFR) but abnormal urine sediment/kidney imaging, or albuminuria. Stages 2–5 have different degrees of GFR reduction and ESRD is mainly used for advanced kidney disease that requires renal replacement therapy. ESRD has the highest mortality within the CKD population. The United States Renal Data System (USRDS) is the national data system that collects, analyzes, and distributes information about CKD and ESRD which provides yearly information. USRDS is funded by the National Institute of Health, National Institute of Diabetes, Digestive and Kidney Diseases. Data from USRDS get updated yearly and reflects events up to the end of 2 years prior to publication. For example, data published in 2016 includes reports up to December 2014. USRDS is a great source of epidemiological data and puts in perspective changes in our CKD and ESRD population over time (Hart et al. 2016; United States Renal Data System 2016).

ESRD Counts; Incidence

From the USRDS data, the number of new ESRD cases in 2014 was greater than 120,000 with an incidence rate of 370 per million per year. This represents an increase of new cases since 2011 and reflects how the burden of kidney failure in the United States continues to increase. On the other hand, adjusted ESRD incidence rates have decreased slightly since 2006, probably reflecting improvement in CKD care despite population aging and increasing diabetes rates. The main decline in adjusted incident ESRD rates has been in the group of 65 years and older. Adjusted ESRD incidence rates have also decreased in diabetics, and glomerulonephritis patients while ESRD incident rates have remained stable in patients with hypertension and cystic disease. The number of new patients diagnosed with ESRD is significantly higher in African Americans, Native Americans, and Asian Pacific Islander when compared to whites despite a continued decline of the adjusted incident rates over the past 20-year period. Adjusted incident rates of ESRD are also nearly 35% higher in Hispanics than among non-Hispanics. The main dialysis modality used by the incident ESRD cases in the United States continues to be hemodialysis, as more than 85% of ESRD incident patients that started renal replacement therapy in 2014 received hemodialysis. Less than 10% of ESRD patients started on peritoneal dialysis, and less than 3% received a preemptive kidney transplant. Despite low numbers of patients starting renal replacement therapy on peritoneal dialysis or home hemodialysis, the use of home therapies has increased in the past few years, with 120% higher use of home dialysis and 72% higher use of peritoneal dialysis in 2014 compared to 2007. Interestingly almost 40% of the patients who started dialysis in 2014 received little or no pre-ESRD care by nephrology.

ESRD Counts; Prevalence

The real burden of kidney disease gets reflected better looking at prevalent ESRD cases, or existing cases of ESRD. At the end of 2014, there were 678,383 prevalent cases of ESRD representing an increase of almost 75% from year 2000. Both unadjusted and adjusted prevalent rates of ESRD have increased yearly since 1996 representing more than 50% increase since the year 2000. In 1972 Medicare extended eligibility to patients with ESRD, when only about 10,000 patients were receiving chronic dialysis. Just between the years 2013 and 2014, Medicare expenditure for patients with ESRD rose by 3.3% for a total of 32.8 million, representing 72% of the overall Medicare paid claim cost. Currently

even though patients with end-stage renal disease only represent 1% of the Medicare population, they account for 7% of Medicare fee-for-service expenditure. The high prevalence rates in the ESRD population reflect both the incident population as well as the growing established population due to the better care of patients with ESRD. Despite a slower incidence, the prevalent population is unlikely to decrease significantly in the near future due to improved ESRD outcomes, and they will continue to require significant resource expenditure. If we stratify prevalent ESRD patients by the type of renal replacement therapies they are receiving, 63% of the prevalent ESRD patients were undergoing hemodialysis, almost 7% peritoneal dialysis, and the rest had a kidney transplant in 2014. Of the three renal replacement therapies, hemodialysis is associated with higher costs per patient than peritoneal dialysis or transplantation.

Global Epidemiology of Renal Transplantation

Transplantation is still the modality of choice for the majority of the patients that suffer from ESRD. Kidney transplantation is associated with better patient survival than dialysis, and this is particularly important in the diabetic patients as they have worse outcomes while on dialysis. In 2014, adjusted mortality rates were 166 per 1,000 patient-years in dialysis patients compared to 30 per 1,000 patient-years for transplant patients by the USRDS report. Also according to the USRDS report in 2009 the 5-year survival of ESRD patients with diabetes was only 30%. Currently the 1-year patient survival after a kidney transplant in a diabetic patient has exceed 90% for both living and deceased donor recipients (Hart et al. 2017; Wolfe et al. 1999; Schnuelle et al. 1998; McDonald and Russ 2002; Lloveras et al. 2015).

This difference in mortality was emphasized in a study by Wolfe et al. where the authors demonstrated that the risk of death after transplantation in a patient with diabetes is reduced by 73% by 18 months compared to diabetic patients that are placed on the transplant waiting list (relative risk 0.27, 95% CI: 0.24–0.30) (Wolfe et al. 1999). Kidney transplantation not only improves patients' life expectancy but also improves quality of life and it is also cost-effective. The main problem faced by the transplant community is the lack of organs. On average, patients have to wait between 3–5 years for kidney transplantation and in some states the waiting time could be as high as 10 years. From the Organ Procurement and Transplantation Network (OPTN), 119,521 people were in need of a transplant by December 2016 while there were only 13,066 donors that facilitated 27,605 transplants. Every 10 min somebody is added to the transplant waiting list and on average 22 people die each day awaiting a transplant. Despite multiple efforts to raise awareness for organ donation, there is still a big gap between supply and demand.

In December 2014, a new kidney allocation system was implemented. The new system gives priority to patients that are sensitized, and patient's dialysis time is now included as waiting time independently of time of listing. A new donor quality metric, the kidney donor profile index (KDPI), replaces the prior categories of extended criteria or expanded criteria donors. KDPI is a combination of several donor characteristics that get translated into a number. The number reflects the likelihood of graft failure after kidney transplant relative to all the kidneys recovered in the USA in the prior year. KDPI factors include donor age, height, weight, ethnicity/race, history of hypertension and diabetes mellitus, cause of death, serum creatinine, HCV status, and donor after cardiac death status.

Recipients are also categorized depending on their expected post-transplant survival score (EPTS). EPTS represents the percentage of kidney candidates in the nation with a longer expected post-transplant survival time. EPTS weighs the candidate time on dialysis, whether or not a candidate has a current diagnosis of diabetes, whether or not the candidate had any prior solid organ transplant, and the candidate age. Currently, kidneys with low KDPI scores (<20%) are

allocated to recipients with the best EPTS scores (<20%). It will take a couple years until USRDS is able to reflect allocation changes in transplant statistics.

Transplant Counts

In 2014 there were 17,914 kidney transplants performed in comparison to 88,231 candidates on the kidney transplant list that year. Of those kidney transplants 17,205 represented kidney transplants alone and the rest were multiorgan transplants. Living donation was less than one third of the transplants performed in 2014. As of January 11, 2016, there were more the 100,000 patients awaiting a kidney transplant and a third of those were listed as inactive. The number of patients waiting for a kidney transplant has been steadily increasing; as a reference, there were 58,000 kidney transplant candidates in 2004 and 98,956 in 2014. In 2014, the kidney transplant waiting list increased by 3% with only 1% increase in kidney transplantation that same year. The time that patients spend on the waiting list has also increased. Patient waiting for more than 5 years were 10.9% in 2004 compared to 14.7% in 2014 and there is a smaller number of patients that wait for less than a year to transplant. Since 2005 the number of kidney transplants overall has remained fairly stable. On the other hand, since the dialysis population continues to increase, the transplant rates of the dialysis population have been decreasing. Deceased donor transplant rates are higher in males than females, patients with diabetes or hypertension, whites, and patients between the ages of 45–64, most likely just resembling the characteristics of the transplant waiting list. The number of living donor transplants increased steadily between the years of 1996 and 2004, but since then there has been a small decline. Annual counts of living donor kidney transplants for patients aged over 65 years, males, and whites are higher than for younger patients, females, and Asian/African Americans despite living transplant rates being overall lower in the current years. Patients with glomerular disorders as main cause of ESRD have higher rates of living transplantation than patients with diabetes and hypertension, and this trend is in contrast to the rates seen with deceased donor transplants. One area in living donation that has improved in numbers significantly is paired exchanged donation. Living pair exchange involves couples of potential donor and recipients that cannot be performed directly due to incompatibilities in blood group or due to preformed antibodies in the recipient. Two living donors with their incompatible recipients can perform an exchange, so the donors give a kidney to their compatible recipients from the other pair. The number of kidney transplants performed by paired donation has continued to increase steeply in the past few years with 552 paired exchange kidneys done in 2014 which represent 10% of the living donor transplants during that year.

Transplant Outcomes

Transplant outcomes continue to improve. In 2013 the probability of all-cause graft failure at 1 year post transplant was 8% and the probability of recipient death was 4% among recipients of kidneys from a deceased donor. In living recipients, the probability of all-cause graft failure at 1 year was 3%, which is lower than in deceased donor recipients, and the probability of death was 1% over the same period, which is also lower than in deceased donor recipients. Improvement in patient's mortality and graft survival may also be seen at 5 and 10 years post-transplantation in both deceased donor and living transplant kidney recipients. Overall, graft failure at 5 years was around 30% in both living and deceased donor kidney recipients and graft failure at 10 years around 55%. For patient mortality, the probability of death by the fifth year post-transplantation was 37% in 2004 compared to 15% in 2009. In general outcomes of living donor transplant recipients have always been better than deceased donor kidney recipients.

Graft survival is lower in recipients of expanded criteria donor kidneys, older recipients,

recipients with hypertension or diabetes mellitus as the cause of kidney disease, or in African American recipients. Rates of rejection have also decreased during recent years, without significant differences between the rates of rejection in diseased donor kidney recipients compared to living donor recipients. During 2008–2009, close to 10% of the patients suffered a rejection episode through the first year post transplantation and this percentage decreased to less than 9% during the years 2012–2013. Kidney function post-transplant has also improved through the years. In 2004 there were 42.4% of the transplant patients that had an eGFR $\geq$ than 60 mL/min/1.73 m^2 at 6 months post-transplant. The rate of transplant patients with eGFR $\geq$ 60 mL/min/1.73 m^2 at 6 months post-transplant increased to 48.2% in 2014 (Hart et al. 2016).

Also, the rates of death censored graft failure have improved over the past decade, but the rates of death with a functional graft have remained stable or even increased at 10 years for both deceased and living donor transplants. This is probably a reflection of the increased age of the population that is receiving kidney transplants. Older patients are more likely to die before they lose the allograft.

Kidney transplantation increases the risk of developing diabetes mellitus and malignancies. Rates of post-transplant diabetes have also declined during the past 8 years. In 2013 the percentage of patients that were diagnosed of diabetes at 1 year was 5% compared to close to 10% in 2006. Ten percent of the patients will be diagnosed with diabetes after 3 years and close to 17% at 5 years. When looking at patients with BMI greater than 35 kg/m^2, the rates of PTDM also decreased from 17% at year one in 2006 to around 8% in 2013. The most common-life threatening malignancy after kidney transplantation is post-transplant lymphoproliferative disorder (PTLD). The risk of PTLD was more common in patients that were EBV negative at the time of transplant with an incidence of 1.7% at 60 months post-transplantation versus 0.5% incidence in patients that were EBV positive. The risk of PTLD has also decreased over time (Caillard et al. 2012).

Conclusion

Despite a stabilization in the CKD population, the number of ESRD patients will not likely decrease in the near future. Due to the great outcomes after kidney transplantation, this modality of renal replacement therapy should be the target for most of the ESRD population. Current transplant epidemiology will most likely change in the incoming years due to the recent changes in the kidney allocation policies. The biggest barrier that we will continue to face will be the lack of sufficient donors to serve the growing ESRD population.

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Ethical Issues in Organ Transplantation

Hector C. Ramos and Jerry McCauley

Contents

Abstract

Organ transplantation is perhaps the only medical venture that creates a situation where the best interests of those in need require direct harm to another human to affect a change in the course of an illness. Most literature on ethics of organ transplantation focuses on specific and practical issues of current interest and addresses the issues with the recipient's well-being prioritized. Therefore, issues such as organ allocation and fairness in the distribution

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of organs tend to flood the literature. Historically, ethical issues were causes of concern for many leading transplant surgeons. Perhaps the most prominent of concerns was the potential for harm to the donor. The potential for harm is inherent in all surgical treatment and in ethical reflection foundational principles such as respect for autonomy, beneficence, nonmaleficence, and justice are and should be resources for ethical action. The donor is a vulnerable human source of the organ necessary for treatment. Effective treatment of the recipient requires an altruistic action on the part of the donor. Therefore, complying with the principle of justice requires more attention to the vulnerable donor. However, the recipient is also a vulnerable human component. Justice for the recipient relates to just allocation of the organ based on medical principles. Characteristics of recipients such as race, gender, and socioeconomic status or cognitive impairment should not have a primary place in the selection of recipients. The ethical treatment of the organ transplant recipient requires a foundational paradigm grounded in justice. Justice for both the donor and the recipient ought to be the grounding principle guiding transplant professionals.

Keywords
Transplantation · Ethics · Justice · Organ donation · Brain death

Introduction

The subject of this chapter is a necessary component to any tome on organ transplantation. However, most of the ethical issues addressed in quotidian reference issues on transplantation review the medical ethics point of view geared toward the practical and not the philosophical. Practical issues are usually centripetal to a system of just allocation of organs. And in our current healthcare environment of scarce financial resources the practical ethical applications appear to overwhelm the literature. However, there are subjects under the rubric of ethical issues that are as important but are often subjugated by the overwhelming attention to organ allocation. The subject of organ allocation comprises more than 70% of the OPTN's webpage on ethical issues in organ transplantation for 2017. It is therefore the subject and purpose of this chapter to address – not only – more philosophical issues but, some of the practical and most of all, the controversial issues related but not directly organ allocation.

Organ transplantation has a unique role in medicine. It is the only medical endeavor that requires the beneficial act of donation to affect the final medical purpose, e.g., the axiom: "the gift of life." Moreover, that single identifiable feature of organ transplantation is the crux of all of its ethical issues for a physician cannot care for a recipient without a presumably altruistic action on the part of a deceased or live donor; human organ transplantation cannot exist without such an act.

The above circumstance encompasses all the principles of bioethics. Those being beneficence, respect for autonomy, nonmaleficence, and justice. However, most ethical debates arising from conflicts applicable to the principle of justice revolve around organ allocation. But in this chapter the subject will be less emphasized. Other important ethical issues will be addressed.

Foundational Principles

Modern bioethics, or more applicable to transplantation, healthcare ethics, is grounded on four foundational principles: respect for autonomy, beneficence, nonmaleficence, and Justice. Each has an important position in the field of organ transplantation. Throughout the chapter there will be associations of the principles with current important issues.

Respect for Autonomy

In our current healthcare environment, respect for autonomy has developed into the core principle guiding medicine. According to Beauchamp and Childress (B&C) (2013), autonomy is primarily self-rule. However, the principle that is presented in bioethics is "respect for autonomy." The latter

requires three conditions: intention, understanding, and noncontrol. The will governs intention. Respect for autonomy requires the healthcare provider to understand the agent (patient, family, etc.) is acting from his will. That exercise of will is based on the Kantian concept of autonomy and is based on reason. According to Kant, a person without the ability to reason is not acting autonomously (Johnson and Cureton 2017, Chap. 10).

The above concept has particular implications in transplantation *vis a vis* the donor, recipient, and the physician. The donor is an individual autonomous person, but is she able to exercise her will? The live donor does, yet the deceased donor cannot exercise her will concurrently with the event of donation, but can make her will known in the form of advance directive, e.g., donor card or living will. If the latter are not present, the exercise of the will becomes more complicated as the family or loved ones take on the role of intentionality. The latter situation creates ample fodder of ethical reflection particularly on the concept of informed consent. Informed consent will be addressed later in the section of live donation.

Beneficence

The principle of beneficence is the quintessential principle guiding the telos of all healthcare endeavors. It is the principle guiding the goal of all healthcare providers to act in the best interest of the patient. Some authors have posited that beneficence is the only foundational principle in medical ethics (Pellegrino 1994). However, Pellegrino's conceptualization of beneficences as a sole principle creates a conflicting paradigm in organ transplantation. The transplant physician/surgeon has often two patients with conflicting benefits. That is not to say that donors would perceive a risk of their life for an altruistic purpose, a benefit. But, is the latter perception one that transfers to the physician? How can the physician have two patients, one has to be harmed (donor) to benefit the other (recipient)? Also, the declaration of brain death for the purpose of organ transplantation is another potential conflict of beneficence. Are we harming the donor for a "greater purpose," e.g., the recipient? The resolution to the previous questions is beyond the scope of this chapter, but the grounding concept is one of conflicting interests/principles. The latter concept begs the question: When the proverbial push comes to shove. What is the ethical physician to do. Later in the chapter these controversial issues will be addressed (Pellegrino and Thomasma 1988).

Nonmaleficence

Nonmaleficence is another foundational concept in health care. The proper telos of any medical intervention being invasive or not is the mitigation or elimination of harm, e.g., the aphorism*: primun non nocere* (first do no harm). Yet, treatment of a disease frequently requires actions which initially cause injury and have significant risk for harm including death. But, outside the realm of transplantation the consequences of the latter endeavors are foreseen and the intention is toward the eventual change in the course of disease or alleviation of suffering for the patient. Contrarily, in transplantation, there are two patients affected by treatment. Arguably, the physician harms the donor for the benefit of the recipient. That is not to say the recipient of the organ does not also incur risk, but the risk is for the self and not another. However, the donors risk is not incurred for self but for the other. Again, a conflict worthy of much ethical reflection (Schoene-Seifert 2014).

Justice

The dominant and most important principle for medical ethics is justice. There are multiple theories of justice identified by moral scholars. The two most dominant theories applicable to transplantation are the deontological and utilitarian theories. Deontology is grounded in duties and obligations. Justice is served based on keeping with prescribed duties toward the patient. Consequences or circumstances may or may not determine the just end of an action. However, the utilitarian theory's foundation is exemplified in the statement: "the end justifies the means."

It is the utilitarian theory that is applied to a greater extent in healthcare today. In organ transplantation, concepts of justice for the recipient are pervasive in media, literature; a fact that brings to the forefront another theory of justice, distributive justice. McCormick (2010) notes that distributive justice applies to situations where the means of treatment is significantly less than the need. The disparity between the number of recipients and donors demands the application of distributive justice. But, what is justice for the donor?

The Donor

Most of the ethical reflection surrounding the transplant process focuses on the donor. However, it is interesting that the focus of practical reflection tends to be on the recipient. It would be accurate to say that it is the recipient that is the goal of therapy. Therefore, financial, legal, political, human resources, etc. are directed toward the benefit of the recipient. Some may say that such endeavors are correctly applied toward the object of treatment, i.e., the recipient. However, to complete the ethical argument requires a philosophical analysis that includes the donor; for it is the donor that provides the means of therapy. It is appropriate that we begin the ethical issues with the donor. As this is chapter on ethics, empiric science will not be addressed unless it specifically pertains to an ethical issue.

Live Donation

Currently there are five solid organs amenable to live donation: kidney, liver, pancreas, lung, and intestine (see chapters ▶ "Live Donor Nephrectomy," ▶ "Living Donor Evaluation and Selection," ▶ "Medical Complications After Kidney Transplantation: Early"). All of them involve significant risk to the donor and notably no donor derives a medical benefit from the procurement. The latter ethical issue was noted even in the beginning of transplantation. Ramsey (1970) provides perhaps the most extensive early assessments on the morality of live donation. Quoting Francis Moore: "Physicians are exceedingly sensitive that for the first time in the history of medicine a procedure is being adopted in which a perfectly healthy person is injured permanently in order to improve the well-being of another" (Ramsey 1970, pp. 173, 197). Ramsey thereby illustrated the ethical dilemma of live donation even in its nascent stages.

The ethical principles governing live organ donation are similar if not identical to principles guiding human experimentation. Particularly human experimentation where the risk of the subject is incurred either for the benefit of humanity or for the benefit of a specific group and not the recipient herself. Therefore, two other principles ought to guide physicians: Respect for persons and informed consent. Informed consent has four modifying components: Voluntariness or freedom from coercion, capacity or the ability to reason, disclosure and understanding all lead to the final component, consent (Beauchamp and Childress 2013, Chap. 4).

Respect for persons includes the consideration of the vulnerability of the patient. In the case of live donation, critics emphasize the possibility of violation of the principle of respect for persons when the emotional attachments to the recipient influences – some would say – coerce the decision to donate as in parent to child donation, donation between married couples, or even sibling donation. The latter situations can also be perceived as violation of one of the major components of informed consent, voluntariness. In the case of live donation, the justification has always been under the principle of proportionality Hermeren (2012). Jonsen (1998) analyzes the opinions of early bioethicists as to the principle of proportionality and advocates that the harm to the donor must be outweighed by the benefit to the recipient (Jonsen 1998, p. 203). The principle of proportionality applied to live donation is defined as the choice between two competing moral values; in the case of live donation, causing harm to one to help another. The Catholic ethical tradition describes the principle of "double effect" where an immoral action is taken to prevent a greater immorality from taking place. While the latter and former definitions do ethically validate live donation in principle, factors such as coercion and vulnerability have only been analyzed through the informed consent

process. The latter ethical quandaries have culminated in our current OPTN guideline/rules for the evaluation of living donors which include stipulations for independent advocacy, analysis, and verification of voluntariness. The entry "▶ The Finance of Kidney Transplantation" addresses the legal and regulatory aspects of a kidney transplant program. However, historically ethical reflection on live donation has not addressed that the current transplantation paradigm's zeal for rescue of the recipient diminishes the importance on the welfare of the donor by a form of "social" coercion. Author's such as Lewis et al. (2017) note the portrayal of organ donation in the media as a form of the latter. Another form of social coercion is how society tends to elevate the live donor to a "hero" level. It is not a conscious elevation but as Chapple (2010) demonstrates, the concept of "rescue" is ingrained in the American culture and those who ascribe to less glamorous endeavors or eschew it individually are seen as less. Chapple (2010) does not specifically address organ transplantation, but her rescue paradigm assertion is easily applied to transplantation. Therefore, while some may view rescuing the recipient as a positive social endeavor, vulnerable persons perceive negative social consequences from not donating. The latter is illustrative of coercion. Societal pressure in favor of recipient rescue is such that any information given to the public that is perceived to lessen live donation is modified, parsed, or even suppressed. Example is subdued public reporting of live kidney donor deaths living kidney donor death and mortality (2017). Fung (2010) stated at the 2010 US Department of Health and Human Services Advisory Committee on Organ Transplantation (ACOT) referring to four live kidney donor deaths in that year: "The fact that there were four kidney deaths with almost no publicity is. . .problematic." Indeed, the subject requires more ethical reflection and definitely more research.

Deceased Donors

The first successful transplantation was a renal transplant performed in 1954 by Murray et al. (1955). Today most transplants performed are from donors declared deceased. In 2015, approximately 81% of the transplants (24,982) involved organs from deceased donors. Deceased donors are brain dead or deceased donors after cardiac death (DCD). DCD are further divided into controlled or uncontrolled. A new and controversial classification is DCD by euthanasia. The three situations that lead to deceased donation reveal issues ripe for ethical analysis and reflection. Three issues will be addressed: declaration of brain death, donation after cardiac death, and euthanasia or suicide by organ donation.

Brain Death

The concept of "Brain Death" did not develop to accommodate, benefit, or considering organ transplantation. Factually, the concept developed as an epiphenomenon and today is almost exclusively under the rubric of organ donation for the benefit of transplantation. This chapter does not intend to relate an exhaustive analysis of brain death; therefore, the subject will be limited only to salient and arguably controversial issues.

Classically, the declaration of death involved the observation of cessation of heartbeat and respiration (Machado 2007, p. 1). In the late 1950s, cessation of circulation to the brain was identified as a cause of apnea and elimination of reflexes. Later, Mollaret and Goulon (1959) coined the term *coma d'epasse'* for an irreversible state of coma and apnea. However, it was Wertheimer's group (72, 73) that described "the death of the nervous system." The group went further to propose stopping ventilation if death of the nervous system was diagnosed clinically and by "the repeatedly verified absence of electroencephalographic (EEG) activity both in the cortex and in the diencephalon, and if resuscitative efforts have been given enough time, 18–24 h." (Wertheimer et al. 1959). Finally, the seminal event that created the currently established concept of brain death was the publication of the "Harvard" criteria in 1968 (Ad Hoc Committee of the Harvard Medical School to Examine the definition of Brain Death [Harvard Committee] 1968).

Still the actual cause of cessation of cerebral activity was not identified as termination – regardless of cause – of circulation to the brain. Crawfoord (1939) stated that

> death was due to "cessation of blood flow to the brain and nothing else." The latter set the grounding concept for today's diagnosis of brain death. Today, clinical diagnosis of brain death is directed almost exclusively at the purpose of determining cessation of blood flow. However, objective maneuvers such as angiography, nuclear medicine blood flow determinations, and positron emission tomography (PET) are seldom used particularly in adult patients. Instead, and arguably due to lack of resources, the less objective and more clinical criteria have been used. The generally accepted clinical criteria stated in the American Academy of Neurology (AAN) core guidelines are shown below. (Wijsdicks et al. 2010, p. 1917)

Clinical Criteria (AAN)

1. Coma, irreversible, and cause known
2. Neuroimaging explains coma
3. CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level,10 mcg/ml)
4. No evidence of residual paralytics (electrical stimulation if paralytics used)
5. Absence of severe acid-base, electrolyte, endocrine abnormality
6. Normothermia or mild hypothermia (core temperature $>36\ ^{\circ}C$)
7. Systolic blood pressure ≥ 100 mm Hg
8. No spontaneous respirations
9. Pupils nonreactive to bright light
10. Corneal reflex absent
11. Oculocephalic reflex absent (tested only if C-spine integrity ensured)
12. Oculovestibular reflex absent
13. No facial movements to noxious stimuli at supraorbital nerve or temporomandibular joint
14. Cough reflex absent to tracheal suctioning
15. Absence of motor response to noxious stimuli in all four limbs (spinally mediated reflexes permissible)
16. **Apnea testing**:
    (a) Hemodynamic stability
    (b) Adjust ventilator to provide normocarbia (Pco_2 35–45 mmHg)
    (c) Pre-oxygenate patient at 100% for 10 min to $PaO_2 \geq 200$ mmHg
    (d) Patient well oxygenated with PEEP of 5 or $<$
    (e) Place on T-Piece or tracheal O_2 at 6 L/min and CPAP of 10 mmHg.
    (f) Discontinue ventilator and insure spontaneous respirations are absent
    (g) Draw arterial blood gas at 8–10 min and assure PCO_2 is ≥ 60 mmHg and no spontaneous respirations and reconnect ventilator

The clinical criteria are extensive and meticulous; however, they are based on levels of evidence considered lower according to evidence-based standards. Admittedly, further research is necessary for the universal acceptance of standards. However, for ethical analysis specifically declaring a human being a cadaver perhaps more objective criterion should be used.

The ethical implications of brain death were eloquently described by Starzl in his comments at the Ciba Symposium of 1966, the first international symposium on ethical and legal aspects of organ transplantation. Dr. Starzl commented: "I doubt if any of the members of our transplantation team could accept a person as being dead as long as there was a heartbeat. We have been discussing this practice in relation to renal homograft. Here, a mistake in evaluation of the 'living cadaver' might not necessarily lead to an avoidable death since one kidney could be left. But what if the liver or heart were removed? Would any physician be willing to remove an unpaired vital organ before circulation had stopped?" Dr. Starzl's comments were prophetic and identified the moral suspicions of the transplant community toward the concept of brain death. His comments also echo a subconscious concern of all transplant surgeons when procuring organs from a brain-dead donor. It is clear from Dr. Starzl's reflections that there is a possibility of causing death by organ procurement. Despite the evolution of brain death from a questionable moral entity to an accepted criterion of death, maintaining ethical consistency and true adherence to the "Dead Donor" rule (the concept that patients undergoing donation of a

"life sustaining organs be declared dead) would require all possible clinical criteria in conjunction with objective tests confirming the diagnosis of brain death to virtual certainty. The modifier "virtual" used as the only true proof of death is putrefaction.

