Chapter 24: Anesthesia for Renal Transplantation

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INTRODUCTION

FOCUS POINTS

1. Congenital and structural abnormalities are the leading causes of pediatric renal failure.
2. The adult approach, curvilinear incision and retroperitoneal placement of the donor kidney, is the current surgical technique.
3. Careful review of preoperative medications is warranted, especially angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) that may affect cardiac hemodynamics intraoperatively.
4. Vascular access can be a challenge and may require a preoperative placement in the interventional radiology suite for successful placement.
5. Sugammadex has been proven to be safe and effective in patients with renal failure, perhaps with slower recovery compared with patients with normal renal function. Sugammadex and sugammadex-rocuronium complexes are cleared by hemodialysis.
6. Providing optimal hemodynamics for graft reperfusion is extremely important; this goal can be accomplished with the administration of crystalloid, colloid, blood products, and/or inotropic infusions.
7. Causes of graft loss in the immediate postoperative period include primary nonfunction of the new organ and thrombosis of vessels.
8. Malignancy is a potential complication after transplant surgery with post-transplant lymphoproliferative disease (PTLD) being the most common, developed from latent Epstein–Barr virus (EBV).

End-stage renal disease (ESRD) is a complex and difficult problem in pediatric medicine. It causes significant metabolic and physiological derangements as the disease progresses leading to growth retardation, chronic anemia, electrolyte abnormalities, and systemic hypertension. Dialysis can be a life-prolonging treatment; however, renal transplant is considered to be the therapy of choice for patients with ESRD. Transplantation has the advantages of better quality of life, increased survival, and decreased health cost over time. Younger patients who undergo transplantation tend to have greater benefit and survival.[1,2]

EPIDEMIOLOGY

The Organ Procurement and Transplant Network (OPTN) manages the national transplant registry of the United States. The 2017 OPTN data shows 1,022 patients ages 17 and under on the active waiting list. This represents 1.05% of the 96,628 patients on the active waiting list.[3,4] The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) group has been following a similar small cohort of patients since 1987 in order to better characterize the epidemiology and outcomes of this unique population. They have obtained voluntary participation from all U.S. and Canadian centers performing a minimum of four pediatric renal transplants per year.[5] As of the 2014 Annual Report, 12,189 transplants have been reported for 11,186 patients (Table 24-1). Congenital and structural abnormalities account for a majority of cases of pediatric renal failure. In contrast, the leading causes of adult renal failure are diabetes mellitus, hypertensive nephrosclerosis, and glomerular disease.

Table 24-1

Recipient and Transplant Characteristics	N	%
Total	11186	100.0
Sex		
Male	6606	59.1
Female	4580	40.9
Race		
White	6605	59.0
Black	1911	17.1
Hispanic	1910	17.1
Other	760	6.8
Primary Diagnosis		
Kidney Aplasia/Hypoplasia/Dysplasia	1769	15.8
Obstructive uropathy	1713	15.3
Focal segmental glomerulosclerosis	1308	11.7
Reflux nephropathy	576	5.1
Chronic glomerulonephritis	344	3.1
Polycystic disease	339	3.0
Medullary cystic disease	305	2.7
Congenital nephrotic syndrome	289	2.6
Hemolytic uremic syndrome	288	2.6
Prune belly	279	2.5
Familial nephritis	247	2.2
Cystinosis	225	2.0
Idiopathic crescentic glomerulonephritis	195	1.7
Membranoproliferative glomerulonephritis type 1	191	1.7
Pyelonephritis/interstitial nephritis	189	1.7
SLE nephritis	172	1.5
Renal infarct	144	1.3
Berger's (IgA) nephritis	135	1.2
Henoch–Schonlein nephritis	115	1.0
Membranoproliferative glomerulonephritis type 2	87	0.8
Wegener's granulomatosis	71	0.6
Wilms tumor	59	0.5
Oxalosis	58	0.5
Drash syndrome	57	0.5
Membranous nephropathy	51	0.5
Other systemic immunological disease	34	0.3
Sickle cell nephropathy	16	0.1
Diabetic glomerulonephritis	11	0.1
Other	1223	10.9
Unknown	692	6.2

