Chapter

29

Renal Transplantation

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The first case in your operating room assignment is a living related donor kidney transplant. The recipient is a 16-year-old Caucasian female with chronic kidney disease (CKD) 5 due to obstructive nephropathy. She initially presented six months ago with progressive fatigue, headaches, nausea, and vomiting.

Initial workup demonstrated a serum creatinine of 7.5, BUN 105, sodium 134, potassium 5.8, bicarbonate 12, calcium 6.2, phosphorus 10.3, hemoglobin 7.2. Vital signs: heart rate 89, BP 148/89, temperature 36.5°C.

Renal ultrasound demonstrated bilateral small kidneys with loss of cortico-medullary differentiation and bilateral severely dilated collective systems. Since the initial diagnosis, she has been treated with sodium bicarbonate tablets, calcitriol, darbepoietin alfa, atenolol, and sevelamer carbonate. The related donor is her mother, a 38-year-old healthy woman with no significant past medical history.

Immediate preoperative vital signs include: blood pressure 138/86, heart rate 62, temperature 36.5°C, SpO_2 100% on room air.

What Is Chronic Kidney Disease (CKD)?

Chronic kidney disease (CKD) is defined by the National Kidney Foundation Kidney Disease and Outcome Quality Initiative (KDOQI) Group in any patient older than two years, with kidney damage lasting for at least three months with or without a decreased glomerular filtration rate (GFR), or any patient who has a GFR of less than 60 mL/min per 1.73 m^2 lasting for 3 months with or without kidney damage.

What Are the Stages of CKD?

The KDOQI Group classifies CKD into five stages based on GFR (Table 29.1).

When Are Patients with CKD Eligible for Kidney Transplantation?

Discussion for renal replacement therapy including renal transplantation starts when the patient reaches stage 4 CKD. Initial workup for renal transplantation is also initiated. Preemptive kidney transplantation is done when dialysis has not been started prior to transplant and it is the optimal treatment to avoid the four-fold increase in morbidity and mortality associated with dialysis.

What Organ Systems Are Affected in Patients with End-Stage Renal Disease (ESRD)?

Multiple systems are affected by ESRD including:

- cardiovascular
- endocrine
- hematologic
- bone and mineralization homeostasis.

What Laboratory Abnormalities Would You Expect in a Patient with ESRD?

Anemia. Anemia of CKD develops as a result of both decreased production secondary to low erythropoietin and increased red blood cell turnover due to uremic toxins in patients with shortened lifespans. It presents as moderate to severe normochromic and normocytic anemia without increased reticulocytes.

Electrolyte Abnormalities. Common electrolyte disturbances include mild hyponatremia due to volume overload and hyperkalemia due to decreased clearance of potassium and acidosis.

Impairment of tubular excretion function results in hyperphosphatemia with hypocalcemia due to

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Table 29.1 Classification of chronic kidney disease (CKD) by glomerular filtration rate (GFR).

CKD Stage	Glomerular filtration rate (GFR) mL/min/1.73 m^2
Stage 1	Kidney disease with GFR greater than 90
Stage 2	60–89
Stage 3	30–59
Stage 4	15–29
Stage 5: End-stage renal disease (ESRD)	<15

secondary hyperparathyroidism and vitamin D deficiency as there is no conversion of 25-hydroxyvitamin D to 1,25 (OH)2D in renal proximal tubules.

Acid Base Disturbance. The high-anion gap metabolic acidosis is a consequence of failure of adequate excretion of acid anions (mainly ammonium but also phosphate and sulfate).

There is also a significant decrease in reabsorption and synthesis of bicarbonate which would serve as body buffer.

The deleterious consequences for metabolic derangements include renal osteodystrophy, arterial calcification, and increased risk of death.

What Are the Most Common Clinical Manifestations of ESRD?

- Neurological: Headaches, dysautonomia, uremic encephalopathy, cognitive alteration, fatigue, muscle weakness, peripheral neuropathy, increased risk of stroke, and in severe cases seizures and coma.
- Cardiovascular: Hypertension, fluid overload, left ventricular hypertrophy, arterial calcifications, early atherosclerosis, increased risk of cardiovascular disease.
- Endocrine: Vitamin D deficiency, renal osteodystrophy, short stature, growth retardation, dyslipidemia, malnourishment, sick euthyroid syndrome, delayed puberty, anovulation.
- Gastrointestinal: nausea, emesis, gastric paresis, insulin resistance.
- Hematologic: anemia, increased bleeding risk (uremia induced platelet dysfunction), immunosuppression due to T and B cell dysfunction.

What Is the Incidence of ESRD in Children?

