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Cystic Diseases of the Pediatric Kidney

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to differentiate among various etiologies of cysts in pediatric kidneys, and assess and counsel the family and patient on the risk of end-stage renal disease and malignancy.

This AUA Update aligns with the American Board of Urology Module on Core/General Urology. Additional information on this topic can be found in the AUA Core Curriculum section on Pediatric Urology.

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INTRODUCTION

Pediatric renal cystic diseases encompass a wide spectrum of sporadic or genetically determined congenital or acquired conditions that include cysts in 1 or both kidneys. These cysts are fluid-filled cavities derived primarily from tubules and enclosed by a layer of epithelial cells. They are uncommon in children and are often incidental findings on radiographic imaging.

The basic process of renal cyst formation involves 3 primary steps: proliferation of epithelial cells within the renal tubules, accumulation of fluid within this tubule segment, and altered arrangement and maintenance of the extracellular matrix. Recently, growing scientific evidence points to several genes defective in the signaling pathway within the primary cilium that result in cyst formation. Primary cilia are nonmotile sensory organelles that monitor the extracellular environment and modulate the proliferation and differentiation of tubular epithelium. Ciliopathies may show an isolated renal phenotype but may also result in extrarenal manifestations since primary cilia are present in nearly every major organ.

The classification of pediatric renal cystic disease is largely determined by whether the disease is heritable or nonheritable. Heritable diseases with renal cyst formation include autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), juvenile nephronophthisis-medullary cystic disease complex, von Hippel-Lindau disease (VHL), tuberous sclerosis complex and Bardet-Biedl syndrome. Table 1 illustrates this list of diseases with their chromosomal defects and renal and extrarenal findings. Nonheritable cystic diseases include multicystic dysplastic kidney disease (MCDK), simple or multiloculated cysts, and pyelogenic and parapelvic cysts.

NONHERITABLE CYSTIC DISEASES

MCDK. MCDK is the most common cause of renal cystic disease and the second most common cause of abdominal mass in a newborn (most common being hydronephrosis). It has an estimated incidence of 1 per 1,000 to 4,000 live births.[1,2] **Typically, the kidney resembles "a bunch of grapes" with noncommunicating cysts of variable size and consists of an underdeveloped pelvicalyceal system, ureter and renal vessels.[3]**

It is important to distinguish the terms multicystic and polycystic. Although both terms mean "many cysts," the term polycystic refers to renal units developed normally without dysplasia, and it is exclusively restricted to inherited entities as such ARPKD and ADPKD. The term multicystic refers to a dysplastic kidney that resulted from aberrant renal development. By definition, the multicystic dysplastic kidney has no function, with a normal contralateral kidney that may exhibit compensatory hypertrophy.

Clinical Features: Most cystic diseases are initially identified on prenatal ultrasonography during routine ultrasound checkups. Postnatal detection without an abnormal prenatal ultrasound is uncommon. The most significant clinical feature in these patients is a functionally solitary contralateral kidney with involution of the MCDK.[4] The contralateral kidney is often associated with anomalies, most commonly vesicoureteral reflux (up to 43%), ureteropelvic junction obstruction (up to 12%) and ureterovesical junction obstruction (2%).[2,5,6] On ultrasound, MCDK typically has a distribution of cysts throughout the kidney with variable sizes without a large central cyst or any visible communications among the cysts (fig. 1, *A*). MCDK can be confused with hydronephrosis secondary to ureteropelvic junction obstruction; however, in hydronephrosis, connections from peripheral cystic structures to a central cyst can be demonstrated (fig. 1, *B*). In addition, radioisotope studies such as dimercaptosuccinic acid or technetium-99m mercaptoacetyltriglycine scans can help differentiate between a nonfunctioning MCDK and a hydronephrotic, obstructed kidney.

End-Stage Renal Disease (ESRD) and Malignancy Risk: Recent studies have demonstrated low rates of hypertension, from 1.5% to 6%.[5] In a review of over 1,000 children with unilateral MCDK, Narchi demonstrated that the risk of hypertension in these patients was not higher than in the general population.[7] As well, a meta-analysis by Narchi revealed no evidence to support any association between MCDK and Wilms tumor.[8] As such, given the benign nature of the disease, invasive procedures such as nephrectomy are no longer indicated as part of the management of MCDK.

Treatment: The natural progression of the MCDK is involution, which may occur prenatally, soon after birth or over several years.[5] By age 10, the probability of an MCDK to involute is over 50%, particularly for an MCDK with initial size less than 5–6 cm.[9] Regarding contralateral renal anomalies, recent series suggest that screening for vesicoureteral reflux with voiding cystourethrogram is unnecessary, as the majority were low-grade and not clinically significant.[10] As such, unless ultrasound demonstrates a significant abnormality, voiding cystourethrogram is not routinely recommended.[4] **Given the benign nature of MCDK and low incidences of malignancy and clinically significant clinical sequelae, conservative management and limited followup are preferred**. Consensus of the current

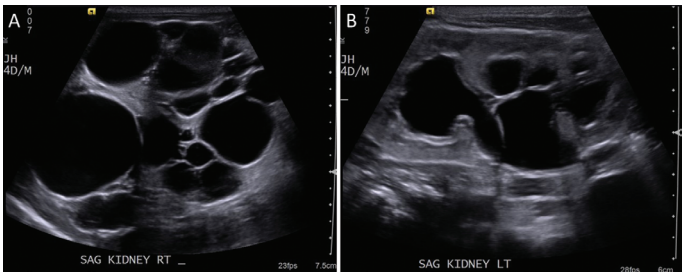

Figure 1. Renal ultrasound of 4-day-old male with right MCDK (*A*) and left urinary tract dilatation (*B*). Note communication of left upper pole dilatation with renal pelvis (*B*), distinguishing this from noncommunicating cysts of variable size (*A*).

