Urologic Considerations in Pediatric Chronic Kidney Disease

Rebecca M. Lombel, Paul R. Brakeman, Bryan S. Sack, and Lavjay Butani

Common causes of pediatric ESRD are distinct from those seen in the adult population. In the pediatric population, the most common are congenital anomalies of the kidney and urinary tract (CAKUT), affecting approximately 30% of children with CKD. These structural anomalies often require coordinated care with the pediatric urology team to address voiding issues, bladder involvement, and the potential need for surgical intervention. For pediatric nephrologists and urologists, common CAKUT that are encountered include antenatal hydronephrosis, obstructive uropathies (eg, posterior urethral valves), and vesicoureteral reflux. As more pediatric patients with CAKUT, CKD, and ESRD transition to adult care, it is important for receiving adult nephrologists to understand the clinical presentation, natural history, and prognosis for these diagnoses. This review outlines the diagnosis and potential interventions for these conditions, including strategies to address bladder dysfunction that is often seen in children with CAKUT. A discussion of these management decisions (including surgical intervention) for CAKUT, which are quite common to pediatric nephrology and urology practices, may provide unique learning opportunities for adult nephrologists who lack familiarity with these pediatric conditions.

Key Words: Congenital kidney disease, Chronic kidney disease, Kidney abnormalities, Bladder abnormalities, Hydronephrosis

Urologic issues in pediatric patients can present at any time from before birth to late adolescence. While some pediatric urologic issues have little to no effect on kidney function, many urologic conditions can cause and contribute to progression of CKD. To optimize kidney outcomes, these conditions need to be well understood both by pediatric and adult nephrologists such that seamless care can be provided and a successful transition of care be achieved from pediatric to adult providers. This paper reviews urologic causes of pediatric CKD with the intent of providing important and practical information that adult nephrologists can use to care for the growing population of pediatric patients with complex urologic conditions and CKD who are surviving into adulthood and transitioning to adult care.

EPIDEMIOLOGIC DIFFERENCES IN CHRONIC KIDNEY DISEASE BETWEEN ADULTS AND CHILDREN

CKD is substantially less common in children than in adults. It is difficult to estimate the incidence of less severe CKD, but in the United States Renal Data System database, the Australia and New Zealand Dialysis and Transplant Registry, and the European Renal Association-European Dialysis and Transplant Association registry, the incidence of ESRD in children ranged between 7 and 11.4 per million people in 2018.[1,2] For comparison, the incidence of ESRD in the United States population, as a whole, in 2018 was 390.2 per million people.[1] Similarly, there are large differences in the causes of CKD and ESRD in pediatric patients compared with adults. The most common causes of ESRD in children are congenital anomalies of the kidney and urinary tract (CAKUT) affecting approximately 30% of children with CKD. An additional 10%-19% of pediatric patients with ESRD have cystic or congenital kidney disease.[2] This contrasts with adults for whom ESRD is associated primarily with diabetes, high blood pressure, and heart disease—with autosomal dominant polycystic kidney disease being the single most common hereditary cause of ESRD.[1]

CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT

CAKUT are disorders of kidney and urologic development that cause a wide range of anatomical and functional defects including abnormal or absent kidneys and abnormal drainage of the kidneys and/or bladder. The prevalence of CAKUT has been estimated to be between 4 and 60 per 10,000 live births, with the large variability occurring due to inconsistencies in diagnosis and possibly variation across different races and ethnicities.[3,4] Common CAKUT phenotypes include renal agenesis, hypoplasia and dysplasia, multicystic dysplastic kidneys, ectopic kidneys, and malformations of the outflow tracts including ureteropelvic junction (UPJ) obstruction, ureterovesical junction obstruction, and posterior urethral valves (PUVs). In most cases, a monogenic abnormality cannot be identified. In 20%, a monogenic mutation can be identified, with the most common mutations being in the *PAX2* and *HNF1b* genes.[4,5] In both mouse and human models of CAKUT, for a specific identified genetic defect, there can be

From the Division of Pediatric Nephrology, University of Michigan, Ann Arbor, MI (R.M.L.); Division of Pediatric Nephrology, University of California, San Francisco, San Francisco, CA (P.R.B.); Division of Pediatric Urology, University of Michigan, Ann Arbor, MI (B.S.S.); Division of Pediatric Nephrology, University of California Davis Medical Center, Sacramento, CA (L.B.)

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Rebecca M. Lombel, MD, C.S. Mott Children's Hospital, Michigan Medicine, 1540 East Hospital Drive, Room 12-250, Ann Arbor, MI 48109. E-mail: rlombel@med.umich.edu

1548-5595
https://doi.org/10.1053/j.ackd.2022.02.006

significant variability in phenotype, making it more difficult to predict outcome and provide counseling.[5,6] At present, genetic testing is not routinely performed in the clinical setting unless there are other organ systems involved, multiple family members with similar CAKUT phenotype, and/or advanced chronic kidney disease.

SINGLE FUNCTIONING KIDNEY

One of the most common outcomes of CAKUT is a solitary functioning kidney. Approximately 0.05% of children have a solitary functioning kidney.[7] A single functioning kidney (SFK) can result from unilateral renal agenesis, renal dysplasia such as a multicystic dysplastic kidney, severe vesicoureteral reflux (VUR) with episodes of pyelonephritis, a severely obstructed kidney, and/or surgical removal of a nonfunctional or poorly functioning contralateral kidney. In general, reduced kidney mass is associated with increased risk for progression of CKD and hypertension independent of the etiology of SFK; however, it is important to note that the likelihood of CKD progression and hypertension does vary somewhat depending on the etiology.[8-11] For unilateral renal agenesis, 1 systematic review identified the prevalence of hypertension as 16% and the risk of glomerular filtration rate <60 as 10%. Interestingly 32% of patients had another associated contralateral CAKUT abnormality, and having another associated CAKUT abnormality was associated with an increased risk of progression.[7] Other factors that contribute to increased risk of progression of CKD in patients with SFK are kidney size, acute kidney injury events, prematurity, presence of hyperfiltration, and genetic risk factors.[10-13] Pediatric patients with SFK kidney are counseled to avoid nephrotoxic medications and to seek early evaluation for significant dehydration events to avoid acute kidney injury episodes that can lead to worsening CKD. In addition, patients with SFK should be monitored routinely with the frequency of monitoring depending on the presence or absence of associated CAKUT, hypertension, albuminuria, and abnormal glomerular filtration rate.[10,14,15] One monitoring strategy is shown in Table 1 from Westland and colleagues.[10]

CLINICAL SUMMARY

- Epidemiology of CKD and ESRD in pediatric patients is different than that in the adult population.
- Approximately 30% of pediatric CKD is due to CAKUT.
- There is close partnership between pediatric nephrology and urology in the care of these patients with structural or anatomic anomalies.
- To provide seamless transition of care for young adult patients, adult nephrologists should be familiar with the presentation, natural history, management, and prognosis of children with CAKUT.