In 2007, the reported incidence of ESRD in the United States was 1.48 per 100,000 children. As per the United States Renal Data System (USRDS) 2016 report, a total of 9,721 children were treated for ESRD by December 31, 2014.

What Are the Most Common Initial Treatment Options in Children with ESRD?

Treatment for ESRD includes renal replacement therapy and renal transplantation. Peritoneal dialysis (PD) was the most common initial ESRD treatment modality in children younger than nine years weighing less than 20 kg. Overall, the most common treatment for children with ESRD is hemodialysis (HD) at 50.4%.

What Are the Most Common Diagnoses Leading to Transplantation for Children with ESRD?

As per the 2014 annual transplant report from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), out of 11,186 pediatric renal transplants:

- Aplastic/hypoplastic/dysplastic kidney disease = 15.8%.
- Obstructive uropathy (15.3%) most common cause of ESRD requiring renal transplantation.
- Focal Segmental Glomerulosclerosis (FSGS) = 11.7%.
  - FSGS is the most frequent cause of ESRD in African American patients.

What Is the Age Distribution for Pediatric Renal Transplants?

Of the 718 listed pediatric renal transplants in 2015:

- Less than 1 year of age: 2 transplants (0.28%).
- 1 and 5 years old: 163 transplants (22.7%).
- 6–10 years: 145 transplants (20.2%).
- 11–17 years: 408 transplants (56.8%).

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What Preoperative Workup Should You Order Before Proceeding?

A deceased donor kidney transplant (DDKT) is considered a semi-urgent procedure in an attempt to decrease the cold ischemia time. Cold ischemic time is the time between cooling of the kidney after organ procurement to the time when the kidney reaches physiological temperature during implantation into the recipient. On the other hand, a living donor kidney transplant is entirely an elective procedure. For both cases, workup should be completed prior to surgery.

Clinical workup should be focused on current vital signs and ever-changing volume status. In patients with hypertension, the blood pressure target should be below goals for stage 2 hypertension.

Hypertension. Preoperative administration of scheduled antihypertensive medications is recommended with the exception of Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARBII), which are still controversial due to risk of intraoperative hypotension. Recently, Roshanov et al. demonstrated that in adults, withholding ACEI/ARBII before major non-cardiac surgery was associated with a lower risk of death and postoperative vascular events. However, no such studies exist in children undergoing renal transplantation regarding ACEI/ARBII administration. The major risk of withholding these medications is postoperative hypertension.

Volume Maintenance. Perioperative volume status is vital during renal transplant. ESRD patients managed by hemodialysis (HD) or peritoneal dialysis (PD) have a specific target weight after dialysis called estimated dry weight. Comparison of actual weight with dry weight gives the best evidence of fluid depletion or fluid overload. In scheduled kidney transplant cases, discussion with a pediatric nephrologist about lower fluid removal during HD or PD before surgery is key. Intravascular volume depletion after dialysis is a risk factor for graft acute tubular necrosis (ATN) or delayed function.

Laboratory Workup. Workup should, at minimum, include:

- Complete blood count (CBC), mainly hemoglobin and platelets
- Electrolytes/chemistry including Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-, BUN, creatinine, and glucose
- Coagulation studies: PT, PTT and INR
- Blood type and screen and/or type and cross-matching.

Imaging Studies. Yearly echocardiogram is usually obtained in patients with CKD 5 and ESRD to monitor for development of left ventricular hypertrophy, ventricular dilation, and both aortic and coronary calcifications. The leading cause of morbidity and mortality in children with ESRD in dialysis and post renal transplantation is cardiovascular disease.

What Are the Transfusion Goals for Patients Undergoing Renal Transplantation?

Most patients undergoing kidney transplant will have mild anemia. The KDIGO (Kidney Disease, Improving Global Outcomes) guidelines on anemia sets a treatment goal hemoglobin of 10–12 mg/dL with erythropoietin-stimulating agent (ESA).

If required, red blood cells should be irradiated (due to immunosuppression) and washed to decrease risk of hyperkalemia.

Are There Any Contraindications to Renal Transplantation in Children?

Children with uncontrolled extrarenal malignancies, sepsis, or multiorgan failure are usually not considered to be candidates for renal transplantation.

Improvements in immunosuppression protocols have permitted transplantation in ABO incompatibility situations but is not frequently seen in pediatrics.

Kidney transplant should be delayed for 12 months in patients with rapid progressive glomerulonephritis due to elevated levels of circulating antibodies and high risk of disease recurrence in the transplanted kidney.

What Monitors Do You Plan to Employ During the Transplant Operation?