ABBREVIATIONS: autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), computerized tomography (CT), end stage renal disease (ESRD), multicystic kidney disease (MCDK), renal cell carcinoma (RCC), von Hippel Lindau disease (VHL)

literature includes performing an initial postnatal ultrasound, an ultrasound at age 1 year and additional imaging based on abnormal contralateral kidney, presence of urinary tract infections, abnormal blood pressure or enlarging MCDK.[9]

Simple and complex cysts. Simple renal cysts are uncommon in children, with an average incidence of less than 1%.[11] These cysts are usually found in nondiseased kidneys and can arise from any portion of the nephron. The pathogenesis of simple renal cysts in children is not well-known, although numerous theories have been proposed, including involvement of calyceal diverticula and obstruction of renal tubules.[12] They can vary in size, are typically oval or round in shape, and can be solitary or multiple. Simple cysts become increasingly common with age, with an incidence as high as 50% after age 60 years, and therefore are often considered as an acquired lesion.[13]

Clinical Features: Most simple cysts are asymptomatic and are discovered incidentally on imaging. However, large cysts can produce abdominal pain, hematuria if ruptured and even hypertension from segmental ischemia.[14] On ultrasound, simple renal cystic lesions have well-defined and thin walls, are anechoic with no elements within the cyst and do not communicate with the renal pelvis. On computerized tomography (CT), simple cysts have density similar to water without enhancement after injection of contrast medium. Enhancement of cystic walls or septa should raise a high index of suspicion for neoplasm.[12]

Treatment: Malignant transformation of renal cysts to cystic renal cell carcinoma (RCC) in children is very rare, unlike in adults. A modified Bosniak classification with risk stratification has been proposed for the pediatric population (table 2), although caution should be used with this modified system, as interrater reliability for intermediate-risk renal cysts in particular has been shown to be inconsistent.[15–17] **In the absence of clinical symptoms, Bosniak categories I and II cysts are usually benign and can be safely followed with periodic ultrasounds, while categories III and IV warrant radical nephrectomy, since over 90% of cases can harbor malignant pathology.** Simple renal cysts are considered Bosniak category I and therefore should not be surgically explored if the patient is asymptomatic. Indications for surgical intervention on simple cysts are primarily related to symptomatology: bleeding, pain, stone formation and superimposed infection.[18] Otherwise, asymptomatic simple renal cysts should be managed conservatively with serial ultrasounds to evaluate for growth and clinical changes.

Multiloculated cysts (cystic nephroma). Benign multilocular cyst, or cystic nephroma, is considered the terminally differentiated, benign spectrum of Wilms tumor, with the most malignant extreme of the spectrum being cystic Wilms tumor. Multiloculated cyst is considered histologically and clinically different from multicystic disease.

Clinical Features: In children, most cases occur before the age of 4 years, and the patient is twice as likely to be male.[19] This differs in adults, where most cases are discovered after the age of 30 and predominantly in females. The most common finding is an asymptomatic abdominal mass. Histologically, these lesions are bulky and typically well-circumscribed. While they can be locally invasive, there has been no evidence to suggest that benign multiloculated cysts can transform into cystic Wilms tumor.[20]

Treatment: Imaging is helpful to distinguish multilocular cysts from multicystic kidneys, but no study can reliably identify benign multilocular cysts from their more malignant counterparts. **Therefore, once a multilocular cystic lesion is diagnosed radiographically, surgical excision is required to determine its histological variant. Partial nephrectomy is a feasible option if there is well-preserved renal tissue.** Any multiloculated cystic lesions with components of Wilms tumor should follow the National Wilms Tumor Study recommendations for staging and management.[21]

Pyelogenic, parapelvic and renal sinus cysts. Pyelogenic cyst, also known as calyceal diverticulum, is an outpouching of the collecting system in the corticomedullary region, and it is typically located in the upper or lower pole. These diverticula are usually asymptomatic unless they develop calculi that obstruct the narrow channel into the calyx. They can be difficult to distinguish radiographically from renal cyst unless contrast medium is given. Parapelvic and renal sinus cysts, on the other hand, are more readily identifiable on imaging as cysts that arise within the parenchyma and hilum, respectively. These cysts are generally discovered incidentally and are considered benign.

