Kidney Transplant Management

A Guide to Evaluation and Comorbidities

Sandesh Parajuli
Fahad Aziz
Editors

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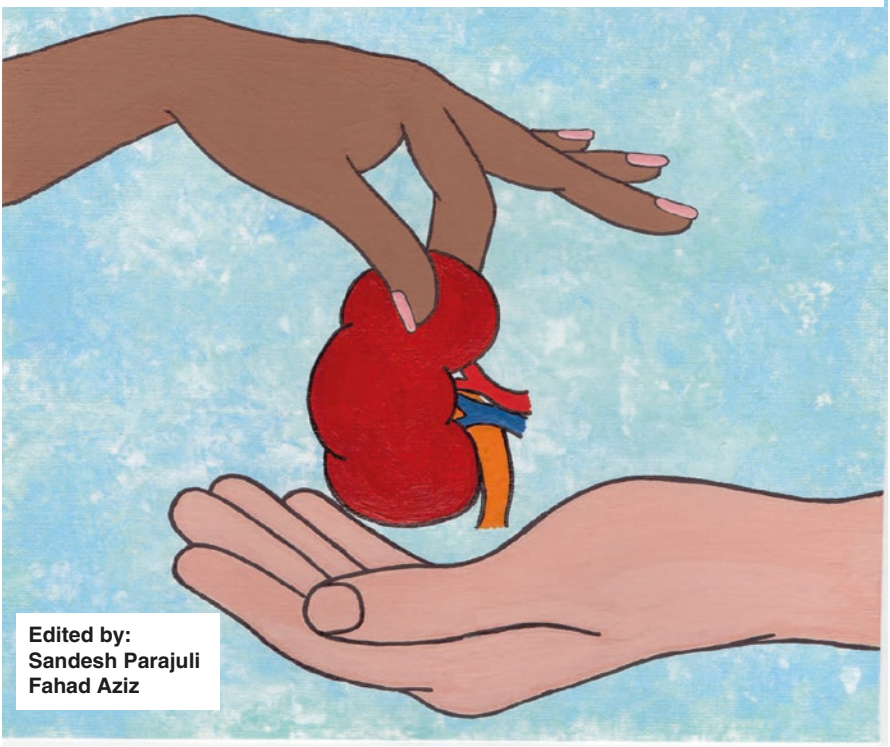

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Preface

Transplant medicine is both science and art. A kidney transplant is a unique modality of treatment with a clear advantage to the patient in terms of survival and quality of life despite being cheaper than dialysis in patients with the end-stage renal disease. Chronic medical conditions are common in transplant recipients. Immunosuppression-related side effects could also play a significant role in overall patients' medical condition.

This book provides an overview of the different problems we face daily while treating our transplant patients. It will discuss the different aspects of transplant nephrology as well as provide a brief look at life after transplant. It will also highlight the importance of proper immunosuppressant adjustment to improve the graft half-life.

We believe various chapters included in this book will provide some knowledge to the health-care providers at the beginning level in their career or anyone who is interested in the transplant medicine or takes care of the kidney transplant recipients. Chapters included in this book were inspired by our patients who we take care and see routinely.

Madison, WI, USA — Sandesh Parajuli
Madison, WI, USA — Fahad Aziz

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Chapter 1
Introduction to Kidney Transplantation

Fahad Aziz and Dana F. Clark

According to the United States Renal Data System (USRDS) 2017 annual report, 124,111 new cases of end stage renal disease (ESRD) were reported in 2015 [1]. The incidence of ESRD rose sharply in the 1980s and 1990s before plateauing in the early 2000's and peaking again in 2006 [1]. In 2003, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that the crude 1-year mortality rate was 21.7% in the United States for patients on dialysis [2]. Depression, sexual dysfunction, and sleep related problems are common among this patient population [3] and medical professionals recognize that dialysis is associated with both poor quality and quantity of life [4–6].