Donation After Cardiac Death (DCD)

Formerly called non-heart beating donation (DCD) has less scrutinized ethical issues than brain death or live donation but the concept is not without controversy. Two ethical issues come to the forefront in DCD. First is the decision to end life support. Second is the process and declaration of death before organ donation.

The grounding ethical problem in the first situation is conflict of interest. Conflict of interest is defined as: "A situation that has the potential to undermine the impartiality of a person because of the possibility of a clash between the person's self-interest and professional interest or public interest" (Business Dictionary.com n.d., p. 1). Both the transplant team and the organ procurement organization have self-interest in the procurement of the organs from the person whose life support is terminated. In our society's recipient-centered transplant environment, the impetus to rescue the recipient is inherent in the philosophy of the transplant team and the organ procurement organization. The possibility of financial incentives will not be mentioned as it is beyond the scope of this chapter. However, the total separation of any relationship of transplant professionals from the physicians terminating life support is necessary for elimination of conflict of interest.

The second situation animates the moral pitfall of the transplant surgeon or team actually hastening or causing the death of the donor for interests other than the donor's. Some may argue that the donor's wishes are respected by terminating life support and organ donation and subsequently any maneuver used to preserve the organs prior to death including during the death process is consistent with respect for the donor's autonomy. Organ donation advocates posit that the surrogate or donors informed consent justifies almost any intervention on either brain dead or DCD during the terminal process. Opponents of any hastening or intervention of the donor's death for procurement purposes cite violation of the donor's dignity and respect as a person. Consider the case of Dr. Hootan Roozrokh who according to Chawkins (2008) was charged with felony adult abuse. Investigational documents indicate it was Dr. Roozrokh who gave the order to the respiratory therapist to remove the donor from life support. The lack of a specific DCD protocol in addition to ethical breaches leads to the physician's arrest.

In 1992, the University of Pittsburgh was one of the first institutions to develop a protocol for retrieving organs from non-heart beating donors. An ad hoc committee excluding organ procurement representatives and transplant service members was formed to develop the protocol. The exclusion was to prevent conflicts of interest. The Pittsburgh protocol is interestingly in contrast to the current UNOS (United Network of Organ Sharing) and the OPTN (Organ Procurement and Transplantation Network) critical pathways which essentially require the OPO staff to be involved in pre-, during, and post-procurement efforts. Proponents of OPO staff involvement assert the OPO's expertise in organ donation and cite their success in obtaining consent for donation. However, the ethical issue is not one of success in procuring the organs. It is one of procuring them ethically or not at all. Only a recipient centric system would exhort the former.

Euthanasia or Assisted Suicide by Organ Donation

Serial review of ICU deaths found that from the 1980s to the 1990s, the percentage of ICU deaths that occurred following withdrawal or withholding of life support increased from approximately 50% to approximately 90%. These statistics remain approximately the same today (Prendergast and Luce 1997).

The viability of solid organs is almost universally compromised in cases of organ donation

after cardiac death. The "Dead donor" rule mandates declaration of death before organ procurement. Traditionally, the 5-min rule has been followed in cases of DCD. However, heart, lung, and liver donation and to a lesser extent kidney has been precarious due to tissue damage by warm ischemia during the mandate 5 min. Some have proposed forgoing the dead donor rule in cases where the patient or surrogate has decided to terminate life support with the purpose of ending their life. In such cases, the organs are procured and death is caused by the procedure of organ donation, e.g., the patient is euthanized for the purpose of procuring the organs. The transplant team becomes an assistant to the patient's wish to terminate their life.

Truog (2013) and others have argued for the suspension of the "Dead Donor Rule" limited to individuals with no possibility of regaining consciousness such as anencephalic infants and patients in a permanent vegetative state. However, Wilkinson and Savulescu (2012) has gone further and proposed a protocol for organ donation euthanasia (ODE) for the United Kingdom to procure a fraction of brain dead (BD) and DCD. In the United Kingdom, Wilkinson and Savulescu (2012) estimates a fraction of approximately 600 donors could potentially increase the donor supply. However, admittedly the supply of organs would have little if any impact on the number of recipients treated.

The above concept is governed under the principle of medical utilitarianism, i.e., the greatest good for the greatest benefit and foregoing the moral implications for the means for the end. The question is, whose benefit; euthanasia by organ donation is again a creation of a recipient centric system. It can be posited that apparent conflicts of interest are numerous and impossible to overcome in a system with such asymmetric focus. The scene of a transplant surgeon ending the life of a patient in the operating room is counter the any concept of a virtuous physician. Such a drastic violation of a long-standing moral framework such as the dead donor rule for a small benefit is counter to the fundamental ethical concepts grounding organ transplantation.

The Recipient

Several ethical controversies exist that are grounded on the recipient side: racial disparities, discrimination based on diagnosis, and regional disparities in organ allocation. The controversies are under the bioethical principal of justice, particularly social justice.

The current system of organ allocation asserts its position of fairness and justice. Organs are allocated based on a system grounded on just distribution. However, gaining access to the organ has not been a priority of the system. In a recipient-centered system, the donor and the organ are viewed as a commodity used to treat the recipient. The disparity between the number of recipients and donors creates a situation ripe for studying and enacting distributive justice. Moreover, the transplant community had designated that organs should be allocated to the most appropriate recipient. Ethical reflection requires analysis of the choice of said recipient as worthy of the organ. In this section, ethical issues relating to the recipient will be addressed.

Racial Disparities in Recipient Selection for Organ Transplants

Kasiske et al. (1991) identified racial disparities in the likelihood of undergoing kidney transplants. The etiology of the disparity was not known at the time; however, the system of allocation based on ABO and mean histocompatibility antigens (MHC) favoring the non-African American was posited. Also, diminished survival statistics, lack of healthcare coverage, and cultural barriers were also identified as potential causes. Arriola (2017) describes eight steps involved in obtaining a kidney transplant. At each of the steps she identified potential sources of racism. The ethical question is whether disparities are due to racism, structural violence, or a complex array of biologic, genetic, psychosocial, and cultural factors. The transplant system is centered on providing the most just distribution of the donor for the recipient on the list. There is, however, little attention paid to justice of access to the "list" itself. The

transplantation literature identified by Arriola (2017) is replete with data identifying racial disparities. However, recommendations for the elimination of disparities are not attended to nor is research directed at them. Recommendations for mitigation of racism include primarily acknowledgment of the existence of structural racism. Education on navigating the system and expanded research aimed at raising consciousness of and elimination of structural racism require self-identification by the transplant community as requiring a fundamental change in behavior and methods. Arriola (2017) eloquently lists potential sources of racism and recommends actions for elimination of said sources (Arriola 2017, Table 1). The latter is the path to applying the principle of justice to transplantation.

Discrimination-Based Diagnoses or Conditions Other than Medical

Historically, the transplantation community has determined patients with certain diagnoses whether causative or allied to their disease as criteria for exclusion from a transplant. The justifications for exclusion have been centered at the risk for graft failure or recipient mortality. Causes cited have been: patient noncompliance with immunosuppressive regimens or low allograft or patient survival for the specified conditions. Excluding patients based on criteria such as the latter is supported by a utilitarian ethic aimed at complying with the dictum of fair distribution for the greatest benefit.

Medical contraindications such as disseminated malignancy, or inability to survive the transplant operation itself have been supported by empirical evidence. However, more subjective contraindications such as lack of social capabilities, the presence of socially undesirable habits such as smoking or diminished intellectual capacity have been a source of ethical controversy.

Senderovich (2016) questioned the ethics of the transplant community's exclusion of smokers and alcoholics and cites the lack of randomized trials supporting the transplant community's assertion that patients that smoke (in the case of renal transplantation) and patients who use alcohol have an increased mortality or decrease allograft survival. The ethical question is whether transplant programs should decide the indication for a transplant based on a social desirability. The World Health Organization (WHO) consensus states: "donated organs should be made available to patients on the basis of medical need and not on the basis of financial or other consideration." It is these other considerations that the WHO does not define. Clearly, discrimination based on behavior alone is not justified. Examples of exclusions based on socially undesirable habits are the exclusion of smokers from transplant lists. Despite the lack of literature supporting exclusion of recipients for smoking in lung transplantation, most programs exclude active smokers. Diamond et al. (2013) reviewed causes of primary graft dysfunction in lung transplantation. Donor smoking history was the only "social" factor that contributed to graft dysfunction. Recipient smoking history was not mentioned as a cause. However, virtually all lung transplant programs exclude candidates who actively smoke. It is understood that patient adherence to specified recommendations (formerly compliance) is an important factor in long-term graft and patient survival. But, should patients be excluded from lifesaving transplants for behavior not empirically proven to be detrimental to survival.

Another controversial nonmedical criterion used for exclusion from transplant lists is cognitive disability. Richards (2009) showed the significant variability in who a transplant program will place on the list. Among the exclusionary criteria for most programs was cognitive disability. However, Ohta (2005), Weightman (2016), and others have shown no difference in allograft nor patient survival for children with intellectual disabilities in renal and heart transplants. Unfortunately, this is yet another biased and subjective indication for exclusion of "undesirable" patients from transplant lists.

Geographic variation in listing and transplantation has long been a subject of controversy and also requiring ethical analysis under the principles of beneficence and justice. It has been generally perceived by the transplant community that

regional prioritization for allocation of organs was due to donor factors such as ischemia time. The latter may apply to currently transplantable thoracic organs where ischemia times are crucial; liver and kidney transplantation do not suffer from the same liability. Yeh et al. (2011) had identified – not only – geographic variation but increase in mortality of and the transplantation of patients who may not benefit from a liver transplant, resulting in the equivalent of organ wastage. Deshpande (2017) analyzed the current system of liver allocation and found the arbitrary system of geographic distribution to be inconsistent with just allocation. Patients with resources can list at multiple centers which, due to geographic variation in number of donors available to the centers, have a lower waiting time and lower mortality than other centers. "Current liver allocation policy favors the wealthy" (Deshpande et al. 2017, p. 165). The latter situation is inconsistent with appropriate stewardship of a scarce resource and further illustrates the multiple areas in transplantation where subtle discriminatory policies yield less benefit to patients.

Conclusion

As stated at the beginning of this chapter, the most important issue necessary of ethical reflection is the great disparity between the number of organs and the number of recipients. In 2017, over 120,000 recipients wait for a transplant. Society, government, the healthcare environment, the transplant community, transplant centers, and finally individual clinician, all have one goal in common: providing care in the best interest of those afflicted. In transplantation, justice is the overarching principle. Unfortunately, due to the very unique situation of human transplantation, the resource (organ) is a scarce gift and requires a concerted and ethical application of distributive justice. The transplant community since inception has functioned under several self-imposed dictums aimed at maintaining the ethical standards of medicine. Among these dictums are: The Dead Donor Rule (donors), Respect of informed consent and freedom from coercion (donors), elimination of nonmedical exclusionary criteria for transplantation (race, religion or culture), and maximization of survival. These self-imposed mandates are not always followed for many reasons. However, it is the role of the individual healthcare provider to identify and mitigate any subversion of our self-imposed ethical mandates. Only through continued education and ethical reflection can such a goal be achieved.

Cross-References

- ▶ Live Donor Nephrectomy
- ▶ Living Donor Evaluation and Selection
- ▶ Medical Complications After Kidney Transplantation: Early
- ▶ The Finance of Kidney Transplantation

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Psychosocial and Personal Financial Aspects of Transplantation

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Contents

Abstract

In addition to end stage renal disease (ESRD) and other medical illnesses, candidates and recipients of renal transplants are faced with a myriad of potential psychosocial problems. It is typically the responsibility of the nephrology and transplant social worker to assess, plan management and follow these patients long term. It has become clear that socioeconomic determinants of health are as important to long-term patient and graft survival as many of the medical aspects of treatment. Poverty, limited social

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networks and inability to pay for transplant medications have direct effects on patient's quality of life, patient, and graft survival. Beginning with the patient's introduction to ESRD through successful transplantation, identification and management of adverse psychosocial issues may make the difference between success and failure. This chapter will outline an example of the psychosocial assessment and discuss personal financial aspects from the patient's perspective. It further discusses other important psychosocial issues such as employment, nonadherence, and patient-related resources from governmental, private, and philanthropic sources.

Keywords

Kidney transplant · Psychosocial assessment · Poverty · Medicare · Medicaid · Employment · Nonadherence · Social networks · Quality of life · Socioeconomic status · Patient survival · Graft survival

Introduction

The patient is a 32-year-old man who presents to the transplant clinic for evaluation for a second renal transplant. He developed focal segmental glomerulosclerosis at age 5 but the nephrotic syndrome was refractory to steroids and cyclophosphamide. He progressed to ESRD by age 12 and underwent a living related kidney transplant from his mother the following year. He was home schooled due to the many hospital admissions to treat nephrotic syndrome. Prior to the transplant his parents divorced and the patient overheard his father say that "I didn't sign up for this sick kid." Thereafter his father was absent from his life. His mother had been a teacher's assistant but lost her job due to the school district's downsizing. The family consisting of the patient, his two sisters, and mother became dependent on welfare and Medicaid for health insurance. They lived in a rural setting and the closest transplant center was in a different state. Despite these problems the patient completed high school only 1 year late and was accepted into a college 200 miles away from home. Prior to college his mother set out and supervised administration of his medicines. His serum creatinine was 0.8 mg/dl at that time. He was short for his age but otherwise had a normal body habitus. Six months after starting college, he noticed increasing tenderness over the transplant site and visited the student health center. He admitted that he had not taken his anti-rejection medication for at least 6 weeks and he had missed taking them frequently before this "due to my classes." Serum creatinine was found to be 5.5 and the renal biopsy revealed mixed humoral and antibody mediated rejection. After aggressive treatment for rejection his creatinine fell and stabilized at 3.9 mg/dl. He resumed his medications and was able to graduate from college within 5 years without recurrent rejection. He experimented with marijuana, cocaine, opioids, and methamphetamines while in college but heroin became his drug of choice "since it was so cheap." He was unable to find a job after college and moved in with his mother again who was off welfare and had a full time job at a nearby diner. His relationship with his mother was tumultuous often ending in physical violence. He would typically stop his anti-rejection medications after fights to "get back at her." After several rejection episodes and progressively rising creatinine he started hemodialysis. He missed dialysis treatment at least once weekly, had 5-kg weight gains and routinely had elevated serum phosphates. In addition, he began injecting heroin into his A-V fistula. He was not referred for re-transplantation due to nonadherence to medications and active drug abuse. After many drug rehabilitation admissions, he was able to stop heroin abuse, took his medications, and stopped missing dialysis treatments. After 2 years of sobriety and compliance with his medical regimen, he was referred for transplantation.

Kidney transplantation has become the most frequently performed and most successful of all solid organ transplantation. The technical aspects of kidney transplantation have been refined such that few patients are not acceptable candidates. Surgical procedures, antirejection medications, and management of post-transplant complications have advanced to the point that kidney transplantation can be safely performed in most areas of the

USA and the world. Although the underlying medical conditions of patients are important, the psychosocial condition of patients is probably equally important. The technically excellent outcomes can be thwarted by patients who are unable or unwilling to take their medications, have underlying untreated psychiatric or social conditions which may flare post-transplant or any number of other psychosocial problems which preexisted the transplant. The psychosocial evaluation is typically performed by a nephrology/transplant social worker who has particular skills in assessing these often complex patients.

The renal social worker does a complete psychosocial assessment on every client that is referred for ESRD care and transplantation (Gaston and Gitlin 2010; Browne et al. 2014). While there are numerous assessment tools available for social workers, there is a basic problem list that should include areas of physical illness, emotional adjustment, disruptions in family relationships, the socioeconomic situation, and the complexities in planning for community living (Table 1). Currently there is no universally accepted psychosocial instrument or formally accepted guidelines although a number have been proposed (Greene 2013; Maldonado et al. 2012). Most transplant programs use some variant of the items noted in Table 1. A psychosocial evaluation is required by federal regulatory agencies in transplantation including the United Network of Organ Transplantation (UNOS) and Centers for Medicare and Medicaid Services (CMS). They also require that a social worker be part of every kidney transplant center.

Table 1 Basic areas covered in psychosocial assessment

• Medical history and adjustment to illnesses
o Renal disease history
▪ Duration
• Since childhood or recent onset
▪ Preemptive?
▪ On dialysis?
o Comorbid illnesses
o Adherence on dialysis with
▪ Medications
▪ Diet
▪ Dialysis treatments missed
o Mental illnesses
▪ Currently controlled?
▪ Risk of exacerbation post-transplant
o Adjustment to illnesses
▪ Renal disease
▪ Other illnesses
o Knowledge of ESRD
o Knowledge of transplantation
o Feelings about ESRD and transplant specifically
• Personal assessment
o Demographic and personal information
▪ Education
▪ Age, lifecycle position, ethnicity
▪ Emotional, sexual and intellectual functioning
▪ Religious beliefs
o Education
▪ Highest grade attained
o Vocation
▪ Work history
▪ Working or unemployed
▪ Interest or need for vocational rehabilitation
o Financial
▪ Employment status
▪ Poverty?
▪ Sources of income
• Disability income
▪ Number of persons supported by patient
▪ Current job jeopardized by ESRD or transplant?
▪ Ability to pay for medications post-transplant
• Support systems
o Family
▪ Members- spouse, children, grandchildren, partner
▪ Quality of relationships
▪ Family support after transplant
o Social
▪ Friends, neighbors, coworkers
▪ Quality of relationships

(*continued*)

Quality of Life After Kidney Transplantation

A major benefit of kidney transplantation has been improvement in quality of life (QoL). A number of instruments have been used to measure QoL including SF-36, World Health Organization QOL instrument (WHOQOL-BREF), and others (Alkatheri et al. 2015). Most studies have found consistent improvements in QoL during the first 3 months after transplantation compared to their

Table 1 (continued)

o Environmental
▪ Distance from transplant center
• Need for transportation
• Neighborhood characteristics
• Need for housing
o Homeless currently
o Housing plans after transplant

dialysis scores in recipients. Some patients, however, do not experience such improvements. Villeneuve et al. reported that patients without improved QoL scores could be distinguished by higher serum creatinine, increased anxiety, and lower muscles mass (Villeneuve et al. 2016). These were likely patients with poor allograft function due to delayed renal recovery, early rejections, and recurrence of their primary renal disease. Increased physical activity has been associated with the best QoL results. Raymond et al. used a combination of surveys and pedometers to assess transplant recipient's activity and QoL (Raymond et al. 2016). Those with the greatest moderate-vigorous physical activity (MVPA) had the best QoL and conversely increased sedentary time was associated with worse QoL including decreased mental functioning. Patients meeting the public health recommendation of 150 mins/week of MVPA had the best QoL. This study emphasizes the importance of encouraging patients not only to return to "normal" life but to make that life physically and mentally active.

The kidney transplant process creates great stress for patients and their families. The level of anxiety predictably increases in uncomplicated patients but may become severe in those experiencing medical or surgical complications and particularly those who lose the allografts. This increase in anxiety develops in donors and recipients alike. Erim et al. used the World Health Organization Quality of Life (WHOQOL-Bref) and resilience scale (Resilience Scale, RS-12) in donors before and after transplantation (Erim et al. 2015). Resilience correlated with QoL in all patients. Donors excluded from donation had lower resilience scores at baseline compared to those allowed to donate. Not surprisingly, all donors experienced a decrease in QoL 3 months after donation. Long-term follow-up was not provided to determine if QoL returned to baseline or improved beyond this level. In other studies, QoL returned to baseline by one year post donation. Interestingly, QoL was greater than the general population in donors prior to donation in most studies.

Psychosocial Assessment

The Patient's Medical Condition

Patients with ESRD may have a multitude of medical illnesses not related to their kidney disease. These comorbid illnesses complicate their assessment, post-operative management, and are associated with worse early and long-term outcomes (Kauffman et al. 2007; Wu et al. 2005). These illnesses in conjunction with poor socioeconomic factors result in particularly poor outcomes. End-stage renal disease alone is associated with higher rates of cardiovascular disease, decreased sexual function, and an array of social and psychological problems that remain poorly characterized even in this modern era. In addition, diabetes, with all its complications, is the leading cause of ESRD in adults. Patients may also have serious illnesses such as lupus, vasculitis, previous cancers, and psychiatric illnesses. Psychiatric illnesses are highly prevalent in transplant candidates including DSM-IV axis I (60%, all psychological diagnostic categories except mental retardation and personality disorder) and axis II (32%, personality disorders and mental retardation) (Chacko et al. 1996). These problems do not necessarily exclude patients from transplantation, but they should be controlled and risks minimized. The psychosocial assessment must explore the patient's adaptation to their illnesses including their understanding of the potential benefits of transplantation. Unrealistic expectations may exist about transplantation improving symptoms of non-renal origin such as relieving pain from diabetic neuropathy or osteoarthritis.

The major medical problem existing in all kidney transplant patients is the end-stage renal

disease (ESRD). The cause of renal disease and rapidity in which it developed may have major influences in the patient's ability to cope with their illness. Social workers may be involved with the patient's care during the progression of their chronic kidney disease (CKD) or they may see the patient initially, while on dialysis and in the case of most kidney transplant evaluations, they may see them for the first time during this initial visit. The frequent interactions with clients enables a long-term trusting relationship for the client as well as the social worker and has been associated with improved medical and social outcomes (Wilkins et al. 2003). This is often the case when the client has been in an outpatient or inpatient dialysis unit as well as a frequent outpatient visitor in renal clinics. The social worker who works in an outpatient renal clinic or hospital dialysis unit and follows the patients while hospitalized is able to see the progression of renal disease and how it affects the patient, as well as the entire family unit. This bond provides the opportunity for intervention on every level necessary to promote the emotional, social, and economic needs of the patient and family unit. ESRD is a progressive illness that requires a compassionate understanding of the patient's challenges as well as the ability to enable the patient and family to adapt to the changes that will affect every member of the family. The social worker's support is vital in helping the patient and family achieve optimum mental functioning and family stability through the arduous process of ESRD to kidney transplantation and post-transplantation care.

Personal Factors

Table 1 outlines a partial list of potential personal factors which may impact on patient's candidacy for transplant and long-term outcomes. Age or stage in life is a major independent factor in the psychosocial assessment. For very young pediatric patients, the assessment is centered on the parents and the child's current or predicted cognitive development. In such cases, the parent may be the kidney donor in addition to the care giver. The intellectual functioning of the child and parent becomes a major consideration. It is not uncommon to have a child with ESRD and one or both parents may be developmentally delayed. The potential cognitive and developmental potential of the child in these cases may span from normal to severely impaired with the expectation that the child will never be independent. Elderly patients are increasingly undergoing kidney transplantation. In these patients, both physical and cognitive functioning may be impaired requiring additional assessment and long-term support. For all patients, an assessment of the ability to follow the medical regimen is vital. In very young children, this will involve the capabilities of the parents, but for older children such as adolescents the assessment includes both the parents' and child's abilities. Adolescents have a high rate of nonadherence to the medical regimen when left to administer medications without adult supervision. They may also have excellent adherence while living at home with parents but may lose the graft to nonadherence when transitioning to college or living alone. The patient's coping style may help predict their reaction to transplantation or graft failure. Religious beliefs and engagement should be assessed as should their sexual functioning and history of prior uses of illicit substances. There has been growing interest in the relationship between patient's religiosity and medical outcomes. VanderWeele has recently reviewed this topic (VanderWeele et al. 2017). Although this area remains controversial, religiosity may be associated with more stable social situations, increased likelihood of adherence to medications, and other benefits to patients. Active intravenous drug users and others should not be transplanted until they have undergone successful drug rehabilitation. Active use of marijuana is discouraged by most transplant programs but may be prohibitive by some.

Education/Vocation/Financial Situation

Education and work history in addition to the patient's current financial situation are important and the financial status for some is vital (Wilkins

et al. 2003). Patients with greater education and stable work histories experience better medical and psychosocial outcomes after transplantation. Poverty is a particularly damaging factor (Butkus et al. 2001). Transplant outcomes can be correlated with the zip codes of patients with those in poor zip codes experiencing inferior transplant outcomes. Such patients may not have adequate resources for clinic visits, out-of-pocket costs not covered by insurance, or immunosuppressant medications. These patients may develop graft loss simply because they are unable to afford their medications. Homelessness is a growing problem in the general population and in patients with ESRD. Lack of stable housing may exclude patients from transplantation in most programs. Increased exposure to extremes in weather for those living on the streets could profoundly increase their risk for medical complications.

Support Systems

Social support is defined as the physical and emotional comfort provided by family and others. The patient's social support system is important in their ability to have a successful functioning graft long term (Borges et al. 2017). Social support networks consist of family, extended family, friends, religious and cultural groups. Strong social networks have been associated with completion of transplant evaluations (Clark et al. 2008) and medication adherence (Chisholm-Burns et al. 2010; Gerson et al. 2004). Gender may also play a role in that support provided by women was positively correlated with patient's intention to adhere to medications but negatively correlated if support originated from males (Scholz et al. 2012). Not surprisingly, the quality of social support and relationship is vital. In a study by Frazier et al., supportive spouses resulted in decreased distress after transplantation compared to unsupportive spouses who actually increased the distress experienced by patients after kidney transplantation (Frazier et al. 1995).

In most cases, the patient's family will provide the majority of support for patients undergoing dialysis or those receiving renal transplants. For children, the parents usually provide extensive support depending on the age of the child. Likewise, elderly patients may require substantial support from their children or other caregivers. In each case, an assessment of the quality of family relations will be crucial. Illnesses may cause previously marginal family relationships to decompensate as the demands of caring for the patient mounts. Some patients may receive substantial social support from friends, partners, and neighbors. The quality and durability of these relationships should be assessed. As mentioned earlier, social networks which consist of family and community members influence the patient's rapidity in completing their transplant evaluation, but they may even determine if patient will allow themselves to be referred for transplantation. In a study by Browne in Chicago, the odds of patients being seen in a transplant center increased with income and having a social network in which members were knowledgeable about transplantation (Browne et al. 2014).

Environmental

Closely associated with patient's personal finances is the environment in which they live. Multiple studies have correlated patient outcomes after transplantation with the area in which they live. Zip code has been used as a proxy for economic status and may also correlate with neighborhood resources, crime, and many other factors. Patients from poor neighborhoods have higher rates of graft loss, nonadherence, and many medical complications. Although economic groups may overlap in Zip codes, it is usually available in large registries and seems to approximate the macroeconomic environment for most neighborhoods. Housing and transportation resources are important factors in patient's transplant experience and outcomes. Patients with unstable housing will have a myriad of challenges. At the extreme, homelessness will pose risks to the transplantation and to the patient's survival. Measures should be taken if possible to find community resources to stabilize the housing situation before transplantation. Special measures may be needed

to provide consistent transportation when the patient does not have the resources or they do not exist in their environment. Patients in urban centers may have access to public transportation to the transplant center and to other medical facilities required but some may be unable to use these due to disabilities. Provision of vouchers may assist some patients if they are available when the price of public transportation is too expensive. They must be capable of getting to clinic visits after transplantation. Rural areas pose extreme transportation challenges when the patient lives in a very remote area. In these cases, relocation closer to the transplant center may be required when frequent post-operative visits are required.

A detailed psychosocial assessment must include environmental factors such as neighborhood characteristics, housing, access to transportation, and distance from the transplant center among others. High poverty neighborhoods can be associated with increased threats of violence which may increase the stress and distress of being evaluated and maintaining a functioning graft. Recommendations to exercise such as walking may be ludicrous for patients living in areas where physical violence is ever present. For patients living in nonthreatening environments, walking may be a perfect solution for weight reduction and stress relief. Transportation may be abundant in urban areas but scant in rural areas. Social services which might assist with transport, child care, drug rehabilitation, and monetary support vary by location. Even access to healthy foods may be limited in "food deserts" found in both urban and rural settings. These are areas in where affordable and nutritious food is difficult to find. They have been linked to unhealthy eating habits and diet-related eating problems such as obesity, hyperlipidemia, and diabetes.

