



Diagnosis and Management of Renal Cystic Disease of the Newborn: Core Curriculum 2021

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Renal cystic disease encompasses a large variety of illnesses with various phenotypic expressions that can manifest in utero, in infancy, and in childhood. These diseases may be unilateral or bilateral and present with single or multiple cysts. Various cystic diseases may also progress to chronic kidney disease (CKD), including kidney failure, and hepatic disease, thus potentially being life threatening. The prevalence and serious complications of CKD in the pediatric population make it vital that health care providers detect these conditions early and provide effective management. This installment of *AJKD's* Core Curriculum in Nephrology discusses various genetic and sporadic kidney cystic diseases, including multicystic dysplastic kidney, nephronophthisis, cystic dysplasia, hepatocyte nuclear factor 1- β (HNF1- β) nephropathy, Bardet-Biedl syndrome, Meckel-Gruber syndrome, Zellweger syndrome, calyceal diverticulum, autosomal recessive polycystic kidney disease (ARPKD), and autosomal dominant polycystic kidney disease (ADPKD). This article discusses the epidemiology, genetics and pathophysiology, diagnosis, presentation, and management for each of these renal cystic diseases, with particular attention to prenatal care and pregnancy counseling.

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Am J Kidney Dis. 78(1):125-141. Published online January 6, 2021.

doi: [10.1053/j.ajkd.2020.10.021](https://doi.org/10.1053/j.ajkd.2020.10.021)

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Introduction

Renal cystic diseases (RCD) can occur in a large variety of illnesses and manifest in utero, in infancy, or throughout childhood and adolescence (Box 1). Overall, the incidence of RCDs can vary from 0.44 cases per 10,000 births for neonatal-onset genetic polycystic kidney disease to 4.1 cases per 10,000 births for sporadic kidney cystic diseases. Certain RCDs are life threatening and may progress to chronic kidney disease (CKD) and hepatic disease. The prevalence and serious complications of this group of diseases in vulnerable populations make it vital that health care providers detect these conditions early and provide effective management.

RCDs may be conceptually grouped in a number of ways. The classification by Liapis and Winyard is the system most commonly referred to for organizing RCDs (Box 2). Alternatively, one can distinguish between genetic and sporadic RCDs or between dysplasias and cilioopathies, with the latter containing hepatorenal fibrocystic diseases (HRFCDs). Collectively, genetic RCDs are a frequent cause of pediatric kidney failure. The most prominent RCD members are autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), glomerular cystic kidney disease, Bardet-Biedl syndrome (BBS), nephronophthisis (NPHP), and hepatocyte nuclear factor 1- β (HNF1- β) nephropathy. Instead of genetic inheritance, some RCDs presenting in

the newborn have a sporadic inheritance including multicystic dysplastic kidney (MCDK), calyceal diverticula (CD), and simple and complex kidney cysts. Additionally, kidney dysplasia has been associated with genetic syndromes such as Meckel-Gruber syndrome (MKS), chromosome anomalies (eg, trisomy 18), vertebral defects—anal atresia—cardiac defects—tracheoesophageal fistula—renal anomalies—limb abnormalities (VACTERL), renal-hepatic-pancreatic dysplasia (RHPD), and splenic disorders.

This installment of the Core Curriculum highlights issues surrounding diagnosis and management, including care during the perinatal period and prenatal counseling for MCDK, cystic dysplasia, HNF1- β nephropathy, Zellweger spectrum disorders, CD, ARPKD, ADPKD, infantile NPHP, BBS, and MKS.

Essential Reading

- Khare A, Krishnappa V, Kumar D, Raina R. Neonatal renal cystic diseases. *J Matern Neonatal Med.* 2018;31(21):2923-2929.
- Kwatra S, Krishnappa V, Mhanna C, et al. Cystic diseases of childhood: a review. *Urology.* 2017;110:184-191.

Renal Development and Prenatal Evaluation of Renal Cystic Diseases

Formation of the urinary system begins during the third week of gestation as the pronephros in the cervical region, which leads to

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Box 1. Renal Cystic Disease Nomenclature and Terminology^a

ADPKD: autosomal dominant polycystic kidney disease
ARPKD: autosomal recessive polycystic kidney disease
BBS: Bardet-Biedl syndrome
CD: calyceal diverticulum
HNF1 β : hepatocyte nuclear factor 1- β
MCDK: multicystic dysplastic kidney
MKS: Meckel-Gruber syndrome
Renal adysplasia: finding of combined renal agenesis and renal dysplasia
Renal agenesis: unilateral or bilateral absence of kidney in a newborn
Renal aplasia: extreme form of dysplasia where a nubbin of dysplastic kidney caps a normal or abnormal ureter
Renal dysgenesis: abnormal development of the kidney regarding size, shape, or structure; there are various forms of dysgenesis, such as dysplasia, hypoplasia, aplasia, agenesis, and dysmorphism
Renal dysplasia: abnormal and disorganized renal structure that can be diffusive, segmental, involuted, or focal; additionally, ectopic tissue may be present
Renal hypoplasia: normal renal structure with reduction in nephron number and size in one or both kidneys with absence of dysplastic elements

Based in part on information in Bonsib (The classification of renal cystic diseases and other congenital malformations of the kidney and urinary tract. *Arch Pathol Lab Med.* 2010;134(4):554-568).

development of the mesonephros. The mesonephric duct forms the ureter and collecting system of the renal pelvis, making urine by 16 weeks. The fetal bladder is visible by ultrasonography at 9 weeks of gestation, and the fetal kidneys (hyperechoic oval structures) can be identified at 11-12 weeks. Kidney echogenicity, in comparison with the liver and spleen, decreases throughout gestation, presenting at birth with typical corticomedullary differentiation. The kidney continues to grow normally with age, unless affected by fetal kidney anomalies.

Kidney malformations can be variable in appearance and severity and may vary by the number of kidneys present, absent, or duplicated; whether they are located normally or in the pelvis; whether they are small or enlarged, and whether they are hypoechoic or hyperechoic. These malformations may be obvious at initial examination, or they may evolve during pregnancy. Prenatal ultrasonography scans are an effective tool for detecting fatal and severe kidney malformations. Ultrasonography should describe the size, location, and echogenicity of the kidneys. Kidney ultrasonography scans are typically evaluated on 2 planes, sagittal (to assess growth) and transverse (to assess the renal pelvis), and are located between the umbilical arteries and veins. Additionally, the bladder should be imaged from 13 weeks on, and the patient is required to have a full bladder for visualization (the bladder fills every 30 minutes).

Cystic diseases are among the most common kidney anomalies. It is useful to determine the extent of renal

Box 2. Classification System for Renal Cystic Diseases

- A. Polycystic kidney disease
 1. Autosomal dominant polycystic kidney disease
 - Classic ADPKD
 - Early-onset ADPKD in children
 2. Autosomal recessive polycystic kidney disease
 - Classic ARPKD in neonates and infants
 - Medullary duct ectasia in older children with hepatic fibrosis
 3. Glomerulocystic kidney disease
 - Familial GCKD
 - Renal hypoplasia and UROM mutation
 - Associated with HNF1B mutations
 - Hereditary GCKD
 - Associated with ADPKD/ARPKD/TSC
 - Syndromic nonhereditary GCKD
 - Sporadic GCKD
 - Acquired GCKD
- B. Renal medullary cysts
 1. Nephronophthisis
 - Nephronophthisis, autosomal recessive
 - Juvenile nephronophthisis
 - NPH1, NPH4
 - NPH1, NPH5 associated with Senior-Løken syndrome
 - Infantile NPH2
 2. Medullary cystic diseases
 - Autosomal dominant MCKD
 - MCKD associated with hyperuricemia
 3. Medullary sponge kidney
- C. Cysts in hereditary cancer syndromes
 1. Von Hippel-Lindau disease
 2. Tuberous sclerosis
- D. Multilocular renal cyst
- E. Localized cystic disease
- F. Simple cortical cysts
- G. Acquired (dialysis-induced) cysts
- H. Miscellaneous
 1. Pyelocaliceal diverticula
 2. Perinephric pseudocysts
 3. Hygroma renalis

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; GCKD, glomerulocystic kidney disease; MCKD, medullary cystic kidney disease; NPH, nephronophthisis; TSC, tuberous sclerosis complex.