PATHOPHYSIOLOGY

The kidneys perform a number of functions, including filtration of metabolic waste products, volume regulation, and hormone production. Dysfunction in any of these roles leads to wide-spread systemic problems. Metabolic derangements are the most common. As the glomerular filtration rate falls, the kidney's ability to remove acids, urea, and potassium decreases. Hyponatremia and volume overload occur due to decreased ability to excrete free water. Initiation of dialysis can help correct electrolyte and fluid levels but can cause significant hypotension from aggressive fluid removal.

Hyperphosphatemia results from the kidney's inability to adequately excrete phosphate. The excess phosphate then binds serum calcium and magnesium, causing levels of both to decrease. Hypocalcemia induces increased production of parathyroid hormone, stimulating osteoclast activity, causing further bone destruction in an attempt to raise serum calcium levels. This ongoing problem leaves the patient prone to fractures.

Damage to the cardiovascular system can occur through multiple routes in patients with chronic renal failure.[6] Hyperkalemia is particularly problematic due to its effects on the cardiac conduction system, leading to potentially lethal arrhythmias if high enough (ECG changes can be seen with potassium levels as low as 6 mmol/L) levels are reached. Systemic hypertension develops due to chronic fluid overload, and increased activity of the renin-angiotensin-aldosterone system in response to diminished renal perfusion. Erythropoietin production is decreased leading to chronic anemia. This decrease in oxygen-carrying capacity further stresses the cardiovascular system with a need for increased output to meet oxygen demand. Young patients with early-onset renal disease often have premature coronary artery calcification.[7] Hyperhomocysteinemia associated with cardiovascular disease in adults is often found in young patients with renal disease, and can be a biomarker for disease progression.[8] Uremic cardiomyopathy as a result of uremia is a cluster of symptoms including left ventricular (LV) hypertrophy, LV dilation, and LV systolic and diastolic dysfunctions.[9]

Besides its effects on the cardiovascular system, uremia also has detrimental effects on the neurological, hematologic, and gastrointestinal systems. Acute uremia can often cause seizures and coma, as well as peripheral neuropathy and encephalopathy in patients with chronic disease.[10] Platelet dysfunction is a multifactorial problem in uremic patients as a result of the underlying disturbance of the α-granules (containing platelet factor 4, transforming growth factor β1, platelet-derived growth factor, fibronectin, serotonin, and factors V and XIII). There is also derangement of the arachidonic acid and prostaglandin metabolism, leading to impaired synthesis and release of thromboxane A_2 which in turn reduces adhesion and aggregation of platelets.[11]

Uremic enteropathy is another serious complication of chronic renal disease. Urea is an irritant to the gastrointestinal mucosal surface causing changes in the microbiome, as well as changes to the gut barrier integrity.[12] This alters nutrient and drug absorption and excretion. Evidence also suggests that mechanical dysfunction (eg, delayed gastric emptying) is part of this syndrome. Anorexia is frequently seen in uremic patients, thus putting the child at significant risk for growth retardation. The need for protein and calories must be carefully balanced against excessive protein intake, which can worsen metabolic acidosis. Recombinant growth hormone has been used as a treatment in children with renal disease to help prevent height deficits without acceleration for the disease process.[13]

SURGICAL TECHNIQUE

Historically, renal transplantation in smaller children (<20 kg) differed in approach from adult renal transplant. A midline incision was made, and the kidney was placed intraabdominally, with vascular connections to the vena cava and aorta. Since the late 1990s, this approach has largely been abandoned in favor of the adult approach which involves a curvilinear right lower quadrant incision and retroperitoneal placement of donor kidney. The right side is favored because of easier access to the vena cava for anastomosis. This approach has been successful in small children and infants. The decision to whether anastomoses are performed to either aorta and vena cava or iliac vessels depends on the size of the patient and the length of the donor vessels present. After revascularization of the kidney, a ureterocystostomy is performed, followed by abdominal closure and completion of the procedure.[14]