The idea of replacing diseased or non-functional body organs has existed for centuries. Although attempts at transplantation began in earnest towards the nineteenth century, the first successful kidney transplant was performed by Dr. Joseph E. Murray in 1954 at Brigham Hospital in Boston between two identical twins [7]. With the improvement in the surgical techniques and immunosuppression over last few decades, kidney transplantation has become the preferred treatment option for patients with ESRD. Kidney transplant recipients enjoy freedom from dialysis with improvement in both quality and quantity of life, and indeed multiple studies have shown that kidney transplant is a superior option in all age groups as compared to being on maintenance dialysis [8–11].

As of the end of 2017, 114,958 patients were waiting for life-saving organ transplants in the United States; of these, 87% are waiting for a kidney transplant [1]. The median wait list for an individual's first kidney transplant is 3.6 years and varies depending on factors such as blood group, geographic location, and organ availability [1]. Generally, there are two types of kidney transplant, living donor transplants and deceased donor transplant. Living donation can be directly from the relatives or

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friends. Living donation can also be part of paired kidney exchange program. Deceased donation occurs after the donor has died.

In 2015, 18,805 kidney transplants took place in US; of these 13,132 (69.8%) came from deceased donors and 5672 (30.2%) came from living donors [1]. Due to organ deficiency, more than 13 people die each day while waiting for a kidney transplant in the United States. Unfortunately, approximately 5000 patients died while waiting for a kidney transplant in 2014 and another 4000 patients became too sick to receive a kidney transplant [1]. The number of patients placed on the transplant waiting list continues to grow, but they still represent only a small fraction of the patients living with ESRD. As per the United Network of Organ Sharing (UNOS) transplant registry of 2014, over the last 10 years, despite increasing efforts by the transplant community, organ shortage remained the biggest hurdle in increasing the number of transplant recipients [12]. Since living donor transplants have a shorter waiting time and longer half-life than deceased donor transplants, they are preferred over deceased donor transplants. It is imperative that we increase awareness regarding the live donation process to increase the organ pool and decrease the number of people on the waiting list.

Although many comorbidities, including anemia and bone and mineral disease. Improve after transplant, kidney transplant recipients continue to have higher a cardiovascular mortality risk and an increased risk of malignancies and infections [13]. Because of this combination of overall improved outcome but increased risk, kidney transplant recipients are unique subset of patients with multiple traditional and transplant-specific risk factors. Appropriate preventive health measures and the monitoring and appropriate adjustment of the immunosuppressants are essential for prolonged allograft and patient survival. Kidney transplant recipients require appropriate, regular adjustment of their immunosuppression to maintain the fine balance between preventing rejection on one hand (if immunosuppression is too low), or infections or malignancies on the other (if too high). With all these considerations, transplant nephrology continues to be an interesting and challenging branch of nephrology. The effective treatment of the different aspects of the transplant population remains a hallmark of this specialty. With increasing number of transplant recipients every year, more transplant nephrologists are needed.

This book provides an overview of the different problems we face daily while treating our transplant patients. It will discuss the different aspects of transplant nephrology as well as provide a brief look at life after transplant. It will also highlight the importance of proper immunosuppressants adjustment to improve the graft half-life.

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Chapter 2
End Stage Renal Disease – Treatment Options: Dialysis Versus Transplant

Sandesh Parajuli and Patrick K. Reville

There are limited treatment options for a patient with end-stage renal disease (ESRD). Options include initiation of dialysis, kidney transplantation or palliative care (Fig. 2.1). Based on the medical conditions and patient's wish, patients opt to choose one or more of the above-mentioned treatment modalities. In patients deemed to be suitable candidates for transplantation, kidney transplantation is usually the preferred treatment modality. There are clear advantages to the patient in terms of survival, cost, and quality of life with transplant compared to dialysis.

Dialysis

Dialysis is one form of treatment option for patients suffering from ESRD. There are two main types of dialysis: Hemodialysis (HD) and peritoneal dialysis (PD) (Fig. 2.2). In the United States of America HD is the most common form of dialysis utilized while in other countries, for example, Mexico, PD is utilized more frequently.