Based on the Liapis and Winyard classification of renal cystic disease as discussed in Bonsib (The classification of renal cystic diseases and other congenital malformations of the kidney and urinary tract. *Arch Pathol Lab Med.* 2010;134(4):554-568).

involvement with the number and size of cysts along with a description of uninvolved normal areas in both kidneys. Dilated renal pelvis is a common finding and may progress to hydronephrosis. Pyelectasis grade is based on severity, with grade IV resembling MCDK. Amniocentesis may facilitate assessment of fetal kidney function in the presence of bladder outlet obstruction. Fetal magnetic resonance imaging (MRI) should be considered in some cases of echogenic kidneys.

Essential Reading

- Gimpel C, Avni FE, Bergmann C, et al. Perinatal diagnosis, management, and follow-up of cystic renal diseases a clinical practice recommendation with systematic literature reviews. *JAMA Pediatr.* 2018;172(1):74-86.
- Whittle M, Simões R. Hereditary polycystic kidney disease: genetic diagnosis and counseling. *Revista da Associação Médica Brasileira.* 2014; 60(2), 98-102.

Genetic Testing and Prenatal Counseling

Prenatal consultation with neonatologists, maternal-fetal medicine specialists, and genetic specialists should be offered whenever a kidney anomaly is identified on prenatal ultrasonography. This consultation should cover the ultrasonographic findings, family history, and any information available for prognosis and likelihood of recurrence, followed by development of the pregnancy management plan. The patient should also be provided with various options for prenatal and postnatal genetic testing. Such testing will vary based on the family history and renal findings and may use nontargeted and targeted next-generation sequencing (NGS) approaches to sequence multiple genes for further diagnostic evaluation. Improving understanding of the genetics of kidney disorders can be expected to enhance the clinical utility of genetic analysis in providing valuable information concerning clinical management, prognosis, and risk of recurrence. Current genetic testing recommendations, as endorsed by multiple kidney, pediatric, and obstetric societies, are described in [Box 3](#). Bilateral fetal kidney involvement with concurrent significant oligohydramnios is frequently associated with Potter's sequence and fetal pulmonary hypoplasia. In the presence of anhydramnios and severe pulmonary hypoplasia, postnatal survival may not be possible, thus termination of a pregnancy before fetal viability with appropriate counseling can be offered. In less severe cases, a close and regular monitoring of fetal kidneys, ureters, bladder, and fetal growth throughout the pregnancy is necessary. Parental counseling is critical and should cover the possibility that the child could require critical care at birth with extensive evaluation and management, including dialysis. Whenever ADPKD or ARPKD, or both, are suspected, appropriate testing including genetic testing should be completed to counsel parents regarding prognosis, any associated extrarenal organ involvement, and recurrence risk in subsequent pregnancies.

Notably, a considerable proportion of patients with ADPKD carries a de novo mutation with practically no risk of a subsequent child being affected (with the very rare exception of germline mosaicism).

A separate set of recommendations exist for counseling and diagnostics for neonatal and pediatric patients with RCDs ([Box 4](#)). The consortium of professional societies behind the recommendations consider ultrasonography to be the most useful imaging modality for diagnosis of

Box 3. Clinical Practice Recommendations for Prenatal Care and Counseling

- Ultrasound recommendations based on causes
 - ◊ Solitary renal cysts
 - A follow-up ultrasound during pregnancy should be performed after 4-6 weeks to assess for newly developed cysts.
 - A fetal MRI should be performed if the cyst appears unusual regarding echo-pattern, size, or if there is suspicion of a tumor.
 - ◊ Multiple unilateral cysts
 - A follow-up ultrasound during pregnancy should be performed after 4 weeks. Follow-up intervals for ultrasound are dependent on presence of contralateral hypertrophy and volume of amniotic fluid.
 - If needed, a fetal MRI should be performed in the third trimester.
 - ◊ Bilateral cysts without oligohydramnios
 - Ultrasonography scans should be repeated every 4 weeks until the end of the pregnancy.
 - An MRI may be performed to provide increased accuracy after 28-30 weeks of pregnancy and may be helpful to be performed earlier if termination of pregnancy is being considered.
 - ◊ Bilateral cysts with oligohydramnios
 - Ultrasonography scans should be repeated every 4 weeks until the end of the pregnancy.
 - MRI is recommended as ultrasound image quality may be severely compromised due to lack of amniotic fluid.
- Nondirected counseling should be provided whenever genetic testing is considered for prenatal cystic kidney disease.
- Prenatal genetic testing is suggested for fetuses with solitary/multiple unilateral cysts if there are extrarenal manifestations.
- Prenatal genetic testing is suggested for fetuses with bilateral cystic kidney disease and/or bilateral hyperechoic or enlarged kidneys (even in the presence of oligohydramnios or extrarenal malformations).
- Parents should be counseled by a fetal medicine specialist and a neonatologist in the case of oligohydramnios.
- Counseling by a pediatric nephrologist should be offered to parents of fetuses with bilateral renal cystic disease.
- Nondirective counseling should be provided to parents when termination of pregnancy is locally available to give realistic perspective of outcome.

Clinical practice recommendations were formulated by aggregating current evidence and expert opinion consensus of the current management of cystic nephropathies before and after birth. Abbreviation: MRI, magnetic resonance imaging.

Based on information from Gimpel et al (Perinatal diagnosis, management, and follow-up of cystic renal diseases a clinical practice recommendation with systematic literature reviews. *JAMA Pediatr.* 2018;172(1):74-86).

underlying disorders and follow-up examinations. The type of testing and on whom are controversial topics in current guidelines. For example, parental anxiety associated with an ADPKD diagnosis before symptoms occur may outweigh any possible benefits, whereas early genetic testing will allow patients to receive early clinical management, such as

Box 4. International Consensus Recommendations for Imaging and DiagnosisRecommendations for measuring and describing renal cysts^a

- Renal cysts should primarily be investigated using ultrasonography with detailed examination and description of the renal parenchyma, urinary tract, and cysts.
- The liver should also be examined via ultrasonography for the initial evaluation of cystic kidney disease.
- Transabdominal genital ultrasonography should be performed in female patients at first examination as disorders such as HNF1 β mutations and Bardet-Biedl syndrome are associated with Müllerian duct irregularities.

Recommendations for standard and contrast-enhanced ultrasonography

- An experienced examiner with specialized training in pediatric ultrasonography should perform the ultrasonography using a curvilinear transducer with a frequency of more than 7 MHz with settings optimized for the child.
- The use of contrast-enhanced ultrasonography is restricted to only a select few cases with complex cysts in experienced centers.

Recommendations for MRI and CT

- MRI is not necessary and should only be used for certain cases of pediatric renal cysts where the ultrasonography results are indistinct.
- CT should not be routinely used for pediatric renal cysts due to radiation exposure. Both ultrasonography and MRI can provide better contrast resolution. However, CT may be beneficial in children with claustrophobia or when MRI is not available.