UROLOGIC CONDITIONS PRESENTING ANTENATALLY

Lower Urinary Tract Obstruction

Lower urinary tract obstruction (LUTO) occurs in 2-3 per 10,000 live births and is caused by a variety of different anatomic conditions that obstruct the urethra.[16,17] The most common cause of LUTO is PUV which occurs in about 60% of patients. Other causes include urethral stenosis or atresia, congenital megalourethra, anterior valves/urethral diverticulum, and obstructing ureteroceles. Approximately 30% of LUTO cases have a genetic or syndromic association such as prune belly syndrome, female cloacal anomalies, VACTERL sequence (*v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheo-*e*sophageal fistula, *r*enal anomalies, and *l*imb abnormalities), and megacystis-microcolon-intestinal hypoperistalsis syndrome.[18-21]

LUTO is usually diagnosed on second-trimester antenatal screening ultrasound and is suspected by the presence of a distended bladder. There have been multiple different staging systems proposed for LUTO that are generally based on bladder size and amniotic fluid volume as a proxy for kidney function.[22,23] LUTO has a wide spectrum of clinical outcomes from normal bladder and kidney function to neonatal death. The latter is often due to pulmonary hypoplasia caused by anhydramnios from lack of urine production or urine exiting the bladder. For severe cases of LUTO, the likelihood of surviving the perinatal period is only about 50%, and 40%-50% of survivors are left with severe CKD or ESRD.[23-25] Current fetal interventions for LUTO include vesicoamniotic shunting (VAS) and fetal cystoscopy with direct valve ablation for PUV.[25-27] There has been 1 randomized controlled trial for VAS that demonstrated improved perinatal survival, but it was unable to demonstrate improved kidney outcome.[27] A case-control trial of fetal cystoscopy with valve ablation also demonstrated improved perinatal survival and a trend toward a higher chance of normal kidney function compared with VAS.[25]

POSTERIOR URETHRAL VALVES

PUV are the most common congenital obstructive pathology of the urethra and is only seen in boys. Prenatally, PUV are suspected if there is bilateral hydroureteronephrosis and a distended bladder. Another common association is the "keyhole sign"—a dilated proximal urethra and a distended bladder.[28] Following delivery, a child who is suspected of having PUV should have an indwelling bladder catheter placed to relieve the obstruction. A voiding cystourethrogram (VCUG) is needed to confirm the diagnosis, with endoscopic fulguration of the valves being the definitive surgical procedure once the diagnosis is confirmed. Despite relief of the obstruction, patients with PUV are frequently left with some element of bladder dysfunction which requires close and ongoing involvement of pediatric urologists.

CKD is common in boys with PUV given the associated renal dysplasia, bladder dysfunction, and infection (VUR

Table 1. Anticipatory Guidance and Counseling for Primary Care Providers and Patients With a Single Functioning Kidney

Parameter	Interval
Blood pressure	Yearly
Proteinuria	Yearly once toilet-trained. If proteinuria detected by dipstick, send first AM urine sample for spot urine protein-to-creatinine ratio (normal <0.20)
Growth chart	Yearly
Kidney function	Every 3-5 y if normal GFR; more frequently as indicated by staging of CKD (if present)
Ultrasound	Every 3-5 y with last ultrasound done following adolescent growth spurt
Anticipatory guidance	Yearly; primary care provider may assist with this at the child's yearly healthy maintenance examination
Avoidance of obesity	
Healthy lifestyle habits	
Prompt recognition and treatment of UTI	
Minimize use of NSAIDs	

Abbreviations: AM, morning; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; UTI, urinary tract infection.
Pediatric nephrologists follow up children with solitary kidney through childhood and adolescence, providing anticipatory guidance and counseling. Modifiable risk factors are discussed and monitored. On intervening years between nephrology visits, primary care providers can monitor for development of hypertension and proteinuria at a child's yearly health maintenance evaluation. Modified from the study of Westland and colleagues.[10]

is present in half or one-third of patients).[29] In 2 studies with a median follow-up of approximately 7 years, 15%-20% of patients with PUV progressed to ESRD.[29,30] In severe neonatal presentations, infants may require dialysis in the first few days of life. Pediatric nephrologists follow up infants with PUV closely in the first 1-2 years of life. As a consequence of the associated renal dysplasia and dysfunction, these children are at risk for developing polyuria; electrolyte abnormalities including hyponatremia, hyperkalemia, and metabolic acidosis.[31] During this period of life, management focuses significantly on nutrition and growth in addition to monitoring for other comorbidities of CKD including mineral bone disease.

ANTENATAL HYDRONEPHROSIS

Antenatal hydronephrosis (AH) is the most common antenatal urologic issue with up to 2% of all fetuses affected at some point during gestation.[32,33] The most common clinically significant causes of AH in descending order of frequency are UPJ obstruction, VUR, and PUV.[32,34] There are various grading systems for hydronephrosis. Historically, classification was done by qualitative description (mild, moderate, and severe), which was subjective or by quantitative measurement based on the anterior-posterior dimension of the renal pelvis.[35] The Society of Fetal Urology system was developed in 1993 and classifies AH by increasing dilatation of the renal pelvis and calyceal systems from grade I to IV.[36] Drawbacks of this classification system are that it is operator-dependent and subjective. In 2014, a consensus grading system was endorsed by multiple stakeholder societies and is known as the upper tract dilation (UTD) classification.[32] This grading system includes both grading for antenatal (UTD A1 and A2-A3) and postnatal hydronephrosis (UTD P1, P2, and P3). The UTD classification includes more specific kidney parenchymal changes (eg, echotexture and thickness) and involvement of the ureters/bladder.[32] Management is dependent upon the UTD classification (Table 2).