Distance from the transplant center can pose significant barriers to obtaining a transplant and post-transplant monitoring. Unlike liver, heart, and lung transplantation, the kidney can sustain longer cold ischemia times before transplantation in deceased donors. The non-renal organs must be transplanted before approximately 12–14 h post donation. Despite this advantage, distance from the transplant center might exclude some patients from kidney transplantation or at least make getting to the center in time more difficult. These challenges range from patients coming from international homes for transplantation in the USA to patients living in urban areas but relatively far based upon their available resources. Patients have been known to take a bus to the transplant center to receive the organ because no other form of transportation was available to them. Likewise patients from Europe or the Middle East have moved close to the transplant center to have access. Patients within the same country may need to relocate near transplant centers in addition. Wirken et al. performed a meta-analysis of studies examining the QoL in donors (Wirken et al. 2015). They also found that QoL decreased after donation but improved at least to baseline by 12 months except for fatigue which was slightly lower than baseline but equivalent to the general population.

Personal Financial Aspects of ESRD and Transplant

The patient's personal financial situation may have profound effects on their ability to complete evaluations, obtain medications or transplantation, and affect their overall quality of life. ESRD care requires that some patients stop working or reduce their working hours. For some this results in a major reduction in family income. For others, who are chronically unemployed this may provide a consistent income in the form of disability income. In the latter, obtaining a transplant may eliminate their disability payments forcing them deeper into poverty. In such cases, getting a kidney transplant may be a luxury they cannot afford. In general, middle class and upper middle class patients fare better economically than the poor. Poor patients may require additional assistance.

Patients starting ESRD care including renal transplantation will likely have many questions about medical insurance coverage and any potential financial assistance which may be available to them. Medicare is a major source of insurance for

dialysis and transplant services in the USA. In general, patients become eligible for Medicare at age 65 or when they develop ESRD regardless of age. Medicare becomes active 90 days after starting in center dialysis, 1 month after starting home hemodialysis or peritoneal dialysis and at the time of admission for renal transplant generally. Not all patients are eligible for Medicare, however. Current regulations require that they qualify for social security by virtue of having worked sufficiently to have the required work credits, If they, a spouse, or child is receiving social security they qualify. These regulations change frequently so one should check with Medicare for the most current requirements. A detailed discussion of medical insurance is beyond the scope of this discussion. Additional details can be found at medicare.gov for the basics of Medicare coverage and to specific private insurers for their details. Table 2 illustrates some of the additional resources available to patients. Some patients may have a need for transportation to the dialysis unit or transplant center, medication programs for indigent patients, and others. For transplant recipients who must fly to obtain a new graft, some charitable organizations may be of assistance. Insurance may consist of private insurers which is usually employer provided or Medicare/Medicaid. Initial information on their insurance options is mandated by CMS to be provided by social workers and insurance counselors (Zumoff 2017). The United Network of Organ Sharing (UNOS 2017a) and others provide a list of financial resources available to patients. Some of these are charitable in nature such as the American Kidney Fund (AKF) which may help pay insurance premiums for private insurers such as Blue Cross BlueShield and other private companies (Zumoff 2017) (American Kidney Fund: Financial Assistance 2017). Recently, however, some insurers have denied payments of premiums by charities for what are likely complex reasons but may force patients ultimately to withdraw from those plans. The AKF and other financial organizations may also assist patients with transportation and prescription medication costs. These funds typically require a grant from the agency which usually requires the social worker's assistance. The National Kidney Foundation (NKF) may also offer small grants to patients and provides information on insurance and other matters of concern to patients with ESRD (NKF 2017).

Employment

Implicit in Medicare policy for renal transplantation is the assumption that patients will return to work. In the USA and other countries, the rate of employment is low. A study in Brazil found that only 29% of the kidney transplant recipients were employed and that employment was associated with pre-transplant employment and higher educational levels (Bohlke et al. 2008). In the USA, Peterson et al. examined employment after transplantation using registry data from the USRDS and UNOS (Petersen et al. 2008). The employment status of these 78,130 patients at the time of transplantation was the following; 41.7% working, 36.7% not working due to disease, and 3% not working by choice. Full-time employment at the time of transplant was associated with better graft survival compared to the other groups at 1 year, but continued work after expiration of Medicare medication benefits was associated with lower graft survival. There were no differences in patient survival and the employment rate did not substantially improve in any employment status. Parajuli et al. reported that 93.5% of their patients were working prior to starting dialysis but only 35% continued to work on dialysis (Parajuli et al. 2016) in this single center study in the USA. Fourteen percent of patients were receiving disability prior to starting dialysis compared to 75% once they started dialysis. After approximately 6–10 years post-transplant, there was no significant improvement in full-time employment (35% vs. 35.5%). From most studies available, the minority of dialysis patients working prior to transplantation and the return to work rate is universally low following transplantation. The assumption that removing patients from dialysis will return them to work appears to be erroneous and health policy measures should take this into account when planning medication and other benefits for transplant recipients.

Table 2 Resources for patients

Federal and other agencies
• **Medicare**: www.medicare.gov
• **Centers for Medicare and Medicaid Services (CMS)**: www.cms.gov
• **Social security disability insurance (SSDI) or SSI (supplemental security income)** if you believe your illness will prevent you from working for a year or longer, contact your local Social Security Administration office to apply for disability. Call (800) 772–1213 for information, to file a claim or to request publications. If you are not collecting Medicare already due to your age or diagnosis of end stage renal disease, you will be eligible for Medicare after collecting 24 social security disability (SSDI) checks. If eligible for SSI, many states include the Medicaid benefit: www.ssa.gov
• **Life options**: www.lifeoptions.org
• **Your local ESRD network**
• **Forum of ESRD networks**: www.esrdnetworks.org
• **Medicare rights center**: www.medicarerights.org
• **The CMS publication** "Medicare coverage of kidney dialysis and transplant services": www.medicare.gov/Publications/Pubs/pdf/10128.pdf
• **State kidney programs –** approximately 15 states provide assistance with outpatient medications and other expenses for kidney transplant or dialysis patients
Transportation
• **Air care alliance** – A list of humanitarian volunteer pilot organizations who provide air transportation to patients free or at low cost. mail@aircareall.org
• **Angel flight** arranges free transportation to medical treatment. angel@angelflight.com
• **Patient airlift services** – volunteer pilot organization providing free air transportation for medical purposes to patients and their families. Northeastern U.S.
Dental services
• **American dental association** keeps a list of volunteer organizations providing low cost dental services
• **Donated dental services (DDS)** https://dentallifeline.org/
• **Community health centers** – dentists may volunteer their services at HRSA approved centers regardless of the patients ability to pay
• **National Institute of Dental and Craniofacial Research** is a research institution – Informational source on dental issues after transplantation including some information on low cost care.
Financial assistance
• **American kidney fund (AKF)** – Provides financial grants to pay for insurance premiums, medications and transportation. https://greatnonprofits.org/org/american-kidney-fund
• **National Kidney Foundation** – may off small one time grants locally https://www.kidney.org/
• **COTA (Children's organ transplant association)** – provides free fundraising assistance for children and adults needing organ transplants. http://cota.org/

Socioeconomic Status and Patient Outcomes

Shortly after kidney transplantation became a standard medical procedure differences in patient and graft survival were noted by socioeconomic status. The most consistent differences have been noted between African Americans and Hispanics compared to Whites. Until recently, African Americans routinely waited approximately three times as long once placed on the waiting list to be transplanted and in most large studies graft survival was inferior. Curiously African Americans had better patient survival on dialysis. Many studies have demonstrated that income, education, and ethnicity were predictors of patient outcomes. African Americans and Hispanics as groups had less income, educational attainment, and were historically in groups experiencing racial and ethnic discrimination. As discussed earlier, poverty, disadvantaged neighborhoods, and limited social supports were associated with extended times to complete transplant evaluations and poor outcome after transplantation. Although the transplant center cannot eliminate societal factors such as discrimination and poverty, measures can be enacted to minimize their effects and improve the chances for successful long-term transplantation.

Who Pays for the Transplant: Long-Term and Short-Term

The costs of transplants vary by organ, but kidney transplants cost the least. Even so, the costs are substantial and most are covered by insurance particularly in the first year. Either private or Medicare insurance pays for the transplant evaluation, hospitalization, and usually the care needed within the first 3 months. Medical costs which are covered by insurance were outlined in the UNOS website and may include: (1) pre-transplant evaluation and testing, (2) surgery, (3) fees for recovery of the organ from the donor, (4) follow-up care and testing, (5) additional hospital stays related to complications of the transplant, (6) fees for surgeons, physicians, radiologist, anesthesiologist, and recurrent lab testing (UNOS Transplant

Living: Financing a Transplant 2017b). The precise coverage varies by the type of insurance, state of residence, and transplant center. Some medical costs are not covered and may include insurance deductibles or copays, lost wages, child care, travel, food, and lodging. Financial difficulties can often be assisted by the transplant social worker. The UNOS website lists the following forms of assistance from social workers for patients with: (1) inability to pay medical bills, (2) lack of funds to meet daily needs, (3) lack of reliable transportation to and from the transplant center, (4) referral for re-employment services, (5) anxiety and depression issues, and (6) help in caring for children and other family members (UNOS Transplant Living: Financing a Transplant 2017a). This list highlights the additional costs of transplant beyond clinic visits and hospital admissions. Many of these costs will be borne out-of-pocket.

Immunosuppressant costs remain a major cost to patients. Currently Medicare covers immunosuppressants only for the first three years post-transplant for younger patients. It covers patients 65 or older indefinitely. For many patients without private insurance, these costs may be unsustainable (James and Mannon 2015). Since Medicare policies may change, check Medicare.gov for updated policies. Most patients receive three immunosuppressant medications (tacrolimus or cyclosporine with mycophenolic acid and prednisone) which may cost $10,000–$14,000/year. Although many transplant programs eliminate prednisone treatments, this is the least costly of all immunosuppressants. Some transplant physicians will add medications known to increase tacrolimus or cyclosporine levels with the intention of lowering drug costs. Agents such as diltiazem or ketoconazole may reduce drug cost by 50% per year. Other maneuvers include using cheaper medications such as Imuran after 3 years when Medicare coverage ends. This may not provide optimal immunosuppression but may be more sustainable for patients with limited incomes. Some pharmaceutical companies have assistance programs which may provide medications at no cost. Ultimately, lifelong coverage of immunosuppression is the only reliable solution and may be cost-effective compared to returning patients to dialysis.

Avoiding Nonadherence

Nonadherence (NA) to medications and other parts of the medical regimen is a major cause of inferior long-term kidney survival. This may range from obvious cases in which the patient stops taking all of their medications to more subtle cases where occasional pills are missed or the patient delays reporting a medical complication until severe illness develops. Nevins et al. found that the strongest risk factors for medication NA were prior history of NA and adolescence or younger age (Nevins et al. 2017). Other factors included minority race/ethnicity, poor social supports, and poor perceived health. In a French study, Couzi et al. found that 17.3%, 24.1%, 30.7%, and 34.6% of patients were nonadherent at 3, 6,12, and 24 months post-transplant, respectively (Couzi et al. 2013). They also found that younger age and adolescence were strong risk factors for graft loss and physicians underestimated the prevalence of NA compared to the patient self-report. Another study examined factors associated with missed or late medications taking (Goldfarb-Rumyantzev et al. 2011). Higher comorbidity index, living (compared to deceased) donor, and full-time employment were associated with forgetting medications or taking them late. Educational level, smoking status, recipient race, dialysis modality, number of medications, and the time since first kidney transplantation were not associated with NA. There was a trend toward older age being associated with lower rates but this was not statistically significant. In a survey of US transplant centers more than 70% of programs report that their patients have an extremely or very serious problem paying for their medications (Evans et al. 2010). Approximately, 47% of the programs reported that more than 40% of their patients were having difficulty paying for their immunosuppressive medications. In addition, 68% of the programs reported that patients had died or lost grafts due to cost-related immunosuppressive medication NA. They also felt that some

of the problems were more "significant" for adults compared to children. Using the US renal data system (USRDS), Jindal et al. found that depression was strongly associated with NA (Jindal et al. 2009). In addition, nonadherence was also associated with black race, younger age, lower HLA mismatches, living donation, and greater time since transplantation. Afsar also found that depression was associated with NA in dialysis patients (Afsar and Akman 2009).

Once patient loses an allograft due to overt nonadherence, retransplantation becomes less likely and some centers will seldom transplant such patients. Dunn et al. reported on a single center experience with retransplanting such patients and found that although the risk of repeated graft loss due to nonadherence (7.9%) was greater than controls (second allograft recipients) (1.2%), the majority could be transplanted successfully after 8 years of follow-up.

Psychosocial Evaluations in Living Kidney Donation

Living kidney donation has become a major source of transplanted organs worldwide. This may occur in a variety of situations including living related, unrelated living donation, spousal donation, altruistic and paired exchange. Guidelines have been advanced for living unrelated donation during a consensus conference organized by UNOS which includes the assumptions and evaluation recommendations of other forms of living kidney donation (Dew et al. 2007). The assumptions reviewed at this meeting included: (1) the need for living donation is driven by the insufficient number of deceased donors; (2) donation should be voluntary; (3) living donation is cost saving to the national health-care system; (4) living donors incur nonmedical costs; (5) buying, selling, or trade of living donor organs is illegal in the USA; (6) public solicitation for donors cannot be regulated and should be allowed; (7) the evaluation and/or determination of eligibility of potential living donors will continue to be the responsibility of the physicians, surgeons, allied health professionals, and living donor programs involved with the donors; (8) living organ donation and transplantation must be undertaken with the highest possible standard of clinical care. At all stages of the evaluation and transplantation process, the donor is as legitimately considered to be a patient as the transplant recipient and thus should be afforded the same level of care and the same protections against undue risks (Dew et al. 2007). The basic principles of donation were also outlined in the report. They included: (1) the donor should be capable of making the decision to donate, be willing to donate, and be free of coercion; (2) the donor is fully informed of the risks to themselves; (3) the donor is fully informed of the risks/benefits to the recipient and alternative treatments for the recipient; (4) the donor should not be called upon to donate in a hopeless situation; (5) medical and psychosocial follow-up should be undertaken by the transplant center in addition to other more obvious principles.

Although the psychosocial evaluation contains the elements mentioned earlier for kidney recipients, specific areas related to living donation must be explored. Both the assumptions and principles form the basis for some of the specific donor portions of the psychosocial assessment. For recipients, the quality of relationship between living related, spousal, and unrelated donors should be reviewed. In particular, evidence of coercion should be ruled out. All centers avoid donation by minors since they may have insufficient autonomy to give true consent. This becomes particularly important when the young person might be donating to a parent from whom they receive financial support, housing, and other support. The latter problem may also occur in adults or others who are dependent on the recipient. Likewise donors and recipients should be questioned to determine if monetary or other exchanges are planned for the donated organ. As mentioned earlier, buying or selling of organs is illegal. In reality donors and recipients may have such arrangements and do not disclose this during their evaluation. Other exchanges may be more subtle such as an assumed promotion when donating to a superior at work or an assumed marriage if one donates the organ. Despite these limitations, every effort

should be made to determine if monetary or other exchanges are planned.

Problematic relationships between donor and recipient should be sought during the evaluation. Similar to the recipient, the donor's outcomes post-donation can be adversely affected by a poor relationship with donors. The recipient may act out by not taking their medications which is particularly common in adolescents. Excessive anger towards the recipient may lead to greater pain post-operatively and loss of the graft may exacerbate a marginally functioning relationship. The stresses of transplantation can lead to divorce or estrangement particularly for spousal donors if major relationship problems existed prior to transplantation. Changes in power balances in relationships may occur where loss of dependence or increased short-term dependence fractures the prior balance. Such problems may not prevent donation but additional measures such as psychological or psychiatric counseling may improve the chances for a smooth post-donation course.

Donors usually have additional nonmedical costs which may not be covered by medical insurance. Travel expenses including airline, hotel, and other out-of-pocket costs may limit some donor's ability to complete the evaluation. This will be particularly challenging for patients with limited incomes. Some transplant centers have special arrangements with hotels or dedicated facilities where patients can stay with major discounts compared to hotels. Limited financial assistance may be available from the sources in Table 2 or the transplant centers may have a limited endowment for this purpose. Proposals to financially compensate donors have not gained wide acceptance in the USA, but this may change if appropriate safe guards can be implemented to avoid unintentional financial coercion particularly in poor donors.

Conclusion

The psychosocial assessment in renal transplant recipients is vital to successful short- and long-term graft survival. Instituting measures to mitigate adverse psychosocial factors begins prior to transplantation and ideally involves social workers, psychologists, and the medical teams during the entire life of the allograft. Understanding which patients are at risk for graft loss due to these factors should be helpful in preemptively supporting these patients. Assisting patients with community resources for transportation, medications, and social support are major functions of social workers. Helping them navigate the insurance systems are also vital functions performed by social workers which should allow patients adequate coverage for their care.

Cross-References

- ▶ Ethical Issues in Organ Transplantation
- ▶ Living Donor Evaluation and Selection
- ▶ Necessary Components of a Living Donor Team
- ▶ Pediatric Transplantation
- ▶ Recipient Selection for Kidney Transplantation
- ▶ Transplant Immunosuppression

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Pediatric Transplantation

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Abstract

Kidney transplantation is a life-saving therapy for children with end-stage renal disease. Several important factors impact the technical aspect of the procedure for children. Their blood vessels are smaller in caliber, making technique an even more critical part of a successful transplant procedure. Discrepancies between the sizes of the donor kidney, which often comes from an adult, into a small pediatric recipient can necessitate substantial modifications to the procedure. Additionally, children with obstructive uropathies can have smaller bladders and conduits, making ureteral implantation more challenging. Despite all of these aspects, renal transplantation is a life-saving operation that allows children with end-stage renal disease to live a higher-quality life than they could expect with dialysis. These patients can be hopeful of graft function in excess of 20 years.

Keywords

Anastomosis · Children · Extraperitoneal · Growth failure · Kidney transplant · Lymphocele · Nephroureterectomy · Neurogenic bladders · Obstructive uropathy · Peritoneal dialysis · Renal replacement therapy · Transplant renal artery stenosis · Ureteral implantation · Ureteroneocystostomy · Ureteroureterostomy · Renal vein thrombosis · Renal artery thrombosis · Bladder augmentation · Vascular reconstruction · Immunosuppression · EBV · BK virus · Posttransplant lymphoproliferative disorder

Introduction

Renal allotransplantation is the gold standard therapy for children with end-stage renal disease. It is applicable in almost every cause of renal failure in children and is a durable therapy. This chapter covers the timing, operative technique, as well as several technical challenges and complications unique to the pediatric population.

Timing of Transplant

Optimal timing of kidney transplantation in children is different than for adults, who have usually reached the need for renal replacement therapy at the time of their transplant procedure. In children, in addition to the need for renal replacement therapy, ensuring adequate growth velocity is an important consideration as well as responsiveness to erythropoietin. Although the goal is to get a child to weight of at least 10 kg prior to transplant with an adult-size kidney allograft, growth failure is one indication to proceed with transplant sooner. Occasionally, preoperative nutritional supplementation and growth hormone administration prior to transplant is beneficial; however, the precious loss of growth potential in these patients is reason enough to proceed with kidney transplantation.

Overview of Operation

Once a patient has been matched with an appropriate organ, he or she is brought to the operating room and prepared for surgery. This involves induction of general anesthesia, placement of a central line, and placement of an arterial line. A three-way Foley catheter is also placed. Next, the patient is positioned on the table in such a way as to make preparation of the site for organ implantation as easy as possible. Usually this would involve putting the kidney rest up on the operating room table and flexing the bed. This opens up the space between the iliac crests and the ribcage and brings the retroperitoneal space closer to the operative field.

The extraperitoneal approach is preferable for many reasons (Tanabe et al. 1998) although the transperitoneal approach is useful in some situations as well (Salvatierra et al. 2006). The vessels are easily approached in the extraperitoneal space especially if the patient has had prior abdominal operations. If the patient was on peritoneal dialysis pretransplant, the peritoneal space is maintained for posttransplant dialysis in the case of delayed graft function.

The incision is made on the abdomen in a transverse-oblique orientation, exposing the fascia lateral to the rectus abdominis muscles. The external oblique fascia is opened to expose the internal oblique muscle. This muscle is divided to expose the retroperitoneal space. In the adult- or near-adult-size child, the external iliac artery and vein are exposed. For children of smaller size, especially those <10 kg, the retroperitoneal space needs to be developed enough to expose the common iliac vessels or even the distal inferior vena cava (IVC) and aorta. The inferior epigastric vessels are ligated and divided. In boys, the spermatic cord is identified and retracted medially. In girls, the round ligament may be divided. For a first transplant, the right side is usually preferred. A self-retaining retractor such as a Bookwalter retractor system may be used to improve exposure (Barr and Brayman 2015).

Preparation of the vessels involves ligating and dividing the small lymphatics that travel with the artery and vein. These should be definitively controlled, as failure to do so may lead to a postoperative lymphocele. The posterior branches of the external iliac vein should be ligated if the vein is deep in the iliac fossa to allow it to rise up and be at the same level as the iliac artery. The artery should be sufficiently mobilized so that it lies lateral to the vein. Enough of the target artery and vein should be mobilized to allow room for proximal and distal control of the vessel, while the arterial and venous anastomoses are being constructed.

Once the vessels are prepared, the patient may be systemically heparinized prior to applying clamps to the vessel. The donor kidney is positioned in the iliac fossa such that the hilum is medial and the ureter is oriented toward the bladder. The venous anastomosis is constructed first, usually in an end-to-side fashion with a fine polypropylene suture. The venotomy is made in the vein to a size that is equivalent to the width of the donor vein. Once this anastomosis is finished, clamps are applied to the recipient artery and the arterial anastomosis constructed in a similar manner. Usually, the venous anastomosis is constructed by the primary operator, who can perform the anastomosis in a running fashion entirely from one side of the table. The arterial anastomosis is more easily done by two people, each operator performing his/her side of the anastomosis. Gentle retraction is often placed on the completed renal vein reconstruction when sewing the back wall of the arterial anastomosis, to allow full visualization of the artery.

Once both anastomoses are complete, the clamps are released, venous before arterial. Anesthesia administers the appropriate dose of diuretic and mannitol prior to reperfusion. Perfusion of the graft should be done in conjunction with the anesthesia team, as the patient may experience blood pressure lability with reperfusion. The kidney is checked for bleeding areas and allowed to warm up to body temperature. The kidney turgor is checked to assess the recipient volume status and to ensure there is no technical problem with the anastomosis that may be causing an outflow or inflow obstruction. For a healthy donor kidney with limited cold time, urine production should start.

Once the surgeon is satisfied that there is adequate hemostasis and that blood flow is appropriate to the kidney (evaluation with a Doppler can be helpful with this), attention is turned to the ureteral anastomosis.

Many factors may impact the technique used for the ureteral anastomosis in children, who are more often in renal failure secondary to obstructive uropathy than adults and who may have undergone procedures on their bladder prior to kidney transplant. Further discussion will follow about technical aspects of the ureteral implantation. For the straightforward case, however, the ureter is cut to an appropriate length and spatulated. The bladder is exposed and filled with irrigant. Exposure of the bladder usually

requires repositioning the retractors. Reflecting the bladder medially to expose the posterolateral surface is valuable, because it allows for ureteral implantation in a place where the bladder is the least mobile.

Once the bladder is exposed, the detrusor muscle is divided carefully to expose the bladder mucosa. A large cystotomy is made with a #11 blade and the corners of the cystostomy controlled with a fine absorbable suture, usually a 6–0 PDS. These sutures are also used to construct the ureteroneocystostomy between the donor ureter and the recipient bladder. Fine bites are usually taken on the ureter and large bites taken on the bladder. A watertight anastomosis is required. It is sometimes beneficial to place a ureteral stent to prevent stricture. The anastomosis is tested for a leak by instilling more irrigant into the bladder. Detrusorrhaphy is performed over the ureteroneocystostomy with a larger absorbable suture.

At this point, the incision is closed in layers, and a surgical drain is usually left near the kidney to prevent any perinephric fluid collection from accumulating. Children with small vessels may be placed on a perioperative heparin drip.

Unique Challenges in the Pediatric Patient

As was mentioned above, a smaller recipient size can impact several key decisions made during the implantation procedure. Patients less than 10 kg may require vessel anastomoses to be performed on the common iliac vessels or even the distal IVC and aorta; although even in small infants, the iliac vessels are most often able to be used (Mickelson et al. 2006). In this situation, the retroperitoneal dissection is carried out more medially to expose these vessels. For exposing the aorta, care must be taken to be alert to the inferior mesenteric artery (IMA), which arises from the distal aorta. A long donor artery may require implantation above the orifice of the IMA. When obtaining circumferential control, care must be taken not to avulse any lumbar branches off the aorta but rather carefully ligate and divide them. When applying a clamp for proximal and distal control, a side-biting clamp that prevents total aortic occlusion may be preferable, if possible. However, if the recipient is small, this may not be possible.

When obtaining control of the distal IVC, care must be taken once again to not avulse any lumbar branches. Any branches that are preventing proper mobilization and control should be ligated and divided, with awareness that failure to control the vessel prior to division may lead to retraction of the distal vessel. Bleeding resulting from this will be arduous to control surgically and add to the blood loss for the procedure. Proximal and distal control would ideally be obtained without total IVC occlusion, but this may not be possible. The anastomoses need to be oriented so that when the donor kidney is implanted the orifice of the anastomosis is not compressed by the weight of the allograft. This may require orienting the venotomy to the side of the IVC rather than in the anterior midline. Another important consideration for this situation is to carry out the vessel anastomoses as quickly as possible to avoid prolonged interruption of lower extremity perfusion. If clamping of the IVC is necessary, once the venous anastomosis is finished, a fine bulldog clamp may be applied to the renal vein and the IVC reperfused. This avoids the metabolic acidosis that may arise from prolonged clamping of the IVC. The aortic anastomosis can then be performed without IVC obstruction. The further advantage of this technique is that it allows the surgeon to ensure hemostasis around the IVC anastomosis prior to the arterial anastomosis, which makes it more difficult to retract or adjust the kidney position to allow for visualization to control any bleeding.

Children with large native kidneys may be best served by undergoing a native nephrectomy or removing the native kidney that is ipsilateral to the allograft implantation at the time of transplantation. For children with enough native nephron mass to avoid dialysis, nephrectomies should not be done too far ahead of transplant. When the allograft is large for the child, it may occupy a large space in the retroperitoneum that exerts a large mass effect on the peritoneal cavity. This can cause a significant ileus not usually experienced by larger recipients.

Nasogastric decompression in the early postoperative period should be considered.

During the closure of the incision, it is possible for the vessels to become compressed in such a way that perfusion of the graft kidney is compromised. Strategies for handling this include peritonealization of the graft by widely opening the peritoneum and positioning the allograft to dwell in the peritoneal cavity. This may limit future options for transplant kidney biopsy, however.

Management of the Vascular Variant Graft

Occasionally, an allograft may have more than one artery or vein. The surgeon must make a decision about how to reconstruct the vessels in this case. A small polar artery or vein may be ligated without clinically significant effect on function. However, in cases where there are two or more major arteries, the decision about how to implant the allograft can be complex. If the vessels originate off of the donor aorta close together, they can be implanted with a common cuff. If there is significant distance of a few centimeters between the renal artery orifices, use of the common cuff is not practical and increases the risk of a vascular complication. In this case a couple of strategies may be used. If there is enough redundancy in the vessels, the arteries may be spatulated together on the back table to create one common orifice. If there is a small accessory artery that still provides significant blood flow to the kidney, it can be sewn into the inferior epigastric artery. For that reason, when dividing the epigastric artery during the opening of the procedure, use of cautery should be avoided. A small accessory artery may be additionally implanted into the side of the major artery on the back table. This is very useful for lower pole accessory arteries where loss of this blood supply may result in ureteral ischemia.

In cases where there is more than one vein, a small draining vein can be ligated without adverse effect. If the donor kidney is a right kidney, an IVC extension graft can be constructed on the back table with fine polypropylene suture or a surgical stapler, although this is likely rarely required in the small pediatric patient. These graft extensions have a higher risk of early thrombosis, so care must be taken when positioning the kidney for implantation. Alternatively, the veins may be implanted separately with good result.