Additional considerations

- Cystic renal diseases often only present with hyperechoic and/or enlarged kidneys prenatally.
- Imaging findings, such as oligohydramnios and external features (eg, congenital malformations and reduced lung volume), are important as they may affect prognosis.
- Regular monitoring and multidisciplinary care are strongly recommended during pregnancy and postnatally.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
^aRecommendations are from the Network for Early Onset Cystic Kidney Disease (NEOCYST) on imaging of cystic diseases in children. These consensus statements were endorsed by the European Society of Pediatric Radiology Task Force on Genitourinary Imaging, the European Federation of Societies for Ultrasound in Medicine and Biology, and the European Society of Pediatric Nephrology, and were reviewed by the European Reference Network for Rare Kidney Disease. Based on information from Gimpel et al (Imaging of kidney cysts and cystic kidney diseases in children: an international working group consensus statement. *Radiology*. 2019;290(3):769-782).

antihypertensive interventions for the prevention of cardiovascular disease, and can help families prepare their child for adulthood. Any framework for diagnostics and counseling should make certain that: 1) parents have the opportunity to discuss the implications in advance of referrals for imaging and genetic testing; 2) if there is no doubt about the correct diagnosis in the family's index patient (keeping in mind that a number of phenocopies may mimic ADPKD, so some caution is recommended), ultrasonography evaluation for ADPKD is considered equal to genetic testing with access to appropriate counseling; 3) the child is

involved in the decision making process if they are mature and well informed enough to do so; 4) parents are enabled to discuss the diagnostic implications of ADPKD in children and are supported by appropriate services and information; and 5) genetic testing is provided where feasible and cost-effective in at-risk children. Table S1 provides a description of syndromes associated with RCDs.

Essential Reading

- Gimpel C, Avni FE, Bergmann C, et al. Perinatal diagnosis, management, and follow-up of cystic renal diseases a clinical practice recommendation with systematic literature reviews. *JAMA Pediatr*. 2018;172(1):74-86.
- Bergmann C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. *Pediatr Nephrol*. 2015;30(1):15-30.

Dysplasias**Multicystic Dysplastic Kidney (MCDK)**

Case 1: A 2.5-week-old male term infant is being evaluated for unilateral cysts in the left fetal kidney seen during prenatal ultrasonography at 20 and 32 weeks of gestation (the right kidney was of normal appearance). Using postnatal renal sonography, a 4.9-cm left kidney and large noncommunicating cysts with absence of normal kidney tissue are revealed. The right kidney measures 6.0 cm with normal corticomedullary differentiation. Blood pressure is 80/40 mm Hg and serum creatinine concentration is 0.5 mg/dL (44.2 μ mol/L). Obstetric records report normal amniotic fluid volume. The parents inquire about future tests and follow-up.

Question 1: Which of the following is the next management step for the infant?

- Diuretic kidney flow scanning
- Conservative follow-up with periodic kidney ultrasonography and blood pressure measurement
- Voiding cystourethrography
- Referral to pediatric urology for possible resection of the cystic kidney

For the answer to the question, see the following text.

Epidemiology. MCDK is a congenital malformation of the kidney identified by multiple, noncommunicating cysts and is a subtype of the broad array of early developmental disorders often termed congenital anomalies of the kidney and urinary tract (CAKUT). MCDK has an incidence of 1 in 4,300 fetuses with 94% of all cases being detected using antenatal ultrasonography.

Genetics and Pathophysiology. MCDK is a form of kidney dysplasia, where smaller and larger cysts are found along with immature, undifferentiated, and primitive tissue, resulting from abnormal kidney morphogenesis due to mutations of developmentally expressed genes, such as TCF2 and PAX2 and those encoding the uroplakins. In addition to cystic elements, there is a hydronephrotic form

that has an identifiable kidney pelvis. MCDK often arises from congenital ureteral obstruction during early nephrogenesis, with malformation of the ureteric bud branches and ampullae. Typically, unilateral MCDK is sporadic, whereas bilateral dysplasia may be suggestive of inherited genetic involvement. Pregnancies associated with early detection of fetal bilateral MCDK should be carefully monitored for oligohydramnios and pulmonary hypoplasia with appropriate parental counseling.

Presentation and Diagnosis. Kidney dysplasia with potential presence of cysts is suggested by large bright kidneys on prenatal ultrasonographic examination. Except for cysts associated with MCDK, which are detected at 20 weeks' gestation, cysts detected later in pregnancy are usually associated with other RCDs. Additional presentation in newborn infants may include findings of small kidneys (due to immature glomeruli formation and primitive tubules) and variable number and size of cysts.

If MCDK is unilateral, it may be associated with a contralateral kidney anomaly approximately 30%-40% of the time. MCDK has been described in association with various genetic disorders, many also affecting other organs, including BBS and other ciliopathies, Zellweger syndrome, VACTERL, renal coloboma syndrome, Eagle-Barret syndrome, branchio-oto-renal (BOR) syndrome, and renal-hepatic-pancreatic dysplasia. MCDK may also occur in association with genital tract anomalies, particularly in females, such as HNF1- β -related or Mayer-Rokitansky disease (Table S1 lists associated syndromes).

The optimal modality to diagnose MCDK is high-resolution ultrasonography, and its routine use during pregnancy monitoring has enabled prenatal identification of most cases. In addition to serial ultrasonographic examinations, diuretic

renograms are helpful postnatally in evaluating and monitoring kidney function. In Fig 1, a prenatal ultrasonogram at 36 weeks' gestation and a postnatal ultrasonogram show multiple noncommunicating cysts present in the left kidney. Under circumstances when an ultrasound study is inadequate, MRI can also be used to complete kidney evaluation.

In addition to imaging, individuals with fetal MCDK may undergo a chromosome microarray analysis (CMA), also often called array-CGH (comparative genomic hybridization). CMA is a relatively new technique in clinical genetics and a first-tier diagnostic test to detect submicroscopic copy number variations (CNVs), in which sections of the genome are deleted or repeated. CNVs often cause complex phenotypes, leading to neurocognitive impairment and additional congenital anomalies. CMA of 30 fetuses with MCDK was reported to detect 6 pathogenic CNVs, with the overall pathogenic CNV detection rate via CMA at 15% in the isolated MCDK group and 20% in the MCDK plus extrarenal abnormalities group. Another study showed that the use of CMA may improve detection rate by an additional 16.7% in patients with multiple congenital anomalies and developmental delays.