PREOPERATIVE EVALUATION

There are two routes for renal transplantation: living donor and cadaveric donor. In the case of a living donor, the operation is an elective surgery with adequate time to optimize any fluid deficits or excess, metabolic derangements, and nil per os (NPO) status. With a cadaveric renal donor, there may not be time to completely optimize the patient for surgery. In either case, a CBC and an electrolyte panel should be drawn the day of surgery to evaluate the degree of anemia and electrolyte derangement prior to proceeding to the operating room. A physical exam should be conducted such as in any other surgery and should include vital signs and weight and assessment of the airway and cardiopulmonary status of the patient. Once obtained, anthropometric parameters and blood pressure should be compared against others in patient's recent past to determine true baselines. Evaluation of fluid status is particularly important. Dialysis history should be reviewed to help determine if the child is volume overloaded, or potentially intravascularly depleted if dialysis has recently occurred. If an arteriovenous fistula is present, this should be noted and protected during all parts of surgery (eg, no arterial or venous lines, or blood pressure cuff on that extremity).

Most chronic medications should be continued up to the time of surgery. Antihypertensive medications in particular, if taken up to the morning of the procedure, may prevent rebound hypertension intraoperatively, though cautious use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) is recommended since they may cause persistent refractory hypotension.

INTRAOPERATIVE MANAGEMENT

Vascular Access and Monitoring

Vascular access can be a challenge even in healthy children. Children with renal failure have been subjected to countless lab draws and peripheral IV placements, causing stenosis and scarring of peripheral veins. Central-line placement may also be difficult if the child has had several dialysis lines placed. If access is estimated to be particularly difficult, arrangements should be made for preoperative assistance from interventional radiology.

Standard, noninvasive monitors should be placed prior to induction of anesthesia to monitor for hemodynamic changes. Invasive monitors (arterial line, central venous catheter) should be placed after induction. A central venous line is important for several reasons. It allows for monitoring of central venous pressure (CVP), infusion of vasoactive medications, and infusion of certain types of immunosuppressive medications. An arterial line should be considered on a case-by-case basis. Smaller children and infants do not tolerate the third-spacing and fluid shifts caused by pre-reperfusion volume loading making an arterial line essential for optimal intra- and postoperative management. Larger children and teenagers tolerate this better, and typically do not require an arterial line. Avoiding an arterial line if possible is also beneficial in that it better preserves a possible future dialysis fistula site. Near-infrared spectroscopy (NIRS) is another measure of tissue perfusion that can help guide intraoperative fluid and inotrope management. It has been proven to correlate with ultrasound data and can be used to monitor the graft postoperatively in real time.[15,16]

Induction

Premedication with oral or intravenous midazolam is often used to decrease preoperative anxiety. The decision between an inhaled induction and intravenous induction depends on the patient's NPO status and overall cardiovascular stability. An inhalational induction with sevoflurane with or without nitrous oxide is an appropriate plan for an NPO-appropriate patient with clinically normal gastric function. In patients with severe systemic hypertension, or suspected volume-depletion from recent dialysis, a carefully titrated intravenous induction with hypnotic and narcotic medications will likely have more hemodynamic stability. A rapid-sequence induction may be needed if a patient is not NPO appropriate or has known gastroparesis.