INHERITABLE CYSTIC DISEASES

ARPKD. ARPKD is a hereditary renal cystic disorder that carries a high mortality rate. The incidence of ARPKD has been estimated to be anywhere from 1 in 10,000 to 50,000 births.[22] However, the true incidence of ARPKD may be higher, since as many as 50% of affected individuals die in the neonatal period prior to a definitive diagnosis.[22] ARPKD is often referred to as infantile polycystic kidney disease, although ARPKD can present at any time from the antenatal period to young adulthood. The most severe forms of the disease appear earliest in life, with milder cases of the disease more apparent later in adolescence.

Mutations of a single gene, PKHD1, which produces a protein called fibrocystin and is located on chromosome 6, are responsible for the disease. Fibrocystin is located in the basal body area of the primary cilium and plays a vital role in microtubule organization and terminal differentiation of the collecting duct and biliary systems.[23] As such, once ARPKD is suspected prenatally, genetic counseling and evaluation are indicated.

Clinical Features: **ARPKD is always associated with some degree of hepatobiliary disease, including congenital biliary dysgenesis and periportal fibrosis**. Patients can develop portal hypertension and nonobstructed dilatation of biliary ducts later in life and ultimately may require liver transplantation.[23] Infants with oligohydramnios in utero often are born with Potter facies, limb deformities and respiratory distress from pulmonary hypoplasia. Oligohydramnios is a poor prognostic factor for renal insufficiency immediately after birth.[24] In addition, at birth, patients usually present with large, palpable flank masses. On prenatal or newborn ultrasound, kidneys can appear severely enlarged, homogeneous and hyperechogenic with poor corticomedullary differentiation. The increased echogenicity on ultrasound is largely due to tightly compacted dilated collecting ducts causing numerous microcysts within the parenchyma (fig. 2).

ESRD and Malignancy Risk: Severe forms of ARPKD typically manifest prenatally, leading to renal insufficiency in utero, oligohydramnios and pulmonary hypoplasia. Peritoneal dialysis may be required within the first few days postnatally to help prolong survival until kidney transplantation is possible.[25] Patients who live past the perinatal period can have some

degree of improvement in renal function due to continued renal maturation.[26] These children will still very likely develop hypertension, although the mechanism of this is unclear. It can be present in patients with normal renal function and sometimes be the only presenting feature for those not diagnosed with ARPKD perinatally.[26] To date, there is no association of ARPKD with any renal neoplasms.

Treatment: There is no cure for ARPKD. If the kidneys are particularly large during the neonatal period, diaphragmatic movement and respiratory expansion can be compromised, which would necessitate removal of 1 or both kidneys to improve oxygenation. Infants without significant renal or respiratory insufficiency should be followed closely. Polyuria and renal concentrating defects are common, making most children prone to significant dehydration, especially during acute bouts of illness.[27] Advances in renal replacement therapy and transplantation have improved survival of ARPKD patients, with over 50% survival rate at age 10 years.[22] Aside from renal complications, surviving children should be monitored and treated for clinical consequences of hepatobiliary fibrosis, such as portal hypertension and esophageal varices.

ADPKD. ADPKD is the most commonly inherited renal cystic disease, occurring at an incidence of approximately 1 in 400 to 1,000.[28] The disease typically is diagnosed between the fourth and fifth decades of life, although the condition has been identified in infants.[29] Renal cysts can form in all tubular segments, with the proximal tubule being the most common site of involvement.[27]

Two mutated genes are responsible for ADPKD. PKD1, which is mapped to chromosome 16 and encodes polycystin-1, is responsible for 85% of cases. PKD2, the gene for polycystin-2 on chromosome 4, accounts for the remaining 15%.[11] Polycystins are transmembrane proteins involved with the function of the primary cilium on renal tubular cells.[30] Like ARPKD, malfunction of primary cilia leads to aberrant proliferation of renal epithelial cells and formation of cysts. Patients with PKD1 mutation have the more rapidly progressive form of the disease and begin developing renal cysts by the age of 20.[11]

Clinical Features: Signs and symptoms of ADPKD typically occur after age 30 years.[31] Pain is the most common presenting symptom in adults, likely from mass effect of the cysts, bleeding within the cysts, stone formation or urinary tract infections. Hematuria is seen in 50% of patients.[32] Similar to ARPKD, ADPKD is a multiorgan disease. Hepatic cysts are the most common extrarenal finding in ADPKD patients, but cysts can also form in the spleen, pancreas, arachnoid membrane and seminal vesicles.[25] Mitral valve prolapse and diverticulitis have also been associated with ADPKD.[33,34] Berry aneurysms of the circle of Willis can be seen in up to 30% of cases, and 9% of these patients die from subarachnoid hemorrhages.[28,35] **Ultrasonographic criteria for diagnosis of ADPKD in individuals with a positive family history include 2 cysts in 1 or both kidneys if under age 30 years, 2 cysts in each kidney if between the ages of 30 and 59, and 4 cysts in each kidney if older than 60 (fig. 3).[36]**

ESRD and Malignancy Risk: ADPKD is a common cause of renal failure, with up to 15% of patients needing hemodialysis