In children with unilateral MCDK, kidney function, imaging such as dimercaptosuccinic acid (DMSA) or technetium-99m-labeled diethylenetriamine pentaacetate (DTPA) scintigraphy is not recommended. The concordance between ultrasonographic and nuclear medicine studies is very high. Voiding cystourethrography or nuclear scintigraphy may be performed in these infants, although there is still debate in the literature. A meta-analysis of children born with MCDK reported that contralateral kidney abnormalities such as vesicoureteral reflux (VUR) were found in 19.7% of patients and that most patients with significant VUR

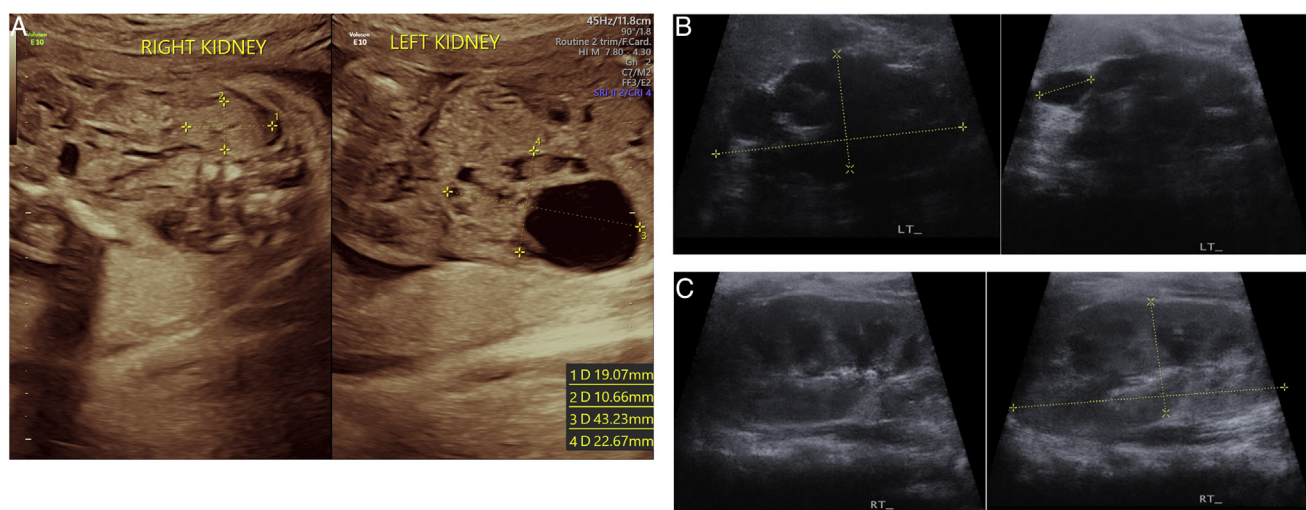


Figure 1. Antenatal and postnatal ultrasound scans of multicystic dysplastic kidney (MCDK). (A) Antenatal scan at 22 weeks' gestation show hyperechoic left kidney and size greater than 95th percentile for gestation, with evidence of multiple noncommunicating cysts. The reniform shape is maintained. The right kidney is normal. (B-C) Postnatal ultrasonography scan. (B) Left kidney shows multiple noncommunicating cysts of various sizes. (C) Right kidney is normal in size and echotexture. Corticomedullary differentiation is well maintained. There is no hydronephrosis or calculus.

developed hydronephrosis. Although VUR resolves spontaneously, voiding cystourethrography should be performed in the presence of contralateral hydronephrosis or a history of urinary tract infection. Follow-up nuclear scintigraphy that shows a lack of blood flow can confirm the diagnosis of MCDK. It is recommended waiting until the infant is 1 month of age before performing a kidney flow scan.

Management and Prognosis. Conservative management and radiographic follow-up for MCDK infants with periodic blood pressure measurements, kidney ultrasonography, and urinalysis are indicated. Infants with unilateral or bilateral MCDK are at an increased risk for CKD and require monitoring of blood pressure, proteinuria, and serum creatinine. Although the incidence of hypertension in MCDK patients 5 or 10 years after diagnosis is similar to that in the general population, routine blood pressure monitoring should be performed as studies have found an increased risk on follow-up of blood pressure greater than the 95th percentile based on age, sex, and height. In children with unilateral MCDK, the contralateral kidney should be monitored with serial ultrasonography at birth and at 2, 5, and 10 years of age to ensure continued appropriate compensatory hypertrophy. Additionally, clinical follow up for hypertension and proteinuria is warranted. Even if kidney ultrasonography indicates no specific concerns regarding the contralateral kidney, periodic urinalysis is indicated to monitor for proteinuria, especially in hypertensive infants. Periodic serum creatinine monitoring should be considered because up to 30% of children with MCDK and compensatory contralateral hypertrophy have a mild degree of reduced kidney function. Despite a very low risk of complications, particularly with laparoscopic procedures, there are scant reasons to perform surgical nephrectomy in the absence of significantly increased risk of hypertension, Wilms tumor, or renal cell carcinoma. Furthermore, longitudinal follow-up studies have shown that the chance of developing kidney malignancy in these patients is extremely low, thus prophylactic nephrectomy is not indicated. Instead, patients should be monitored by using screening ultrasonography. It is crucial to monitor for the presence of VUR, as this can result in urinary tract infections that may endanger the functioning contralateral kidney.

The answer to question 1 is therefore (b).

Essential Reading

- Sharada S, Vijayakumar M, Nageswaran P, Ekambaram S, Udani A. Multicystic dysplastic kidney: a retrospective study. *Indian Pediatr.* 2014;51(8):641-643.
- Bleich AT, Dashe JS. 15–Multicystic Dysplastic Kidney. In: Copel JA, D’Alton ME, Feltovich H, et al, eds. *Obstetric Imaging: Fetal Diagnosis and Care*. 2nd edition. Elsevier: Baltimore, MD: 2018:58-62.

Cystic Dysplasia

Cystic dysplasia is characterized by the presence of at least 1 cyst within an abnormal fetal kidney, hyperechogenic

parenchyma, loss of corticomedullary differentiation, and smaller kidney size. Cystic dysplasia often involves the whole kidney but may also be isolated as segmental dysplasia (associated terminology is provided in [Box 1](#)). Cystic dysplasia can occur in isolation or may be associated with urologic abnormalities, such as posterior urethral valve (PUV) disease or Eagle-Barret syndrome. Additionally, dysplasia and hypoplasia may be associated with multiple congenital abnormalities and syndromes, including BOR syndrome (caused by mutations in *EYA1*, *SIX1*, and *SIX5*), renal-coloboma syndrome (caused by mutations in *PAX2*), VACTERL, CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital and ear abnormalities), and MURCS (Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia).

Patients with cystic dysplasia should be referred to a pediatric nephrologist and undergo evaluation of kidney function, proteinuria, and hypertension. Additionally, differentiation between dilated calyces and dysplastic cysts may be challenging and thus may lead to confusion and misdiagnosis of kidney cysts in patients with high-grade urinary obstruction. This warrants further examination for urinary flow impairment by mercaptoacetyl triglycine (MAG3) scintigraphy.

Essential Reading

- Gimpel C, Avni EF, Breysem L, et al. Imaging of kidney cysts and cystic kidney diseases in children: an international working group consensus statement. *Radiology.* 2019;290(3):769-782.

Hepatocyte Nuclear Factor 1- β Nephropathy

HNF1-, (also known as HNF1 homeobox B or transcription factor 2, and encoded by the *HNF1B* gene) is a homeodomain-containing, tissue-specific transcription factor important in nephron development. It transactivates a variety of genes, such as those encoding albumin, fetoprotein, fibrinogen, transthyretin, glucose transporter 2, and various targets for cystic and polycystic kidney disease. Heterozygous mutations or complete deletions of *HNF1B* and adjacent genes on chromosome 17q12 lead to HNF1- β -nephropathy, where unilateral or bilateral kidney cysts are the clinical features most frequently observed. Individuals may also present with early-onset diabetes mellitus, single kidneys, kidney hypoplasia, electrolyte abnormalities (particularly hypomagnesemia), pancreatic hypoplasia, uterine abnormalities, and early-onset gout. HNF1- β nephropathy presents with hyperechogenic kidneys on kidney ultrasound and may mimic ARPKD or ADPKD and other cystic nephropathies. Thus, kidney imaging alone is not adequate for the diagnosis of HNF1- β -associated disease and requires confirmation by genetic testing. Kidney ultrasound finding from the parents (due to autosomal dominant inheritance of the disease), a family history of maturity onset diabetes of the young (MODY) type 5, and presence of hyperuricemia,

gestational diabetes, or concurrent hypomagnesemia would strengthen the diagnosis of HNF1- β -associated disease.