Several medications depend on the kidney for metabolism or clearance of metabolites. Not only can immediate graft function after transplant not be assumed, but protein-binding and volume status will not be immediately normalized as well. Medications should be planned with this in mind. Drugs with organ-independent elimination, those that do not depend on the kidney for metabolism or elimination of metabolites, and those with inactive metabolites, are excellent choices for patients in renal failure. Succinylcholine can be used in patients with normal serum potassium levels. Sugammadex has been proven to be safe and effective in patients with renal failure; however, the recovery was slower than that of patients with normal renal function. Sugammadex and sugammadex-rocuronium complexes are cleared by hemodialysis.[17–19]

Intraoperative Management

Maintenance of anesthesia can be accomplished with either a general, or general and regional anesthesia approach. Children who had epidural analgesia for renal transplantation did receive larger volumes of fluid intraoperatively, but also demonstrated a tendency toward better hemodynamic stability.[20] There is some evidence that a continuous transversus abdominus plane (TAP) block can be used to effectively reduce the need for narcotic pain medications postoperatively, but that has not been studied in the pediatric population.[21] As with all abdominal cases, nitrous oxide should be avoided to prevent abdominal distention.

Immunosuppressive therapy is typically started in the operating room. An immuno-induction agent is selected by the transplant team prior to commencement of the operation. Induction agents include polyclonal antibodies—antithymocyte globulin (thymoglobulin), and monoclonal antibodies—basiliximab (Simulect, *Novartis*) and daclizumab (Zenapax, *Biogen*). Thymoglobulin is a rabbit polyclonal antibody against human lymphocytes used to cause lymphocyte depletion. This allows for administration of calcineurin inhibitors (maintenance agent), which can be nephrotoxic to the new graft, to be delayed. Thymoglobulin should be given over 4 hours via a central venous catheter to prevent chemical thrombophlebitis of smaller peripheral veins. Premedication with diphenhydramine and hydrocortisone can reduce cytokine-release reactions associated with it. Basiliximab and daclizumab are monoclonal antibodies against the IL-2 receptor, targeting the proliferative T-cell response of the immune system. These agents have the advantage of not causing a cytokine-release reaction and are thus better tolerated by the patient. Alemtuzumab (Lemtrada, *Boyer*) is a newer monoclonal antibody that targets the CD-52 surface protein. Maintenance immunosuppressive agents are administered later in the postoperative period.[22,23]

Providing optimal hemodynamics for graft reperfusion is extremely important. Patients require volume-loading to augment their mean arterial pressure to combat the decrease in blood pressure due to diversion of volume into the new organ. This can be particularly problematic in small children and infants where this represents a much larger fraction of their total blood volume. Recommendations for CVP range from 8 to 12 mm Hg to 16 to 20 mm Hg, with most centers targeting the middle of these ranges (12 to 15 mm Hg). Mean arterial pressure should be raised to greater than 65 mm Hg. Crystalloid, colloid, blood products, and potentially inotropic infusions may be required to achieve this. After aortic unclamping, sodium bicarbonate may be needed if acidosis is severe. Mannitol and/or furosemide may be given to promote diuresis.

Immediate Postoperative Management

At the end of the operation anesthetic agents should be discontinued, neuromuscular blockade reversed, and the patient assessed for extubation. Extubation may be delayed in smaller patients with ongoing need for volume or pressor infusion to maintain organ perfusion pressure or in patients who have had significant volume loading and resulting pulmonary edema. This is generally less of an issue in larger children with more size-matched kidneys. Intravenous and enteral fluid supplementation may be required long into the postoperative period to adequately maintain perfusion pressure. Decreased perfusion pressure carries higher risk of acute tubular necrosis (ATN) and graft loss.