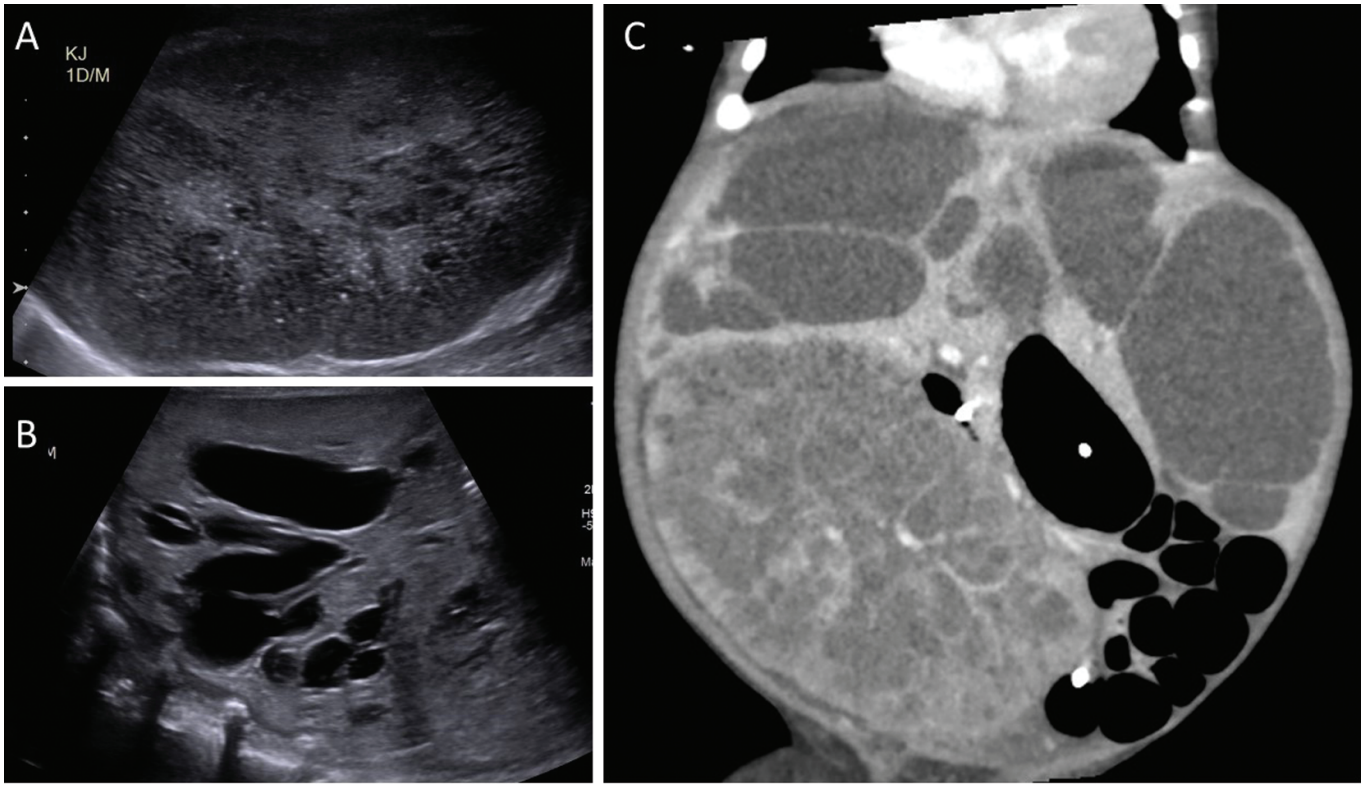

Figure 2. *A*, renal ultrasound of newborn child with ARPKD demonstrates a markedly enlarged kidney measuring 7.5 cm with cylindrical cysts in medulla and cortex, representing ectatic collecting ducts. *B*, liver ultrasound reveals multiple cystic spaces of varying sizes, likely dilated intrahepatic bile ducts. *C*, CT of abdomen and pelvis with contrast of same child at 3 months old. Liver and right kidney (13 cm) have enlarged considerably since birth, causing significant abdominal distention and stomach and bowel compression, as well as upward displacement of diaphragm with low lung volumes. Left kidney is surgically absent.

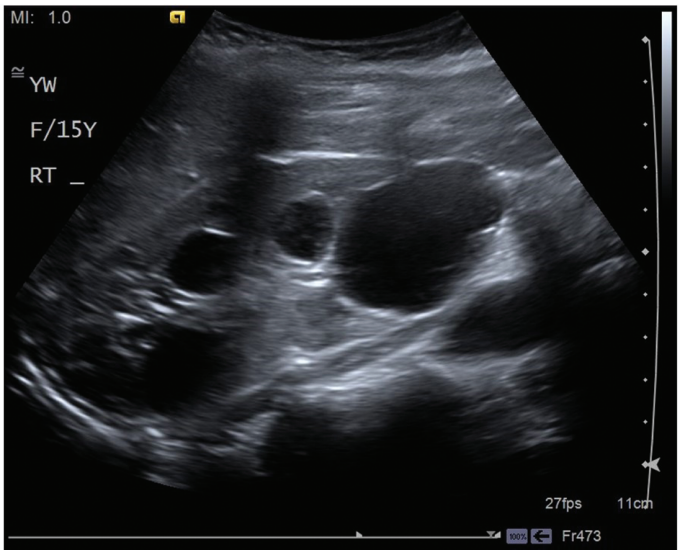

Figure 3. Fifteen-year-old asymptomatic female with ADPKD. Multiple anechoic, cortical cysts of varying size are present.