Essential Reading

- Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated kidney and extra-renal disease—an expanding clinical spectrum. *Nat Rev Nephrol.* 2015;11(2):102-12.
- Bergmann C. Early and severe polycystic kidney disease and related ciliopathies: an emerging field of interest. *Nephron.* 2019;141(1):50-60.

Zellweger Syndrome

Zellweger spectrum disorders (ZSDs), also known as Zellweger syndrome or cerebro-hepato-renal syndrome, comprise a varied group of autosomal recessive disorders. ZSDs are characterized by a defect of peroxisomal biogenesis due to mutations in 1 of the 14 currently identified PEX genes and result in severe metabolic abnormalities (Table S1). The incidence of ZSDs in the United States has been reported to be 1 in 50,000 births. ZSDs in neonatal and infantile patients are often characterized by dysmorphic facial features, severe hypotonia, epileptic seizures, neocortical dysplasia, macro- or microcephaly, skeletal abnormalities, and subcortical kidney cysts (seen in 70% of cases). If ZSDs are suspected, biochemical testing of plasma and urine, including measurement of very-long chain fatty acids (VLCFAs), plasmalogen levels in erythrocytes, peroxisomal bile acid intermediates di- and trihydroxycholestanoic acid, phytanic acid, pristanic acid, and pipecolic acid should be performed to confirm the diagnosis. In the past, prenatal diagnosis was often performed through direct analysis of VLCFA levels and bile acid intermediates in the amniotic fluid or by cytochemical staining of peroxisomes in a sample of chorionic villus, but due to some diagnostic uncertainties, testing is now usually accomplished by genetic testing. Currently, there are no effective treatments for ZSDs, although management does include supportive symptomatic care.

Essential Reading

- Klouwer FC, Berendse K, Ferdinandusse S, Wanders RJ, Engelen M, Poll-The BT. Zellweger spectrum disorders: clinical overview and management approach. *Orphanet J Rare Dis.* 2015;10:151.
- Kheir AE. Zellweger syndrome: a cause of neonatal hypotonia and seizures. *Sudan J Paediatr.* 2011;11(2):54-58.

Calyceal Diverticula (CD)

Case 2: A 4-year-old girl was admitted to the hospital due to fever. At age 5 months, ultrasonography examination had revealed a simple cyst in a central part of the left kidney. Three days before admission, she reported pain in the dorsal region and had fever up to 40.5 °C with poor response to antipyretic therapy. Laboratory test results showed elevated

inflammatory markers and urinary tract infection. Ultrasonography revealed a thin-walled cyst 24 mm in diameter filled with nonechogenic fluid in the central part of the left kidney. After 3 days, follow-up ultrasonography revealed that the cyst contained a thick, heterogeneous sediment with fluid, leading to a suspicion of cyst infection. Her case was diagnosed as acute pyelonephritis accompanied by left-sided renal cyst infection.

Question 2: Which of the following is the next management step?

- a. Antibiotic therapy
- b. Scintigraphy
- c. X-ray urography
- d. All of the above

For the answer to the question, see the following text.

Epidemiology. CDs are rare and present as out-pouchings of the calyx into the renal parenchyma, predisposing to the formation of kidney stones and related infection. CD has been found in 0.2%-0.6% of intravenous urograms (IVU) performed in children.

Genetics and Pathophysiology. Currently, the exact pathophysiology of CD development is unknown. Inflammation-related failure of regression of uretic buds or infection or VUR-related obstruction is postulated to have causative roles. The CD is lined with transitional epithelium, which allows for passive filling of urine through the narrow diverticular neck. Acquired CD may arise due to obstructive, neuromuscular, traumatic, or fibrotic causes. Although CD has not been strictly categorized as a genetic kidney cystic disease, it has been related to mutations in developmental genes such as EYA1 and SIX1 causing BOR syndrome or other reasons for CAKUT.

Presentation and Diagnosis. CD can present at any time during pregnancy including as early as 35 days. CDs are classified as type I or type II. Type I CDs are more common, communicate with a minor calyx or an infundibulum, and are often found in the upper pole. In comparison, type II CD are larger, tend to be symptomatic, communicate with the kidney pelvis/major calyx, and are found in the central part of the kidney. Most patients with CDs have mild or no symptoms. However, some patients do develop flank pain, urinary tract infections, or gross hematuria. Initial ultrasonographic assessment may not be able to definitively diagnose CD due to initial morphological appearance as simple or complex cysts. However, intravenous or computed tomography urography (CTU) studies can further help define the cystic lesion. Although multiphase contrast-enhanced CTU has been used to examine benign CD, a technetium-99m-labeled DTPA diuretic kidney scan seems to be more sensitive.

Management and Prognosis. Although there is no standardized treatment for managing CD in newborn infants with stones, shockwave lithotripsy is the preferred

initial treatment. In patients with small endophytic diverticula, an endoscopic, minimally invasive procedure can be performed. In contrast, more extensive laparoscopic interventions may be required for a larger exophytic diverticula.

The answer for question 2 is (d).

Essential Reading

- Waingankar N, Hayek S, Smith AD, Okeke Z. Calyceal diverticula: a comprehensive review. *Rev Urol*. 2014;16(1):29-43.
- Bombiński P, Warchoń S, Brzewski M, et al. Calyceal diverticulum of the kidney - diagnostic imaging dilemma in pediatric patients—case report. *Pol J Radiol*. 2015;80:27-30.

Hepatorenal Fibrocystic Diseases (HRFCDs)

Overview

HRFCDs consist of monogenic disorders characterized by the fibrocystic abnormalities of the kidney and dysgenesis of the portobiliary tract. Mutations leading to HRFCDs often involve gene encoding proteins that function in the primary cilium or centrosome, which suggests a key role for these organelles in the pathogenesis of HRFCDs. This is the reason HRFCDs are categorized in a larger group of disorders known as the ciliopathies (Fig 2). The most common type of HRFCDs are ARPKD and ADPKD, followed by NPHP, BBS, MKS, and Joubert syndrome (Table S1).

The hepatic pathology of HRFCDs can be separated into 3 main components and include defective remodeling of the ductal plate, abnormal portal veins, and progressive fibrosis of the portal tracts, which can result in portal hypertension, abnormal liver function test results, esophageal varices, and ascending cholangitis. Portal hypertension is often defined by splenomegaly, with the spleen palpable >1 cm larger than the upper limit of normal for age or >2 cm below the left costal margin, and pancytopenia or thrombocytopenia (platelet count $<150 \times 10^3/\mu\text{L}$); or presence of varices, ascites, or hepatopulmonary syndrome. Additionally, hepatic involvement in HRFCDs can manifest as: 1) congenital hepatic fibrosis, which affects microscopic bile ducts; 2) Caroli disease, which refers to the presence of focal macroscopic saccular or fusiform dilations of the medium and large intrahepatic bile ducts; and 3) polycystic liver disease, which is the presence of multiple macroscopic cysts in the liver, mostly associated with ADPKD.