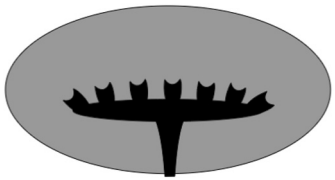
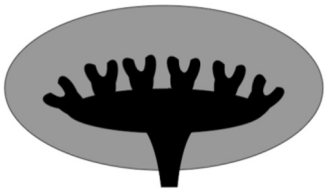
About 60% of patients with the most severe degree of AH will have a significant urologic pathology (UPJ obstruction or PUV).[34] The severity of hydronephrosis, its laterality, and associated kidney or bladder anomalies guide decision-making for further evaluation. For the highest risk category of AH (A2-A3), early VCUG is recommended with further imaging such as diuretic renal scintigraphy at the discretion of the clinician.[32] The outcome of AH is highly varied, with mild AH (UTD A1 and UTD P1) usually resolving with no kidney consequence and bilateral severe AH causing significant CKD in some patients. Ultrasound remains the imaging modality of choice to follow up patients with hydronephrosis. This modality is noninvasive and allows for monitoring parameters over time including kidney growth and changes in degree of dilation.

VCUG is the diagnostic test of choice for diagnosing VUR and PUV. During this study, contrast material is instilled into the bladder, and multiple images are obtained fluoroscopically.[37] VUR is documented if contrast material has retrograde flow into the ureters. PUV has a characteristic appearance at the posterior urethra. If there is concern for an obstructive process (other than PUV), a nuclear medicine functional renal scan (also called diuretic renal scintigraphy) is indicated. The most common radioisotope used is technetium-99m-mercaptoacetyltriglycine since it is taken up by the cortex, filtered across the glomerular basement membrane, and excreted. This study is typically performed after 2-3 months from birth as kidney immaturity in the neonate affects the handling of the radioisotope.[38] The cortical uptake phase provides quantitative information on split kidney function; this may inform surgical planning. The excretion phase is augmented by furosemide and measures the "washout." Typically, if the washout time is more than 20 minutes, the pattern is consistent with obstruction.[38,39] Technetium-99m-diethylenetriaminepentaacetic acid can also be used to evaluate function and drainage; however, technetium-99m-dimercaptosuccinic acid can only be used to assess renal parenchymal anatomy and evaluate differential renal function because it is not excreted.[40]

VESICOURETERAL REFLUX

Primary VUR is a relatively common urologic finding in children. The presentation can vary from an asymptomatic diagnosis made at the time of evaluation for AH or following a febrile urinary tract infection (UTI). The prevalence of VUR is variable depending on presentation—up to 15% for those with AH and upwards of 45% for those presenting with febrile UTIs.[41,42] Primary reflux is attributed to insufficient closure of the ureterovesical junction,

Table 2. In 2014, a Multidisciplinary Consensus Was Published on Classification of Postnatal Urinary Tract Dilation (UTD)

	UTD P1	UTD P2	UTD P3
Ultrasound findings			
APRPD	10-15 mm	>15 mm	>15 mm
Calyceal dilation	Central	Peripheral	Peripheral
Parenchymal thickness	Normal	Normal	Abnormal
Parenchymal appearance	Normal	Normal	Abnormal
Ureters	Normal	Abnormal	Abnormal
Bladder	Normal	Normal	Abnormal
Example			
Risk	Low	Intermediate	High
Management			
Follow-up US	1-6 mo	3-6 mo	1 mo
VCUG	Consider	Consider	Recommended
Antibiotics	Consider	Consider	Recommended
Functional scan	Not recommended	Consider	Consider

Abbreviations: UTI, urinary tract infection; VCUG, voiding cystourethrogram.
The UTI classification system is based on 6 categories of ultrasound findings. For postnatal presentations, the characteristics are listed above. The stratification is based on the most concerning finding, ie, even if the anterior-posterior renal pelvis diameter (APRPD) is <15 mm, the presence of bladder abnormalities designates UTD 3 classification. Based on the UTD classification, findings are risk-stratified, and this information management as indicated. Modified from the study of Nguyen and colleagues.[32]

with the submucosal tunnel being too short to allow for adequate closing. Secondary reflux is associated with functional or anatomic bladder issues. There are 5 grades of VUR with increasing severity from I to V.

Patients with VUR are at risk for repeated episodes of pyelonephritis, and there are data to suggest that recurrent pyelonephritis is associated with kidney scarring.[43,44] Kidney scarring can cause both CKD and hypertension. The risk of scarring increases with the severity of reflux. To reduce the risk of recurrent pyelonephritis, most pediatric nephrologists and pediatric urologists will start antibiotic prophylaxis for children with VUR grades III-V based on data from the Randomized Intervention for Children with Vesicoureteral Reflux trial.[45] In this randomized, multicenter trial, antibiotic prophylaxis reduced the risk of recurrent UTI by 50% although there was no statistically significant difference in kidney scarring.[45] Another factor that has gained increasing recognition as a contributing factor to scar formation is the presence of genetic polymorphisms. Specific genetic polymorphisms or their various combinations modulate the inflammatory response after pyelonephritis.[46] At present, these do not have routine use in clinical practice but may in the future.

Primary VUR resolves spontaneously in a large proportion of patients,[47,48] but those with high-grade reflux and/or recurrent episodes of pyelonephritis will require evaluation for bladder dysfunction and may ultimately require surgical intervention. This can include ureteral reimplantation (tunneling a ureteral segment through the detrusor to create a longer submucosal tunnel) and endoscopic correction by injecting a periureteral bulking agent (Deflux procedure).[49]

UPJ OBSTRUCTION

UPJ obstruction is the most common anatomic cause of severe AH. The incidence of UPJ obstruction is 1 in 500 live births.[50] Most commonly, UPJ obstructions in children are due to intrinsic stenosis instead of external compression, as is more commonly the case in adults. There are no randomized controlled trials to guide management in pediatric patients with asymptomatic UPJ obstruction. The decision is much more clear-cut in school-age patients who develop symptoms (unilateral flank pain and hydronephrosis at the time of pain). For asymptomatic patients or those that cannot communicate their symptoms (ie, babies, cognitively delayed patients), the goals of care are to use our current imaging modalities to predict need for surgical intervention in order to preserve kidney function. Deciding when to intervene with pyeloplasty can be difficult as many patients can have stable kidney function and stable or improving hydronephrosis in the long term.[51,52] Finally, there are limited data on long-term outcomes of children with prenatally diagnosed UPJ obstruction. In 1 series of 49 children, all who underwent pyeloplasty had improved relative kidney function, and all but 2 had improvement in hydronephrosis on imaging.[53]