The majority of hemodialysis is performed in a dialysis center, where patients spend 3–5 h on the machine 2–4 times a week. For dialysis, patients need good vascular access with arteriovenous (AV) fistulas being the preferred method of vascular access. Unfortunately, in certain circumstances and patients, an AV fistula may not be possible. These patients will require another form of vascular access in the form of an AV graft or less preferred, a centrally placed dialysis catheter. Home

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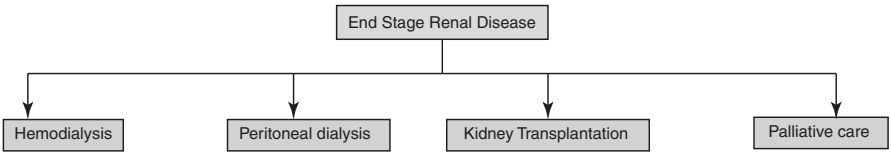

Fig. 2.1 Options for patient with End stage renal disease

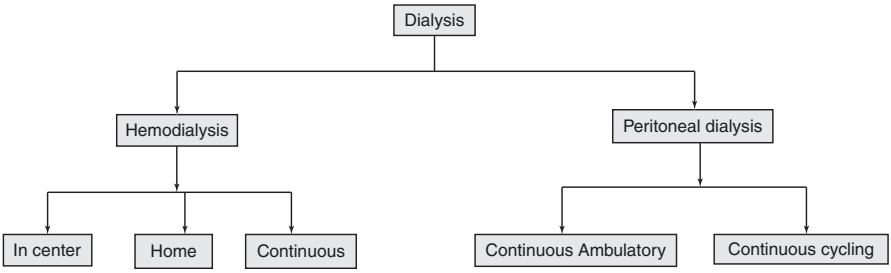

Fig. 2.2 Different types of dialysis

hemodialysis is also becoming more popular, where a patient can perform dialysis at home 4–5 times a week generally at night after work. For patients in hemodynamic shock that require dialysis treatment, continuous veno-venous hemodialysis (CVVHD) is performed with slower blood and dialysate flow rates for prolonged periods of days or weeks.

Peritoneal dialysis is another form of treatment for patients with ESRD. Peritoneal dialysis consists of a highly concentrated glucose containing solution instilled in the peritoneal cavity which creates an osmotic gradient and convection to remove uremic toxins and fluid. A PD catheter is required to perform PD. There are two types of PD: continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD). In CAPD, the dialysate solution stays in the peritoneal cavity for about 4–6 h. After which, the solution is drained from the peritoneal cavity and recycled 4–5 times a day. In CCPD, a machine automatically fills and drains the dialysate for 10–12 h a day. Most of the patients that perform CCPD, do so at). night during sleep. Generally speaking, PD is cheaper and more convenient than HD for patients with ESRD.

Transplantation

Kidney transplantation is another form of treatment for patients with ESRD. Transplantation is generally a better treatment for ESRD than dialysis, but it is also no cure for ESRD. There are clear advantages to the patient in terms of survival, quality of life, and cost. Although it is the often-preferred method, there are adverse effects of transplantation including increased risk of cancer, infections,

obesity, to name a few. There are two general types of kidney transplants, one from a living donor and another from a deceased donor. A living donor transplant is preferred to the deceased donor because these tend to be better quality kidneys in that the waitlist times tend to be low and graft survival is longer than deceased donor kidneys. The half-life of living kidneys is around 12–14 years while that of the deceased donor is around 9 years. The longer people wait for transplantation while on dialysis, the more unfavorable their outcomes are after transplant. Ideally, patients would be transplanted before initiating dialysis, referred to as pre-emptive transplant, or as soon as possible after initiating dialysis. Patients can be listed for transplant when their glomerulus filtration rate is below 20 mL/min/m^2.