Regarding diagnosis and screening, anticipatory guidance for clinical manifestations of congenital hepatic fibrosis should be provided as any delay can lead to an increased risk of morbidity and mortality. Characteristics of portal hypertension are the earliest manifestation of congenital hepatic fibrosis and can help anticipate further

complications, thus care should be taken to assess for splenomegaly on physical examinations, annual complete blood and platelet count, and ultrasonography with doppler evaluation of the portal and splenic veins, splenic measurement, and potential intra- and extrahepatic biliary dilation. If portal hypertension or biliary anomalies are suspected, the patient should be referred to a pediatric gastroenterologist/hepatologist for verification. Cholangitis should also be considered in any infant with HRFCD presenting with unexplained fever; however, HRFCD can be challenging to diagnose definitively. The suspicion of cholangitis is highly warranted in kidney transplant recipients or when immunosuppression activity is high. Cholangitis often requires a prolonged course of intravenous antibiotics, which in itself could worsen the prognosis of congenital hepatic fibrosis. The Liver Work Group suggests that routine antibiotic prophylaxis is not indicated and recommends that antibiotic therapy should only be considered for 6-12 weeks after a cholangitis episode, immediately after transplantation, or under conditions of heightened immunosuppression. If there is recurrent cholangitis, this may be indicative of need for liver transplantation.

Essential Reading

- Johnson CA, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. *J Med Genet*. 2003;40(5):311-319.
- Bergmann C. Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. *Front Pediatr*. 2018;5:221. <https://doi.org/10.3389/fped.2017.00221>

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Epidemiology. ARPKD usually presents as an early-onset HRFCD, characterized by nonobstructive cystic enlargement of the kidney collecting ducts (10%-90%). ARPKD has an incidence of 1 in 20,000 births among White populations and equal occurrence in boys and girls, although a higher incidence of up to 1 in 8,000 births has been reported in isolated or consanguineous populations. ARPKD is a major cause of morbidity and mortality and has a perinatal death rate of 30%. Kidney survival in ARPKD patients has been reported to be 86% and 42% at age 5 and 20 years, respectively. Morbidities reported to be associated with ARPKD include systemic hypertension (up to 80% of patients within the first year of life), hyponatremia (in 6%-26%; due to impaired urinary diluting leading to water overload), and urinary tract infections (20%-50% of patients).

Genetics. ARPKD is most commonly caused by mutations in PKHD1, a large (~500 kilobase) gene encoding

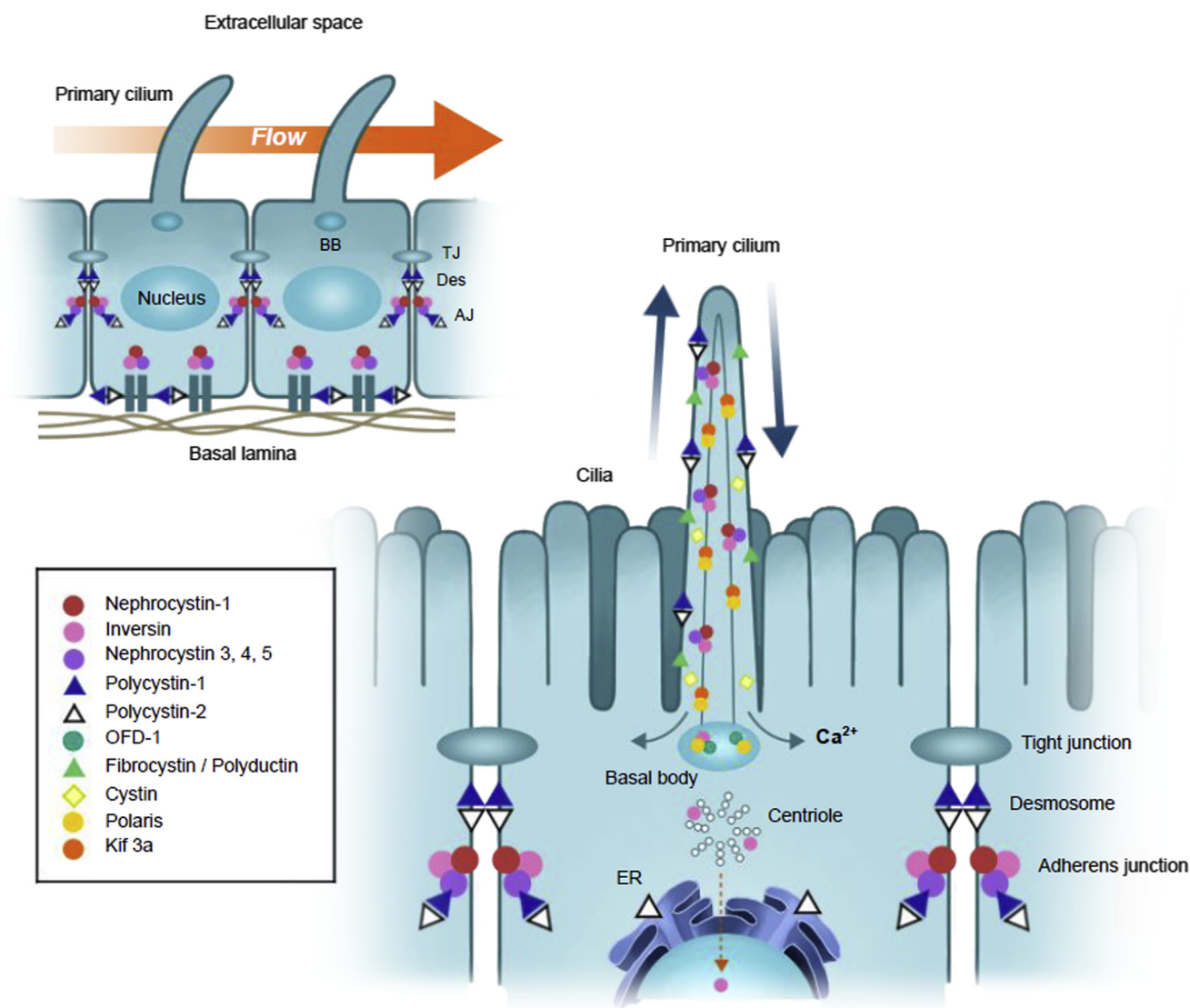


Figure 2. Cystoproteins and their associated functions in the kidney tubular cell. Cystoproteins are the product of genes mutated in RCDs. These proteins are expressed in primary cilia, basal bodies, and centrosomes and can be localized to multiple intracellular domains. A few of these proteins can localize to the adherens junction based on the cell cycle stage. Abbreviations: AJ, adherens junction; BB, basal body; Des, Desmosomes; ER, endoplasmic reticulum; KIF3a, kinesin family member 3a; OFD1, orofacioidigital syndrome type 1; RDC, renal cystic diseases; TJ, tight junction. Graphic created by Joshua Colina based on information in Hildebrandt and Weibin (Nephronophthisis-associated ciliopathies. *JASN* 2007;18(6):1855-1871).

fibrocystin/polyductin (FPC). FPC is a single-membrane-spanning protein that localizes to the apical membranes, mitotic spindle, and primary cilium/basal body on epithelial cells in the bile ducts and kidneys. Missense mutations of in PKHD1 are frequently reported in ARPKD cases. In addition, ARPKD patients with biallelic truncating mutations usually have a more severe phenotype associated with a high rate of perinatal or neonatal death. Affected patients who survive the neonatal period usually carry at least 1 missense mutation.