by adulthood.[28] Renal cysts can become quite large and compress the renal vascular system, consequently activating the renal-angiotensin-aldosterone system.[31] Risk factors for early onset of ESRD include PKD1 mutation, onset of hypertension prior to age 35 years, sickle cell trait, male gender and first episode of hematuria prior to age 30.[37] There is currently no evidence to suggest any association between ADPKD and RCC. However, RCC is often diagnosed at a younger age in patients with ADPKD and is more commonly bilateral, multicentric and sarcomatoid.[38]

Treatment: **Treatment for ADPKD centers around delaying the onset of ESRD by tightly controlling blood pressure. Even in the absence of renal insufficiency, over 60% of these patients have hypertension, which increases their risk of cardiac disease and intracranial hemorrhage.[31]** Hypertensive management is particularly important in patients with intracranial aneurysms. Screening for asymptomatic berry aneurysms is currently not recommended, except for those individuals who have a family history of aneurysm or subarachnoid hemorrhage or prior medical history of aneurysm rupture, or those being screened in preparation for major surgery or work in a high-risk occupation.[39] In general, conservative management of renal cysts is preferred, unless the patient experiences chronic pain or recurrent infections, in which case imaging-guided cyst aspiration or minimally invasive cyst unroofing is recommended.

Juvenile nephronophthisis-medullary cystic disease complex. This complex describes 2 diseases that share common histological and gross pathological features. They are both defined by the presence of small cysts at the corticomedullary junction as well as interstitial fibrosis and damage that usually lead to ESRD.[40] Juvenile nephronophthisis is an autosomal recessive disease that has been linked to mutations in chromosome 2.[41] Meanwhile, medullary cystic kidney disease is inherited in an autosomal dominant fashion and mutated genes have been mapped to chromosomes 1 and 16.[42]

Clinical Features: Due to a tubular concentration defect, most cases of both disorders have common symptoms of polydipsia and polyuria. Juvenile nephronophthisis presents earlier, usually within the first decade of life. Only juvenile nephronophthisis is associated with extrarenal findings, with up to 20% of cases associated with retinitis pigmentosa, a combination known as the Senior-Løken syndrome.[40] Other concomitant conditions may include ocular motor apraxia, hepatic fibrosis, Joubert syndrome and Bardet-Biedl syndrome.[43]

ESRD and Malignancy Risk: ESRD develops early in patients with nephronophthisis, usually 5 to 10 years after initial presentation and almost always before the age of 25 years.[43] ESRD in medullary cystic kidneys develops later in life, during the third or fourth decade. Treatment of this complex is primarily supportive, with emphasis on preserving renal function, and delaying dialysis and transplantation for as long as possible.

Malformation syndromes associated with renal cysts. Tuberous sclerosis, with an incidence of 1 in 6,000 children, is classically described as a triad of epilepsy, mental retardation and adenoma sebaceum.[44] In 25% to 40% of patients, it is transmitted as an autosomal dominant trait. Mutations in TSC1 on chromosome 9 and TSC2 on chromosome 16 are responsible for this disorder.[45] Renal features include cysts, angiomyolipoma and RCC. Renal cysts can occur in 20% of patients and often appear in children younger than age 3 years. In children with multiple cysts but no family history of polycystic kidney disease, tuberous sclerosis should be considered. Angiomyolipomas can occur in 40% to 80% of tuberous sclerosis patients and are usually multiple and bilateral.[46] Most tuberous sclerosis patients do not develop ESRD unless the growths of the cysts and angiomyolipoma compromise renal function.

VHL is a neoplastic disorder that has been linked to the tumor suppressor VHL gene on chromosome 3.[47] Classically, VHL manifests as hemangioblastomas in the eye and central nervous system, cysts within the kidneys, pancreas and epididymis, pancreatic tumors, pheochromocytomas and clear cell RCC. The most common indicator of VHL is renal cysts, which are seen in over 75% of affected people.[48] These cysts are usually multiple, bilateral and hypothesized to be precancerous if larger than 2 cm.[48] RCC occurs in up to 50% of patients and is the leading cause of death for many. Careful surveillance is necessary by the urologist, with the goal of treatment as cancer control and renal preservation.

SURVEILLANCE

Routine monitoring of the above-described cystic lesions depends primarily on the potential for cystic growth and malignant transformation. Table 1 includes general surveillance guidelines for inheritable renal cystic diseases.[49–53] Unfortunately surveillance protocols have not yet been formally established for several of these diseases due to their rarity, but the general consensus advocates routine annual (more frequent) renal imaging as well as urinalysis, blood pressure and renal function measurements.