In addition to the ASA standard monitors, providers should consider a 5 lead EKG, central venous pressure (CVP), and possible beat-to-beat invasive arterial blood pressure monitoring (IABP). The noninvasive blood pressure (NIBP) cuff should be placed on the upper extremity contralateral to the AV-fistula site. In

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addition to protecting the fistula, should great vessels need to be clamped, lower extremity blood pressure will not be accurate.

CVP is useful for intraoperative fluid management and can be monitored using an existing dialysis catheter or after placement of an internal jugular central line (ideally multilumen).

The IABP placement should be discussed with the Pediatric Nephrologist because of the possibility of a future need for an arterio-venous (AV) fistula. It should be considered in children less than 12 years of age, renal transplant requiring anastomosis of allograft into aorta and inferior vena cava, history of stage 2 hypertension, significant coronary and aortic calcifications, moderate to severe cardiac valvular disease, and heart failure. If IABP is needed, we recommend use of ultrasound guided placement and avoidance of brachial vessels with goal of placement one attempt, distal radial artery (in order to prevent damage) or dorsalis pedis artery.

How Would You Induce Anesthesia in This Patient?

Most patients will have intravenous access (IV) as usually they are admitted for prehydration, laboratory workup, and blood cross-match. Premedication with IV midazolam is generally safe and will alleviate anxiety in already highly medicalized patients.

Patients should be NPO except for medications including oral immunosuppression agents such as tacrolimus and mycophenolate mofetil, in addition to regular antihypertensives. Induction with opioids and propofol should commence with the goal of avoiding hypotension, followed by a short-acting non-depolarizing neuromuscular blocker (NDMR) (unless need for rapid sequence intubation) like rocuronium or ideally cisatracurium which is neither metabolized nor excreted by the kidney. Intermittent doses of NDMR should be continued to maintain 1–2 twitches for adequate relaxation during the procedure. After adequate placement of endotracheal tube if needed an arterial line should be placed and baseline arterial blood gas should be sent along with baseline hemoglobin. If the patient does not have an existing HD catheter to monitor CVP, placement of a right internal jugular catheter should be considered. As most patients typically have undergone prior IJ vascular access for HD catheters, vessels should be scanned with ultrasound for patency and to rule out thrombus presence.

What Are the Options for Intraoperative Analgesia?

Epidural analgesia has been safely used for perioperative and postoperative pain management but concerns for both hypotension and possible platelet dysfunction secondary to uremic platelets have decreased significantly the use of this type of pain management. The best approach is multimodal analgesia including non-opioids, opioids, NMDA receptor blockers, and local anesthetics at the incision site.

Perioperative opioids should be used with caution. Meperidine is not recommended due to accumulation of the active metabolite normeperidine, which decreases the seizure threshold and may cause convulsions. Morphine should be used with caution due to accumulation of morphine-6-glucuronide, an active metabolite that increases sedation and can cause respiratory depression. Morphine-3-glucuronide accumulation can cause neuroexcitation. Hydromorphone and fentanyl are the recommended opioids. Hydromorphone needs to be administered with caution as patients with ESRD can accumulate hydromorphone-3-glucuronide which may also cause neuroexcitation. Fentanyl is one of the opioids of choice for renal transplantation and is considered safe in ESRD with its lack of active metabolites. However, fentanyl clearance may be slightly decreased. Methadone is considered relatively safe, as it has no active metabolites and does not result in plasma accumulation.

Other analgesics have been used including: IV acetaminophen, NDMA receptor blockers, ketamine (0.5 mg/kg can be repeated every two hours or via infusion at 4–8 mcg/kg/min) in addition to other medications such as dexmedetomidine for their opioid sparing effects. Dexmedetomidine has the theoretical benefit of increasing urine output with the possible side effect of hypotension which is undesirable during renal transplantation.

How Would You Manage Intraoperative Fluids?

Intraoperative IV fluid management during pediatric renal transplant has been controversial. In the past, an isotonic solution without added potassium has been recommended to prevent hyperkalemia. Historically, normal saline 0.9% (NS 0.9%) has been used for this purpose. Potura et al., in a prospective randomized control trial in adults, demonstrated that use of NS

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0.9% during deceased-donor renal transplant (DDRT) increased the incidence of hyperkalemia by 17% between groups compared to an acetate-buffered balanced crystalloid. This worsening hyperkalemia is likely secondary due to high chloride concentration, lack of base or buffer, low pH of 5.5, and high doses during transplant, producing a hyperchloremic metabolic acidosis.