Comparison of Clinically-Relevant Outcomes of ESRD Treated with Dialysis Compared with Transplantation

Anemia

The prevalence of anemia is very high in chronic kidney disease (CKD) populations. As CKD progresses, the prevalence of anemia also increases affecting almost every patient with ESRD [1]. The kidney is the main source for erythropoietin production, the hormone most responsible for erythropoiesis. Anemia in CKD is multifactorial, but mainly due to a reduction in the erythropoietin production along with short lifespan of red blood cells [2]. Additionally, there is an increased iron loss of approximately 1–3 grams per year in a dialysis patient due to chronic blood loss from uremic platelet dysfunction, frequent phlebotomy, and/or blood trapping in the dialysis machine [3]. In ESRD patients, oral iron has been shown to be no better than placebo in treating anemia; intravenous iron is preferred in the ESRD patient with iron deficiency, which in turn reduces the need for erythrocyte stimulating agents [3]. However, intravenous iron supplementation is not without risk, it has been associated with increased atherosclerosis and risk of infections, which are the two major causes of mortality in ESRD patients [4]. Anemia in ESRD also poses a significant financial burden. In 2005, erythrocyte stimulating agents were the largest expenditure within the Medicare program approaching $2 billion, by 2007 they cost Medicare $3.9 billion and these costs continue to increase [5].

After a kidney transplant, anemia is not uncommon with the prevalence of 20–57%, with prevalence higher in patients with impaired or poor renal function after transplant [6]. In patients with well-functioning kidney allografts, anemia usually resolves by 3–6 months after transplantation [7]. However, some patients develop persistent anemia caused by immunosuppressive medications which can cause or exacerbate anemia [6]. In one study, post-transplant anemia was associated with poor patient and graft survival along with increased risk of rejections [8]. Although the prevalence of anemia is lower after kidney transplantation, it is still common and an important contributing factor in allograft function.

Cardiovascular Risk

Chronic kidney disease is a well-known risk factor for cardiovascular disease and has been confirmed in many epidemiological studies. After adjusting for traditional risk factors, impaired renal function and albuminuria increase the risk of cardiovascular disease by two to four-fold [9]. In a large cohort of 16,958 people and median follow up of 24 years, after adjusting for conventional risk factors, the hazard ratio for cardiovascular disease were 1.55 for CKD stage 1 and 1.72 for CKD stage 2 patients [10]. This indicates that even mild renal impairment is a risk for cardiovascular disease. The risk of cardiovascular mortality is even higher in ESRD with 10–100 fold increased risk compared to matched control population [11]. The majority of cardiovascular mortality in ESRD patient is due to sudden cardiac death [12]. Left ventricular hypertrophy, heart failure, rapid electrolyte shifts, hypervolemia, and hyperphosphatemia are common in ESRD patients, all of which are associated with sudden cardiac death [13].

Cardiovascular disease and mortality decrease after kidney transplantation but still remains higher than the general population. Risk of cardiovascular mortality is worse with renal transplant compared with dialysis in the early transplant period with a relative risk of 2.84, but the risk equals out by 3–4 months and after that, there is reduced risk and a long-term survival benefit [14]. In the long term, annual cardiovascular mortality drops to two times higher than the general population [15, 16]. It is estimated that by 3 years post-transplant approximately 40% of transplant recipients experience cardiovascular events- mainly related to congestive heart failure (CHF) which is the second most common cause of hospital admission after infection in this population [17]. Myocardial infarction is more common in elderly and diabetic transplant recipients [17]. Other risk factors for cardiovascular events in kidney transplant recipients are unique to immunosuppressive medications. Prevalence of hyperlipidemia in kidney transplant recipients is 40–60% [18]. Most of the commonly used immunosuppressive medications are known to cause hyperlipidemia. Corticosteroids, even at low maintenance doses are related to hyperlipidemia [19]. Tacrolimus, cyclosporine, and to the greatest extend sirolimus are all known to cause hyperlipidemia [20, 21]. Newer immunosuppressive agents such as belatacept appear to have improved cardiovascular and metabolic risks when compared to traditional calcineurin inhibitors [22]. Although cardiovascular risk and mortality are significantly higher in kidney transplant recipients compared to the general population, their risk is much lower related to the immunosuppressive medications, with novel immunosuppressive medications expected reduce this risk.