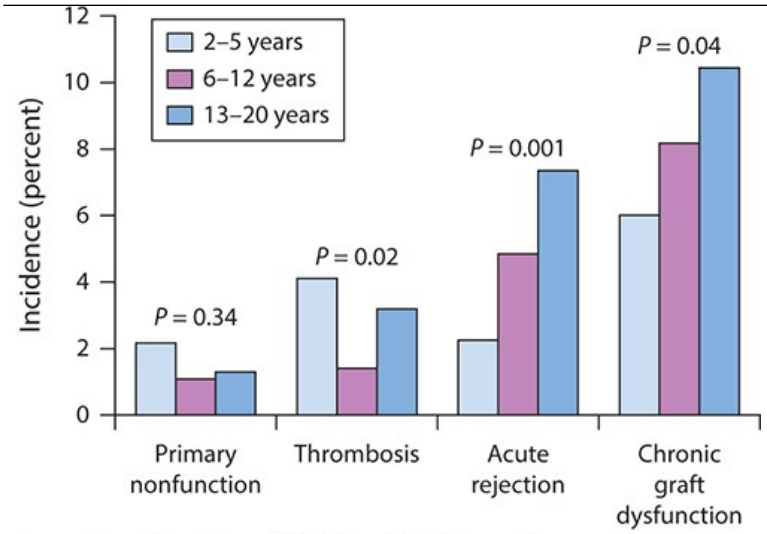
POSTOPERATIVE COMPLICATIONS, LONG-TERM ISSUES, AND OUTCOMES

Graft Loss

Causes of graft loss in the immediate postoperative period include primary nonfunction of the new organ and thrombosis of vessels, though these can also occur at any time. Patients are often monitored in an intensive care setting to closely follow hemodynamics, track urine output, and periodically check the vessels by ultrasound. Acute rejection can occur at any time but can often be reversed with prompt and aggressive treatment. The overall frequency of acute rejection reactions has been decreasing over time as improvements in immunosuppressive regimens have been made (Table 24-2). The frequency of chronic graft dysfunction is a more insidious and long-term issue. Incidence of each of these increases over time (Figure 24-1).[24]

Figure 24-1

Causes of graft loss, relationship with recipient age. (Reproduced with permission, from Hwang AH, Cho YW, Cicciarelli J, et al. Risk Factors for Short- and Long-Term Survival of Primary cadaveric renal allografts in Pediatric Recipients: a UNOS Analysis. *Transplantation*. 2005; 80: 466-70.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Table 24-2

Frequency of Acute Rejections Over Time and Comparing Source of Graft

Frequency of Acute Rejections						
1987–2013						
	Total*		Living Donor		Deceased Donor	
	N	%	N	%	N	%
All transplants	12116	100.0	6100	100.0	6016	100.0
Transplants with at least 1 rejection	5399	44.6	2449	40.2	2950	49.0
Number of acute rejections						
0	6717	55.4	3651	59.9	3066	51.0
1	2801	23.1	1329	21.8	1472	24.5
2	1285	10.6	606	9.9	679	11.3
3	665	5.5	270	4.4	395	6.6
≥4	648	5.4	244	4.0	404	6.7
Transplants with at least 1 rejection by transplant era	1874/2692	69.6	780/1210	64.5	1094/1482	73.8
1987–1991	1754/3169	55.4	807/1603	50.3	947/1566	60.5
1992–1996	1000/2720	36.8	537/1599	33.6	463/1121	41.3
1997–2001	548/2151	25.5	249/1133	22.0	299/1018	29.4
2002–2006	223/1384	16.1	76/555	13.7	147/829	17.7
2007–2013						