EVALUATING BLADDER ABNORMALITIES

For pediatric patients with urologic issues, the pediatric urology team plays a major role in evaluating bladder abnormalities and addressing these. Bladder dysfunction can arise from any issue that disrupts the normal voiding process. These can include issues with bladder capacity or compliance, or abnormal innervation to and function of the detrusor muscle and urethral sphincter complex. The main categories of dysfunction are anatomic, neurogenic, and functional.[54]

Estimated bladder capacity (in mL) is based on the age of the patient using the following equation: (age of the patient in years + 2) × 30 mL (>1 year of age).[55] During the filling phase, there must be active detrusor muscle relaxation with concomitant bladder neck and external urinary sphincter tone to ensure continence. Normal bladders have high compliance and can store urine at low pressures. Bladder pressures that exceed and persist above 40 cm H_2O during filling are associated with increased risk of kidney injury.[56,57] The etiology of this injury could be secondary to persistent upper tract backpressure and/or retrograde passage of bacteria from the bladder resulting in infection. During the voiding phase, there is coordinated contraction of the detrusor muscle and relaxation of the bladder neck and external urethral sphincter to allow for urine passage.

First and foremost, a detailed voiding and stooling history is vital to assess bladder function. For children who are toilet-trained, having families keep a voiding log is helpful to understand voiding patterns at home. A significant contributing factor to voiding dysfunction is constipation, and this needs to be aggressively managed for patients with bladder dysfunction.

Ultrasound is the most common imaging study to evaluate bladder dysfunction. In addition to providing anatomic detail, images performed before and after the patient voids can provide estimates of bladder capacity and postvoid residual, a marker of bladder emptying. A thickened bladder wall is suggestive of an anatomic or functional abnormality; however, this is highly dependent on bladder volume at the time of measurement. A VCUG, in addition to diagnosing VUR and PUV, also provides information on the bladder size, configuration, capacity, and ability to empty.

Measurements of urinary flow (uroflowmetry) can provide data on bladder emptying. During voiding, a urinary flow curve is produced and, if abnormal, can point toward specific pathologic processes. Also, perineal electromyography can be used to understand urethral sphincter activity during the micturition cycle.

Urodynamic studies are more invasive tests that involve placing urethral and rectal catheters to detect abnormalities during both filling and voiding phases. Information obtained includes compliance, filling and voiding bladder pressures, bladder capacity, postvoid residual, and urine flow rates. Fluoroscopy can be performed concomitantly to understand bladder shape and presence of VUR.

NEUROGENIC BLADDER

In addition to children with primary kidney or urologic conditions, patients with neurogenic bladder dysfunction

(eg, secondary to spina bifida, spinal cord injury, infection, or spinal tumors) require close surveillance and timely management by pediatric nephrologists and pediatric urologists. Up to 25%-50% will develop CKD,[58] and those that develop ESRD requiring kidney replacement do so at a much younger age.[59] Unfortunately, CKD in this patient population has an independent association with increased mortality.[60] For these reasons, close monitoring for kidney dysfunction (eg, blood pressure measurement, urinalyses, and serum studies) is included in neurogenic bladder guidelines, like the one designed for the urologic care of people with spina bifida.[61]

MANAGING BLADDER DYSFUNCTION

For patients who are toilet-trained and neurologically intact, urotherapy with timed voids with double voids is recommended to maintain low bladder volumes and achieve complete bladder emptying. Recommendations provided to families include voiding every 2-3 hours during the day and attempting an additional void after a first void. To protect the upper urinary tract, the goal is to maintain low bladder pressures and ensure complete bladder emptying. As mentioned above, addressing constipation is an important part of management given the contribution of bowel dysfunction to bladder dysfunction. For patients who fail conservative measures and those that empty to completion, anticholinergic agents can be added to decrease nonvoiding contractions during filling and improve compliance by decreasing detrusor tone.[62] Oxybutynin is the most commonly used anticholinergic medication.

Issues with incomplete bladder emptying may require the use of clean intermittent catheterization (CIC). CIC is an effective way to completely empty the bladder and avoid consequent risk for symptomatic infection and, most importantly, protect the upper urinary tract from a sustained high-pressure system.[63] Due to the anatomy, however, CIC can be difficult particularly in boys with PUV and those with a sensate urethra. If bladder decompression is necessary to preserve the upper tract and kidney function, surgical options may be considered. Other indications for surgical management include patients who have progressive kidney damage despite maximal conservative management and those with extremely noncompliant bladders. Most surgical procedures are designed to enable low-pressure bladder storage and complete emptying. It is worth noting that those who perform CIC are likely to develop chronic bacterial colonization of the bladder without symptoms of infection. This is called asymptomatic bacteriuria and should not be treated with antibiotics in the absence of symptoms or a urinalysis suggestive of an infection such as the new presence of, or increase in, pyuria and signs of inflammation (such as hematuria and proteinuria).

A vesicostomy is an incontinent diversion of the bladder to the abdominal wall. It is continuously draining and is best suited for patients who are not toilet-trained. A vesicostomy allows for continuous decompression of the bladder, and as such, low bladder pressures. A vesicostomy is typically performed in infants or toddlers, but at some point, social continence may become important for these children as they grow. Creation of a urinary diversion using a continent catheterizable channel between the bladder and the abdominal wall allows for bladder emptying away from the patient's urethra. This is ideal for patients with abnormal urethral anatomy or mobility limitations (eg, wheelchair-bound patients). The Mitrofanoff and Yang-Monti channels use appendix (appendicovesicostomy) or small intestine (continent ileovesicostomy), respectively, to surgically create these continent channels. The channel is nonrefluxing so when a catheter is not in the channel, the patient remains continent. Diagrams of these urologic surgical procedures are in Figure 1.[64,65]

Patients with PUV and other CAKUT often have concomitant renal dysplasia and, consequently, are frequently polyuric. As such, even a frequent catheterization regimen is insufficient to keep the urinary bladder volumes low enough to protect the upper tract. Initial conservative management in these patients can include overnight continuous drainage of the bladder. Alternately, a child's bladder capacity may be very small, resulting in socially unacceptable incontinence and/or prolonged high pressures resulting in kidney injury. In these circumstances, intravesically injected botulinum toxin or an augmentation cystoplasty may be necessary. For botulinum toxin injection, up to 300 units are injected into multiple locations in the bladder wall endoscopically. This requires repeat injection as the duration of action varies—dependent on the etiology of underlying bladder dysfunction—but on average, symptoms return 6 months after injection.[66] Bladder augmentation involves using a portion of the gastrointestinal tract (most commonly the ileum) to enlarge the capacity of the native bladder. Because the gastrointestinal portion does not have the innervation of the native bladder, a patient who requires bladder augmentation is committed to lifelong intermittent catheterization.