Mutations in the *DZIP1L* gene, responsible for the ciliary membrane translocation of the ADPKD proteins polycystin 1 (PC1) and polycystin 2 (PC2) can result in ARPKD

pathogenesis. Likewise, mutations in several other cystogenes can phenocopy early PKD and cause severe PKD, resulting in overlapping in differential diagnosis (Fig 3). Molecular genetic testing is the gold standard and should be performed to identify the underlying mutations and verify the diagnosis of ARPKD. Mutation analysis has been reported to detect mutations in more than 90% of ARPKD patients with strong clinical and radiological evidence. According to the Genetics Work Group, single-gene testing should be avoided as a first-line diagnostic approach for infants suspected of having ARPKD. Instead, more robust methods such as NGS have become the mainstay of genetic testing as these techniques can simultaneously and

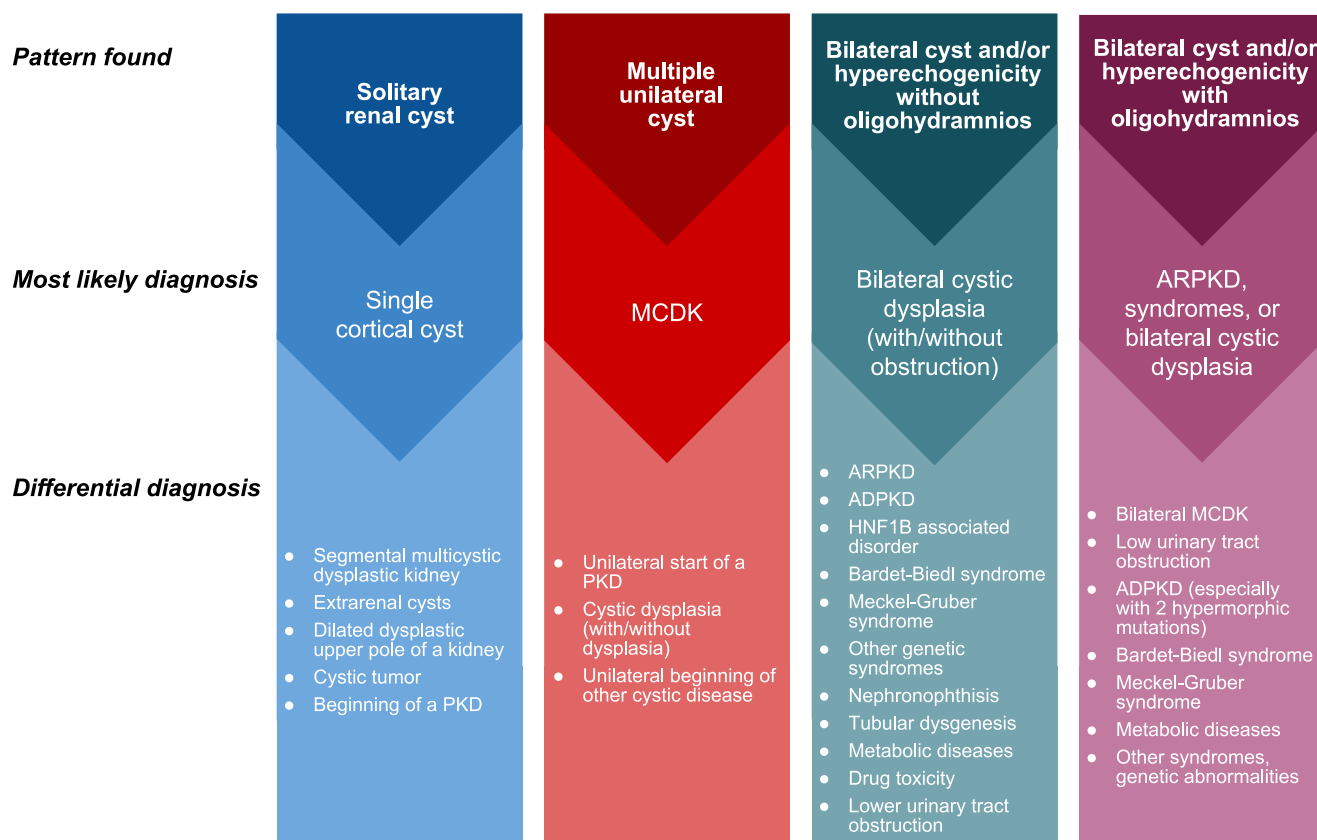


Figure 3. Various patterns of prenatal renal cystic disease with likely and differential diagnosis. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; MCDK, multicystic dysplastic kidneys; PKD, polycystic kidney disease. Graphic created by Joshua Colina based on information in Gimpel et al (Imaging of kidney cysts and cystic kidney diseases in children: an international working group consensus statement. *Radiology*. 2019;290(3):769-782).

efficiently analyze multiple HFRCD genes by using a single test at a relatively low cost with the capability to detect bi-allelic mutations in most patients. Overall, genetic testing is a crucial tool for affirming ARPKD diagnosis prenatally, although it is typically offered to families with a known risk of ARPKD as it requires invasive techniques such as chorionic villus sampling or amniocentesis.

Preimplantation genetic diagnosis, where fertilized embryos are tested for ARPKD by genetic analysis, can be performed for early prenatal diagnosis in affected families. In the case of prenatal genetic testing, it is crucial that all physicians and parents carefully review the medical and ethical implications. The physician should perform genetic testing only if there is informed consent from the parents.

Diagnosis. ARPKD is most often diagnosed in the prenatal period due to early and severe manifestations and vigilance due to the high risk of recurrence (25%). Antenatal ultrasonography during the second or third trimester may present findings of bilaterally enlarged echogenic kidneys, possibly with oligohydramnios, or a small/non-visualized bladder with no urine. Bilateral tiny cysts (5-7 mm) may be found in ultrasonography as they are reported in 29% of ARPKD cases, whereas macrocysts (>10 mm) in the fetal ARPKD kidney are uncommon and

may instead be indicative of MCDK, HNF1- β -related disease, ADPKD, or other ciliopathies. In neonates, ultrasonographic features may include enlarged echogenic kidneys with reduced corticomedullary differentiation, oligohydramnios, microcysts confined to the distal tubules and collecting ducts, and diffusely increased hepatic parenchymal echogenicity with fibrous tissue (Fig 4). In cases where severe oligohydramnios is present, imaging by ultrasonography can be challenging, and MRI may better identify the kidney anomaly. ARPKD can be suspected if one or more of the following are present: 1) absence of kidney cysts on ultrasonography in both parents; 2) clinical/laboratory signs of congenital hepatic fibrosis; 3) characteristic hepatic pathology; 4) pathoanatomical proof of ARPKD in an affected sibling; and 5) parental consanguinity. However, it is important to recognize that these older guidelines need critical reflection, given that precise and unequivocal diagnosis of ARPKD requires genetic testing.

Presentation and Management. Presentation may include enlarged kidneys, oligohydramnios, and Potter sequence due to reduced amniotic fluid. Patients may also present with hyponatremia, urinary concentration defects, and pulmonary hypoplasia. Hepatic involvement is often



Figure 4. Ultrasonography imaging of a 2-month-old female patient with autosomal recessive polycystic kidney disease (ARPKD) presenting as neonatal hypertension. In sagittal views of the (left panel) left and (right panel) right kidneys, both appear enlarged and echogenic with the presence of small cysts.

present in all ARPKD patients and may manifest as Caroli disease and complications of congenital hepatic fibrosis, such as portal hypertension and cholangitis.

Optimal management of ARPKD patients is centered on proper surveillance to minimize morbidity and mortality, procedures to improve quality of life, and informed methodologies for diagnosis and treatment. Clinical management should be guided by a multidisciplinary care team that involves perinatologists, neonatologists, hepatologists, nephrologists, and geneticists to organize care for the patient from the perinatal period to adulthood. Infants with ARPKD are at risk for the clinical manifestations of CKD, such as anemia, osteodystrophy, and cognitive deficits. Some patients may develop symptomatic kidney failure or portal hypertension and may require kidney replacement therapy, with peritoneal dialysis being the preferred modality. A multivariate model-based analysis of data from the international ARegPKD registry (<https://aregpkd.org/>) reported that risk factors for requiring dialysis within the first year of life included the presence of oligo/anhydramnios, prenatal kidney enlargement, a low 10-minute Apgar score, and the need for postnatal breathing support.