Graft Laterality

In general, the donor left kidney is considered to be the more technically easy to implant, as the renal vein is longer than with a donor right kidney. In the pediatric patient, a right renal vein can usually be utilized without shortening it much as the vein becomes extremely thin-walled closer to the hilum which can complicate the vascular reconstruction. Complications with right kidneys are slightly more common, perhaps because of the tendency of the renal artery to exert some compression on the renal vein. Usually the right iliac fossa is the first choice for implantation of the allograft as the iliac artery is lateral to the iliac vein. However, implantation on the left side is also feasible, although more preparation of the vein, which may lie deeper in the pelvis, on the left side may be required. This may require ligation of pelvic branches or even the internal iliac vein. However, there is sufficient collateral circulation from the contralateral side that this does not cause a clinically significant problem.

Patients with Prior Bladder or Ureteral Operations

As many children suffer end-stage renal disease secondary to urinary obstructive processes or other lower urinary tract abnormalities, they often present for transplant after having undergone one or multiple procedures to preserve, augment, or create a proper urinary reservoir. This can complicate the ureteroneocystostomy, and the pediatric transplant surgeon needs to be prepared. Preoperatively these patients should have definition of their

urologic anatomy with ureterocystoscopy or contrast studies. Voiding cystourethrography (VCUG) can help define whether preoperative correction of posterior urethral valves (PUV) has been adequate. Patients with known hydronephrosis or hydroureter should be considered for preoperative nephroureterectomy (Salvatierra et al. 2008). If pretransplant nephrectomy is to be performed (usually considered when the patient urine cannot be sterilized), the approach should be different than that planned for transplant, retroperitoneal approach if intraperitoneal implantation is planned or vice versa. This keeps the dissection planes around the vessels untouched for the later operation. Several anti-reflux techniques are used, including the nipple valve, the Lich technique, and a tunnel in the muscular layer of the bladder (Van Arendonk et al. 2015). Stents should be used where appropriate, with plans to remove them 6–12 weeks after transplant. Collaboration with the patient's pediatric urologist may be beneficial if prior urologic procedures have been extensive (Torricelli et al. 2015; Yamazaki et al. 1998).

Generally, utilization of the patient's native bladder is desirable, even when the bladder volume is small. An obstructive or neurogenic process should be ruled out in the pretransplant evaluation. In these situations, even in patients with small bladders, use of the native bladder is associated with a better outcome, and this is well substantiated (DeFoor et al. 2003). For patients with neurogenic bladders, a short ileal conduit or bladder augmentation may be beneficial.

Patients with a Prior Transplant

As management of the transplant patient becomes more complex, more patients are presenting for their second or third kidney transplant. These patients warrant careful consideration, as repeat transplants can be at higher risk for graft loss. Patients presenting for repeat transplant are sensitized and may have high panel-reactive antibodies (PRA) or donor-specific antibodies (DSA). Therefore, performance of a technically pristine operation is imperative. As children have much potential longevity to be restored with a kidney transplant, they are more likely to present for a repeat transplant at some point in their lives. For a second transplant, a transplant nephrectomy is usually not necessary, provided the child has grown enough to accommodate the mass effect of a second graft. Repeat transplant can also be a reason for utilizing the distal aorta and IVC for engraftment. Vessels that have been used for implantation may have significant adhesions or inflammation around them, making them difficult to use. In these cases, allograft implantation on the opposite side from the original transplant, or the use of extra donor vessels may be useful to expand options for vascular reconstruction.

Vascular Complications

Vascular complications of the pediatric kidney transplant are dreaded and difficult to treat. The risk of a vascular complication increases with the decreasing size of the child. Renal vein thrombosis is a dreaded complication that, unless recognized very early, will cause loss of the graft. It can be recognized by the sudden loss of urine output, increased distension of the kidney caused by the sudden vascular outflow obstruction, or feeling the vessel and noting it to be hard or not compressible. For renal vein thrombosis that occurs outside of the operating room, emergent evaluation with ultrasound is useful and can be used as a confirmatory study. Immediate reoperation is required if the graft is to be saved.

The surgical team needs to be alert for the possibility of inferior vena cava thrombosis. This should be suspected and preoperatively evaluated in children who have had resection of large dysplastic kidneys, have had central vein cannulation in the femoral veins, or have had a hypercoagulable condition. For this patient, multiple strategies for management are described for this complicated problem (Salvatierra et al. 2008). If IVC thrombosis is suspected pretransplant, an MRA or CT angiogram can be obtained for planning and diagnosis. MRA is risky in patients with little or no kidney function, and careful use of CT contrast with dialysis afterwards is often used

in these patients. These studies will confirm the presence of IVC thrombosis and will demonstrate the dilated collaterals that are providing the outflow. These vessels can be used for venous reconstruction. Adult-size grafts are difficult to use in these patients, as sufficient outflow cannot be provided for the graft.

If one is unfortunate enough to discover the caval thrombus at the time of transplant, this can be managed with an end-to-end anastomosis with the subhepatic IVC that has been divided (Dinckan et al. 2015). Renal vein implantation into the inferior mesenteric vein, splenic vein, and ovarian vein has also been described. This condition should be suspected in a child who has undergone femoral vein cannulation for dialysis access, and the IVC evaluated in the pretransplant period with Doppler US (Kumar et al. 2014).

The most common vascular complication involving the renal artery is transplant renal artery stenosis. This can be recognized on ultrasound or may require an angiogram. When recognized, the stenosis can be treated with angioplasty or stent. Early renal arterial thrombosis has been described, and the graft can only be salvaged with prompt re-exploration of the graft and thrombectomy (Mickelson et al. 2006).

Urological Complications

Urologic complications remain a steady source of morbidity for the pediatric kidney recipient (Routh et al. 2013). Widespread adoption of the extravesical ureteroneocystostomy or ureteroureterostomy has been accompanied by a decrease in complications, but some series still report a 21% rate of obstruction or leak (Irtan et al. 2010). Patients with posterior urethral valves have a significantly higher rate of postoperative leak, obstruction, or vesicular reflux (Routh et al. 2013). Complications involving the ureter can be either obstruction or leak. An obstruction is most common, and this can be managed with stents, nephrostomy tubes, pyeloplasty, or ureteral reconstruction. Replacement of a necrotic ureter with native appendix is even described (Corbetta et al. 2012). If a stricture is treated with a nephrostomy tube, the tube is usually internalized after several weeks and then removed. If a leak is present, it could be due to an unrecognized ureteral injury at the time of transplant or a technical error in the ureteral neocystostomy. Leaks can be managed with drains and diversion with nephrostomy tube. A ureteral injury can also be treated with a stent.

Lymphoceles

Lymphoceles are a nuisance complication in the postoperative period, arising in 1–7% of pediatric patients (Giessing et al. 2007). Lymphoceles may require laparoscopic fenestration for definitive management (Giuliani et al. 2014).

Noninvasive Strategies for Graft Salvage

Modern radiological techniques allow for several options for management of a number of graft complications. Keeping in mind that the pediatric patient is small and therefore can tolerate less contrast than an adult, contrast studies can diagnose vascular and ureteral complications with great sensitivity, and then interventional techniques can be used to correct the problem without repeat operation. Occasionally a persistent ureteral stricture will require surgical exploration with reconstruction of the ureteral anastomosis.

Immunosuppression Initiation and Maintenance

For the most part, induction of immunosuppression of the pediatric patient is similar to the adult population. A triple-drug induction with thymoglobulin, mycophenolate, and steroids is typical. All medications are dosed according to weight or body surface area. Typically a dose of 5 mg/kg thymoglobulin is given. For recipients that have significant donor-specific antibodies in circulation, perioperative administration of intravenous immunoglobulin (IVIG) is common. For maintenance of immunosuppression, a

combination of IL-2 inhibitor (most commonly tacrolimus), an antimetabolite such as mycophenolate, and prednisone is used. Tacrolimus dosing is aimed at particular serum levels, usually 8–12 ng/mL. In some situations, a rapid wean of steroids is possible. When it is feasible, it is desirable given the significant adverse effects of long-term steroid use, such as weight gain, Cushing-type facies, osteopenia, mood changes, and poor wound healing, among others.

Treatment of Rejection

Monitoring of kidney function is necessary to be appropriately vigilant for rejection, which is usually a clinically silent phenomenon. An increase in serum creatinine levels, or increased protein, or albuminuria will signal a patient is having a rejection episode. Prompt diagnosis is crucial, as episodes of rejection are directly correlative with graft longevity.

Rejection is definitively diagnosed by kidney biopsy and can be either B or T cell mediated. Acute cellular rejection (T cell-mediated) is treated with further T cell depletion with thymoglobulin and increased immunosuppression. Antibody-mediated (B cell) rejection is treated with plasmapheresis and exchange transfusion in order to bring down the amount of circulating antibody that injures the graft. Rituximab (anti CD-20 antibody) is also used to treat antibody-mediated rejection, as well as posttransplant lymphoproliferative disorder (PTLD).

Posttransplant Viral Infections

After transplantation with a kidney, the immunosuppressed state makes the patient more susceptible to opportunistic viral infections. The most common viruses affecting the pediatric transplant age group are Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and BK virus. It is routine to monitor patients for these viruses by following viral loads, as infections caused by these viruses can be somewhat clinically silent.

Epstein-Barr Virus and Posttransplant Lymphoproliferative Disorder

Epstein-Barr virus (EBV) is a member of the herpes virus family and has a high incidence in the human population. Its major morbidity in the transplant population is its causal relationship with posttransplant lymphoproliferative disorder (PTLD). Pediatric solid organ transplant recipients are at particular risk of EBV infection, owing to their frequent seronegative status at the time of their transplant (Laurent et al. 2018).

PTLD is a lymphoma-type malignancy that affects 1–7% of pediatric transplant recipients DeFoor et al. (2003). There is no widely agreed upon method for monitoring viral loads or the best chemoprophylaxis for EBV. Plasma or whole blood can be used to measure viral loads. Prophylaxis with valganciclovir has been shown in trials to lower the incidence of PTLD in kidney recipients (Hocker et al. 2012), and it is sometimes recommended in EBV-negative recipients who receive a kidney from an EBV-positive donor. However, this is not a universal practice and is potentially controversial (Yamada et al. 2018).

When EBV levels rise or a recipient seroconverts to EBV positivity, immunosuppression may be lowered as a first response to rising viral levels. When levels increase, cross-sectional imaging may be undertaken to look for evidence of lymphadenopathy, to complement physical examination in the clinic. A biopsy may be performed to confirm or corroborate the diagnosis. Rituximab can be used as treatment for high EBV viremia as well and is often used as a treatment for PTLD.

BK Virus

The BK polyoma virus is a double-stranded, nonenveloped virus that infects the uroepithelium and establishes latency there. In the renal transplant recipient, it can cause ureteral stenosis, hemorrhagic cystitis, or BK viral nephropathy (Smith and Dharnidharka 2015). Because BK viruria and viremia appear before injury, prospective surveillance is recommended. Monitoring viral levels

in the urine is sufficient, with assessment of blood levels undertaken when BK viruria occurs (Smith and Dharnidharka 2015). Most BK viral infections occur within the first 2 years after transplant, with only 5% occurring in 2–5 posttransplant years. Because they may be clinically silent, BK virus should be considered in the differential diagnosis for any decline in renal function from baseline. BK virus infection is usually addressed with a reduction or adjustment in immunosuppression.

Outcomes

Outcomes in pediatric renal transplantation are excellent, offering high quality of life for recipients, with many returning to school or work. Transplantation is considered to be the gold standard for the treatment of pediatric end-stage renal disease. Five- and 10-year graft survival is excellent, and repeat transplantation is possible in most cases. One study has reported 15-year graft survival of 86% (Ferraresso et al. 2008). Highly sensitized children or children with complex genitourinary anatomy represent vulnerable populations for whom a careful, individualized approach is critical to ensure the best long-term graft function.

For children weighing less than 15 kg, outcomes have also improved. One- and 10-year graft survival in these patients improved to 94% and 86%, respectively, in patients transplanted after the year 2000. For patients transplanted prior to the year 2000, graft survival at 10 years was 58%. Likewise, patient survival has improved to 94% and 91% at 1 and 10 years, respectively (Chiodini et al. 2017).

Conclusions

Renal transplant is a highly successful procedure in pediatric patients. Due to the relatively smaller size of the recipients compared to the adult population, and the relatively different kinds of etiologies of renal failure in this population, there are several specific aspects to the transplant operation itself that must be approached carefully. Though in the vast majority of cases the operation can proceed quite similarly to an adult recipient, the surgeon must keep in mind the various technical challenges that might be encountered and be flexible to meet them in such a way that still allows a good result for the patient. This chapter has covered the technical aspects of vascular reconstruction, ureteral drainage, and the complications that may arise from the kidney transplant procedure itself, such as lymphocele formation. Renal transplantation remains a vital part of the treatment of children with end-stage renal disease and has the potential to extend the life quality and expectancy for the children who suffer from these diseases.

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Pregnancy After Kidney Transplantation

Lisa A. Coscia, Dawn Armenti, Serban Constantinescu, and Michael J. Moritz

In Memoriam
This manuscript is dedicated to Vincent T. Armenti, MD, PhD (1952–2014), the founding principal investigator of the NTPR. His guidance and leadership allowed the NTPR to flourish and provide countless transplant recipients with scientific information on which to base their family planning decisions.

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Abstract

Successful pregnancy after kidney transplantation has been reported worldwide since the 1960s and much of the clinical guidance regarding post-transplant pregnancy is derived from the experience in kidney recipients. This chapter includes a review of the relevant literature plus data from the National Transplantation Pregnancy Registry (NTPR) regarding pregnancy, maternal and newborn outcomes in this population and clinical management guidelines for the care of kidney transplant recipients before, during, and after pregnancy. Fertility is often restored soon after successful kidney transplantation; therefore, appropriate contraception and pregnancy counselling should be key components of pre- and post-transplant care. Conception planning is strongly recommended. If the recipient's immunosuppressive regimen includes a mycophenolic acid (MPA) product, modifying the medication regimen prior to conception should be seriously considered as exposure confers substantial risks to the fetus. Close monitoring of the recipient, the transplant function, and her medications should continue throughout the pregnancy and postpartum. Post-transplant pregnancies are high-risk and warrant close collaboration among multiple disciplines to provide the best possible outcome for mother, her graft, and child.

Keywords

Kidney transplantation · Pregnancy · Immunosuppression · Mycophenolate · High-risk · Fetus · Prenatal · Birth defects · Breastfeeding · Contraception

Introduction

The first pregnancy after kidney transplant occurred in 1958 resulting in the delivery of a healthy infant with no adverse effects on the recipient's kidney function (Murray et al. 1963). The recipient went on to have a second pregnancy and maintained her kidney graft function until she died from complications of dementia at the age of 76. She was the first woman in the identical twin series from the Brigham Hospital and was

not immunosuppressed. The first recipient with a pregnancy exposed to immunosuppression (azathioprine and prednisone) was reported in 1967 and delivered a healthy infant with no malformations. At the time of the report, the mother's graft function at 1.5 months postpartum and the infant's health at 5 months were favorable (Board et al. 1967).

For years, pregnancy in transplant recipients was discouraged due to concerns about the effect of pregnancy on transplant kidney function and survival and potential teratogenic or long-term effects of immunosuppressive drugs on the offspring. As experience in this population accrued, many of these concerns have been allayed and others have been clarified to the point that healthcare providers ought to no longer automatically dissuade kidney recipients who meet certain criteria from considering pregnancy. These guidelines are based upon the many case and series plus database reports regarding the outcomes of pregnancies in kidney transplant recipients and other issues of special interest in this population (Kashanizadeh et al. 2007; Sibanda et al. 2007; Al Duraihimh et al. 2008; Wyld et al. 2013). The National Transplantation Pregnancy Registry (NTPR), which is one of the largest repositories of data regarding pregnancy after transplantation, analyzes pregnancy outcomes in solid organ transplant recipients and in pregnancies fathered by male transplant recipients (NTPR Annual Report 2015). This chapter is a condensed overview of over 50 years of experience regarding pregnancy after kidney transplantation with a discussion of recommendations for counselling the kidney transplant recipient of child-bearing potential and her partner, as well as guidelines for antenatal care.

Overview of Immunosuppressive Agents

Virtually all kidney transplant recipients take immunosuppressive medications to prevent organ rejection, including during pregnancies. Most take two or three immunosuppressives, and the most potent one is termed the "primary" immunosuppressant. Pregnancy outcomes reported to the NTPR are listed in Table 1 by primary immunosuppressant.

When weighing the need for a medication during pregnancy against the potential effects the medication may have on the developing fetus, the scale unequivocally tilts toward kidney recipients remaining on their immunosuppressive medication(s) during their pregnancy. It is, however, possible that recipients may be able to switch to different medications that are safer in pregnancy.

A description of common maintenance immunosuppressive agents with their potential for teratogenicity follows.

Prednisone

Prednisone at conventional transplant maintenance dosages poses minimal risk to the developing fetus and is generally considered safe for use during pregnancy. A meta-analysis of non-transplanted women who took oral corticosteroids during the first trimester did not show a higher rate of major anomalies. The 3.4-fold increase in oral clefts was not confirmed by later analyses (Park-Wyllie et al. 2000; Hviid and Mølgaard-Nielson 2011).

Azathioprine

Azathioprine in combination with steroids has been used for the prevention of rejection since 1962. In early animal studies, when administered at doses similar to the human primary immunosuppressant dose of >2 mg/kg/day, azathioprine was associated with embryonic resorption and/or fetal anomalies and thus was listed as an FDA Category D agent (i.e., positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks). Results from these animal studies have not been supported by clinical outcome data. Since the introduction of calcineurin inhibitors (CNI), azathioprine is most

Table 1 NTPR: pregnancy outcomes in female kidney transplant recipients

	Azathioprine and/or prednisone[a]	Cyclosporine-based[b,c]	Tacrolimus-based[b,c]
Recipients	**243**	**482**	**254**
Maternal factors (*n* = pregnancies)	**(448)**	**(822)**	**(427)**
Mean transplant-to-conception interval (years)	6.8 ± 4.9	4.7 ± 3.5	4.8 ± 3.3
Hypertension during pregnancy (%)	25	60	53
Diabetes during pregnancy (%)	5	9	9
Infection during pregnancy (%)	16	21	20
Preeclampsia (%)	22	32	35
Rejection episode during pregnancy[d] (%)	1	1	2
Mean serum creatinine (mg/dL)			
Before pregnancy	1.1 ± 0.4	1.4 ± 0.4	1.2 ± 0.3
During pregnancy	1.2 ± 0.5	1.4 ± 0.6	1.3 ± 0.9
After pregnancy	1.2 ± 0.6	1.5 ± 0.8	1.3 ± 0.5
Graft loss within 2 years of delivery (%)	4	7	9
Outcomes (*n*)[e]	**(463)**	**(852)**	**(439)**
Terminations (%)	4	5	2.3
Miscarriages (%)	12	16	24.4
Ectopic (%)	1	1	0.5
Stillborn (%)	2	2	1.4
Live births (%)	81	76	71.5
Live births (*n*)	**(374)**	**(645)**	**(314)**
Mean gestational age (weeks)	36.4 ± 3.3	35.8 ± 3.4	35.4 ± 3.6
Premature (<37 weeks) (%)	47	52	52
Mean birthweight (g)	2734 ± 718	2507 ± 749	2522 ± 821
Low birthweight (<2500 g) (%)	35	44	42
Cesarean section (%)	51	51	58
Newborn complications (%)	37	42	52
Birth defects (%)	2.2	4	8[b]
Neonatal deaths, *n* (%) (within 30 days of birth)	6 (1.3%)	11 (1.7%)[f]	5 (1.6%)

[a]No calcineurin inhibitor
[b]MPA exposure during pregnancy: cyclosporine (4%); tacrolimus (23%)
[c]Cyclosporine-based regimens (brand name or generic formulations of cyclosporine and cyclosporine-USP modified) and tacrolimus-based regimens (brand name and generic formulations of tacrolimus and brand name tacrolimus extended release); regimens may include azathioprine or MPA and/or prednisone
[d]Biopsy-proven acute rejection only
[e]Includes multiple births
[f]Includes 24-week quadruplet pregnancy; all newborn died

often used as adjunctive therapy at doses of 1 mg/kg/day. At this level, azathioprine is considered a safe option for use during pregnancy. Preterm delivery and fetal growth restriction have been noted, but without any predominant structural malformation pattern (Cleary and Kallen 2009). Data from the NTPR and other large cohorts shows no increase in the incidence of malformations or any obvious pattern of malformations among offspring exposed to azathioprine (Davison et al. 1985; Armenti et al. 1994; Langagergaard et al. 2007).

Cyclosporine

Cyclosporine, a CNI introduced in the 1980s, supplanted azathioprine as the primary

immunosuppressant of choice due to lower rejection rate and increased graft survival. The teratogenic risk of cyclosporine is minimal, although there is a potential risk of fetal growth restriction (Paziana et al. 2013). In animal studies, fetal abnormalities and toxicities were noted at higher dosages than those used clinically (Mason et al. 1985). Early reports raised concerns about the safety of cyclosporine use during pregnancy (Pickrell et al. 1989), but clinical data have not demonstrated an increased incidence or pattern of birth defects with exposure to cyclosporine (NTPR Annual Report 2015).

Tacrolimus

In the 1990s, tacrolimus, another CNI, was introduced and is currently the most common primary immunosuppressive prescribed to kidney transplant recipients. Data from the NTPR and other large reports have not revealed an increase in the incidence of malformations or a specific pattern of malformations among offspring exposed to tacrolimus in utero (NTPR Annual Report 2015; Kainz et al. 2000). In animal studies, fetal resorptions occurred at doses higher than those in clinical use. In a lower dosage group (0.16 mg/kg/day) commonly used in clinical practice, surviving fetuses appeared no different than controls (Farley et al. 1991).

Mycophenolic Acid Products

Two oral mycophenolic acid (MPA) products are available, the mofetil ester (MMF) and enteric coated mycophenolate sodium (EC-MPS). MPA products have widely replaced azathioprine as an adjunctive immunosuppressive and are most often used in conjunction with a CNI, with or without prednisone.

MPA products are *not* considered safe for use during pregnancy. It is recommended that females of child-bearing potential use two forms of effective contraception while taking MPA and whenever possible it should be discontinued prior to conceiving. When a patient approaches her healthcare provider to plan a pregnancy, strategies such as temporary replacement of MPA with azathioprine along with adding or increasing prednisone should be considered in an attempt to balance the risks to the transplanted kidney and the risks to the fetus (Coscia et al. 2015b). In a recent NTPR study, there was no increase in acute rejections during pregnancy or postpartum in kidney transplant recipients who discontinued and/or switched MPA preconception (Constantinescu et al. 2016a).

Animal studies revealed developmental toxicity, malformations, intrauterine death, and intrauterine growth restriction at MPA doses within the recommended clinical range based on body surface area. NTPR data demonstrated that exposure to MPA during pregnancy is associated with an increased incidence of miscarriage and a specific pattern and increased incidence of malformations (Sifontis et al. 2006). In a 2015 review article, the MPA phenotype was described to include the embryopathies listed in Table 2 (Coscia et al. 2015b).

These risks have *not* been noted in pregnancies fathered by transplant recipients taking MPA (Jones et al. 2013; Constantinescu et al. 2016b). Listed in Table 3 is a comparison of fathered pregnancies with and without MPA exposure. There was no difference in live birth, fetal loss, or birth defect rates.

Sirolimus and Everolimus

Sirolimus and everolimus are used in both primary and adjunctive immunosuppressive roles. In animal studies, in utero sirolimus exposure resulted in decreased fetal weights and delayed ossification of skeletal structures, but no teratogenicity was noted. When administered in combination with cyclosporine to pregnant animals, there was increased fetal mortality, increased numbers of resorptions, and decreased numbers of live fetuses, suggesting increased toxicity in conjunction with a CNI. To date, limited NTPR data and reports in the literature have not demonstrated a specific pattern of birth defects in offspring exposed to sirolimus (Framarino dei Malatesta et al. 2011; NTPR Annual Report 2015).

Sirolimus taken by male transplant recipients may reduce fertility (Kaczmarek et al. 2004; Zuber et al. 2008). However, there are pregnancies fathered by male transplant recipients taking sirolimus. Based on the 16 pregnancies reported to the NTPR (18 live births; no reported birth defects), there does not appear to be increased risks for pregnancies fathered while taking sirolimus.

Similarly, everolimus administration to pregnant rats at 0.1 mg/kg/day before mating through organogenesis resulted in increased preimplantation loss and early fetal resorptions. The area under the curve (AUC) in rats at this dose was approximately one-third that of the starting human clinical dose. Everolimus administered to pregnant rabbits resulted in increased late fetal resorptions. No malformations were noted in the case reports of pregnancy exposure to everolimus to date (Carta et al. 2014; Margoles et al. 2014). Whether everolimus has the same effect on male fertility as sirolimus is an open question.

Table 2 Frequency of mycophenolate embryopathies

Embryopathies	Fetuses with defect ($n = 35$)	%
Microtia/external auditory canal defect	20	57
Cardiac anomalies	11	31
Clefts	11	31
Eye anomalies	9	26
Skeletal anomalies	8	23
Hypertelorism	7	20
Kidney abnormalities	7	20
Micrognathia	7	15
Brain anomalies	5	14
Trachea/esophageal anomalies	5	14

Belatacept

Belatacept, introduced in 2011, is given intravenously monthly as maintenance immunosuppression in combination with MPA and prednisone. As data regarding human pregnancy exposure are limited, use during pregnancy is not recommended. In animal studies, when administered to female rats during pregnancy (and throughout the lactation period) at doses four times the human dose, belatacept was associated with maternal toxicity (infections) in a small percentage of rats, resulting in increased pup mortality. At doses >20 times than the human dose, surviving pups displayed no abnormalities or malformations. The NTPR has reported on one recipient who received belatacept throughout two unplanned pregnancies. During her first post-transplant pregnancy, she was on tacrolimus and MPA and miscarried. Prior to her next pregnancy, tacrolimus was switched to belatacept. She remained on MPA through the first 3 weeks of this pregnancy and miscarried at 11 weeks. During her third post-transplant pregnancy, she was also maintained on belatacept and MPA was continued until the pregnancy was discovered in the second trimester. She delivered a healthy 38-week 3090 g infant with no reported birth defects (NTPR Annual Report 2015). To date, no other reports of pregnancies exposed to belatacept have appeared.

Fertility and Contraception After Kidney Transplantation

- Fertility returns soon after successful transplant.

Table 3 NTPR fathered pregnancies: MPA exposed versus unexposed

	Exposed (n)		Unexposed (n)		p-value
Pregnancies	268		251		
Outcomes	278		263		
Live births	250	89.9%	244	92.8%	0.29
Fetal losses	28	10%	18	6.8%	0.22
Birth defects	7	2.8%	6	2.5%	1

- Appropriate birth control and pregnancy counselling should occur before and early after transplant.

The return of fertility post-transplantation is an important discussion point during transplant counselling, as nearly half of the women who suffer from chronic kidney disease have menstrual abnormalities or amenorrhea with reduced fertility (Pietrzak et al. 2007). In a survey of 209 solid organ transplant recipients (including 73 kidney recipients), 44% were not aware pre-transplantation that they could become pregnant after their transplant (French et al. 2013).

The likely rapid return of fertility after kidney transplantation makes it essential to have adequate contraception in place, especially in the first post-transplant year (McKay et al. 2005; Constantinescu et al. 2014a). One survey found that when compared to the general population more post-transplant pregnancies were planned, ascribed to the recipients' health concerns. However, only 50% of the transplanted respondents of child-bearing age were using contraception (French et al. 2013). The safety and efficacy of contraceptive methods for solid organ transplant recipients are rated in the 2010 Centers for Disease Control Prevention Report based on inferences from their use in the general population and published case and series reports in the transplant population (Curtis 2010).