Other less-frequent surgical interventions for bladder dysfunction include diversion of urine flow from the bladder such as cutaneous pyelostomy. This procedure involves attaching the renal pelvis directly to the abdominal wall and cutaneous ureterostomies, which decompresses the upper tract by attaching the ureters to the abdominal wall. These are used very selectively in patients with bilateral or solitary kidney UTD where bladder drainage does not result in improvement in hydronephrosis and where kidney compromise is of great concern.

Peritransplant Urologic Management of CAKUT

Given that CAKUT are the most common cause of ESRD in pediatric patients,[67] the issue of pretransplant (Tx) urologic assessment in pediatric recipients is of paramount importance. The question of whether and how best to assess bladder anatomy and function has also been debated in children who present with ESRD of unclear etiology. A retrospective study explored the utility of routine pre-Tx VCUG and ultrasound in children referred for Tx, separated by etiology of ESRD.[68] On routine screening, in the cohort with nonurologic causes of ESRD, VUR was noted in only 1 patient (2.4%). None of the patients in this group underwent any pre-Tx

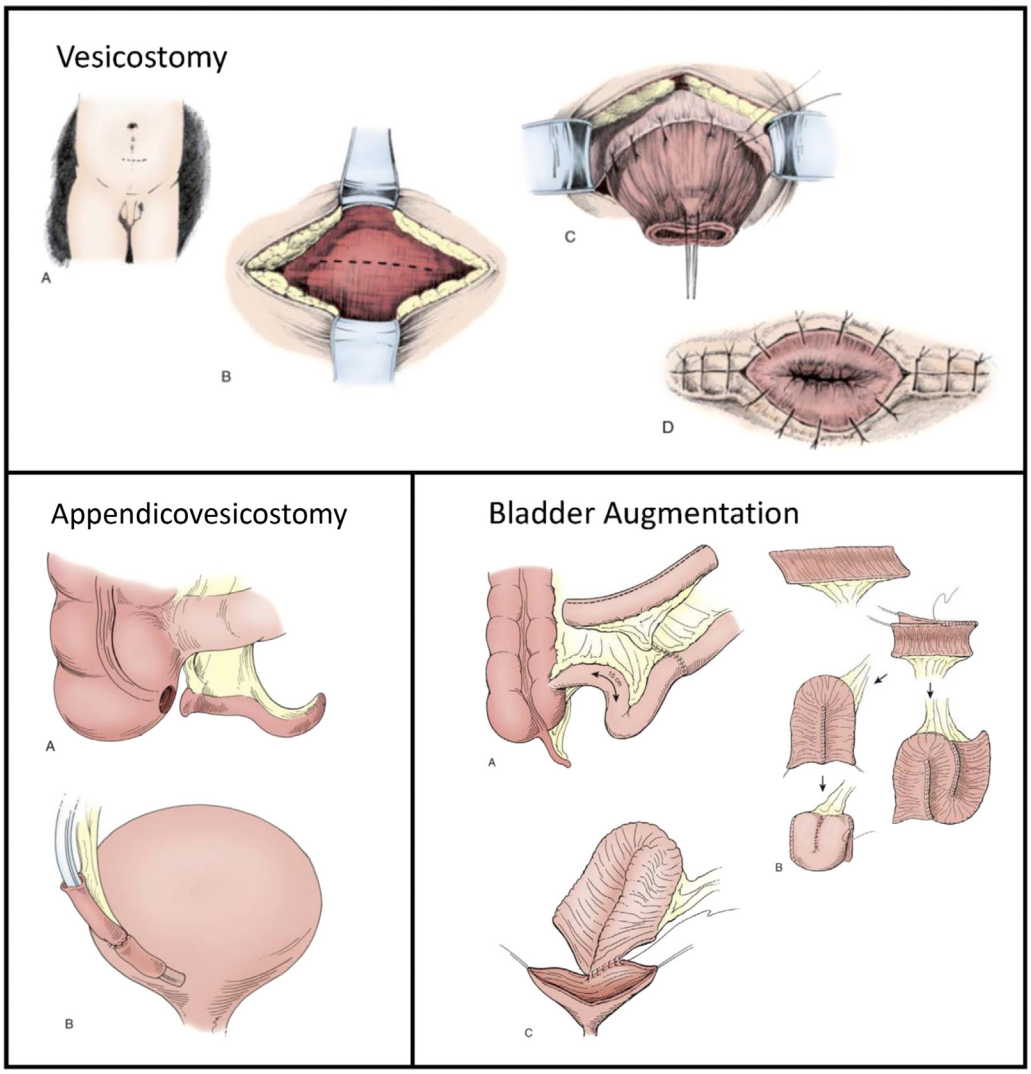


Figure 1. Urologic surgeries to address bladder issues. Panel 1: Vesicostomy. (A) Vesicostomy is placed between the umbilicus and pubis that corresponds to the upper limit of the filled bladder. (B) The bladder is exposed after making an incision through the rectus fascia. (C) The bladder is opened at the dome and delivered out of the body and secured to the rectus fascia. (D) The bladder opening is sutured to the skin. Panel 2: Appendicovesicostomy. (A) The appendix is harvested off of the cecum. (B) The distal appendix is tunneled into the bladder to provide continence after the end is amputated. The proximal end of the appendix is brought to the umbilicus or right lower quadrant as a catheterizable stoma. Panel 3: Bladder augmentation. (A) A segment of ileum at least 15 cm from the ileocecal valve to preserve vitamin B12 absorption is removed. (B) The ileal segment is opened and can be fashioned in 1 of multiple configurations. (C) The reconfigured ileal segment is anastomosed to the native bladder. (Reprinted from Campbell-Walsh-Wein Urology, 12th Edition, Copyright 2020,[64,65] with permission from Elsevier).

surgical interventions, even when found to have abnormalities on VCUG, and the predictive value of pre-Tx urologic studies for post-Tx interventions in this group was 0%. As can be expected, the incidence of abnormalities and the need for pre- and post-Tx surgical interventions were higher in the cohort with known urologic causes of ESRD although the predictive value of routine pre-Tx urologic studies for post-Tx interventions in this group was very low. Based on this study and others, there appears to be little value in obtaining routine pre-Tx urologic studies (VCUG and urodynamic studies) in children with nonurologic causes of ESRD.