Congenital anomalies of the kidney and the urinary tract can lead to many of these children having a congenital or acquired solitary functioning kidney after unilateral nephrectomy. In these children, monitoring of the solitary functioning kidney is important to minimize risk of hypertension, proteinuria and chronic kidney disease. While there are no evidence-based guidelines for long-term monitoring of renal function in this young population, the general consensus is that followup should include yearly nephrology visits for blood pressure

measurements, urinalysis to monitor for microalbuminuria, serum glomerular filtration rate and creatinine levels, as well as ultrasounds as indicated.[54] Frequency of followup should increase to every 3 to 6 months in children showing early signs of renal deterioration. In addition, the American Academy of Pediatrics recommends that while these children should have no restrictions for noncontact sports, they should exercise caution on contact and limited-contact sports.[55] Individual assessment should be made based on the type of sport, and protective equipment should be used at all times during the activity to reduce risk of injury in the remaining kidney.

SUMMARY

Renal cysts in children can be found in a wide spectrum of inheritable and sporadic disorders. Many inheritable diseases, in particular ones associated with multisystem anomalies, have strong associations with dysfunctions of the primary cilium. A careful, concerted effort from various medical and genetic disciplines is needed to counsel affected parents on long-term goals such as renal preservation, improved quality of life and survival.

DID YOU KNOW?

- A multidisciplinary approach is necessary for hereditary complex multisystem cystic disorders and should include nephrology, gastroenterology, neonatology and genetics counseling.
- MCDK is characterized by multiple, noncommunicating cysts of variable size, usually involutes over time without intervention and is often associated with contralateral renal anomalies.
- All affected ARPKD individuals have some degree of hepatobiliary fibrosis at birth, while ADPKD patients are more likely to have liver cysts as they increase in age.
- Juvenile nephronophthisis and medullary cystic disease complex is a duo of disorders that share common clinical symptoms (polyuria, polydipsia, hypertension) and histological pathologies (interstitial fibrosis and cysts at the corticomedullary junction).
- Dysfunctions of the primary cilium are often the primary cause of cyst development and are responsible for disorders such as ARPKD, ADPKD, juvenile nephronophthisis and Bardet-Biedl syndrome.

Table 1. Characteristics of inheritable renal cystic diseases

Inheritable Disease	Chromosome Defect	Renal Findings	Extrarenal Findings	Malignancy Risk	ESRD Risk	Recommended Surveillance
ARPKD	6	Echogenic, large kidneys	Hepatobiliary involvement (portal fibrosis, biliary dysgenesis)	None	Very high; hypertension and concentrating defects	Routine surveillance of hypertension, hyponatremia, renal function (no recommended protocols due to rarity of disease)
ADPKD	PKD1: 16 PKD2: 4	Cysts located in parenchyma; large kidneys	Intracranial aneurysms; liver, spleen and/or pancreatic cysts; mitral valve prolapse	None, but RCC often diagnosed at younger age and bilateral	Up to 15% of pts require dialysis by adulthood	Annual urinalysis and blood pressure, renal ultrasounds every 3 years
Juvenile nephronophthisis-medullary cystic disease complex	2	Cysts located at the corticomedullary junction	Juvenile nephronophthisis only: retinitis pigmentosa (Senior-Løken syndrome), hepatic fibrosis, ocular motor apraxia, Bardet-Biedl syndrome	None	Nephronophthisis responsible for 10%–20% ESRD in children and leads to early ESRD; medullary cystic disease leads to ESRD in 3rd or 4th decade	Routine urinalysis, blood pressure, renal function panel and hematological studies; routine renal ultrasounds (no recommended protocols due to rarity of disease)
Tuberous sclerosis	TSC1: 9 TSC2: 16	Cysts, angiomyolipoma, RCC	Adenoma sebaceum, mental retardation, epilepsy, cranial tumors	3% incidence, often female, younger, bilateral	Low unless cysts and angiomyolipoma are large	Annual blood pressure, renal function panel; magnetic resonance imaging of abdomen every 1–3 yrs
VHL	3	Cysts, adenomas, clear cell RCC	Pancreatic/epididymal cysts, cerebellar hemangioblastomas, pheochromocytomas, retinal angiomas	About 50% of VHL pts	Less likely with nephron-sparing surgery	Annual blood pressure, annual plasma-free or fractionated 24-hour urinary free metanephrines starting at age 5 yrs; annual magnetic resonance imaging of abdomen starting at age 15

Table 2. Modified Bosniak classification for pediatric renal cysts

Risk Category	Bosniak Category	Description		Management
		Ultrasound	CT	
Low	I	Round, smooth, thin-walled; no echogenic foci	Homogeneous consistent with water density; no enhancement after intravenous contrast injection	No surgery
	II	Thin septa with or without minimal thickening of cyst wall	Calcifications and/or high attenuation on CT; no enhancement after intravenous contrast injection	No surgery
High	III	Thick/irregular septations; detectable flow by Doppler ultrasound may be present	Calcifications on CT; enhancement of septa or wall	Radical nephrectomy
	IV	Cystic mass with thick wall; solid internal components or nodular areas with detectable flow by Doppler ultrasound	Enhancement and marked heterogeneity after contrast administration	Radical nephrectomy