The most common methods of contraception reportedly used by kidney transplant recipients are tubal ligation and barrier methods (Guazzelli et al. 2008; Xu et al. 2011; Rafie et al. 2014); however, long-acting effective and reversible contraceptives, such as IUDs and the progesterone implant, may be the best choice for female transplant recipients (Krajewski et al. 2013). Progesterone-only hormonal contraceptives are considered safe for transplant recipients (Curtis 2010).

It is reasonable to consider estrogen-containing contraceptives for kidney transplant recipients with well-controlled hypertension and stable graft function, who do not have other contraindications, such as thromboembolic risks (Krajewski and Sucato 2014). In one study, 36 kidney recipients used either oral or transdermal low-dose hormonal contraception. Two recipients discontinued the contraceptive, one due to thromboembolic event and the other due to liver test abnormalities. Overall, contraception was 100% effective with no pregnancies occurring and despite the risks, i.e., hypertension and altered liver function, hormonal contraception should be considered (Pietrzak et al. 2007). An American Society of Transplantation (AST) consensus conference found no evidence that combined oral contraceptives were associated with adverse consequences among transplant patients whose hypertension was well controlled (McKay et al. 2005). Similarly, the theoretical concern that estrogen-containing contraceptives could affect immunosuppressant drug levels has not been shown to be clinically significant, thus it has been concluded that combined oral contraceptives are suitable for solid organ transplant recipients when appropriately monitored (Estes and Westhoff 2007). Combined oral contraceptives are contraindicated for recipients with a more complicated course. No restrictions have been placed on the use of emergency contraception for solid organ transplant recipients (Curtis 2010).

Much of the published data regarding IUD use in solid organ transplant recipients is derived from kidney recipients. The theoretical risks of IUD use in all transplant recipients are the potential for infection and the possible reduction in efficacy due to interactions with immunosuppressives (Zerner et al. 1981; McKay et al. 2005; Estes and Westhoff 2007). At least two studies have shown no reduction in efficacy of IUDs due to immunosuppression (Xu et al. 2011; Bahamondes et al. 2011). It has been proposed that IUDs be recommended for transplant recipients with uncomplicated courses or for those who are maintaining IUDs that were inserted pre-transplantation; the restriction applies only for the initiating of IUDs in those recipients with a complicated course (Curtis 2010).

In transplant recipients desiring a pregnancy where fertility is compromised, there is guidance from limited reports on the use of assisted reproductive techniques (ART) in kidney transplant recipients (Termini et al. 2011; Wyld et al. 2013;

Kennedy et al. 2012; Norrman et al. 2015). An NTPR study (Termini et al. 2011) assessed in vitro fertilization (IVF) in transplant recipients including data from 11 kidney recipients who had 12 pregnancies after IVF, with 14 pregnancy outcomes (86% live births). The mean gestational age of the 12 infants was 36 weeks; their mean birthweight was 1984 g. At last follow-up, one child had been diagnosed as autistic and had a seizure disorder and the remaining children were reported healthy and developing well. There had been no graft losses in the mothers. Norrman et al. from Sweden, conducted follow-up of seven children of kidney recipients who conceived by IVF, comparing this group to children of transplant recipients conceived naturally and to children of non-transplanted mothers conceived by IVF (Norrman et al. 2015). As noted in previous studies, the outcomes of pregnancies conceived by IVF in this small group of kidney transplant recipients were similar to those infants conceived naturally. These limited reports are encouraging for recipients eligible to consider the use of ART following transplantation. Practitioners should be aware that healthy offspring conceived by ART in *any* woman might later display systemic and pulmonary vascular dysfunction (as evidenced by endothelial dysfunction) which does not appear to be related to parental factors but to the ART procedure itself (Scherrer et al. 2012; Rexhaj et al. 2014).

Transplant to Conception Interval (TCI)

- It is recommended that kidney recipients wait at least a year after transplantation before conceiving if they meet criteria in clinical guidelines.

In the first guidelines for pregnancy after kidney transplantation published in 1976, based on a literature review and their own case report, Davison et al. recommended that kidney transplant recipients be in good general health for at least 2 years post-transplant before conceiving. Over time, the AST and others have considered 1 year as a reasonable TCI (Kim et al. 2008; McKay et al. 2005). Analyses by Kim et al. comparing pregnancies with a TCI <1 year to those with a TCI >1 year revealed that there was no difference in pregnancy outcomes between the two groups. The authors also noted that if a kidney recipient has stable graft function and conceives within the first year after transplant, the pregnancy may be maintained with acceptable results for mother, her transplant, and the fetus. An NTPR study of different TCIs among CsA treated kidney recipients revealed that there were more terminations and fewer live births in a group with TCI <6 months compared to those with longer TCIs (Gaughan et al. 2001). Rose et al. suggest that a TCI >2 years is associated with more favorable graft survival in kidney recipients based on an observational study of administrative data (Rose et al. 2016).

The NTPR also analyzed pregnancy outcomes in kidney transplant recipients with TCIs greater than the recommended 2-year wait period (NTPR 2015). Kidney recipients' first pregnancies were grouped into three categories: TCI between 2 and 5 years, 5 and 10 years, or >10 years post-transplant. The TCI >10 group was transplanted at a significantly younger age, conceived at an older age, and had less treated hypertension during pregnancy. Graft function during pregnancy and postpartum was similar among the groups, as were pregnancy outcomes (Table 4). The analysis did not reveal significant differences in outcomes of pregnancies among the three groups. It was concluded that kidney recipients should not be discouraged from conceiving based on longer TCI.

Pregnancy Outcomes

- The majority of post-kidney transplant pregnancies have successful maternal and newborn outcomes.
- These are high-risk pregnancies and close collaboration among specialists is necessary.
- Comorbid conditions should be monitored and treated appropriately.
- Higher incidences of hypertension and preeclampsia are noted compared to the general population.
- The newborn have higher incidences of prematurity and low birthweight.

Table 4 NTPR comparison of kidney transplant recipients with different transplant to conception intervals

Transplant to conception interval (range (mean ± SD))	2–<5 years (3.3 ± 0.9 years)	5–<10 years (6.9 ± 1.4 years)	>10 years (13.3 ± 3 years)	*p*-value[a]
Recipients/pregnancies	320/320	168/168	84/84	
Maternal factors				
Pre-transplant pregnancy	32%[b]	14%[b]	5%[b]	<0.001
Age at first transplant (years)	24.6 ± 5.9	21.9 ± 5.2	17.4 ± 5.6[b]	<0.001
Age at post-transplant conception	28.8 ± 5.4	29.2 ± 5.2	30.9 ± 5.6[b]	0.003
Planned pregnancy	62%	71%	64%	NS
Pregnancy after two or more transplants	15%	11%	6%	0.048
Living donor	57%	52%	72%[b]	0.012
Diabetes during pregnancy	8%	10%	9%	NS
Hypertension during pregnancy	57%	54%	40%[b]	0.028
Preeclampsia	33%	33%	40%	NS
Creatinine before pregnancy (mg/dL)	1.28 ± 0.4	1.23 ± 0.4	1.28 ± 0.4	NS
Creatinine during pregnancy (mg/dL)	1.38 ± 0.7	1.32 ± 0.7	1.39 ± 0.5	NS
Creatinine postpartum (mg/dL)	1.47 ± 0.8	1.34 ± 0.6	1.4 ± 0.7	NS
Acute rejection during pregnancy	1%	1%	0%	NS
Graft loss within 2 years of pregnancy	7%	6%	5%	NS
Pregnancy outcomes[c]	$n = 330$	$n = 173$	$n = 88$	
Miscarriages	10%	12%	8%	NS
Termination of pregnancy	2%	2%	2%	NS
Ectopic	1%	1%	0%	NS
Stillbirths	2%	2%	2%	NS
Live births (*n*)	85% (280)	83% (143)	88% (77)	NS
Mean gestational age (weeks)	35.4 ± 4.0	36.2 ± 2.9	35.9 ± 3.6	NS
Premature (<37 weeks)	54%	53%	48%	NS
Mean birthweight (g)	2475 ± 817	2659 ± 723[b]	2429 ± 811	0.03
Low birthweight (<2500 g)	44%	39%	51%	NS
Neonatal deaths	$n = 5$	$n = 0$	$n = 0$	NS
Birth defects	3.6%	8.4%	3.9%	NS

[a]Chi or ANOVA
[b]$p < 0.05$ compared to each other group
[c]Includes multiple births

Since the first report of pregnancy after kidney transplant, thousands of pregnancies have been reported. Some larger series are summarized in Table 5. Overall, pregnancy is well tolerated with 75% resulting in a live birth delivery. Although there are high incidences of preeclampsia, hypertension, preterm delivery, and cesarean section, pregnancy does not appear to affect long-term kidney function (Fischer et al. 2005; Rahamimov et al. 2006), which is discussed further in the next section of this chapter.

As of December 2015, 1005 kidney transplant recipients participate in the NTPR and have reported 1874 pregnancy outcomes. These outcomes are listed in Table 6 (Coscia et al. 2016).

Deshpande et al. (2011) in a meta-analysis compared pregnancy outcomes in kidney transplant recipients to that of the general US population. Data from the NTPR comprised the majority of the outcomes in this meta-analysis. The overall live birth rate of 73.5% was higher than the general US population. Overall pregnancy complication rates, preeclampsia, cesarean section, preterm birth, and low birthweight infants were higher than the general US population. The pooled acute rejection (4.2%) and 2-year graft loss rates

Table 5 Comparison of pregnancy outcomes in kidney transplant recipients

	Recipients (*n*)	Pregnancies (multiples)	Live births (%)	Mean gestational age (weeks)	Mean birthweight (g)	Preeclampsia (%)	Acute rejection (%)
USA							
NTPR (2015)[a]	1005	1874	75	35.9	2567	30	0.8
Australia[b]							
Wyld et al. (2013)	447	692	76	35	2485	29	NR
UK[b,c]							
Sibanda et al. (2007)	176	193	79	35.6	2316	NR	NR
Bramham et al. (2013b)	101	105	91	36 (median)	NR	24	2
Middle East[d]							
Al Duraihimh et al. (2008)	140	234	74.4	33.2	2458	26.1	NR
Mexico							
Cruz Lemini et al. (2007)[e]	60	75	84	37.1	2439	8	5.3
Poland							
Dębska-Ślizień et al. (2014)[e]	17	22	77	35	2552	6	0
Germany							
Blume et al. (2013)[e]	34	53	62	35 (median)	2290 (median)	26.4	NR
Japan							
Abe et al. (2008)[e]	20	29	72	35.4	2229	38.1	NR
Iran							
Kashanizadeh et al. (2007)	86	NR	72	NR	NR	10	NR
Ghafari and Sanadgol (2008)	53	61	NR	NR	NR	26.4	NR

[a]North America
[b]Country's data
[c]Potential overlap of cases
[d]Data pooled from five different countries
[e]Single center report
NR not reported

(8.1%) were similar across the analysis. The authors caution that these pregnancies should be considered high-risk and be cared for by a multidisciplinary team.

Two studies were performed using data from the United States Renal Data System (USRDS) (Arab et al. 2015; Gill et al. 2009). Gill et al. looked at 530 pregnancies occurring between 1990 and 2003 and noted that the pregnancy rate among kidney recipients declined from 5.9% in 1990 to 2% in 2000. The overall live birth rate was 55.4%; however, the study had several limitations as it included only Medicare-insured recipients during their first 3 years post-transplant. Conclusions regarding immunosuppression were not possible because the only known medications were from the time of transplant and not during pregnancy. There was also no information available regarding the incidence of birth defects. Similarly, Arab et al. obtained data from the

Table 6 NTPR: pregnancy after kidney transplant

	Kidney			
Recipients	1005			
Mean age at first transplant (years)	24 ± 6			
Pre-transplant pregnancy (%)	31			
Pregnancies	1810			
Mean transplant-conception interval (years)	5.3 ± 4			
During pregnancy				
Primary immunosuppressant[a]	Aza	CsA	Tac	Others
	26%	47%	27%	<1%
MPA exposure (%)	8			
Hypertension treated (%)	49			
Diabetes treated (%)	8			
Preeclampsia (%)	30			
Rejection[b] (%)	0.8			
After pregnancy				
Postpartum rejection[b] (%)	1.8			
Graft loss within 2 years of delivery (%)	5.8			
Outcomes[c]	1874			
Live births (%)	75			
Neonatal deaths (%)	1.6			
Miscarriages (%)	18			
MPA exposure (%)	21			
Stillbirths (%)	2			
Ectopic pregnancies (%)	1			
Terminations (%)	4			
Live births	1414			
Mean gestational age (weeks)	35.9 ± 3.4			
Premature (<37 weeks) (%)	51			
Early preterm (<34 weeks) (%)	21			
Mean birthweight (g)	2567 ± 766			
Low (<2500 g) (%)	42			
Very low (<1500 g) (%)	11			
Cesarean section (%)	54			
Birth defects (%)	4.3			
Child follow-up (years)	13.7 ± 9.3			
Adult follow-up (years)	14.3 ± 9.5			
Maternal deaths (%)	18.2			
Average age of child at maternal death (years)	16 ± 7.9 214 children			
Adequate graft function at last follow-up (%)	63			

[a]Azathioprine and/or prednisone (*Aza*); cyclosporine or its modified form (*CsA*); tacrolimus (*Tac*); sirolimus, everolimus, mycophenolic acid products, or belatacept (other); mycophenolic acid products (*MPA*)
[b]Biopsy-proven treated acute rejection
[c]Includes multiple births

Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) for the period 2003–2010, to study obstetrical and neonatal outcomes in kidney transplant recipients. They identified pregnancies in 375 renal transplant recipients and compared outcomes to 7,094,025 patients without transplant. Kidney recipients in this analysis were at an increased risk for preeclampsia, preterm labor, and postpartum hemorrhage compared to those without a transplant. Prematurity, intrauterine fetal death, congenital anomalies, and intrauterine growth restriction (IUGR) were common complications in the newborn of the transplant recipients. The authors noted a strong correlation between preexisting maternal hypertension and the risk of IUGR. Again, the authors acknowledged the limitations of such a study however, recommended counselling these women regarding the high-risk nature of these pregnancies.

Long-Term Transplant Outcomes After Pregnancy

- When recipients enter pregnancy with stable graft function, the pregnancy is unlikely to affect transplant function.

Well-designed, case–control studies in kidney transplant recipients have demonstrated that pregnancy does not cause deterioration of graft function when prepregnancy graft function is adequate and stable. Long-term graft function also does not appear to be affected by pregnancy (Fischer et al. 2005; Rahamimov et al. 2006; Kashanizadeh et al. 2007). In the study by Rahamimov et al., there was no difference in graft (61.6%) and recipient (84.8%) survival between those who had a pregnancy versus matched controls (68.7% and 78.8% respectively). In another case–control study, Fischer et al. demonstrated no difference in 10-year postdelivery graft survival (pregnancy 62.5% vs. control 67%) or recipient survival (pregnancy 93.4% vs. controls 88.7%) (Fischer et al. 2005).

An NTPR analysis of recipients with and without graft loss after a pregnancy concluded that a high serum creatinine at any time surrounding pregnancy was associated with an increase in postpartum graft loss (Armenti et al. 1998). This study compared 40 recipients with graft loss versus 81 with no graft loss. Additionally, rejection during and postpartum along with low birthweight newborn were also associated with graft loss postpartum. A serum creatinine before pregnancy greater than 2.5 mg/dL was associated with a three times higher likelihood of postpartum graft loss compared to recipient with serum creatinine below 1.5 mg/dL. Recipients must be advised of the potential for increased postpartum graft loss when the serum creatinine is higher before pregnancy.

The NTPR studied the predictors of graft loss within 5 years postpartum (Constantinescu et al. 2011). Recipient race, donor source, cesarean section, and live birth percentage were similar between recipients with graft loss and those without graft loss within 5 years postpartum. Gestational age and birthweight were lower in the offspring of those recipients who lost their graft within 5 years postpartum. The study found that graft loss within 5 years postpartum was significantly associated increased serum creatinine before pregnancy as well as with rejection during and/or within 3 months after pregnancy.

Pregnancy After Living Donor Kidney Transplantation

- Pregnancy outcome does not differ between recipients of living versus deceased donors.

An NTPR analysis compared post-transplant pregnancy outcomes in 259 females who received either live donor or deceased donor kidney transplants (Table 7)(Constantinescu et al. 2010). All recipients were maintained on a calcineurin inhibitor based regimen during pregnancy. There were no significant differences in maternal complication and rejection rates during pregnancy, graft loss within 2 years after delivery, live birth rate or neonatal outcomes between pregnancies in living or deceased donor kidney transplant recipients.

Pregnancy After Pediatric Kidney Transplantation

- Successful pregnancies have been reported in recipients transplanted as children.

Wyld et al. from Australia performed an observational cohort study of kidney transplant recipients who received their transplant under the age of 18 (Wyld et al. 2015). There were a total of 66 recipients with 101 pregnancies. The authors compared this cohort to a group of 401 women who received their transplants as adults and had 626 pregnancies. They concluded that there were no differences in the pregnancy outcomes of the two groups and that complication rates were similar no matter how long the recipients had their transplant.

The NTPR analyzed the 50 pregnancy outcomes of 41 pediatric kidney transplant recipients who conceived 49 pregnancies before the age of 20 (Coscia et al. 2015a). Outcomes included 34 (69%) live births, 9 miscarriages, 5 terminations, and 2 stillbirths. There were 72% unplanned pregnancies; 43% were conceived within 2 years of transplant. Fifteen percent of those who conceived within 2 years of transplant experienced biopsy-acute rejection within 3 months postpartum; two of

Table 7 NTPR: comparison of pregnancy outcomes in kidney recipients by donor source

	Live donor	Deceased donor	*P* value
Recipients	148	111	
Pregnancies	240	165	
Pregnancy outcomes[a]	251	170	
Maternal conditions			
Transplant to conception interval (years)	5.2 ± 3.5	5.2 ± 3.7	NS
Hypertension during pregnancy	56%	63%	NS
Preeclampsia	28%	35%	NS
Infections during pregnancy	21%	22%	NS
Rejection during pregnancy	2%	2%	NS
Serum creatinine before pregnancy (mg/dL)	1.3 ± 0.4[1]	1.2 ± 0.4	<0.01
Serum creatinine during pregnancy (mg/dL)	1.4 ± 0.5	1.2 ± 0.95	0.03
Serum creatinine after pregnancy (mg/dL)	1.5 ± 0.6[2]	1.3 ± 0.8	<0.01
Graft loss within 2 years of delivery	8%	7%	NS
Neonatal outcomes			
Live births	77%	74%	NS
Gestational age (weeks)	35.5 ± 3.7	35.8 ± 3.2	NS
Birthweight (g)	2470 ± 809	2501 ± 765	NS

[a]Includes twins
1 versus 2, $p < 0.01$; *NS* not significant

the four recipients who lost their graft within 2 years of delivery also conceived within 2 years of transplant. Although recommended for all transplant recipients with child-bearing potential, adolescent recipients especially should receive appropriate counselling regarding fertility, contraception, and the risks of conceiving too soon after transplant.

The literature on successful pregnancies in kidney transplant recipients transplanted as children is reassuring. When discussing pregnancy with these women, the potential risks for mother and newborn, inheritable disease conditions, and long-term maternal survival need to be stressed with the recipient and/or the parents of the recipient after pediatric kidney transplantation. Studies regarding fertility in this population are warranted.

Successive Pregnancies After Kidney Transplantation

Several case reports describe kidney transplant recipients who have had more than one pregnancy after their kidney transplant (Sibanda et al. 2007; Al Duraihimh et al. 2008; Wyld et al. 2013).

In an NTPR review of 478 renal recipients who had a first pregnancy, 189 had between one and four subsequent pregnancies (Table 8). The proportion of live births was not statistically different among the groups. With successive pregnancies, there was a trend toward increased gestational age, leading to a significant decrease in the prematurity rate. As a result, there was a significant decrease in the proportion of infants with low and very low birthweights. Female kidney recipients with successive pregnancies had similar rejection rates during each pregnancy and no difference in graft loss within 2 years after delivery. Successive pregnancies in kidney transplant recipients are not associated with adverse fetal outcomes and/or increased maternal graft loss. Transplant recipients with adequate allograft function who wish to have more than one pregnancy should not be discouraged to conceive (Constantinescu et al. 2007).

Breastfeeding

Although breastfeeding while taking immunosuppressive medications is not recommended on product labelling, transplant recipients have

Table 8 NTPR outcomes of subsequent pregnancies after kidney transplant

	First pregnancy	Second pregnancy	Third pregnancy	Fourth pregnancy	Fifth pregnancy	*p* value[a]
No. of recipients	478	189	68	19	6	
Age at conception (years)	29 ± 5	30.2 ± 5.1	31.3 ± 4.8	32.8 ± 4.4	31.2 ± 4.5	
Pregnancy outcomes[b]	495	191	70	20	6	
Live births	78%	72%	83%	65%	67%	NS
Miscarriages	13%	19%	13%	20%	17%	NS
Stillbirths	3%	3%	1%	10%	0	NS
Therapeutic abortions	6%	6%	3%	5%	0	NS
Neonatal deaths	1.3%	0.5%	0	0	0	NS
Mean gestational age (weeks)	35.6 ± 3.4	36 ± 3.4	36.6 ± 3	36.8 ± 2.5	37.6 ± 1.3	0.01
Prematurity (<37 weeks)	54.7%	48.5%	46.4%	41.7%	25%	0.01
Mean birthweight (g)	2426 ± 772	2578 ± 749	2613 ± 752	2646 ± 816	3076 ± 831	0.002
Low birthweight (<2500 g)	49.7%	40.2%	39.7%	30.8%	25%	0.001
Very low birthweight (<1500 g)	14.8%	9.5%	5.2%	15.4%	0%	0.04
Rejection during pregnancy	1.5%	1.6%	4.5%	0%	0%	NS
Graft loss within 2 years after delivery	8%	7.5%	7.4%	5.3%	0%	NS

[a]Linear trends
[b]Includes twins, triplets

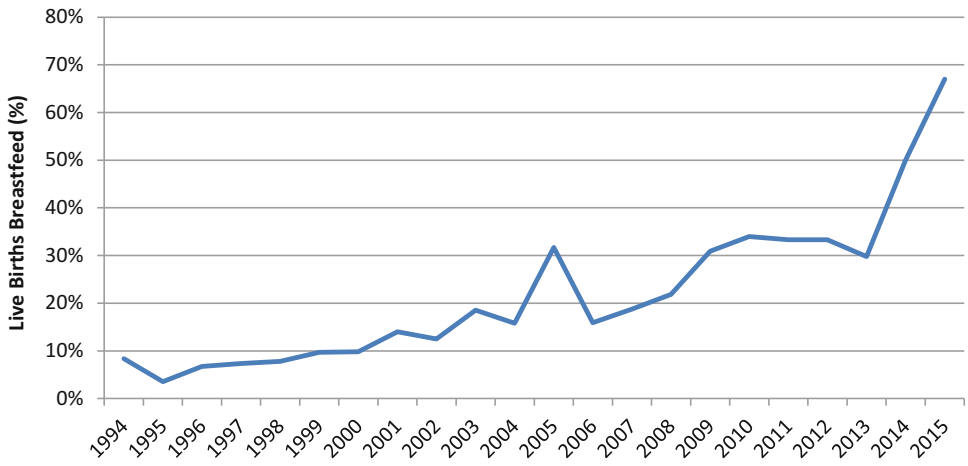

Fig. 1 NTPR trend in breastfeeding practices among transplant recipients

chosen to breastfeed at a steadily increasing rate (Fig. 1).

Short-term follow-up of the development and health of children of transplant recipients who have been breastfed while their mothers were taking immunosuppressive medications did not reveal any adverse effects due to breastfeeding (Constantinescu et al. 2014b). Over the years, several studies, which measured levels of prednisone, azathioprine, and cyclosporine in maternal or infant serum and in breast milk samples, showed that the amount ingested via breast milk was much less than that to which the fetus had been exposed in utero. Subsequent studies have found that the level of tacrolimus in infant blood drops quickly after birth and at equivalent rates, whether the baby is breastfed or

bottle-fed, a finding that led authors to conclude that transplant recipients should not be discouraged from breastfeeding while on tacrolimus, particularly if monitoring of immunosuppressive content in infant blood and breast milk is available (Bramham et al. 2013a). Due to the lack of information regarding breastfeeding on MPA, sirolimus, everolimus, and belatacept, breastfeeding should be avoided while taking these agents. Although long-term studies are warranted, researchers are cautiously optimistic that breastfeeding can be considered safe while taking prednisone, azathioprine, cyclosporine, and tacrolimus (Bramham et al. 2013a; Constantinescu et al. 2014b).

Management Guidelines

Although pregnancy is well tolerated by many kidney transplant recipients with the majority resulting in a healthy newborn, these women must be considered a high-risk pregnancy group requiring specialized multidisciplinary team care in a tertiary center, with the facilities necessary to ensure the best outcomes for mother, her graft, and her child (Rao et al. 2016; Deshpande et al. 2013). The initial clinical guidelines for pregnancy after kidney transplantation were developed by Davison et al. (1976); these guidelines have been expanded and refined based on data accumulated over the last 40 years (Rao et al. 2016). As with all transplant recipients, it is recommended that any transplant recipients use adequate contraception to defer pregnancy for at least 1–2 years after transplantation and that such "active preparation for pregnancy" should be individualized to each woman's needs and should involve her partner.

There should be prepregnancy assessment of kidney function, comorbid conditions, latent viral infections, vaccination history, as well as a consideration of the etiology of the original renal failure and the potential for any genetic predisposition in the offspring. Medications should be reviewed and adjusted as necessary both before and during pregnancy, including avoidance of fetal MPA exposure whenever possible. The risks of IUGR, prematurity, and a low birthweight infant should be discussed.

Once pregnancy is discovered, monitoring of kidney function and immunosuppressive drug levels is recommended at 4-week intervals until 32 weeks gestation, then more frequently until delivery (Rao et al. 2016). Monitoring of immunosuppressive drug levels during pregnancy is essential due to the physiologic changes of pregnancy, including an increase in plasma volume, and changes in drug distribution and drug metabolism. Comorbidities, including bacterial and viral infections, hypertension, proteinuria, diabetes, and graft dysfunction, should be diagnosed appropriately and treated promptly. Hypertension and the potential onset of preeclampsia must be closely managed because of the threat to the health of the mother and compromise of fetal development (Bramham et al. 2013b).

Vital postpartum concerns include maternal medication adherence, measurement of drug levels and dose adjustments, vigilance for postpartum depression, discussion regarding the safety of breastfeeding, and appropriate counselling regarding contraception (Rao et al. 2016; Krajewski and Sucato 2014). For those mothers who had preeclampsia, continued attention to normalizing blood pressure is important, in light of the long-term cardiovascular risks which include a 1.8–3.7 increase in the relative risk of cardiovascular disease (hypertension, ischemic heart disease, stroke, venous thromboembolism) (McDonald et al. 2008; Yinon et al. 2010).

Conclusion

Successful pregnancy after kidney transplantation is possible; however, these are high-risk pregnancies that require close coordination among the various disciplines that care for these complex patients. Continued reports to registries and to the literature are encouraged. Further information can be obtained from the NTPR by contacting their office by email at NTPR@giftoflifeinsitute.org.

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Cross-References

- A History of Kidney Transplantation
- Ethical Issues in Organ Transplantation
- Medical Complications After Kidney Transplantation: Late
- Pediatric Transplantation
- Psychosocial and Personal Financial Aspects of Transplantation
- Transplant Immunosuppression

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The Finance of Kidney Transplantation

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Contents

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Abstract

Hospitals provide many expensive and complicated services to patients all across the country, with organ transplantation ranking among the top of the list. The daily operations of transplant programs involve varied disciplines and numerous payment methodologies, contract types, and reimbursement methods. Medicare and private commercial insurers provide the major sources of payment for kidney transplantation, with differing payment structures per each insurer. Medicare's payment system consists of three parts: the inpatient prospective payment system for the transplant admission, the Medicare cost report for allowable organ acquisition costs, and the outpatient prospective payment system. While Medicare's payment system is a threefold process, commercial payers work through managed care organizations (MCOs) to contract with specialty transplant networks. Although commercial payers, Medicaid, and self-pay are other payment sources, Medicare remains the largest single primary payer for kidney transplantation because of the 1972 end-stage renal disease entitlement.