For those with a known urologic etiology of ESRD, prior routine care has most likely included imaging. For those patients with unclear etiology of ESRD and no previous renal imaging, renal imaging with ultrasound or some other imaging modality is indicated, and a VCUG may be indicated if history or physical exam suggests an issue with bladder function or anatomy. Abnormalities, especially of bladder function (such as a high-pressure bladder with low compliance or an unstable bladder with incomplete emptying) must be corrected before Tx, to minimize the risk of UTIs and optimize long-term graft function and survival. Whether intervention is necessary in all children

with VUR before Tx remains controversial. In our opinion, only children with pre-Tx VUR diagnosed in the context of recurrent UTIs may warrant consideration for interventions. In such instances, a nephrectomy should be considered on the side where VUR is present, either before Tx or at the same time as the Tx.

For dysfunctional bladders—typically seen in children in the context of PUV, spina bifida, and a nonneurogenic neurogenic bladder—a decision regarding the nature and timing of the optimal intervention is essential before Tx proceeds. For very unstable and high-pressure systems, where the risk of UTIs and transmission of pressure upstream to the Tx kidney are high, pre-Tx interventions are necessary as discussed above. For these patients, input from their pediatric urologist is essential to provide clearance.

Infections are a common cause of morbidity and mortality in children after Tx, with UTIs being the leading infectious complication requiring hospitalization.[69] A predisposing factor to UTIs in this population is the presence of VUR into the Tx ureter and kidney. The incidence of Tx VUR varies based on the type of ureteral reimplant and is much lower when an antirefluxing reimplant (ie, a tunneled ureteroneocystostomy) is performed into the recipient bladder.[70] However, even when an antirefluxing reimplant is performed, VUR remains common (12%-20% incidence).[70,71] Children with recurrent UTIs after Tx should be maintained on antimicrobial prophylaxis, and a VCUG should be considered to look for VUR. If VUR into the Tx ureter/kidney is detected, options to reduce recurrent infections include long-term antimicrobial prophylaxis[72] (recognizing the associated risk of selecting resistant organisms) and correcting any obvious predisposing factors such as incomplete bladder emptying. For patients with Tx VUR, surgical ureteric reimplantation should be considered if patients have breakthrough UTIs on prophylaxis or are not suitable candidates for long-term prophylaxis. While endoscopic subureteric injections of dextranomer/hyaluronic acid may be considered, success rates in correcting post-Tx VUR have been low, and their use has been associated with many complications.[71,73]

POSTTRANSPLANT OUTCOMES

When comparing outcomes in children with and without urologic causes of ESRD, most studies have shown comparable graft or patient survival in children with CAKUT,[74] in spite of higher risk of post-Tx UTIs, even in the presence of severe bladder dysfunction.[75,76] Therefore, for pediatric patients with advanced CKD and ESRD due to CAKUT, Tx is the goal for renal replacement therapy because of the better long-term survival, growth and development, and quality of life after Tx than remaining on maintenance dialysis.[35,77,78]

CONCLUSIONS

As we have described, the pediatric urologic conditions that contribute to CKD are widely varied with differential impacts on adult kidney health. While many urologic issues in pediatric patients that contribute to CKD require ongoing urologic monitoring and treatment, some conditions such as VUR can contribute to significant childhood CKD and then improve to the point of requiring no ongoing urologic interventions. Pediatric patients with CKD and chronic bladder dysfunction are a unique population and require intensive ongoing urologic monitoring and treatment to attain the best kidney outcome in adulthood. Unfortunately, for many of these patients, even optimal care cannot forestall progression of CKD to ESRD. Kidney transplant remains the optimal treatment for ESRD, and many of the pediatric urologic issues we have described continue to affect kidney outcomes after kidney Tx. Ultimately, achieving the best clinical outcome for pediatric and adult patients with CKD and urologic issues requires multidisciplinary care with collaboration between nephrology and urology providers.

REFERENCES

1. System USRD. *2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
2. Harada R, Hamasaki Y, Okuda Y, Hamada R, Ishikura K. Epidemiology of pediatric chronic kidney disease/kidney failure: learning from registries and cohort studies. *Pediatr Nephrol.* 2022;37(6):1215-1229.
3. Tain YL, Luh H, Lin CY, Hsu CN. Incidence and risks of congenital anomalies of kidney and urinary tract in Newborns: a population-based case-control study in Taiwan. *Medicine (Baltimore).* 2016;95(5):e2659.
4. Murugapoopathy V, Gupta IR. A primer on congenital anomalies of the kidneys and urinary tracts (CAKUT). *Clin J Am Soc Nephrol.* 2020;15(5):723-731.
5. Kohl S, Habbig S, Weber LT, Liebau MC. Molecular causes of congenital anomalies of the kidney and urinary tract (CAKUT). *Mol Cell Pediatr.* 2021;8(1):2.
6. Westland R, Renkema KY, Knoers N. Clinical Integration of Genome diagnostics for congenital anomalies of the kidney and urinary tract. *Clin J Am Soc Nephrol.* 2020;16(1):128-137.
7. Westland R, Schreuder MF, Ket JC, van Wijk JA. Unilateral renal agenesis: a systematic review on associated anomalies and renal injury. *Nephrol Dial Transpl.* 2013;28(7):1844-1855.
8. Lankadeva YR, Singh RR, Tare M, Moritz KM, Denton KM. Loss of a kidney during fetal life: long-term consequences and lessons learned. *Am J Physiol Ren Physiol.* 2014;306(8):F791-F800.
9. Marzuillo P, Guarino S, Grandone A, et al. Outcomes of a cohort of prenatally diagnosed and early Enrolled patients with congenital solitary functioning kidney. *J Urol.* 2017;198(5):1153-1158.
10. Westland R, Schreuder MF, van Goudoever JB, Sanna-Cherchi S, van Wijk JA. Clinical implications of the solitary functioning kidney. *Clin J Am Soc Nephrol.* 2014;9(5):978-986.
11. Groen In't Woud S, van der Zanden LFM, Schreuder MF. Risk stratification for children with a solitary functioning kidney. *Pediatr Nephrol.* 2021;36:3499-3503.
12. Urisarri A, Gil M, Mandiá N, et al. Retrospective study to identify risk factors for chronic kidney disease in children with congenital solitary functioning kidney detected by neonatal renal ultrasound screening. *Medicine (Baltimore).* 2018;97(32):e11819.
13. La Scola C, Ammenti A, Puccio G, et al. Congenital solitary kidney in children: size Matters. *J Urol.* 2016;196(4):1250-1256.
14. Corbani V, Ghiggeri GM, Sanna-Cherchi S. 'Congenital solitary functioning kidneys: which ones warrant follow-up into adult life?'. *Nephrol Dial Transpl.* 2011;26(5):1458-1460.
15. Westland R, Schreuder MF, Bökenkamp A, Spreeuwenberg MD, van Wijk JA. Renal injury in children with a solitary functioning