We recommend the use of a buffered balanced solution, such as plasmalyte. IV fluids should be titrated to achieve euvolemia with a CVP of 8–10. Many transplant surgeons will request administration of supra-physiologic amounts of crystalloids and colloids in order to obtain a CVP 12–15 prior to unclamping vein and artery with the theoretical purpose of improving graft perfusion. However, Taylor et al. demonstrated that this practice may result in pulmonary edema.

After reanastomosis of the transplanted ureter, fluid management can be switched to two infusions, one at fixed rate for insensible losses (600 mL/m^2/day or about 2.5 mL/kg/h) and the other infusion to replace urine output at a rate of 1 ml of fluid per ml of urine output per hour. This fluid management will usually be adapted by the pediatric nephrologist in the pediatric intensive care unit to better maintain fluid homeostasis.

The Perioperative Immunosuppression Required for Renal Transplantation

Timing of the induction of immunosuppression is crucial in order to prevent acute graft rejection which is highest during the perioperative period. The choice of induction therapy remains controversial in children and is institution dependent. It generally includes intravenous/central anti T-cell antibodies combined with conventional immunosuppression agents. In some instances, it is initiated during the preoperative period by administering conventional oral immunosuppression agents like macrolides, such as tacrolimus or sirolimus along with antimetabolites like azathioprine or mycophenolate. Specific medications will be determined by institutional protocol. Again, good communication among the pediatric nephrologist, anesthesiologist, and transplant surgeon is key.

The pediatric anesthesiologist is involved by administering the perioperative antibody induction. These medications may include polyclonal antilymphocyte antibodies like rATG-thymoglobulin (Thymoglobulin, rabbit-derived) and antithymocyte globulin (ATGAM, horse-derived). The antiinterleukin-2 receptor monoclonal antibody (IL-2 RB) like basiliximab may also be used as an induction agent. Infusion of polyclonal antibodies may cause a massive cytokine release causing fever, rash, tachycardia, and chills. Pretreatment with acetaminophen, diphenhydramine and steroids usually prevents these side effects. IL-2 RB agents generally do not have this response.

The Specific Management Immediately Prior to Kidney Reperfusion

During the procedure, the surgeon may request heparin during recipient vessels cross-clamping. The patient will need to be well hydrated and obtain at least a normal CVP ~ 8–10 mmHg before reperfusion. Depending on center specific protocols, the surgeon may request supra-physiologic CVP ~12 along with mannitol and 1–2 mg/kg or furosemide and even a low dose dopamine infusion (1–5 mcg/kg/min) prior to unclamping of the vessels. However, none of these interventions have demonstrated improved outcomes on graft perfusion, prevention of delayed function, and graft survival.

Once the kidney is reperfused, urine output from the graft can be confirmed in the surgical field. The final stage is reanastomosing the graft ureter with the native ureter, which in some cases may be performed by a pediatric urologist. After an uncomplicated transplant course in the absence of severe pulmonary or cardiac disease, most patients may be extubated at the end of the case. If extubation criteria are not met or intraoperative complications like pulmonary edema or severe fluid shifts are present, extubation should be delayed and the patient transferred to the pediatric intensive care unit (PICU), intubated, and sedated. Most patients are usually managed in the PICU where adequate pain control and hemodynamic and fluid management are ensured.

How Would You Manage Hypotension During Ureteral Reimplantation?

Hypotension management during renal transplant is one of the most controversial subjects in the field. Patients with CKD 5 or ESRD are at high risk of hypotension during anesthesia due to calcification and decreased compliance in both arteries and veins.

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Vasodilation due to inhaled anesthetics is more pronounced and response to vasoconstrictors such as direct peripheral Alpha-2 agonists like phenylephrine is decreased. These effects may be especially pronounced in patients taking antihypertensives such as ACEI or ARBII.

Historically, dopamine has been the medication of choice as the vasoconstriction effect is minimal at low doses and theoretically improves renal perfusion. This statement has been rejected by several publications although a recent review of the management in pediatric renal transplant patients demonstrated that intraoperative use of dopamine was an independent risk factor for delayed time to creatinine nadir in all grafts 9.5 days versus 6.5 days in patients without dopamine. In deceased donor grafts, the difference was even greater, 12.9 days versus 7.4 days.

The use of other vasoactive medications is not recommended due to possible renal artery constriction and decreased renal perfusion. Primary treatment of hypotension should initially be managed with intravenous crystalloid or colloid boluses to achieve normal CVP. Discussion with the surgeon should occur about starting vasopressor agents to treat hypotension after normal CVP is achieved with fluids. No specific agent has shown outcomes improvement versus the other, so the choice has to be made by the surgical and anesthesia team. Theoretical decreased graft perfusion due to vasoconstriction as a consequence of vasoactive medications has been described.

Suggested Reading

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