REFERENCES

1. Kalyoussef E, Hwang J, Prasad V et al: Segmental multicystic dysplastic kidney in children. Urology 2006; **68:** 1121.e9.
2. Feldenberg LR and Siegel NJ: Clinical course and outcome for children with multicystic dysplastic kidneys. Pediatr Nephrol 2000; **14:** 1098.
3. Bisceglia M, Galliani CA, Senger C et al: Renal cystic diseases: a review. Adv Anat Pathol 2006; **13:** 26.
4. Cardona-Grau D and Kogan BA: Update on multicystic dysplastic kidney. Curr Urol Rep 2015; **16:** 67.
5. Schreuder MF, Westland R and van Wijk JAE: Unilateral multicystic dysplastic kidney: a meta-analysis of observational studies on the incidence, associated urinary tract malformations and the contralateral kidney. Nephrol Dial Transplant 2009; **24:** 1810.
6. Atiyeh B, Husmann D and Baum M: Contralateral renal abnormalities in multicystic-dysplastic kidney disease. J Pediatr 1992; **121:** 65.
7. Narchi H: Risk of hypertension with multicystic kidney disease: a systematic review. Arch Dis Child 2005; **90:** 921.
8. Narchi H: Risk of Wilms' tumour with multicystic kidney disease: a systematic review. Arch Dis Child 2005; **90:** 147.
9. Eickmeyer AB, Casanova NF, He C et al: The natural history of the multicystic dysplastic kidney—is limited follow-up warranted? J Pediatr Urol 2014; **10:** 655.
10. Ismaili K, Avni FE, Alexander M et al: Routine voiding cystourethrography is of no value in neonates with unilateral multicystic dysplastic kidney. J Pediatr 2005; **146:** 759.
11. Chakraborty S and McHugh K: Cystic diseases of the kidney in children. Imaging 2005; **17:** 69.
12. Gleason DC, McAlister WH and Kissane J: Cystic disease of the kidneys in children. Am J Roentgenol Radium Ther Nucl Med 1967; **100:** 135.
13. Laucks SP and McLachlan MSF: Aging and simple cysts of the kidney. Br J Radiol 1981; **54:** 12.
14. Papanicolaou N, Pfister RC and Yoder IC: Spontaneous and traumatic rupture of renal cysts: diagnosis and outcome. Radiology 1986; **160:** 99.
15. Saltzman AF, Carrasco A, Colvin AN et al: Can a modified Bosniak classification system risk stratify pediatric cystic renal masses? J Urol 2018; **200:** 434.
16. Wallis MC, Lorenzo AJ, Farhat WA et al: Risk assessment of incidentally detected complex renal cysts in children: potential role for a modification of the Bosniak classification. J Urol 2008; **180:** 317.
17. Frumer M, Konen O, Shapira Rootman M et al: The modified Bosniak classification for intermediate-risk renal cysts in children. Urology 2021; **149:** 206.
18. Terada N, Arai Y, Kinukawa N et al: The 10-year natural history of simple renal cysts. Urology 2008; **71:** 7.
19. Eble JN and Bonsib SM: Extensively cystic renal neoplasms: cystic nephroma, cystic partially differentiated nephroblastoma, multilocular cystic renal cell carcinoma, and cystic hamartoma of renal pelvis. Semin Diagn Pathol 1998; **15:** 2.
20. Banner MP, Pollack HM, Chatten J et al: Multilocular renal cysts: radiologic-pathologic correlation. AJR Am J Roentgenol 1981; **136:** 239.
21. D'Angio GJ, Breslow N, Beckwith JB et al: Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 1989; **64:** 349.
22. Kaplan BS, Fay J, Shah V et al: Autosomal recessive polycystic kidney disease. Pediatr Nephrol 1989; **3:** 43.
23. Bergmann C: ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. Pediatr Nephrol 2015; **30:** 15.