Vascular Calcification

Vascular calcification is a very common finding in a patient with CKD and has been linked with mortality [23]. It is the most common extra-osseous calcification in a patient with ESRD affecting both medial and intimal layers of arteries [24]. The greater the number of blood vessels that are calcified, the greater the risk for death in

patients with ESRD [25]. Vascular calcification is an independent predictor of all-cause and cardiovascular mortality after kidney transplant [26]. The exact mechanism of vascular calcification is poorly understood but multiple risk factors are involved. These include the high total burden of calcium and phosphorus, low levels of circulating and locally produced inhibitors, impaired renal excretion which can induce vascular smooth muscle cells to become a chondrocyte or osteoblast-like cell [27].

Vascular calcification improves after kidney transplantation. It was found that kidney transplantation leads to better control of calcium-phosphorus metabolism and control of uremia and progression of coronary artery calcification slows by 6–12 months post-transplantation [28]. Most of the studies have shown vascular calcification slows but does not stop altogether after transplantation [29]. In one study, after 1 year of follow-up, coronary artery calcification regressed in 14.5% of the patients after transplantation [30]. Vascular calcifications are common findings in ESRD patients and are related to both mortality and graft survival. Unfortunately, there is no effective therapy to consistently reverse calcifications but transplantation often leads to decelerating calcifications.

Quality of Life

Quality of life (QOL) is a crucial clinical outcome measure, with some claims that it is better than traditional clinical outcome measures [31]. ESRD patients on dialysis often are concerned with the poor quality of life from perpetual feelings of fatigue and increased rates of depression that can be debilitating [32]. In clinical practice, patients on hemodialysis often compare being on dialysis as having a part-time job, they spend 9–15 h per week on the machine excluding travel and preparation time. Moreover during and after dialysis patients often feel drained and quite awful. The prevalence of depression, sexual dysfunction, and sleep-related problems are very common and under-diagnosed in ESRD patient [33]. Sleep quality has been associated with decreased QOL and mortality in ESRD patients [34]. In one study, QOL scores were decreased overall but comparable between patients with advanced CKD and dialysis [35]. Dialysis patients are often unsatisfied with complex aspects of care such as information provided about dialysis and when choosing a dialysis modality, and accuracy of this information and instructions [36].

Health-related QOL measures improve after successful kidney transplantation [37]. After a kidney transplant, young recipients are well adapted socially and often satisfied with their current life situation; however, they report lower QOL on most scales than the general population [38]. In one survey among 200 successful kidney transplant recipients, patients were more satisfied with their health condition, were involved more in social and leisure activities, and were traveling more after kidney transplant compared to while on hemodialysis [39]. In clinical practice, patients oftentimes express their happiness and realize how unwell they felt and were while on dialysis only after kidney transplantation. Overall patients are more satisfied with the better quality of life after kidney transplantation compared to dialysis.

Cost

Medicare cost to manage CKD is rising. In 2013, Medicare spending for CKD in patients aged 65 and older was more than $50 billion, which represented about 20% of all Medicare spending in this age group [40]. Compared to the previous year, total Medicare fee for service declined by 0.2% in 2013, but spending for ESRD patients increased by 1.6% to $30.9 billion [41]. In 2013, per patient per year (PPPY) peritoneal dialysis was $69,919 and hemodialysis was $84,550 [41].

Transplant is a cost-effective ESRD treatment. After the first year of transplant, PPPY in 2013 was $29,920 [41]. The financial impact of other medical comorbidities after transplantation, especially cardiovascular events is less studied but presumably lowers than compared with dialysis given the lower event rates [42]. After adjusting for inflation, the annual cost of immunosuppressive drugs peaked in 2007 but then declined due to generic competition [43]. There are clear direct and indirect cost-effective benefits of kidney transplant compared to dialysis.