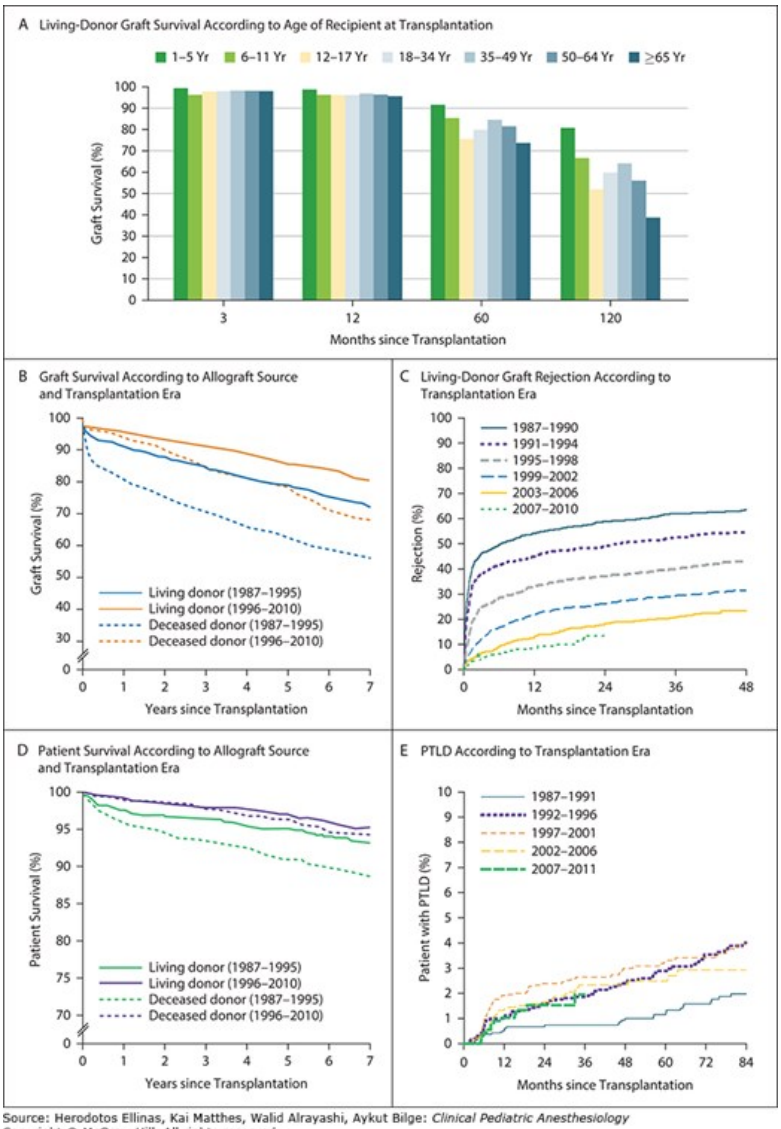
* Total with known donor source.

Malignancy

Malignancy is a potential complication after transplant surgery. Many of these malignancies are due to opportunistic viral infection, or reactivation of latent virus from immunosuppressive therapy. Post-transplant lymphoproliferative disease (PTLD) is the most common type. This develops from latent Epstein–Barr virus (EBV), from prior infection, that is allowed to go unchecked with immunosuppressive therapy. Latent EBV can be present in the patient prior to transplant, but a seronegative recipient can be exposed by a graft received from a seropositive donor. The risk of developing PTLD increases over time. Comparing across multiple years, the overall incidence of PTLD increased, and seemed to coincide with more powerful immunosuppressive medications coming into use[25] (Figure 24-2E). Human papilloma virus (HPV)–related malignancies (anal, perineal, cervical) and human herpes virus 8–related malignancies (Kaposi sarcoma) can also occur with immunosuppression.[26,27]

Figure 24-2

A–E. Pediatric graft and patient survival after kidney transplant. (Reproduced with permission, from Dharnidharka VR, Fiorina P, Harmon WE. Kidney transplantation in children. *N Engl J Med.* 2014; 371(6):550–558.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Outcomes

Overall, both graft and patient survival rates have improved since the 1980s when pediatric renal transplant became a more common operation (Figure 24-2A–C). Improvements in surgical technique, immunosuppressive therapy, and donor selection have contributed to this success. Living-donor recipients tend to fare better over time compared to cadaveric-donor recipients (Figure 24-2D).[28]

Unfortunately, despite these advances, adolescents have the worst outcomes based on graft survival and represent higher risk for retransplant. A likely reason for this is medication noncompliance. More research needs to be done into methods of education and tracking to help improve the outcomes in this group.[29]

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