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 post-transplant lymphoproliferative disorder (PTLD).

**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, non-enveloped 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 post-transplant 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 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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