Keywords

Kidney transplant · End-stage renal disease (ESRD) · Medicare · Managed care · Diagnosis-related group · Medicare cost report · Affordable Care Act (ACA)

Introduction

The United States has seen great improvements in access to care for patients suffering from kidney disease. In 2016, 19,061 adult and pediatric kidney transplants were performed in the United States. Based on Organ Procurement and Transplantation Network (OPTN) data as of March 31, 2017, 253 transplant centers are members of the OPTN. Of the 253 transplant centers, there are 240 centers that perform adult and/or pediatric kidney transplantation. Until 1972, severe limitations existed for the number of persons able to receive treatment due to high costs and limited dialysis availability. Today individuals with end-stage renal disease (ESRD) who need dialysis or transplantation to maintain life can utilize Medicare benefits through the National End-Stage Renal Disease Program. In 2016, Medicare made up 59% of the kidney payer attribution when accounting for Medicare fee-for-service and Medicare Advantage Plans, while commercial payers account for an additional 31% of the kidney transplant payer population. The evolution of public and commercial payers has created numerous payment methodologies, contract types, and reimbursement methods for the domain of kidney transplantation. Transplant administration must stay vigilant in cost and revenue management, as it is crucially important in sustaining transplant programs.

National End-Stage Renal Disease Program

The Social Security Amendments of 1972 created the National End-Stage Renal Disease Program that extended Medicare benefits to individuals with ESRD who need either dialysis or transplantation to maintain life. Prior to the creation of the ESRD program, severe limitations existed for the number of persons able to receive treatment due to high costs and limited dialysis availability. As a result, the ESRD patient profile of today is much different than preceding 1973. In 1967, the dialysis population was predominantly young, white males. Males accounted for 75%, Caucasian persons 91%, and only 7% of patients were over the age of 55. By 1978, access to treatment was equally proportional between males and females, and the African-American and elderly populations were more adequately represented, 35% and 46%, respectively (Eggers 2000).

The basic entitlement provisions of the 1972 legislation creating the ESRD Program still remain in place today; however there have been a number of legislative changes since that time. The first ESRD Program amendment passed in 1978 to extend the Medicare entitlement, increase coverage of kidney acquisition costs, and provide for more complete at home dialysis costs coverage. The amendment extended the Medicare entitlement to 3 years following a successful transplant from the original legislation, which was limited to 1 year (Eggers 2000).

Since the program's inception, the National ESRD Program has grown far beyond the initial estimates of expenditure. Projections of annual program expenditures were originally quite low at about $250 million but by 1979 had already reached $1 billion. By 1990, the program had reached $5 billion and by 1998 had grown to over $12.3 billion. Much of the unexpected increase can be accounted for through enrollment increases and the high cost associated with beneficiaries of increased age and diabetic patients. Compared to other Medicare programs, ESRD has been fairly successful at restraining per capita costs even despite the large increase in overall expenditures (Eggers 2000).

Organ Supply

The kidney supply comes from two sources, deceased donors and living donors. In 2016, nearly 30% of kidney transplants performed in the United States were from living donors (OPTN 2017b). Figure 1 illustrates living kidney donation from 2012 to 2016, as well as the total kidney transplants performed in the United States. Separate policies and procedures for management of living donors are required by the Organ Procurement and

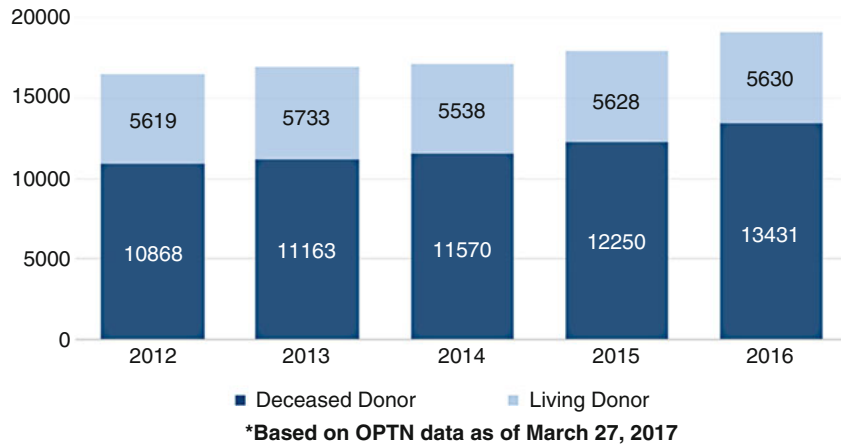

Fig. 1 Total deceased and living donor kidney transplants performed annually, 2012–2016

Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), including separate quality assessment practices and performance improvement processes. Centers for Medicare and Medicaid Services (CMS) and OPTN/UNOS both survey living donor programs for specific criteria to be sure high standards of care are taken for the donors.

Four Phases of Transplantation

The process of transplantation involves four phases of care (Table 1).

Phase One: Pre-transplant Evaluation

The first phase includes all pre-transplant clinical visits, multiple tests, and evaluations to determine a patient's candidacy for kidney transplant. All work involved in screening the patient for candidacy to the point of a decision by the multidisciplinary patient selection committee is considered to be part of the pre-transplantation evaluation phase.

Phase Two: Candidacy and Maintenance Phase

The patient selection committee approves the patient to be placed on the kidney transplant waiting list. While on the kidney transplant waiting list, patients may have to undergo minimal maintenance testing and other procedures to ensure a continuation of transplant candidacy.

Phase Three: Day of Transplantation

The patient is admitted to the hospital for the transplant procedure. This phase comprises all services related to the transplant episode itself and includes such items, based on the payer, as the hospital and professional fees, organ acquisition, and transportation costs. This phase usually begins 24 h prior to the transplant and concludes the day of discharge.

Table 1 Four phases of transplantation

Phase 1	Patient evaluated for transplant
Phase 2	Patient accepted and listed with OPTN/UNOS. Patient is now in the maintenance or candidacy phase
Phase 3	Patient admitted to hospital for organ transplant procedure and subsequent inpatient stay. This is typically the diagnosis-related group (DRG) component of the transplant process
Phase 4	Patient discharged from hospital and post-transplant follow-up care period begins

Table 2 Four phases of living donation

Phase 1	Patient evaluated as living donor
Phase 2	Patient accepted as living donor and begins candidacy phase
Phase 3	Patient admitted to hospital for living donor procedure and subsequent inpatient stay
Phase 4	Patient discharged from hospital and post-donor follow-up care period begins

Phase Four: Post-transplant

This phase begins the day after discharge and ends after a contractually predetermined amount of time. Patients are followed closely to ensure proper organ function.

Living donation follows similar phases for pre-donation, acceptance as a living donor, donor surgery, and post-donation follow-up (Table 2). The phases of transplant and living donor care are important as they are directly related to payer methodology.

Transplant Payers

Medicare

Medicare is the largest single primary payer for kidney transplant services in the United States. Based on OPTN/UNOS data as of March 29, 2017, in 2016, Medicare comprised as much as 59% of the kidney payer attribution when accounting for Medicare fee-for-service and Medicare Advantage. Medicare fee-for-service and Medicare Advantage Plans numbered 8,000

and 3,228, respectively, of a total number of 19,062 kidney transplants in 2016 (OPTN 2017a).

Medicare is a federally funded program that provides health insurance to those aged 65 and older, a subset of younger individuals with disabilities, and individuals with end-stage renal disease. Medicare ESRD coverage for kidney transplant patients can begin as early as the first day of the month a patient receives a kidney transplant or the date the patient diagnosed with ESRD begins dialysis treatment and applies for Medicare. For individuals entitled to Medicare based on ESRD for a coordination period of 30 months, Medicare is the secondary payer to group health plans (GHPs) regardless of the number of employees and whether the coverage is based on current employment status (CMS 2013). Medicare is also secondary to retirement plans and GHPs provided through the Consolidated Omnibus Budget Reconciliation Act (COBRA) (CMS 2013). Medicare ESRD coverage includes kidney transplant, simultaneous kidney/pancreas, and pancreas after kidney transplant, coverage for living donors, and immunosuppressive drugs for 3 years post-transplant. However, Medicare coverage only applies to Medicare patients transplanted in a CMS-certified facility.

There are four main components of Medicare:

Part A – Hospital insurance coverage for inpatient services, outpatient diagnostic services, and extended care after hospitalization
Part B – Medical insurance coverage for physician services and outpatient services
Part C – Medicare Advantage Plans that allow private health insurance companies to provide Medicare benefits
Part D –Insurance coverage for Medicare recipient's outpatient prescription drugs

On March 30, 2007, CMS published the final rule for hospital Conditions of Participation (CoP) for approval and re-approval of transplant centers to perform organ transplants. These regulations effective June 28, 2007, established Medicare CoP for kidney, pancreas, liver, intestine, heart, lung, and heart-lung transplant centers and provided clear expectations for transplant centers to participate in the Medicare program (U.S. Department of Health and Human Services (DHHS) 2007).

As previously stated, Medicare coverage for transplant services is limited to those centers that have been certified by CMS and have met the CoP. Without this certification, Medicare will not reimburse hospitals for transplant-related services, including the transplant surgery, organ acquisitions costs through the Medicare cost report, and immunosuppressive medication under Part B. A transplant center must be located within a hospital that has a Medicare provider agreement, meet the CoPs, and meet all other hospital CoPs. One CoP for a transplant center is to be a member of the OPTN and abide by their approved rules and requirements. For the volume requirements to become Medicare approved, a kidney transplant program must perform at least three transplants over a 12-month period prior to its request for initial approval. During the re-approval period, kidney transplant centers must generally perform an average of ten transplants per year (DHHS 2007). Medicare uses a threefold payment process to cover the cost of a kidney transplant throughout the transplant phases. Payment components include (1) Medicare's inpatient prospective payment system for the transplant admission, (2) the Medicare cost report for allowable organ acquisition costs, and (3) the outpatient prospective payment system for outpatient post-transplant services.

Inpatient Prospective Payment System

Section 1886(d) of the Social Security Act sets forth a system of payment for the operating costs of acute care hospital inpatient stays under Medicare Part A based on prospectively set rates. This payment system is referred to as the inpatient prospective payment system (IPPS). Under the IPPS, each case is categorized into a diagnosis-related group (DRG). Each DRG has a payment weight assigned to it, based on the average resources used to treat Medicare patients in that DRG. The base payment rate is adjusted geographically to account for wage differences across

metropolitan locations. The adjusted base payment rate is then multiplied by DRG relative weight to determine the applicable reimbursement. The DRG payment weight for a kidney transplant, as of October 1, 2016, is 3.2964 and reflects a relative cost difference of slightly more than three times that of the average cost of a Medicare inpatient episode.

If the hospital treats a high percentage of Medicaid/low-income patients, it receives a percentage add-on payment applied to the DRG-adjusted base payment rate. This add-on, known as the disproportionate share (DSH) adjustment, provides additional Medicare payment for hospitals. This adjustment may vary based on the outcome of the statutory calculation. Also, if the hospital is an approved teaching hospital, a separate add-on payment is included for each case paid through IPPS. This add-on, known as the indirect medical education (IME) adjustment, varies depending on the count of allowable interns and residents. Finally, for individual cases that are atypically costly as compared to like DRG cases, known as outlier cases, an additional payment is provided. This additional payment is based upon a cost-threshold, and Medicare reimbursement is at 80% of the difference. The purpose of this additional payment is to lessen the financial losses for high-cost cases. Any outlier payment due is added to the DRG-adjusted base payment rate, plus any DSH or IME adjustments (CMS 2016).

Under the IPPS, MS-DRG 652 is used to identify kidney transplant. In 2007, CMS refined its DRG system to account for the significant variation in costs within a DRG family due to the presence of complications and comorbidities. Unlike heart and liver transplant, there is no separate MS-DRG for kidney transplant related to medical severity. Consequently, all kidney transplants receive the same MS-DRG payment regardless of the complexity of the case.

Medicare Cost Report

The Medicare cost report is an annual report of hospital costs for services provided to Medicare beneficiaries. The Medicare cost report separately accounts for organ acquisition costs from MS-DRG costs and provides additional reimbursement, a significant advantage unique to transplant programs. Allowable Medicare organ acquisition costs include certain pre-transplant recipient and living donor candidate evaluation expenses incurred during transplant phases 1 and 2 (i.e., until the point of admission for transplantation). Also included are inpatient costs associated with living donors and the cost of deceased donor organs received from the Organ Procurement Organizations (OPOs). Collectively, these expenses are known as the organ acquisition costs (Figs. 2 and 3). The Medicare cost report payment

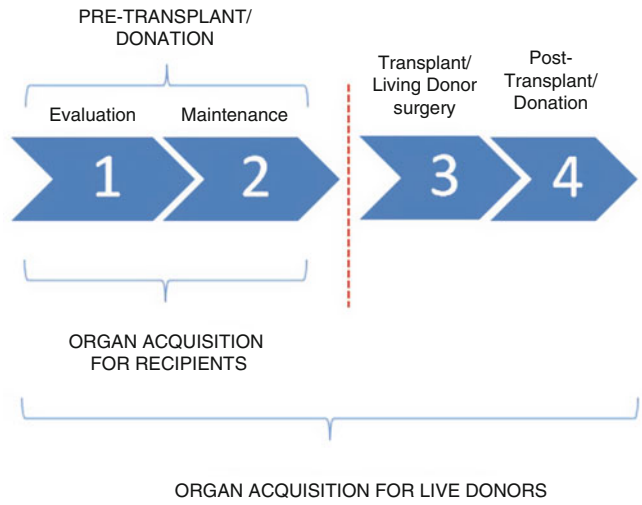

Fig. 2 Organ acquisition phases 1–4 for transplant recipients and living donors

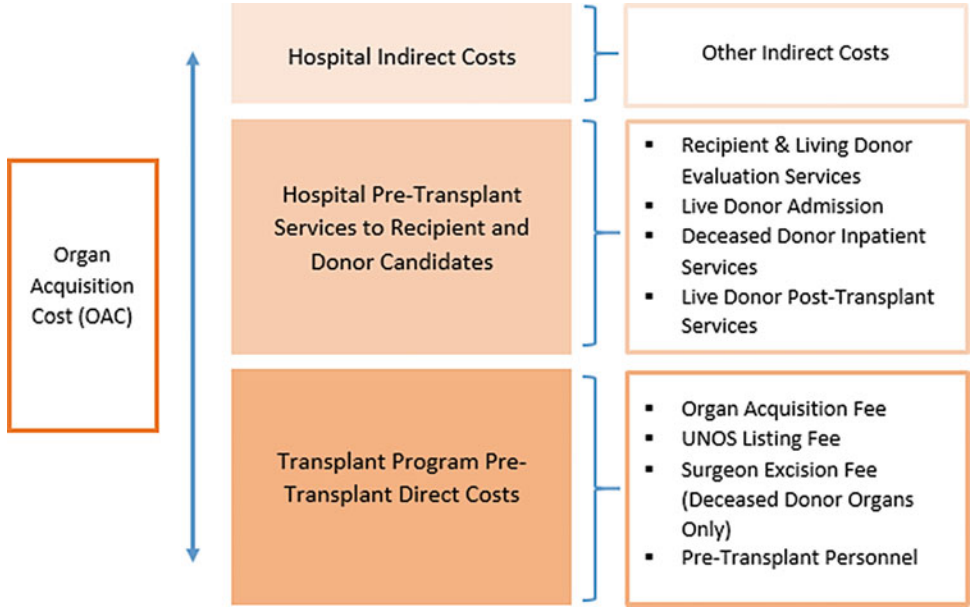

Fig. 3 Components of direct and indirect costs accounted for in organ acquisition

methodology for organ acquisition is predicted on first calculating 100% of the costs for all patients, then applying a Medicare utilization factor, known as the Medicare ratio, to determine the amount payable to Medicare to the transplant hospital.

Organ acquisition cost centers were established by CMS as a method to compensate hospitals for reasonable expenses related to organ procurement and potential recipient and living donor evaluation and selection costs, including costs incurred by the hospital while maintaining potential recipients on the transplant waiting list (Fig. 3) (Abecassis 2006). Organ procurement costs include the cost of the organ and transportation fees incurred to recover the organ; however, treatment and disease management of the transplant patient during pre-transplant phases 1 and 2 are not considered organ acquisition costs. Organ acquisitions costs paid by Medicare are separate from the MS-DRG payment for the hospital for inpatient stay and the physician fees associated with the transplant.

Organ acquisition is comprised of direct costs and indirect costs. Direct costs are those that are attributable to the evaluation and maintenance of pre-transplant recipient and donor candidates and also include salaries and benefits of administrative and clinical kidney transplant staff that have documented pre-transplant responsibilities. Indirect costs (often referred to as hospital overhead) are hospital administration, finance facilities, housekeeping, and medical records, which benefit all hospital clinical departments including kidney acquisition (Norris 2014). The kidney transplant staff documents their pre-transplant time through monthly time studies that alternate weekly each month to allow for an average of the overall pre-transplant time throughout the year. The time studies are typically completed by transplant staff and physicians to include medical directors, transplant coordinators, social workers, financial coordinators, dieticians, pharmacists, and administrative personnel (Rogers 2013). Since transplant physicians bill for their pre-transplant clinical services, only the time spent on pre-transplant administrative tasks may be included on the cost report. Medicare reimburses hospitals for physician administrative costs incurred at the lesser of actual costs or the reasonable compensation equivalent (RCE). The RCE ensures limits are placed on the amount of physician administrative compensation claimed on the Medicare cost report. CMS sets RCE limits based on physician specialty and was initially adjusted for geographic size (large metropolitan and all other) (Norris 2014). In 2015, CMS eliminated the large

metropolitan adjustment and moved to improve the accuracy of the RCE limits overall (DHHS 2016a). For example, a kidney transplant surgical director is compensated $50,000 for administrative duties and logs 300 h of pre-transplant time annually with a 2015 surgeon RCE limit rate of $246,400 (DHHS 2014). Using the provided values, the following calculation illustrates the allowable compensation under the Medicare cost report:

$$\begin{aligned}&\mathrm{RCE\,limit\,rate}(\$246,400/2080\,\mathrm{hours\,per\,year})\\&=\$118.46\,\mathrm{per\,hour}\ \$118.46/\mathrm{hour}\times 300\,\mathrm{hours}\\&=\$35,538\end{aligned}$$

Therefore, only $35,538, not $50,000 for the physician's administrative tasks would be included on the cost report as allowable organ acquisition costs. The portion reimbursed by Medicare would be dependent on the ratio of Medicare kidneys to total kidneys for that year.

Living donors for kidney transplant are also included as allowable organ acquisition costs in the Medicare cost report. The costs included for living donors comprise the donor evaluation provided by the physician and hospital, the hospital admission for the donor kidney excision, and routine follow-up provided by the hospital (Fig. 2). All other living donor services such as the physician services for live donor nephrectomy and post-donation complications are billed to the Medicare program and reimbursed based on Part B physician fee schedule. It should be noted that the hospital may not bill the donor. Travel and lodging for pre-donation needs are not allowable organ acquisition costs in the Medicare cost report for recipients, donors, or family members (Rogers 2013).

Pre-transplant Recipient and Donor Services Provided by Other Hospital Departments

Organ acquisition costs include charges for services provided to recipient and donor by hospital departments other than transplant (i.e., diagnostic radiology and laboratory services). These charges must be tracked for claiming in the Medicare cost report rather than billed to the Medicare program. Conversely, commercial pre-transplant services should be billed to commercial insurance payers. The Medicare organ acquisition payment formula requires that both Medicare and commercial (non-Medicare) charges be reported in the Medicare cost report as the total charges will be adjusted to cost and further adjusted for Medicare utilization based on the Medicare ratio formula. In order to optimize both Medicare organ acquisition reimbursement and commercial payments for pre-transplant hospital services, the following process flow should be utilized (refer to Fig. 4).

Transplant programs maintain an organ acquisition cost center and a billing system report to accumulate hospital pre-transplant services charges to report on the hospital's Medicare cost report at year end for reimbursement. The Medicare cost report uses CMS mandated cost finding methods to calculate allowable direct, indirect and hospital pre-transplant charges into allowable organ acquisition costs. The Medicare ratio is then applied to total allowable pre-transplant expenses to determine the amount Medicare will reimburse to hospitals.

The Medicare Ratio

The Medicare ratio is used to calculate the proportion of total allowable organ acquisition costs that are payable by Medicare to the transplant hospital. The basic Medicare ratio formula is the number of Medicare organs to total organs. This fraction is applied to total allowable organ acquisition costs (i.e., the organ acquisition costs associated with both Medicare and non-Medicare patients) to determine the amount of organ acquisition reimbursement from Medicare. Medicare organs include four categories. The first is the count of kidney transplant recipients transplanted with Medicare fee-for-service as the primary payer. Medicare fee-for-service refers to patients with Medicare Part A coverage as the primary payer (Medicare Part C Advantage Plans do not apply). The second Medicare organ count determinant is the number of kidney transplant recipients that Medicare has paid, or should have paid, as a secondary payer. This pertains to patients that had Medicare Part A as a secondary payer to the

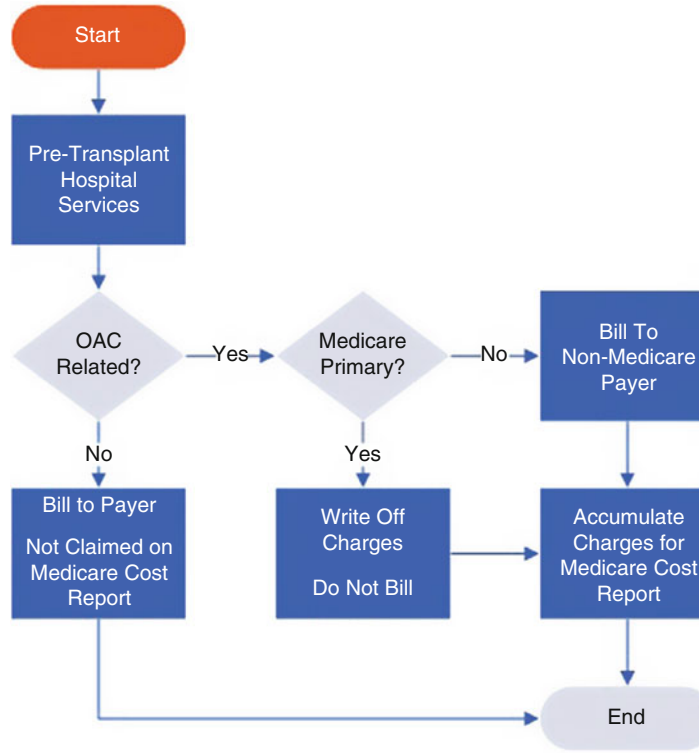

Fig. 4 Algorithm to account for organ acquisition costs

patient's primary commercial insurance. The third determinant is the number of deceased donor kidneys procured in the transplant hospital for the OPO. The fourth determinant is the number of live donor kidneys procured for other transplant hospitals (i.e., paired kidney exchanges and adult kidneys procured for pediatric kidney transplants). Live donor organs procured for the transplant hospital's own recipients are excluded as they will be counted based on recipient's insurance coverage. Total organs include total transplants, deceased donor kidneys procured for the OPO, and live donor kidneys procured for other transplant hospitals. Applying these factors creates the following ratio:

$$\frac{\text{Medicare Primary} + \text{Medicare Secondary} + \text{Deceased Donor Kidneys} + \text{Live Donor for Others}}{\text{Total Kidney Transplants} + \text{Deceased Donor Kidneys} + \text{Live Donors for Others}}$$

An illustration of what the Medicare ratio determinants mean for a transplant program's Medicare reimbursement is shown using an example of a kidney program performing 150 transplants per year, with hypothetical pre-transplant costs for 1 year of $10 million (see Tables 3 and 4). Accounting for the Medicare ratio determinants accurately is critical to ensure that all allowable cost reimbursement is received by the transplant hospital. In this hypothetical example, the Medicare ratio is 15% greater and the cost-based reimbursement is $1,464,000 greater than if the transplant hospital used only the Medicare primary kidney transplant patients as the determinant in the formula.

As the example shows, when transplant programs appropriately capture pre-transplant services, the Medicare cost report can produce significant

Table 3 Determinants to calculate Medicare kidney ratio

Organ description	Medicare Organs	Total Organs	Medicare Ratio (%)
Medicare primary payer transplants	100	100	61
Qualifying Medicare secondary payer transplants	10	10	6
Non-Medicare transplants (incl. Medicare Advantage)	0	40	0
Deceased donor kidneys procured for OPO	8	8	5
Live kidney paired exchange procured	2	2	1
Live kidney procured for Children's Hospital	4	4	2
Total	124	164	76

Table 4 Medicare ratios from Table 3 applied to 10 million dollars of organ acquisition costs

Organ description	Medicare Ratio (%)	Medicare OAC Reimb[a]
Medicare primary payer transplants	61	6,098,000
Qualifying Medicare secondary payer transplants	6	610,000
Non-Medicare transplants (incl. Medicare Advantage)	0	0
Deceased donor kidneys procured for OPO	5	488,000
Live kidney paired exchange procured	1	122,000
Live kidney procured for Children's Hospital	2	244,000
Total	76	7,562,000

[a]Does not include cost report offset for revenue received for Medicare organs

reimbursement for the program that goes beyond the cost of the kidney transplant. However, it is crucial that transplant programs are able to accurately support and verify all cost submissions, as overreporting can result in significant audit adjustments. Transplant programs may be audited by Medicare Administrative Contractors (MACs) and the Office of the Inspector General (OIG) for compliance with CMS regulations. Common noncompliance discoveries by the OIG include inappropriately reporting organ acquisition costs related to post-transplant and non-transplant activities, inadequate documentation, medical director fees exceeding reasonable compensation equivalent limits, and improper documentation of Medicare organs (DHHS 2006).

Outpatient Prospective Payment System

The third component includes reimbursement for post-transplant hospital services, which are covered under Medicare Part B. Reimbursement is through the outpatient prospective payment system (OPPS), and payment is based upon Ambulatory Payment Classifications (APCs) that group services of similar clinical intensity and resource use. APCs are analogous to MS-DRGs under IPPS. CMS uses the Healthcare Common Procedure Coding System (HCPCS) which includes certain Current Procedural Terminology (CPT) codes to identify and group the services within each APC. The OPPS includes payment for most hospital outpatient services, except those designated by the secretary to be paid under a different methodology (Social Security Administration n.d.). Examples of excluded services from OPPS include the professional services of physicians and non-physician practitioners paid under the Medicare physician fee schedule (MPFS), certain laboratory services paid under the clinical laboratory fee schedule (CLFS), services for beneficiaries with end-stage renal disease (ESRD) that are paid under the ESRD prospective payment system, and services and procedures that require an inpatient stay that are paid under the hospital IPPS (see CMS regulations at 42 CFR 419.22). Similar to IPPS, the OPPS base payment rate is adjusted for geographic wage differences for the locality in which the hospital is located.