kidney–the KIMONO study. *Nephrol Dial Transpl.* 2011;26(5):1533-1541.
16. Malin G, Tonks AM, Morris RK, Gardosi J, Kilby MD. Congenital lower urinary tract obstruction: a population-based epidemiological study. *Bjog.* 2012;119(12):1455-1464.
17. Anumba DO, Scott JE, Plant ND, Robson SC. Diagnosis and outcome of fetal lower urinary tract obstruction in the northern region of England. *Prenat Diagn.* 2005;25(1):7-13.
18. Clayton DB, Brock JW 3rd. Lower urinary tract obstruction in the fetus and neonate. *Clin Perinatol.* 2014;41(3):643-659.
19. Taghavi K, Sharpe C, Stringer MD. Fetal megacystis: a systematic review. *J Pediatr Urol.* 2017;13(1):7-15.
20. Fontanella F, Maggio L, Verheij J, et al. Fetal megacystis: a lot more than LUTO. *Ultrasound Obstet Gynecol.* 2019;53(6):779-787.
21. Reinberg Y, Chelimsky G, Gonzalez R. Urethral atresia and the prune belly syndrome. Report of 6 cases. *Br J Urol.* 1993;72(1):112-114.
22. Ruano R, Dunn T, Braun MC, Angelo JR, Safdar A. Lower urinary tract obstruction: fetal intervention based on prenatal staging. *Pediatr Nephrol.* 2017;32(10):1871-1878.
23. Fontanella F, van Scheltema PNA, Duin L, et al. Antenatal staging of congenital lower urinary tract obstruction. *Ultrasound Obstet Gynecol.* 2019;53(4):520-524.
24. Sananes N, Cruz-Martinez R, Favre R, et al. Two-year outcomes after diagnostic and therapeutic fetal cystoscopy for lower urinary tract obstruction. *Prenat Diagn.* 2016;36(4):297-303.
25. Ruano R, Sananes N, Sangi-Haghpeykar H, et al. Fetal intervention for severe lower urinary tract obstruction: a multicenter case-control study comparing fetal cystoscopy with vesicoamniotic shunting. *Ultrasound Obstet Gynecol.* 2015;45(4):452-458.
26. Nassr AA, Shazly SAM, Abdelmagied AM, et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2017;49(6):696-703.
27. Morris RK, Malin GL, Quinlan-Jones E, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet.* 2013;382(9903):1496-1506.
28. Chitrit Y, Bourdon M, Korb D, et al. Posterior urethral valves and vesicoureteral reflux: can prenatal ultrasonography distinguish between these two conditions in male fetuses? *Prenat Diagn.* 2016;36(9):831-837.
29. DeFoor W, Clark C, Jackson E, Reddy P, Minevich E, Sheldon C. Risk factors for end stage renal disease in children with posterior urethral valves. *J Urol.* 2008;180(4 Suppl):1705-1708. discussion 1708.
30. Sarhan O, Zaccaria I, Macher MA, et al. Long-term outcome of prenatally detected posterior urethral valves: single center study of 65 cases managed by primary valve ablation. *J Urol.* 2008;179(1):307-312. discussion 312-303.
31. Misurac J. Chronic kidney disease in the neonate: etiologies, management, and outcomes. *Semin Fetal Neonatal Med.* 2017;22(2):98-103.
32. Nguyen HT, Benson CB, Bromley B, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system). *J Pediatr Urol.* 2014;10(6):982-998.
33. Livera LN, Brookfield DS, Egginton JA, Hawnaur JM. Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme. *Bmj.* 1989;298(6685):1421-1423.
34. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. *Pediatrics.* 2006;118(2):586-593.
35. Fennell EB, Fennell RS, Mings E, Morris MK. The effects of various modes of therapy for end stage renal disease on cognitive performance in a pediatric population–a preliminary report. *Int J Pediatr Nephrol.* 1986;7(2):107-112.
36. Nguyen HT, Herndon CD, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol.* 2010;6(3):212-231.
37. Frimberger D, Mercado-Deane MG. Establishing a Standard Protocol for the voiding Cystourethrography. *Pediatrics.* 2016;138(5) https://doi.org/10.1542/peds.2016-2590
38. Taylor A Jr, Clark S, Ball T. Comparison of Tc-99m MAG3 and Tc-99m DTPA scintigraphy in neonates. *Clin Nucl Med.* 1994;19(7):575-580.
39. Gordon I, Dhillon HK, Gatanash H, Peters AM. Antenatal diagnosis of pelvic hydronephrosis: assessment of renal function and drainage as a guide to management. *J Nucl Med.* 1991;32(9):1649-1654.
40. Viteri B, Calle-Toro JS, Furth S, Darge K, Hartung EA, Otero H. State-of-the-Art renal imaging in children. *Pediatrics.* 2020;145(2) https://doi.org/10.1542/peds.2019-0829
41. van Eerde AM, Meutgeert MH, de Jong TP, Giltay JC. Vesico-ureteral reflux in children with prenatally detected hydronephrosis: a systematic review. *Ultrasound Obstet Gynecol.* 2007;29(4):463-469.
42. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med.* 2003;348(3):195-202.
43. Mattoo TK, Chesney RW, Greenfield SP, et al. Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. *Clin J Am Soc Nephrol.* 2016;11(1):54-61.
44. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics.* 2010;126(6):1084-1091.
45. Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med.* 2014;370(25):2367-2376.
46. Zaffanello M, Tardivo S, Cataldi L, Fanos V, Biban P, Malerba G. Genetic susceptibility to renal scar formation after urinary tract infection: a systematic review and meta-analysis of candidate gene polymorphisms. *Pediatr Nephrol.* 2011;26(7):1017-1029.
47. Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol.* 1997;157(5):1846-1851.
48. Estrada CR Jr, Passerotti CC, Graham DA, et al. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol.* 2009;182(4):1535-1541.
49. Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev.* 2019;2(2):Cd001532. https://doi.org/10.1002/14651858.CD001532.pub5
50. Liang CC, Cheng PJ, Lin CJ, Chen HW, Chao AS, Chang SD. Outcome of prenatally diagnosed fetal hydronephrosis. *J Reprod Med.* 2002;47(1):27-32.
51. Arena S, Chimenz R, Antonelli E, et al. A long-term follow-up in conservative management of unilateral ureteropelvic junction obstruction with poor drainage and good renal function. *Eur J Pediatr.* 2018;177(12):1761-1765.
52. Heinlen JE, Manatt CS, Bright BC, Kropp BP, Campbell JB, Frimberger D. Operative versus nonoperative management of ureteropelvic junction obstruction in children. *Urology.* 2009;73(3):521-525. discussion 525.
53. Chertin B, Pollack A, Koulikov D, et al. Does renal function remain stable after puberty in children with prenatal hydronephrosis and improved renal function after pyeloplasty? *J Urol.* 2009;182(4 Suppl):1845-1848.
54. Bauer SB. Special considerations of the overactive bladder in children. *Urology.* 2002;60(5 Suppl 1):43-48. discussion 49.
55. Koff SA. Estimating bladder capacity in children. *Urology.* 1983;21(3):248.
56. Houle AM, Gilmour RF, Churchill BM, Gaumond M, Bissonnette B. What volume can a child normally store in the bladder at a safe pressure? *J Urol.* 1993;149(3):561-564.

57. McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. *J Urol.* 1981;126(2):205-209.
58. Malakounides G, Lee F, Murphy F, Boddy SA. Single centre experience: long term outcomes in spina bifida patients. *J Pediatr Urol.* 2013;9(5):585-589.
59. Streur CS, Moloci NM, Kraft KH, Sarma AV, Shahinian VB, Hollingsworth JM. Trends in procedures to Initiate renal replacement therapy among people living with spina bifida. *J Urol.* 2021;205(1):250-256.
60. Greenwell MW, Mangold TM, Tolley EA, Wall BM. Kidney disease as a predictor of mortality in chronic spinal cord injury. *Am J Kidney Dis.* 2007;49(3):383-393.
61. Joseph DB, Baum MA, Tanaka ST, et al. Urologic guidelines for the care and management of people with spina bifida. *J Pediatr Rehabil Med.* 2020;13(4):479-489.
62. Nijman RJ. Role of antimuscarinics in the treatment of nonneurogenic daytime urinary incontinence in children. *Urology.* 2004;63(3 Suppl 1):45-50.
63. Pohl HG, Bauer SB, Borer JG, et al. The outcome of voiding dysfunction managed with clean intermittent catheterization in neurologically and anatomically normal children. *BJU Int.* 2002;89(9):923-927.
64. Thomas JCCD, Adams MC. Lower urinary tract Reconstruction in children. In: Partin AWPC, Kavoussi LR, Dmochowski RR, Wein AJ, eds. *Campbell-Walsh Urology.* 12 ed. New York, NY: Elsevier; 2020:680-713.
65. Shukla ARSA. Posterior urethral valves. In: Partin AWPC, Kavoussi LR, Dmochowski RR, Wein AJ, eds. *Campbell-Walsh Urology.* 12 ed. New York, NY: Elsevier; 2020:602-623.
66. Gamé X, Mouracade P, Chartier-Kastler E, et al. Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *J Pediatr Urol.* 2009;5(3):156-164.
67. Chua A, Cramer C, Moudgil A, et al. Kidney transplant practice patterns and outcome benchmarks over 30 years: the 2018 report of the NAPRTCS. *Pediatr Transpl.* 2019;23(8):e13597.
68. Kim JK, Lorenzo AJ, Raveendran L, et al. Utility of pre-transplant lower urinary tract investigation in pediatric renal transplant population after referral: a 16-year institutional experience. *Pediatr Transpl.* 2021;25(4):e14006.
69. Hogan J, Pietrement C, Sellier-Leclerc AL, et al. Infection-related hospitalizations after kidney transplantation in children: incidence, risk factors, and cost. *Pediatr Nephrol.* 2017;32(12):2331-2341.
70. Hanevold CD, Kaiser BA, Palmer J, Polinsky MS, Baluarte HJ. Vesicoureteral reflux and urinary tract infections in renal transplant recipients. *Am J Dis Child.* 1987;141(9):982-984.
71. Sheth KR, White JT, Stanasel I, et al. Comparing treatment modalities for transplant kidney vesicoureteral reflux in the pediatric population. *J Pediatr Urol.* 2018;14(6):554.e551-554.e556.
72. Ranchin B, Chapuis F, Dawhara M, et al. Vesicoureteral reflux after kidney transplantation in children. *Nephrol Dial Transpl.* 2000;15(11):1852-1858.
73. Wu HY, Concepcion W, Grimm PC. When does vesicoureteral reflux in pediatric kidney transplant patients need treatment? *Pediatr Transpl.* 2018;22(8):e13299.
74. Cornwell LB, Ingulli EG, Mason MD, Ewing E, Riddell JV. Renal transplants due to congenital anomalies of the kidney and urinary tract (CAKUT) have better graft survival than non-CAKUT controls: analysis of over 10,000 patients. *Urology.* 2021;154:255-262.
75. Sierralta MC, Gonzalez G, Nome C, et al. Kidney transplant in pediatric patients with severe bladder pathology. *Pediatr Transpl.* 2015;19(7):675-683.
76. Koo HP, Bunchman TE, Flynn JT, Punch JD, Schwartz AC, Bloom DA. Renal transplantation in children with severe lower urinary tract dysfunction. *J Urol.* 1999;161(1):240-245.
77. Potter DE, Najarian J, Belzer F, Holliday MA, Horns G, Salvatierra O Jr. Long-term results of renal transplantation in children. *Kidney Int.* 1991;40(4):752-756.
78. Morel P, Almond PS, Matas AJ, et al. Long-term quality of life after kidney transplantation in childhood. *Transplantation.* 1991;52(1):47-53.