Infections

Patients with CKD are at increased risk for hospitalization due to infectious complications, pneumonia, or sepsis. Acute infection is one of the most common causes of hospitalization in ESRD patient [44]. Uremia has been associated with immunodeficiency in CKD patients and the immune system is chronically activated leading to immune dysfunction in uremia [45]. Mortality due to infections is very high in the ESRD patient ranging from 7% to 30% [46]. Risk factors for infections in CKD or ESRD include advanced age, multiple comorbid conditions, low albumin level, uremia, malnutrition, and anemia [44].

Risk of infection is significantly higher after kidney transplantation and is a common cause of morbidity and mortality. After cardiovascular disease, infection is a second most common cause of death in kidney transplant recipients [47]. Urinary tract infections are the most common bacterial infection requiring hospitalization in kidney transplant recipients [47]. Many viral infections in kidney transplant recipients are due to reactivation of a latent viral infection [48]. Recently with increased prophylactic strategies and early diagnosis, the negative impact of infection on transplant-related outcomes has been improving [47]. Although the risk of infection is high in kidney transplant recipients, with proper prophylaxis and early diagnosis most infections can be managed without significant morbidity.

Malignancy

Chronic kidney disease and malignancy are associated in different ways. ESRD patients carry a 10–80% increased risk of malignancy than the general population [49]. Although exact mechanisms of increased malignancy risk in CKD is not well

understood, uremia induced immune dysfunction and increased circulating toxins are commonly speculated to contribute [50]. A graded relationship between severity of CKD and malignancy mortality has been found with higher mortality risk for liver, kidney, and urinary tract cancers [51]. In a longitudinal population-based study, an association between elevated albumin-to-creatinine ratio and malignancy incidence has been shown [52].

The incidence of malignancy is significantly higher after kidney transplant than on dialysis. The overall incidence of malignancy is 3–5 times higher in kidney transplant recipients compared to the general population [53]. The risk of malignancy in kidney transplant recipients is higher than patients on dialysis or those on the waiting list for transplant [54]. Malignancy is the third leading cause of death in kidney transplant recipients. Death from cardiovascular disease and infections are decreasing in the frequency due to aggressive screening and prophylaxis while mortality from malignancy is rising [55]. It is speculated that malignancy will surpass cardiovascular disease as a leading cause of mortality in the near future [56]. Increased risk of malignancy is associated with more intense immunosuppressive medications and longer duration of immunosuppressive exposure [57]. There are multiple risk factors for malignancy in kidney transplant recipients including chronic uremia, immunosuppressive medications, and increased rates of oncogenic viral infections [58]. Risk of malignancy is significantly increased in kidney transplant recipients and incidence is on the rise making it one of the leading causes of the mortality in the post-transplant period.

CKD After Transplantation

Although after kidney transplant patients do better in many aspects of their clinical and personal life, allografts have limited lifespans. Patient death with a functional graft is a major cause of kidney allograft failure, occurring in approximately 40% of transplant recipients [59]. The majority, however, develops CKD and some return to the dialysis and/or get re-transplanted. It is estimated that 4–10% of all dialysis patients and 20–40% of patients listed for a kidney transplant were previous kidney transplant recipients [60].

Kidney transplant recipients are a unique subgroup of patients with CKD due to the presence of single functional kidney, immunosuppressive medications, and disease vintage. Patients receive kidney transplant when their eGFR is less than 20, either in CKD stage 4 (eGFR <30) or stage 5 (eGFR <15). After kidney transplantation, their CKD can regress to any CKD-T stage 1 through 5. After transplant surgery, the majority of the transplant recipients' renal function stabilizes between CKD-T stage 2 and 3 [61, 62]. These patients are always at risk for CKD progression due to unique transplant-related complications including clinical or subclinical rejections, infections, immunosuppressive medication induced damage, or due to traditional risk factors for CKD progression. There is an independent and graded association between rate of decline in GFR and risk for death in