Medicare Advantage Plans

Medicare Advantage Plans are a type of Medicare health plan offered by private insurance companies to individuals that meet the age requirement of

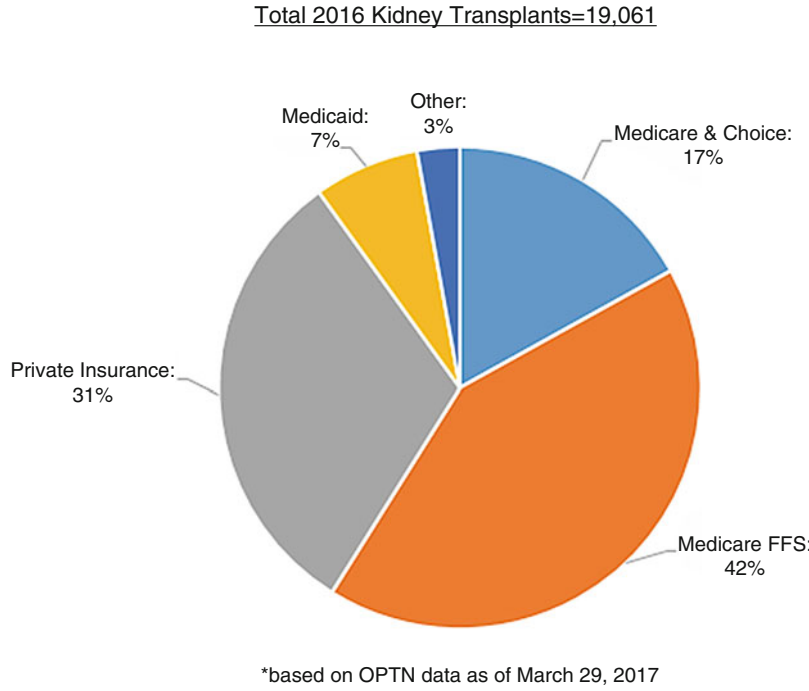

Fig. 5 Primary source of payment for kidney transplantation in 2016

65 years. The private company contracts with Medicare to provide Part A and Part B benefits management to the enrollee. These plans are managed by commercial payers and are, therefore, considered commercial plans. Due to the commercial designation, Medicare Advantage Plan transplant patients cannot be used in calculating the Medicare ratio for the annual Medicare cost report. Additionally, the payments for transplant services to transplant hospitals are negotiable just like a commercial managed care plan with providers negotiating rates for pre-transplant costs, organ acquisition, DRG, and post-transplant outpatient reimbursement.

Commercial Managed Care

Although the majority of kidney transplant patients are insured through Medicare, a portion of patients use commercial insurance companies. According to OPTN/UNOS data, 31% of kidney transplant patients had a private insurance company as their primary payer in 2016 (OPTN 2017a). In most cases, transplant reimbursement from commercial payers is based through managed care, where the financial risk is shared between the payer and the provider. Transplant-specific contracts are created by MCOs to provide access to transplant services regardless of referring physician affiliation. The development of national networks over the last couple decades has helped MCOs anticipate and decrease costs. National networks also provide the opportunity to improve quality of care in transplantation as MCOs direct business to a limited number of providers. In contracting with MCOs, transplant programs look to obtain long-term consistent volumes with satisfactory reimbursement rates (Scharlin 2014) (Fig. 5).

Centers of Excellence

Centers of Excellence (COE) or Institutes of Excellence (IOE) are transplant networks established by MCOs. This designation is given to institutions with high clinical, administrative, and financial competence. With a COE designation, transplant programs are typically able to receive higher reimbursement rates and increase patient volumes. To be designated as a COE, a transplant program must be certified by CMS, be a member in good standing with OPTN/UNOS, meet annual transplant volumes, have

acceptable patient and graft survival outcomes as verified by the Scientific Registry of Transplant Recipients (SRTR), and complete an OPTN/UNOS standardized request for information (RFI). The OPTN/UNOS RFI requires information on facilities, quality, volumes, outcomes, staff coverage, and credentials of a transplant program, as well as descriptions of unique qualities and initiatives to demonstrate the strength of the program (Scharlin 2014). It is important to note that while some MCOs review applications for inclusion in their COE networks throughout the year, others will only review applications during their annual review cycle. In addition to completing the RFI and other credentialing requirements, most organizations will require a site visit to assess the facility and staff in its entirety. Once a program meets the MCO's criteria, the program can begin the contract negotiations through its managed care department as a designated COE.

Managed Care Contracts

MCOs reimburse all transplantation services based on predetermined case rates, with the exception of "carved out" services. Carved out services are typically services that are either very costly, do not occur in the majority of cases, or that the hospital does not provide. Examples of common carved out services for transplant include high-cost pharmaceuticals, ventricular assist devices (VADs), and organ acquisition cost (Scharlin 2014). For reimbursement purposes, services that are carved out should not be included in the stop loss or outlier calculation if paid separately from the case rate. Communication within the contractual language, as well as with the hospitals finance department, is important to the financial success of any transplant program.

Four Popular Models of Transplant Contracting

Model 1: Evaluation and pre-transplant hospital and physician services paid at a percent of charges; transplantation procedure, inclusive of hospital and physician services, paid at a case rate; and post-transplant hospital and physician services paid at a percentage of charge.

Model 2: Outpatient pre-transplant hospital and physician services paid at a percentage of charge; inpatient pre-transplant services paid at an all-inclusive per diem rate; transplantation procedure, inclusive of hospital and physician services, paid at a case rate; outpatient post-transplant services paid at a percent of charges; and inpatient post-transplant services paid at an all-inclusive per diem.

Model 3: Global rates for phases 1–4 with a defined post-transplant time period of risk for transplant-related routine care and complications (i.e., 3–18 months). Global pay includes some carve outs and one fixed price for hospital and physician services.

Model 4: Hybrid of the previous three models and other nuances from the payer. Figure 6 highlights the billing processes of the hybrid model for commercial reimbursement using percentage of hospital and physician charges, broken down by phase of care.

Stop Loss

Stop loss, also known as outlier protection, is specified in payment contracts as a protection mechanism to help programs recover from outlier cases, cases such as procedural complications or long lengths of stay (LOS) that create additional unanticipated costs. Stop loss provides additional reimbursement to cover those costs when the case rates are not sufficient. Stop loss is an important part of the reimbursement agreement and can have a huge impact on the transplant program's profitability. A significant role that stop loss plays is sharing financial risk with the MCO. Financial risk should be shared and should not solely burden the provider.

Varying types of stop loss exist, with multiple factors influencing a hospital's preferred stop loss methodology. Factors that may influence a hospital's preference can be case mix and length of stay variances or simply geographical differences in contracting methodologies. Reliable data on cost and LOS help determine what works best for facilities and enables negotiations to be made from a

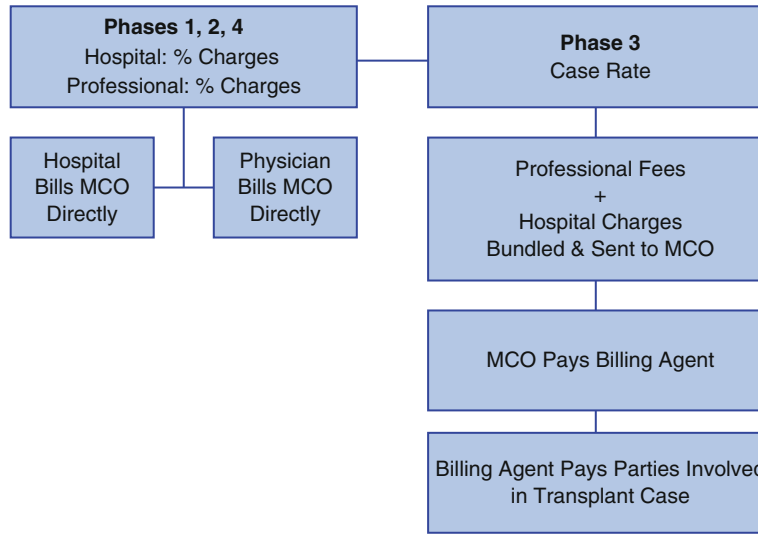

Fig. 6 Hybrid model of commercial reimbursement using percentage of hospital and physician charges pre- and post-transplant and a case rate for all charges during transplant admission

position of strength and knowledge (Scharlin 2014). For Medicare, the reimbursement converts from a fixed payment to a percentage of changes once the charges exceed the specified DRG payment. Meanwhile MCOs establish a stop loss provision that takes effect at a defined ceiling of costs above the global case rate payment. Common stop loss methodologies used by MCOs are first dollar, second dollar, per diem outlier, and floor outlier. Stop loss methodologies based on charges see a higher reimbursement than those based on number of days a patient remains in the hospital (Scharlin 2014).

While additional reimbursement from stop loss helps with extra costs, a gap typically exists between the case rate and stop loss payment threshold. Costs that fall within the gap go unpaid with transplant programs and their hospitals inheriting the financial burden. Additionally, it is still possible that even when the threshold payment is met, the program is not sufficiently paid to allow for a margin or even to cover the costs of the hospitalization and transplant procedure. To help transplant programs remain competitive and profitable, they can use a risk pool, the risk pool or consultant pool generated by a percentage of the global payment being set aside into a special general ledger account. The risk pool can help cover unforeseen costs such as the stop loss gap and can be applied to a global arrangement or to individual agreements in which payment is due. Risk pools have predetermined upper limits that, if reached, no additional withholdings would be held against future accounts until the pool sufficiently decreases (Marshall and Swearingen 2007).

Single Case Agreements

As previously mentioned, not all insurance companies have managed care contracts with each transplant program. In some cases, transplant patients may be referred to a program without managed care contracts with the patient's insurance provider. Single-case agreements can be established with the payer when a transplant program is considered out of the managed care network. Reasonably negotiated reimbursement rates can be mutually beneficial for both provider and payer, as local transplant programs are more cost-effective for insurance companies.

Medicaid

Medicaid is a dually funded program by federal and state governments that provides health insurance to low-income adults, children, pregnant women, elderly adults, and people with disabilities. While the significant majority of kidney transplants are covered by Medicare and private payers, Medicaid also reimburses for transplant

services. As Fig. 5 shows, nearly 7% of kidney transplants were covered by Medicaid, including Children's Health Insurance Program, in 2016 (OPTN 2017a). Individual states administer Medicaid, and, as such, each state determines whether Medicaid will pay for organ transplantation and the reimbursement rate. The Medicaid approval process can be lengthy to determine if a patient will be covered for transplantation and there may be qualifying conditions and criteria that apply. Additionally, most state Medicaid plans will not cover a transplant if a patient receives the transplant in a different state (Norris 2014).

Self-Pay

While not a common option, some patients may choose to pay out of pocket for their transplant procedure. International patients, those who are uninsured, underinsured, and self-insured, typically make up the self-pay population. In many cases, self-paying patients are provided a discounted rate for their procedure. To ensure complete payment, transplant programs may require a deposit prior to evaluation and full payment prior to wait-listing patients (Marshall and Swearigen 2007).

There is no limit to the number of self-paying patients that can be listed. However, the OPTN has oversight to review all citizenship data and request additional information about registrations or transplants of non-US citizens/non-US residents to enhance the transparency in the listing and transplantation of candidates whose sole intent for being in the United States was to receive a transplant (OPTN 2014).

Multiple-Payer Complexity

As shown earlier, the major payers for kidney transplant services are Medicare and commercial plans. As transplant programs grow, they can see the addition of multiple payers. The complexities of Medicare and commercial reimbursement for phases 1–4 for a kidney transplant recipient and living donor can be seen in Tables 5 and 6. This reimbursement includes hospital inpatient, outpatient, professional fees, and organ acquisition. While Medicare has its complexities, a lot can be said for their consistency. In the commercial arena, multiple payers exist, each with their own payment methodology and way of contracting.

Transplant Physician Billing

Similarly to hospital technical reimbursement, physician reimbursement differs based on payer. Medicare reimburses the physician differently based on phase of care. During phases 1 and 2, the physician is reimbursed through the organ acquisition costs and through Medicare Part B for phases 3 and 4 (Tables 5 and 6). For MCOs the actual amount of the case rate that should be directed to the hospital and to the physicians may not be specified in the contract. It is beneficial if the contract includes the breakdown of costs so that reimbursement teams are able to allocate the

Table 5 Multiple-payer complexity for transplant candidate/recipient Medicare and commercial reimbursement

Phases of transplantation		Medicare		Commercial	
		Facility	M.D.	Facility	M.D.
Phase 1	Patient evaluated for transplantation	Organ acquisition	Organ acquisition	Based on contract	Based on contract
Phase 2	Patient accepted and listed with OPTN/UNOS and is now in the maintenance or candidacy phase				
Phase 3	Patient admitted to hospital for organ transplant procedure and subsequent inpatient stay. This is typically the DRG component of the transplant process	DRG	Part B		
Phase 4	Patient discharged from hospital and post-transplant follow-up care period starts	APC			

Table 6 Multiple-payer complexity for living donor Medicare and commercial reimbursement

Phases of donation		Medicare		Commercial	
		Facility	M.D.	Facility	M.D.
Phase 1	Patient evaluated as transplant donor	Organ acquisition (excludes post-donation complications which should be billed to the recipients health insurance claim no.)	Organ acquisition	Based on contract	Based on contract
Phase 2	Patient accepted as living donor and now in candidacy phase				
Phase 3	Patient admitted to hospital for living donor procedure and subsequent inpatient stay		Part B		
Phase 4	Patient discharged from hospital and post-donor follow-up care period starts				

payments appropriately. Generally, the physician and hospital case rate split varies by payer and organ. The transplant program needs to review multiple years of data based on volumes and organ type to determine this case rate split. After the review, the percentage of total charges attributable to hospital services and to physician services for each type of organ can be determined. This percentage can then be included in future contracts or used to develop a negotiated case rate split between hospital and physician services.

Kidney Procurement

In addition to the payment to the certified transplant center for the organ transplant procedure, transplant centers are also reimbursed based on standard acquisition charges for the reasonable and necessary costs associated with acquiring the organ. Costs associated with organ acquisition are included on the organ acquisition cost center of the Medicare cost report. The standard acquisition cost reflects an average of the total actual costs associated with procuring an organ, classified by type of organ. There are two types of standard acquisition charges, one for acquiring a living donor organ and the other for acquiring a deceased donor organ. To bill Medicare for the transplant, a transplant center must use the standard acquisition charge (SAC) for the transplanted organ. Transplant centers have the option of billing a standard acquisition charge or actual charges converted to cost for a procured organ provided to an OPO or another transplant hospital. The costs of procuring an organ are reimbursable; however, when procuring the organ for a Medicare covered transplant, the interim procurement costs are paid and then reconciled through the Medicare cost report at the end of a transplant program's cost reporting period. There are specified expenses that can be included in both the deceased donor and living donor standard acquisition costs. The only consistent surgical recovery fee set by Medicare is for deceased donor kidneys limited to $1,250 (DHHS 2016b).

Estimated Charges for Kidney Transplantation

Milliman Research Report produces a triennial summary that includes an estimate of billed charges for US organ transplants. Charges referred to in this report represent the amount billed, which may differ from the actual amount paid for transplant services. The presence of case rates or other negotiated arrangements for reimbursements may have been made to account for incongruities between amount billed and actual amount paid. While the estimations for billed charges may not accurately reflect the amount paid for transplant, they do represent the expense surrounding transplantation. In the case of many

patients, they are faced with the choice of lifelong dialysis or a kidney transplant. Although the cost of transplantation is high, renal transplantation has been found to be more cost-effective than dialysis and produce higher quality-adjusted life years (Rosselli et al. 2015). The estimated Milliman Research Report US billed charges for kidney transplantation are shown in Table 7.

It is vital that transplant programs understand the costs involved in providing kidney transplantation to better manage the finances of the program, as well as to effectively contract with MCOs. Milliman Research Report of (2017) indicates an increase in billed charges for organ transplantation since 2011. The estimated US average 2011 billed charges per transplant were $262,900 compared to a total of $334,300 in 2014 and $414,800 in 2017.

Increased Cost of Kidney Allocation System

A new kidney allocation system (KAS) was implemented by the OPTN in December 2014 with a few goals in mind: reduce disparities in access to transplant, increase access to sensitized patients, reduce the unnecessary discard rate of kidneys, and align expected survival of the allograft with expected survival of the recipient. An analysis of data by the OPTN 18–20 months after KAS implementation has already shown a number of patterns. Namely, utilization of recovered kidneys has not shown improvement under the new system, an impact on pediatric transplant patients has been observed, and post-implementation 6-month graft and recipient survival are slightly lower than pre-implementation of KAS (Stewart et al. 2016).

Table 7 US organ and tissue transplant charge estimates per 2017 Milliman Research Report

Kidney transplant		
Inpatient services	Procurement	$ 96,800
	Hospital transplant admission	$ 159,400
	Physician during transplant	$ 24,900
Subtotal		$ 281,100
Outpatient services	30 days pre-transplant	$ 30,100
	180 days post-transplant discharge (includes physician professional fees)	$75,000
	Immunosuppressants and other Rx	$ 28,600
Subtotal		$ 133,700
Total		$ 414,800

With changes in key factors that affect patient survival and transplant rates, understanding the effects of these changes on cost is important. Change in the current rates of maintenance dialysis and kidney transplant could alter costs positively if improvements in transplant access are made. This decrease in cost would be expected from shorter time on dialysis and higher transplant rates. Inversely, fewer transplants performed or longer dialysis time could cause costs to rise (Smith et al. 2015). However, thus far, the impacts of KAS on perioperative outcomes and costs have not been favorable. A study conducted by David Taber and colleagues using University HealthSystem Consortium (UHC) data shows substantial changes as a result of the KAS implementation. The KAS has led to a substantial increase for in-hospital costs, a significant increase in comorbid conditions and recipient risk, and higher rates of delayed graft function and increased 7-, 14-, and 30-day readmissions. Total costs, direct costs, cost index, and costs related to organ procurement, surgery, and pharmacy all showed an increase from the impact of KAS (Taber et al. 2017). The findings of Taber et al. show the notable cost impact policy changes can have on transplant programs.

Affordable Care Act's Impact on Kidney Transplant Finance

Public policy decisions can have a dramatic effect on transplant regulations and on programs' financial outcomes. The most profound health policy change of recent years is the Patient Protection and Affordable Care Act (ACA) signed March 23, 2010 by President Obama. The ACA is changing

the organization and financing of the American health-care system by striving for affordability and increased coverage to Americans.

Effects on Insurance Coverage

The ACA seeks to expand access to private health insurance for Americans who can afford it and increase access to Medicaid for Americans who cannot. To date the ACA has had a measurable effect on the availability of health insurance and access to care. Expansion in health-care coverage has provided a number of Americans with the opportunity for more affordable and accessible options. Patients with chronic conditions can no longer be denied covered because of preexisting conditions. Young adults are eligible to remain covered under their parents' health plan until the age of 26. Most notably is the expansion of Medicaid eligibility to many adults previously outside of the criteria to qualify. As of January 2017, 32 states, including the District of Columbia, have expanded Medicaid to adults. By 2015, about 14 million Medicaid enrollees were adults in the expansion group accounting for 18% of Medicaid enrollees. This number has likely risen as additional states have expanded since 2015 (Kaiser Family Foundation 2017). Unintended consequences of the implementation of the coverage provisions of the ACA have occurred. Some marketplace plans restricted access to providers, major insurance companies have dropped out of the marketplace, and Americans saw companies cancel their health plans that did not meet minimum ACA standards (Blumenthal et al. 2015).

Although there is enhanced access to care for transplant patients, potential to further strain the already limited organ supply is possible with an increase in the population of insured patients with earlier access to transplantation. This possibility leads to a rise in organ waitlists and thus waitlist mortality which could expand the use of marginal organs and result in worsening post-transplant outcomes (Axelrod et al. 2010a).

Effects on Patient Costs

Patients may also see a change in healthcare-related costs from the ACA implementation. Medicare beneficiaries with Part D medication coverage stand to benefit from the policy's aim at closing the existing "donut hole" (Axelrod et al. 2010b).

Decreased Medicare Reimbursement for Kidney Transplantation

The DRG and the cost report are the two primary mechanisms through which Medicare pays for transplant services. The DRG is the actual surgical procedure payment (DRG 652) and is billed to Medicare at the time of transplant. A national model approach to determine the estimated decrease in kidney transplant DRG 652 is shown in Table 8. Zavala et al. 2017) calculated a national average Medicare reimbursement for transplant DRGs and then applied the projected ACA reductions and 2% Budget Control Act sequestration reduction to the total DRG reimbursement. For DRG 652, the estimated decrease is $2,136 at a 7.6% reduction.

The second mechanism of Medicare payment is through the organ acquisition cost

Table 8 Kidney transplant DRG modeled payment reductions

Transplant DRG modeled payment reductions				
DRG/ organ	Total Medicare DRG payment prereductions	Total Medicare DRG payment postreductions	Modeled reduction	Percentage decrease
652 kidneys	$28,088	$25,952	($2,136)	−7.6%

Table 9 Transplant cost analysis template for the kidney transplant admission

Patient ID	1	2	3	4	5	6	Averages
Length of stay	0	0	0	0	0	0	0.00
Medical/surgical room cost	$0	$0	$0	$0	$0	$0	$0
Radiology cost	$0	$0	$0	$0	$0	$0	$0
Operating room cost	$0	$0	$0	$0	$0	$0	$0
Pharmacy cost	$0	$0	$0	$0	$0	$0	$0
Organ acquisition cost	$0	$0	$0	$0	$0	$0	$0
Blood transfusion cost	$0	$0	$0	$0	$0	$0	$0
Other department cost	$0	$0	$0	$0	$0	$0	$0
Phase 3 transplant cost	$0	$0	$0	$0	$0	$0	$0

center comprised of the organ from the OPO plus direct and indirect expenses that can be allocated to the pre-transplant portion of activity prior to the admission of the patient. Throughout a given year, the hospital maintains an organ acquisition cost center to accumulate charges and reports them on the hospital's Medicare cost report at year end for reimbursement at the level of the hospital's costs. In 2013, The Budget Control Act sequestration reduced Medicare reimbursement for organ acquisition hospital payments by 2 % projected through 2023 (Zavala et al. 2017).

Analyzing and Reducing the Costs of Kidney Transplantation

Transplant programs should routinely review and analyze their costs for performing kidney transplants. Some operating indicators to help monitor financial performance are number of referrals, waitlisted patients, number of transplants, cost per case, and payer mix (Norris 2014). Key information to assist in a transplant admission review is noted in Table 9. This is not an all-inclusive list but does contain many of the cost categories for performing kidney transplant. Reviewing patient costs in detail may reveal opportunities to reduce costs without affecting the patient outcome. Kidney transplant programs will have an ever-increased focus on cost reduction in the face of decreased reimbursement. Programs will need to work as a clinical and administrative multidisciplinary team to identify opportunities for meaningful cost reductions. The varied clinical and business disciplines encompassed in kidney transplantation are shown in Fig. 7. The figure provides an overview of the many disciplines involved in the daily operations of a kidney transplant program but is not intended to be an inclusive list.

Conclusion

Solid organ transplant finances harbor a number of complex financial aspects that are unique to hospitals with transplant programs. These complexities require dedicated and trained professionals in transplant financial processes to continually work for optimization of costs and revenue. With Medicare and MCOs being such a crucial component of the success of a transplant program, it is important to understand the numerous payment methodologies and reimbursement methods. Transplant programs must continue to increase focus on quality and efficiency while maintaining a firm grasp on the financial management. The integration of both the multidisciplinary clinical and business teams is and will continue to be an important role in transplantation in an era of evolving healthcare reform.

Fig. 7 The kidney transplant enterprise showing the multidisciplinary clinical and administrative function

Cross-References

- ▶ Organ Procurement Organization and New Kidney Allocation
- ▶ The Regulatory and Legal Environment of a Contemporary Kidney Transplant Program

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Quality Measurement of a Contemporary Kidney Transplant Program

Maria McCall and Linda S. Wright

Contents

Abstract

In the era of increasing oversight of transplantation, which includes a prescriptive framework for quality monitoring, transplant centers have been provided some necessary blueprints for developing a basic Quality Assurance/Assessment and Performance Improvement (QAPI) program. Missing from the regulatory framework for the QA portion of QAPI is the inclusion of structure and value as quality indicators in addition to process and outcomes. A meaningful and effective method of both measuring and monitoring quality in a kidney transplant program involves incorporating structure and value as additional quality measures. This achieves monitoring of minimum program requirements as well as program efficiency, and it meets the goals of multiple stakeholders such as payers, providers/programs, regulators, and patients. In order to make the QAPI program successful and to establish ownership with the transplant team, goal setting and benchmark establishment should be a collaborative process.

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In effective QAPI programs, the PI portion is equally critical. Meaningful PI not only meets minimum regulatory requirements of established methodologies for monitoring but also incorporates PI monitoring secondary to adverse event occurrences and the recognition of negative trends. All QA measures and PI methodology, along with pertinent policies and documentation, should be incorporated into the program's annual Quality Plan.

Keywords
QAPI · SPO paradigm · Performance improvement · Adverse events

Introduction

Quality in healthcare is often defined based on the constructs of outcomes, process, or structure. These constructs are measured either individually, or in combination. In organ transplant, quality was historically based on only outcome measures. Specifically, a quality program was based on patient and graft survival indicators. A more recent paradigm shift, driven by regulatory requirements, has expanded quality measurement to include processes. In addition, structural requirements set forth by regulators have necessitated the addition of monitoring of this construct. Further, commercial payers and the shift towards accountable care have redirected hospitals and transplant programs to focus on efficiencies and cost relative to outcomes and add value as a fourth construct in defining quality. This chapter will describe best practices in the measurement and monitoring of quality in a modern kidney transplant program which will satisfy the priorities of all stakeholders involved hospitals/programs, patients, regulators, and payers. In addition, this chapter will review the steps necessary for establishing an effective and compliant QAPI program starting with best practices in choosing quality measure. This chapter will also provide guidelines for developing performance improvement plans that meet regulatory guidelines and provide structure for adverse event reviews.

Regulatory Oversight Driving Transplant Quality Monitoring

Transplant programs have experienced sweeping regulatory changes in the past 10 years. These regulatory requirements, high-profile media stories, and the era of online research and the educated consumer have been the impetus for the development of comprehensive QAPI programs in solid organ transplant. The federal government has recently begun surveying transplant programs strictly for the purpose of assessing their QAPI program amidst known outcome issues. This process has been coined fQAPI and has driven transplant programs to dedicate significant staffing and resources to their transplant-specific QAPI programs. The emergence of the fQAPI onsite survey has placed even further emphasis on the importance of a quality program to the extent that there are multiple annual QAPI webinars hosted by the transplant professional organizations and an annual conference dedicated strictly to transplant quality management. The new level of sophistication in QAPI development and awareness has not only driven changes in staffing models but it has also encouraged true multidisciplinary collaboration and bridged the gap between programmatic quality programs and hospital administration-level quality management.

Prior to 2007, hospitals had minimal oversight of organ transplantation in terms of maintaining quality. The Organ Procurement and Transplant Network (OPTN) required maintenance of outcomes as a quality measure; however, the remainder of oversight was documentation driven and no requirement for a formalized QAPI program existed. On June 28, 2007, the Centers for Medicare and Medicaid Services (CMS) published the final rule on organ transplant certification and oversight in the Code of Federal regulations. Among the requirements was a specific Condition of Participation for QAPI. Upon publication of these regulations, Thomas Hamilton, the Director of the Survey and Certification Group of CMS's Division of Medicaid and State Operations, described the QAPI Condition of Participation as one of the most important aspects of the new era of oversight in transplantation (Hamilton 2008). Hamilton explained that the requirement was meant to be

action oriented and feedback systems for adverse events will be analyzed for effectiveness along with the data-driven measurement aspect of QAPI.

The QAPI Condition of Participation (42 CFR § 482.96) states that "Transplant centers must develop, implement, and maintain a written, comprehensive, data-driven QAPI program designed to monitor and evaluate performance of all transplantation services, including services provided under contract or arrangement." It further lists a standard that requires the QAPI program to measure "outcomes" as well as a standard requirement for adverse event monitoring. The condition is very broad overall and provides little specific guidance to maintaining this requirement. One year after the regulations were effectuated, CMS released a formal guidance letter to the State Survey Agency Directors, which included the Interpretive Guidelines for all of the Transplant Conditions and Standards (CMS 2008). This provided some further assistance for transplant programs wishing to develop and enhance their QAPI programs. This guidance was necessary as 24% of all programs surveyed by the state agencies were found to be out of compliance for the QAPI Condition at that time (Abecassis et al. 2008). Transplant programs, however, continued to struggle with the QAPI condition and inconsistent application of the rules by state and contract surveyors. In 2009, CMS awarded a contract to Catapult Consultants LLC to develop guidance meeting three goals including "1. The national need to ensure transplant surveyors understand the QAPI regulations and survey guidelines; 2. Further describe CMS expectations for a comprehensive transplant QAPI program; and 3. Provide surveyors with a tool that provides/promotes a consistent application of the QAPI regulation (Catapult Consultants 2010)." The consulting group released a 37-page guideline and accompanying worksheet in 2010 which provided delineated steps for transplant centers to craft meaningful QAPI programs aimed at not only meeting CMS expectations but also at measuring and maintaining quality in a way that is objective and provides proven results. Figure 1 describes the steps necessary for development of an effective QAPI program that takes into account the consultant's recommendations and also incorporates best practices pertinent to a modern transplant program and its strengths and challenges. These further recommendations are described in the sections below.