24. Roume J and Ville Y: Prenatal diagnosis of genetic renal diseases: breaking the code. Ultrasound Obstet Gynecol 2004; **24:** 10.
25. Kagan KO, Dufke A and Gembruch U: Renal cystic disease and associated ciliopathies. Curr Opin Obstet Gynecol 2017 **29:** 85.
26. Cole BR, Conley SB and Stapleton FB: Polycystic kidney disease in the first year of life. J Pediatr 1987; **111:** 693.
27. Macrae Dell K: The spectrum of polycystic kidney disease in children. Adv Chronic Kidney Dis 2011; **18:** 339.
28. Grantham JJ: The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: recent advances. Am J Kidney Dis 1996; **28:** 788.
29. Proesmans W, van Damme B, Casaer P et al: Autosomal dominant polycystic kidney disease in the neonatal period: association with a cerebral arteriovenous malformation. Pediatrics 1982; **70:** 971.
30. Sessa A, Ghiggeri GM and Turco AE: Autosomal dominant polycystic kidney disease: clinical and genetic aspects. J Nephrol 1997; **10:** 295.
31. Gabow PA: Autosomal dominant polycystic kidney disease. N Engl J Med 1993; **329:** 332.
32. Delaney VB, Adler S, Bruns FJ et al: Autosomal dominant polycystic kidney disease: presentation, complications, and prognosis. Am J Kidney Dis 1985; **5:** 104.
33. Lumiaho A, Ikäheimo R, Miettinen R et al: Mitral valve prolapse and mitral regurgitation are common in patients with polycystic kidney disease type 1. Am J Kidney Dis 2001; **38:** 1208.
34. Scheff RT, Zuckerman G, Harter H et al: Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. Ann Intern Med 1980; **92:** 202.
35. Ryu SJ: Intracranial hemorrhage in patients with polycystic kidney disease. Stroke 1990; **21:** 291.
36. Ravine D, Sheffield L, Danks DM et al: Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet 1994; **343:** 824.
37. Yium J, Gabow P, Johnson A et al: Autosomal dominant polycystic kidney disease in blacks: clinical course and effects of sickle-cell hemoglobin. J Am Soc Nephrol 1994; **4:** 1670.
38. Keith DS, Torres VE, King BF et al: Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1994; **4:** 1661.
39. Pirson Y, Chauveau D and Torres V: Management of cerebral aneurysms in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2002; **13:** 269.
40. Hildebrandt F and Omram H: New insights: nephronophthisis-medullary cystic kidney disease. Pediatr Nephrol 2001; **16:** 168.
41. Saunier S, Calado J, Heilig R et al: A novel gene that encodes a protein with a putative Src homology 3 domain is a candidate gene for familial juvenile nephronophthisis. Hum Mol Genet 1997; **6:** 2317.
42. Scolari F, Viola BF, Ghiggeri GM et al: Towards the identification of (a) genes(s) for autosomal dominant medullary cystic kidney disease. J Nephrol 2003; **16:** 321.
43. Neumann HPH, Zäuner I, Strahm B et al: Late occurrence of cysts in autosomal dominant medullary cystic kidney disease. Nephrol Dial Transplant 1997; **12:** 1242.
44. Lagos JC and Gomez MR: Tuberous sclerosis: reappraisal of a clinical entity. Mayo Clin Proc 1967; **42:** 26.
45. Dabora SL, Kwiatkowski DJ, Franz DN et al: Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet 2001; **68:** 64.
46. Chonko AM, Weiss SM, Stein JH et al: Renal involvement in tuberous sclerosis. Am J Med 1974; **56:** 124.
47. Kondo K and Kaelin WG: The von Hippel-Lindau tumor suppressor gene. Exp Cell Res 2001; **264:** 117.
48. Poston CD, Jaffe GS, Lubensky IA et al: Characterization of the renal pathology of a familial form of renal cell carcinoma associated with von Hippel-Lindau disease: clinical and molecular genetic implications. J Urol 1995; **153:** 22.
49. Gimpel C, Bergmann C, Bockenhauer D et al: International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol 2019; **15:** 713.
50. Guay-Woodford LM, Bissler JJ, Braun MC et al: Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. J Pediatr 2014; **165:** 611.
51. VHL Alliance: Active Surveillance. Available at https://www.vhl.org/clinicians/surveillance/. Accessed April 18, 2021.
52. Krueger DA, Northrup H, Krueger DA et al: Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; **49:** 255.
53. Simms RJ, Eley L and Sayer JA: Nephronophthisis. Eur J Hum Genet 2009; **17:** 406.
54. Westland R, Schreuder MF, van Goudoever JB et al: Clinical implications of the solitary functioning kidney. Clin J Am Soc Nephrol 2014; **9:** 978.
55. Rice SG, Small EW, McCambridge TM et al: Medical conditions affecting sports participation. Pediatrics 2008; **121:** 841.

Study Questions Volume 40 Lesson 38

1. A newborn infant girl has a renal ultrasound to follow up on an abnormal right kidney seen on a prenatal ultrasound. She is diagnosed with a right MCDK. A urinalysis is normal. The next step is
   a. observation
   b. voiding cystourethrogram
   c. mercaptoacetyltriglycine/furosemide renogram
   d. CT urogram

2. A 3-year-old girl is seen for polydipsia and polyuria. On a renal ultrasound there are multiple small cysts bilaterally at the corticomedullary junction. She is an otherwise normal healthy child. Her maternal grandmother has known cysts in her kidneys, but otherwise the family history is negative for cystic diseases. The most likely diagnosis is
   a. autosomal recessive polycystic kidney disease
   b. medullary cystic kidney disease
   c. juvenile nephronophthisis
   d. Senior-Løken syndrome

3. A 28-year-old woman has a renal ultrasound after her father is diagnosed with ADPKD at age 51. To meet the ultrasonographic criteria for ADPKD in individuals with a positive family history, she must have
   a. 1 cyst in each kidney
   b. 2 cysts in each kidney
   c. 2 cysts in 1 or both kidneys
   d. 4 cysts in either kidney

4. A 10-year-old girl has a renal ultrasound performed for recurrent nonlateralized abdominal pain. The ultrasound shows a 1.5 cm renal cyst in the lower pole of the right kidney. The cyst is round and anechoic with a single thin septation. The cyst does not communicate with the collecting system. According to the modified Bosniak system for pediatric cysts, the grade of this cyst is
   a. I
   b. II
   c. III
   d. IV

5. The genitourinary anomaly most commonly associated with von Hippel-Lindau syndrome is
   a. chromophobe RCC
   b. epididymal angioma
   c. epididymal cysts
   d. Wilms tumor