Quality Assessment Beyond the Regulatory Requirement

The historical monitoring of just survival outcomes to monitor program quality is outdated and insufficient. The Catapult Consultants report provided specific instructions for ensuring that transplant programs also analyze process measures. They further describe the need to implement quality measurement at all phases of transplantation including the pretransplantation phase (during evaluation and while waitlisted), the inpatient and perioperative phase, and the posttransplantation phase. Their guidelines necessitate a minimum of nine quality measures per organ program with at least three measures per phase of transplant, at least one of which is an outcome measure and at least one of which is a process measure. This guideline, although tremendously helpful for both transplant centers as well as surveyors in setting forth clear expectations, is not exhaustive of all necessary Quality Assessment practices for Transplant Centers, nor does it provide practical guidance to transplant programs for building their Quality Plan in a collaborative and meaningful way. For example, their guidelines cover process and outcome requirements but do not encompass structure monitoring or value monitoring.

Avedis Donabedian's work on the structure, process, and outcome (SPO) paradigm has been frequently cited as the necessary comprehensive framework for quality measurement in healthcare (Donabedian 1988). Specific structural parameters have long been required in order for a transplant program to obtain and maintain institutional membership in the OPTN. In addition, the majority of the CMS Conditions for Coverage can be categorized as either structure, process, or outcome requirements. Given that both the OPTN rules and CMS rules are required (OPTN for

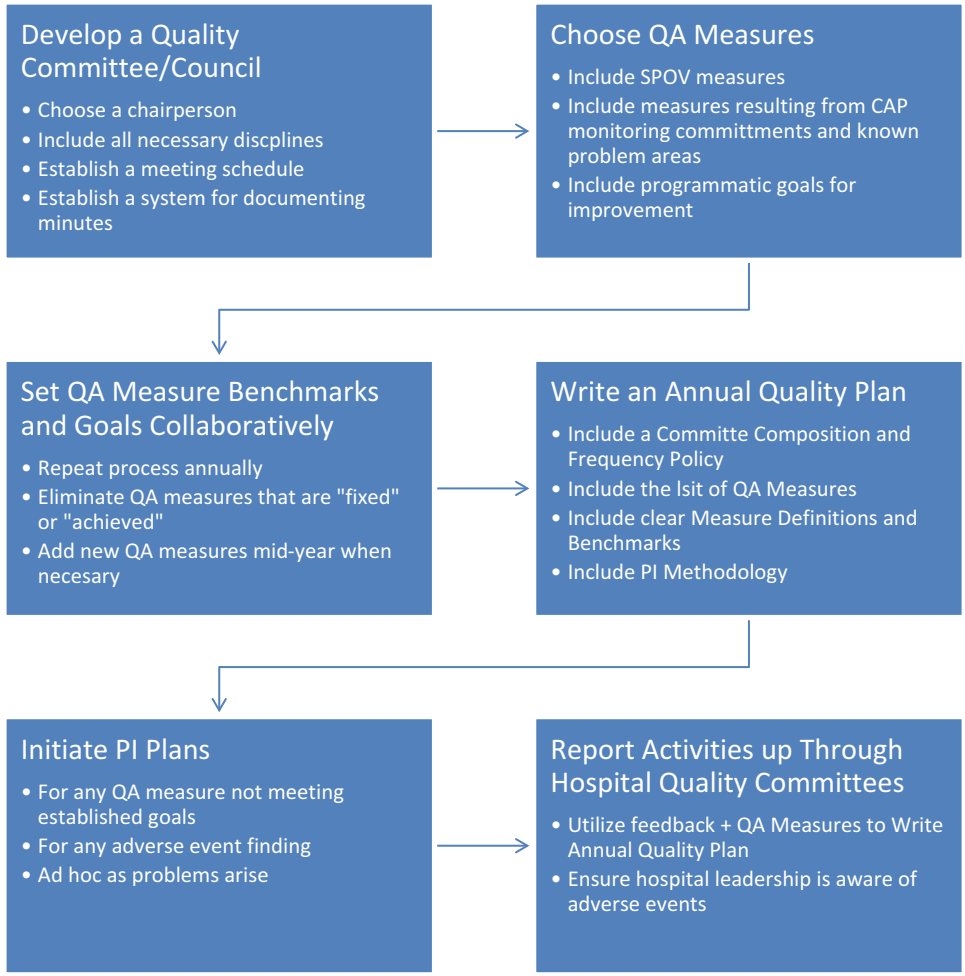

Fig. 1 Steps for successful quality plan development and implementation

membership and CMS for reimbursement), it is a worthwhile safeguard to include measurement of these rules as part of a comprehensive QAPI program. Donabedian (1988, 2005) describes structure variables/ measures as the setting in which care is delivered including adequate facilities and equipment and qualifications of personnel. This data is often readily accessible and objective making it an easy opportunity for data gathering. For example, it should be relatively easy for a transplant program to gather and monitor data on maintenance of competencies for personnel (a CMS requirement), monitoring of appropriate personnel on nursing units (a CMS requirement), and appropriate vessel storage units (an OPTN requirement).

Value in healthcare is defined as outcomes relative to costs (Porter and Teisberg 2010). Value has been recognized as the one goal that is overarching for all stakeholders involved in transplantation: hospitals and healthcare providers, regulators, payers, and patients (Porter and Teisberg 2010). As organ transplantation costs are very closely monitored within the hospital setting due to Medicare Cost Report requirements, obtaining this data should be practical and accessible for transplant programs. Monitoring costs as the denominator in the value equation can assist a program in ensuring that care is delivered efficiently and responsibly. In organ transplantation, process measures are very telling indicators of

efficiency and utilizing a process measure relative to cost will also be an effective tool for measuring value in this setting. For example, if a kidney transplant program uses coordinators for organ call, it may be an area they wish to analyze to explore the cost savings and efficiencies relative to outsourcing this function. Therefore, looking at the cost for on-call pay and lost productivity time post-call can be a useful value measure. As an additional example, graft survival at 1 month is a common outcome measure. To look at this in terms of value, a simplified measure would be 1-month graft survival relative to a cost measure such as posttransplant costs at 1 month. Having an understanding of costs at different phases of transplant and relative to different processes and outcomes from within the program is very useful in understanding how the program provides high value to the patients.

In summary, utilizing the Donabedian SPO paradigm plus the addition of V (value) as a more modern construct, a best practice for a transplant program is to have SPOV quality assessment measures at all phases. Please refer to Table 1 below as an example of quality measures to meet minimum regulatory guidelines for QAPI (at least three measures per organ per phase with at least one process and one outcome) while also capturing structural indicators and value-related indicators.

Development of the Quality Plan and the Quality Committee

Although the examples illustrated in Table 1 may be useful for a program, it is important for transplant programs to have a Quality Committee or Council tasked with collaborative agreement on

Table 1 Sample of quality assessment measures for a kidney transplant program meeting the SPOV suggested framework

Kidney transplantation phase	Example quality measures	Measure type	Regulatory required minimum?	Additional measure for best practice?
Pretransplant	Average time from referral to waitlist	Process	**X**	
	Psychosocial assessment complete before waitlisting	Process	**X**	
	Waitlist mortality rate	Outcome	**X**	
	Transplant-coordinators maintain annual competencies	Structure		**X**
	Lost productivity time for coordinators post-call	Value		**X**
Peri-op/inpatient	Preimplant ABO verification completed accurately	Process	**X**	
	High-risk donor consent completed	Process	**X**	
	Unplanned return to OR	Outcome	**X**	
	Multidisciplinary discharge planning documented	Structure		**X**
	Average cost of inpatient stay for patients with infections	Value		**X**
Posttransplant	Removal from the waitlist occurred within 24 h	Process	**X**	
	One year graft survival	Outcome	**X**	
	One year patient survival	Outcome	**X**	
	Average wait time for patient clinic appointments	Structure		**X**
	Average cost of readmission within 30 days	Value		**X**

Quality Measures. The CMS guidelines recommend establishing a quality committee whose membership is clearly defined in terms of disciplines, roles, and format and frequency of meetings. The recommended functions of a Quality Committee (Norris 2008) are as follows:

1. Hold routine meetings in accordance with program QAPI policy/plan
2. Maintain and update Quality Plan annually and as needed
3. Form consensus on Quality Measures being analyzed
4. Establish goals and benchmarks for all Quality Measures
5. Provide a format for report out of Performance Improvement plans
6. Assign Performance Improvement plan owners and provide feedback on determining new plans
7. Provide a format for reporting adverse events and results of Root Cause Analyses
8. Document meeting minutes
9. Provide a member(s) to report to higher-level hospital Quality Committees

CMS requires that key personnel be included on the Quality Committee. Key personnel are defined as medical and surgical directors, and all key members of the multidisciplinary team such as transplant coordinators, etc.

The Quality Plan developed by the Quality Committee should be updated annually to ensure that it is effective. It should be considered a program "policy" and adhered to as such. CMS defines in its Interpretive Guidelines what the Quality Plan should include. In addition to defining the team members by title and role, the Quality Plan should include explanation of decision-making methodology such as committee vote, subcommittee vote, etc. The plan should list the measures you choose, list the benchmarks and goals chosen, and list the methodology by which data will be analyzed to obtain each measure. For example, the Quality Plan associated with the example measures above in Table 1 would list the measures and the numerator and denominator for each one established. Average time from referral to waitlist, for example, should include information in the plan as to what date is considered the referral date and where the referral date is being obtained. The purpose of this is to ensure that measures are truly objective data driven and are not estimates or subject to collection bias.

The Quality Plan should also list the frequency with which the Quality Committee will meet and how often new measures will be established. Reporting methodology from the Quality Committee to the Hospital-Wide QAPI program or Quality Committee is important to be defined in the plan as well. Specifically, the plan should include what is being reported, how often it is being reported, and to whom. The program should be prepared to have available documentation to demonstrate that this is happening. Any recommendations from the Hospital-Wide QAPI Committee should be documented.

CMS requires that a person be designated to be responsible for monitoring the Quality Plan and this person should be listed within the plan document. Commonly this position is considered a quality coordinator or a QAPI coordinator. This person also does not need to be the same as the QAPI Chairperson. The Chairperson's role can be a clinical lead or a decision-maker. The trend nationally, as demonstrated by the UNOS staffing survey of 2015, is for this position to be embedded within the transplant program and for at least one full-time equivalent be dedicated to the program in this capacity. The QAPI Coordinator should ensure that data required for analysis is readily available, valid, and comprehensive. The QAPI Coordinator should coordinate Quality Committee meetings, maintain the Quality Plan, represent the program for hospital-level quality meetings, and work towards bringing consensus to the team on matters of quality decision-making. The QAPI Coordinator should have readily available all documents related to the Quality Plan for immediate dissemination in the event of an onsite visit from CMS. These documents, although accessible to the transplant team, should be kept in a secure location due to the sensitivity and peer-protected nature of the information.

Also required within the Quality Plan is evidence of tracking and implementing

recommendations for improvements, evidence of ongoing compliance with changes as recommended by the committee and broad representation of transplant program issues across disciplines. In order for the Quality Committee to achieve all that is laid out in the plan, plus meet the SPOV framework, choosing measures is the next step.

Additional Quality Plan items include the program's adverse event policy and policy for tracking of complaints and incidents. A recommended Table of Contents for the Quality Plan includes the following.

1. Quality Committee Composition
2. Member roles and responsibilities
3. Meeting frequency
4. Plan Year's QA Measures
   (a) Definitions
   (b) Goals
   (c) PI Plan triggers
5. PI methodology
6. Methodology for reporting up through Hospital Quality Committee
7. Adverse Events Policy
8. Complaints and Incidents Tracking Policy
9. Appendix – Prior Year's Meeting Minutes
10. Appendix – Prior Year's Adverse Event's Reports
11. Appendix – Prior Year's QA Measures and PI Plans
12. Appendix – Add on/new measures for Plan Year
13. Appendix – Ongoing PI plans with responsible parties Plan Year

How to Choose Quality Measures

Quality measures meeting the SPOV framework should be chosen based on areas in which the program is struggling, issues for which the program has been cited by a regulatory agency, and programmatic goals that include major changes or shifts in activities or processes.

Because QAPI is aimed at continuous improvement, quality measures should not be chosen based on what is a known programmatic strength. For example, if the program has the resources to utilize a fast-track evaluation that has had years of proven success in evaluating patients expeditiously, it is not helpful to measure program evaluation timeliness as a pretransplant process. Conversely, if a program is struggling in any area, this should be a target for quality measurement. Whenever possible, cited deficiencies from regulatory agencies should be monitored as QA measures. A commonly cited deficiency by the OPTN is the use of incorrect dialysis start date. As part of a Corrective Action Plan (CAP), a program must often commit to monitoring that this error is remedied. Adding this monitoring to the program Quality Plan as a QA measure is an effective way to achieve this. Dialysis start dates based on standardized documentation can be analyzed in an objective way, utilizing readily available data, to fulfill a pretransplant process QA requirement, as well as ensure that a past deficient practice is being monitored.

In addition to areas of struggle for the program, QA measures should be chosen based on broader programmatic goals for improvement. For example, if volumes are a key growth goal for a kidney transplant program, QA measures can be chosen with ambitious goals and benchmarks in order to achieve success. A kidney transplant program may have a goal of a percentage increase in transplant growth for a given fiscal year. To achieve this growth, the program may surmise that outreach events are key to engaging referring physicians. Therefore, a measure of outreach events per month could be utilized to achieve this programmatic goal. This particular measure is more effective than a referral count measure because a related PI plan can be put in place to achieve the number of outreach events.

QA Measures should not be permanent. As numbers improve and are consistently "good," the Quality Committee should consider eliminating the measure and replacing it with a new measure. Also, as issues crop up throughout the Quality Plan year, a program should not feel as though they are trapped with their list of chosen measures. The program can and should add new measures in an ad hoc manner as issues arise that require monitoring.

Critical to any measure chosen, whether it be a result of a deficiency citation, a CAP commitment, or a programmatic goal, is Quality Committee participation and collaboration. The process of QAPI can be intimidating for the team in particular if measures are specifically related to individual work functions. It is critical that meetings are conducted in a collaborative and encouraging format for programmatic betterment as opposed to a tone that is punitive when goals are not met. That is not to say that team members are given a "free pass" when it comes to QAPI and for measures that require them to perform at a high level. However, team members who are directly affected by measures (and PI plans) should be part of the planning and goal setting in order to feel ownership rather than intimidation.

Collaboration is also key in establishing the QA numerator and denominator, the data source, the personnel responsible for collecting the data, and the goal or benchmark.

Table 2 Examples of QA measures defined in quality plan

Measure name	Ratio of length of stay for transplant admission vs. goal
Measure type	Peri-operative/inpatient outcome measure
Definition	Average number of inpatient days per transplant admission, starting with admission date and ending with discharge date at (transplant) hospital divided by UHC number, for the same population, for patients discharged during the prior (measured) quarter
Exclusions	Transplants occurring on patients who were already admitted, i.e., admission were not specifically for the transplant event, current inpatients
Goal	Less than or equal to 1.0. A PI plan is necessary when (1) this measure is at least 0.1 above the established goal or (2) the measure shows an increase in ratio in three sequential quarters
Data source	Inpatient EMR, admit date and discharge date fields. UHC quarterly report using (predefined DRGs)

Defining Measures and Setting Goals

The quality plan should have each QA measure chosen clearly defined. For example, if length of stay is a concern for a kidney transplant program, and it is chosen as a peri-op/inpatient outcome measure, it should be clearly defined. The QA measure should indicate if this is measured in days, if it is an average, during which time period is the data collected, for which population of patients, when the time period begins and ends, and if there are any patients who should be eliminated from the measure due to outlier scenarios. Collaboration in defining these measures so specifically is important as it often uncovers how team members may interpret the use of a data field differently.

The QA Measure definition in the quality plan should resemble the example in Table 2, which uses the University Hospital Consortium (UHC) as a goal benchmark.

Once a measure has been defined clearly, then a goal must be set by the Quality Committee. The purpose of the goal is to determine when a PI plan must be initiated. In Table 2, a goal is defined based on a numeric trigger. It is not uncommon for the team to wish to alter the goal after a QA measure results unfavorably. And although it is permissible to change goals, all efforts should be made to adhere to the original goal established collaboratively by the team. Situations in which changing the goal would be permissible include known errors in the QA measurement or benchmark and major shifts in priorities (where goals become stricter or more ambitious).

QA Measures must also be objective and data-driven. For example, lab-values, dates, timeframes, etc. are objective data elements that can be utilized in setting measures.

Performance Improvement

When a QA Measure goal is not met and a PI plan is triggered, the Quality Committee should choose a responsible party(ies)/PI Champion to develop the plan. Oftentimes a team member will volunteer for this role, especially if the measure not meeting goal is pertinent to their role. However, for some PI plans it will be necessary for a

responsible party/champion to be assigned. The QA Committee Chairperson can take on the role of assigning someone. To avoid overwhelming any one individual, work should be distributed as much as possible. Further, to encourage participation, it is recommended that participation in QAPI be incorporated into the job descriptions of team members and team members and participation be assessed as part of an annual performance appraisal. As recommended by CMS, hospital-wide methodology should be utilized for the Performance Improvement (PI) portion of the Quality plan. Common in most hospital settings today is the use of six sigma, Failure Modes Effects Analysis (FMEA), Plan Do Study Act (PDSA), and Define Measure Analyze Improve Control (DMAIC) methodologies. It is critical for the Quality Committee to have a working knowledge of the approved methodology. It is useful for hospital quality or PI staff to conduct a training session for the transplant Quality Committee before embarking on the program's first PI planning.

Using the DMAIC methodology as an example and assuming a QA measure of readmissions within 30 days with an unmet stablished goal, the Quality Committee would assign a PI responsible party/champion. After potential PI plans are suggested during the meeting, the PI responsible party would initiate DMAIC for this measure. Table 3 provides an example of the use of DMAIC methodology for Transplant QAPI.

Throughout the stages of the PI plan, Quality Committee meetings should take place and progress with the plan should be clearly documented in the meeting minutes. A sophisticated and proven quality methodology allows for alteration of plans as needed and ensures that plans are monitored for effectiveness. Implementing a "fix" for a problem without analysis and remeasurement risks the "fix" not working without brining awareness to the program.

Similar to how QA Measures should be chosen based on regulatory deficiency citations, PI plans can also be chosen based on CAP commitments. For example, a CMS citation may include a lack of consistently documenting a comprehensive psychosocial evaluation prior to addition to the kidney transplant waitlist. A transplant program will be required to demonstrate a plan of correction or CAP and would commonly include a commitment to measuring and auditing this as well as a commitment to a new process to mitigate this. The new process can be converted to a PI plan. Table 4 provides an example of a PI plan that could result from a deficiency citation.

Table 3 Using DMAIC methodology for transplant QAPI

Define	Quality Committee Meeting Reports QA Measure – Readmissions within 30 days is not meeting the Committee's previously established goal
Measure	
Analyze	A PI responsible party/PI champion is assigned and suggested PI plans are discussed at the committee meeting
	The PI responsible party/champion establishes a plan for calling patients at defined time points after discharge
Improve	The PI responsible party/champion presents the plan to quality committee for consensus, necessary resources, and comment. Plan is implemented
Control	The QA measure of readmissions within 30 days is remeasured to evaluate effectiveness of the PI plan and this is repeated and refined

Similar to how QA measures can and should be added to the quality plan in an ad hoc format given issues that arise throughout the plan year, PI plans can and should be added this way as well. Adverse event occurrences are a good example of where a PI plan is required and is not associated with a particular QA measure.

Adverse Events

CMS requires that transplant programs not only track and trend patient complaints and incidents but also have an established policy on transplant-specific adverse events. The policy should define what an adverse event is, include specifics related to the phase of transplantation, and include how adverse events will be analyzed, e.g., process for root cause analyses.

Table 4 Example of PI plan using DMAIC resulting from deficiency citation

Define	CMS cites transplant program for lack of consistently documenting a comprehensive psychosocial evaluation prior to waitlisting
Measure	Transplant program submits a plan of correction or CAP committing to ensuring that (a) psychosocial assessment documentation is measured as part of the QAPI process, and
Analyze	(b) a checkbox is developed for the listing worksheet which triggers a check of the psychosocial assessment prior to listing
Improve	
Control	The PI process continues with remeasuring the completeness of psychosocial assessments and adjusting the PI plan if not found to be an effective remedy

Table 5 Example of adverse event policy definition by phase of transplant

Pretransplant, predonation	Serious complications or death of an intended living donor Any error/omission/action causing death or harm to a pretransplant recipient while at Transplant Hospital
Transplant, perioperative	Any error/omission/action causing death or harm to a patient during the transplant or donation procedure and immediately following including but not limited to: 1. Unintended ABO incompatible transplant 2. Hyperacute rejection 3. Unintended disease transmission
Posttransplant	Any error/omission/action causing death or harm to a patient during the post-transplant/post-donation phase while at Transplant Hospital including but not limited to: 1. Medication errors 2. Serious infections acquired in the hospital that have the potential to cause death or graft failure Notification by an OPO of a (previously not known) disease transmission to a transplant recipient

The CMS definition of an adverse event is, "*. . .an untoward, undesirable, and usually unanticipated event that causes death or serious injury, or the risk thereof. As applied to transplant centers, examples of adverse events include (but are not limited to) serious medical complications or death caused by living donation; unintentional transplantation of organs of mismatched blood types; transplantation of organs to unintended recipients; and unintended transmission of infectious disease to a recipient.*" The transplant program's Quality plan adverse event policy should specifically address this adverse event definition. Further, the policy must address (1) the procedure for reporting an adverse event by transplant program personnel, the hierarchy of reporting, and for conducting analysis based on the reports; (2) The required timeframe for reporting, investigating and analyzing adverse events; (3) The corrective action process after the completion of the analysis and the timeframes for the action; (4) Use of analysis of reported adverse events in prevention; (5) External reporting of events to external agencies as required and applicable; (6) Reporting to, or inclusion of, Institutional Review Board (IRB)/ Western Institutional Review Board (WIRB) if the adverse event occurred within the context of an approved study; (7) For suspected medical device-related deaths or serious injury, reporting to the Food and Drug Administration (FDA) and the device manufacturer as required by federal law; (8) Reporting to the OPTN if the adverse event caused, or may have caused, transmission of an infectious disease, and reporting to the Centers for Disease Control (CDC), if CDC requires such reporting to them; and (9) Reporting to the Organ Procurement Organization (OPO) if the adverse event was related to an infectious disease present in a recovered organ from a deceased donor that could have been transmitted to other recipients who received organs from that same donor, or an otherwise compromised organ that was not detected either through the donor screening or organ transport processes (CMS 2008). This can be placed in the policy verbatim with the interpretive guidelines from CMS. An example of incorporating the CMS definition into a program's policy is found in Table 5.

CMS also requires that the analysis used for adverse events be described in the policy. Root cause analyses in transplantation are especially challenging given the multidisciplinary nature of the process and the multiple phases throughout

Table 6 Sample adverse event root cause analysis worksheet

Transplant RCA worksheet report (confidential and peer protected)		
Organ		
Meeting date		
Attendees		
Patient name		
MRN		
Transplant date		
RCA event trigger (death, graft failure, disease transmission, etc.)		
Date of event		
Case description, presentation		
RCA contributing factor summary - each contributing factor category must be completed, enter "no findings" if the category is found to be not applicable)		
Contributing factor	**Findings**	**Action/ follow-up plan**
Recipient selection/ waitlist management		
Donor selection		
Surgical/Peri-op		
Anesthesia		
Patient medical management (includes infection)		
Patient pharmacological management		
Post/op follow-up care		
Psychosocial		
Nursing		
Nutrition		
Support staff		
Communication		
Competency/training		
Equipment/resources		
Policies and procedures		
Other		
Approval		
Surgical director	Medical director	Administrator

which errors can occur. Successful root cause analyses for transplant adverse events address all areas. Table 6 shows a recommended worksheet to be used while conducting a root cause analysis. This worksheet allows for all disciplines to be addressed and all hospital areas throughout which the transplant recipient could have "touched" to be covered. The checklist also ensures that associated PI plans are documented at the plan is approved. Following adverse event root cause analyses, any PI plans established should be reported back to the next Quality Committee for documentation in the meeting minutes.

When an adverse event occurs that meets policy criteria, the worksheet should be utilized to work through a Root Cause Analysis meeting. The meeting should be coordinated by the QAPI Coordinator and should be chaired by the Quality Chairperson or his/her delegate. Preparation is necessary for a successful Root Cause Analysis meeting. In advance, a lead clinician responsible for care of the patient should assist in preparing a brief case summary. This should be presented at the beginning of the meeting. All disciplines should be present and be prepared to speak to their portion of care of the patient. For example, a death that is linked to medical complications may not appear as though a social work representative be necessary to the meeting; however, the complications could stem from a psychosocial high-risk patient who did not meet criteria for inclusion. At this point, a follow-up may be necessary to revise selection policies and social work representation is important for this step. Similarly, a patient death may be linked to an error at the bedside. The outpatient team may be responsible for reinforcing education or educating the inpatient team and their participation, although initially may not seem important, now becomes critical for understanding all processes related to the evaluation and care of the patient through all stages. Although all disciplines should be represented, it is not necessary for all team members to be present and limiting the Root Cause Analysis meeting to only representatives for each discipline can help set an environment for candid sharing and critical dialogue.

Follow-up actions are usually required after a Root Cause Analysis. The worksheet should list the individuals responsible for the follow-up and required dates. Follow-up meetings may be required to reconvene as well. Usually an adverse event will necessitate PI plans. The same methodology used for QA Measures not meeting goals

should be used for PI plans related to adverse events. Finally, when the Root Cause Analysis is complete and PI planning and follow-up actions are underway, this should be reported to the Quality Committee and up through the hospital-level quality committee.

The adverse event requirement does not address near misses. A near-miss can be defined as an event or occurrence that, if not detected and/or abated by a staff member, could have readily resulted in an adverse event. Near-misses, along with substantiated patient complaints, and unfavorable trends should be indicators for an ad hoc meeting of the Quality Committee to discuss the occurrences and determine if a PI plan or after-action is necessary. A near-miss can be treated like an adverse event for analysis purposes. An unfavorable trend or patient compliant can be treated this way but more often will necessitate a focused review with a smaller group. For example, if waitlist mortality is not a programmatic QA measure and it is indicated that waitlist mortality has been trending unfavorably, a meeting should to be convened or a portion of the Quality Committee time should be dedicated to discussing this and mitigating further issues with this.

Conclusion

In order for a modern kidney transplant program to ensure quality, a Quality Plan must be developed. The composition of the Quality Plan is driven heavily by regulatory factors but also requires further diversity in quality measurement development to develop best practices. Specifically, quality measures should be chosen following a Structure, Process, Outcome, and Value format. QA measures should be chosen based on areas of struggle, deficiency citations, and programmatic goals. QA measure goals and benchmarks should be established via committee and in a collaborative nonintimidating manner to ensure that team members have a sense of ownership. PI planning should be conducted in a format that is consistent with the hospital-wide methodology. Team members should have a working knowledge of the PI planning methodology. The annual Quality Plan should include detailed descriptions of the QA measures, the PI planning methodology, the program's adverse event's policy, and all pertinent changes made throughout the year. Also, the Quality Plan should contain previous year's meeting minutes and documentation pertaining to all interventions taken throughout the year. It is important for a QAPI program to go beyond the regulatory required minimum and include best practices for actual quality improvement that resonate with team members, payers, and patients.

Cross-References

- A History of Kidney Transplantation
- The Finance of Kidney Transplantation
- The Regulatory and Legal Environment of a Contemporary Kidney Transplant Program

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