Some ARPKD patients may progress to or present with kidney failure and require kidney transplantation whereas others may present with severe kidney and hepatic complications and should be considered for combined liver-kidney transplantation, which is associated with longer-term survival and decreased morbidity and mortality.

ARPKD patients often present with severe hypertension, which manifests during the first year of life in 80% of cases. Expert consensus recommendations for diagnosing and managing ARPKD from the Renal Work Group, an international team of multidisciplinary specialists, includes administration of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). However, the combination of ACEIs and ARBs is not recommended due to the increased risk of side effects without clear added benefit. The treatment

should be aimed at optimizing blood pressure control while preventing further decline in glomerular filtration rate (GFR). This was shown in a study by Dell et al, where a cohort of ARPKD patients was compared to control groups with other congenital cystic kidney diseases. That study reported that the annual rate of decline in GFR in ARPKD patients was 1.4 mL/min/1.73 m² (−6%) with a greater decrease (−11.5%) noted in patients older than 10 years of age. There were no significant differences in GFR decline noted between the 2 groups, with rates of hypertension and left ventricular hypertrophy that were similar. Significantly more ARPKD patients than control group patients with aplastic/hypoplastic/dysplastic disorders (A/H/D) and obstructive uropathies (OU) were taking 3 or more antihypertensive medications (32% vs 0% vs 0%, respectively; $P < 0.0001$) and were using ACEIs (82% vs 27% vs 36%, respectively; $P = 0.0005$). The urinary protein-to-creatinine ratio was significantly lower in the ARPKD patients (0.1 vs 0.6 mg/mg, respectively; $P = 0.005$). The relatively slow rate of decline in GFR and absence of proteinuria in that study suggests that standard clinical measurements have a limited role in assessing therapeutic interventions and further highlights the need for other ARPKD progression biomarkers.

Essential Reading

- 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(3):611–617.
- Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. *Nat Rev Dis Primers*. 2018;4(1):50.
- Dell KM, Matheson M, Hartung EA, Warady BA. Kidney disease progression in autosomal recessive polycystic kidney disease. *J Pediatr*. 2016;171:196–201.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Case 3: A NICU consult was obtained for a 1-week-old female neonate due to cystic appearance of fetal kidney detected at 20 weeks of gestation age by prenatal ultrasonography. Following an uncomplicated delivery, the baby underwent abdominal ultrasonographic imaging that showed bilateral increased echogenicity, with the right kidney measuring 4.9 cm and the left kidney measuring 4.1 cm. Several macrocysts were present in both kidneys. The family history was unremarkable, though after detailed questioning, the patient's mother reported that she was once told she had a cyst on her kidney and that "it was not an issue." The presence of echogenic, mildly enlarged kidneys with several macrocysts resulted in a diagnosis of ADPKD.

Question 3: Which of the following statements is not true?

- a. Neonatal presentation of ADPKD is rare and may be clinically indistinguishable from ARPKD
- b. ADPKD patients often progress to kidney failure, but prognosis for patients who present as neonates is not well established
- c. Family history may not be present due to unrecognized disease in the parent
- d. A majority (85%) of ADPKD patients will not have a positive family history and are presumed to have a de novo mutation
- e. Extrarenal manifestations, such as liver cysts and cerebral aneurysms, rarely present in infants

For the answer to the question, see the following text.

Epidemiology. ADPKD is the most commonly inherited kidney disease with an autosomal dominant pattern. Typically, ADPKD is an adult-onset disease; however, a small proportion (~2%-5%) of patients can manifest ADPKD symptoms during childhood or even prenatally.

Genetics and Pathophysiology. Genetically resolved ADPKD is mainly due to mutations in either PKD1 (85%) or PKD2. PKD1 is a complex gene (46 exons) that encodes the membrane-bound protein PC1. PKD2 is a smaller gene (15 exons) that encodes PC2, a cation channel that interacts with PC1 to form a receptor channel. The mechanosensory function of PC1 facilitates the opening of the calcium-permeable channel whereas PC2 facilitates a series of calcium-dependent signaling cascades. Mutations in PKD1 and PKD2 can lead to disruption of calcium signaling, leading to fluid secretion into tubules, formation of cysts, and vascular sclerosis and interstitial fibrosis. Furthermore, it has been reported that patients with mutations in PKD1 tend to progress to kidney failure at an earlier age than in patients with mutations in PKD2 (mean age, 54.3 vs 74.0 years). Regardless of whether PKD1 or PKD2 is affected, there is significant inter- and intrafamilial phenotypic variability in disease progression and extrarenal complications.

ADPKD may also be caused by mutations in other more recently described genes. Patients may present with

additional features of tuberous sclerosis complex (TSC); the causative TSC2 gene lies adjacent to PKD1. In some patients, a mutation can impact both TSC2 and PKD1, resulting in a contiguous gene deletion syndrome with TSC and severe ADPKD often presenting in utero or during infancy. Notably, patients harboring this TSC2-PKD1 deletion syndrome (or a single point mutation in 1 of 2 known TSC genes) can present with an ADPKD phenotype lacking any extrarenal pathology. Various factors can affect the severity of cyst formation including the timing of PKD1 inactivation and the influence of 1 cyst on neighboring nephrons, which can potentially lead to cyst development in the adjacent tubules.

Diagnosis. Kidney ultrasonography is considered the optimal option for ADPKD diagnosis because it is the most cost-effective and least invasive imaging modality. Ultrasonography scans may present enlarged polycystic kidneys with hyperechoic parenchyma, with or without diminished corticomedullary differentiation and multiple (sometimes tiny) cysts (Fig 5). However, ADPKD can phenocopy ARPKD; therefore, both prenatal ultrasonography and a positive family history are crucial for proper diagnosis in these cases. In instances where there is a patient with unknown or negative family history, genetic testing by mutation analysis or NGS should be used. Notably, approximately 10%-25% of ADPKD patients lack a positive family history; their disease is mainly caused by de novo mutations that may present as atypical disease (eg, when associated with mosaicism). Genetic testing can also be helpful in the evaluation of potential kidney donors in the family, genetic counseling, and future family planning for couples with ADPKD. Bergmann et al have provided specific indications for when genetic testing can be used for these patients (Box 5).

Presentation and Management. ADPKD may present in utero with Potter phenotype and kidney cysts detected by prenatal ultrasonography. Neonates and infants may be asymptomatic or present with bilaterally enlarged cystic kidneys, loss of corticomedullary differentiation, multiple cysts of variable sizes, gross hematuria, nephrolithiasis, and decreased kidney function.

Treatments are currently limited to supportive management of complications and prevention of disease progression, similar to patients with ARPKD. Hypertension, which often precedes clinical manifestations of ADPKD, is a presenting feature that can be detected in the newborn period and strongly correlates with kidney size and reduced function. Ongoing studies have demonstrated that cardiovascular manifestations such as arterial stiffness and hypertrophic vasculopathy often precede decline in kidney function, regardless of blood pressure status. One postulated mechanism of hypertension is through the activation of the intrarenal renin-angiotensin system. The International Consensus Statement on the Diagnosis and Management of ADPKD in Children and Young People recommends that patients should be aggressively treated with ACEIs or ARB therapy to prevent the risk of end-organ damage and should have blood pressure measured annually.

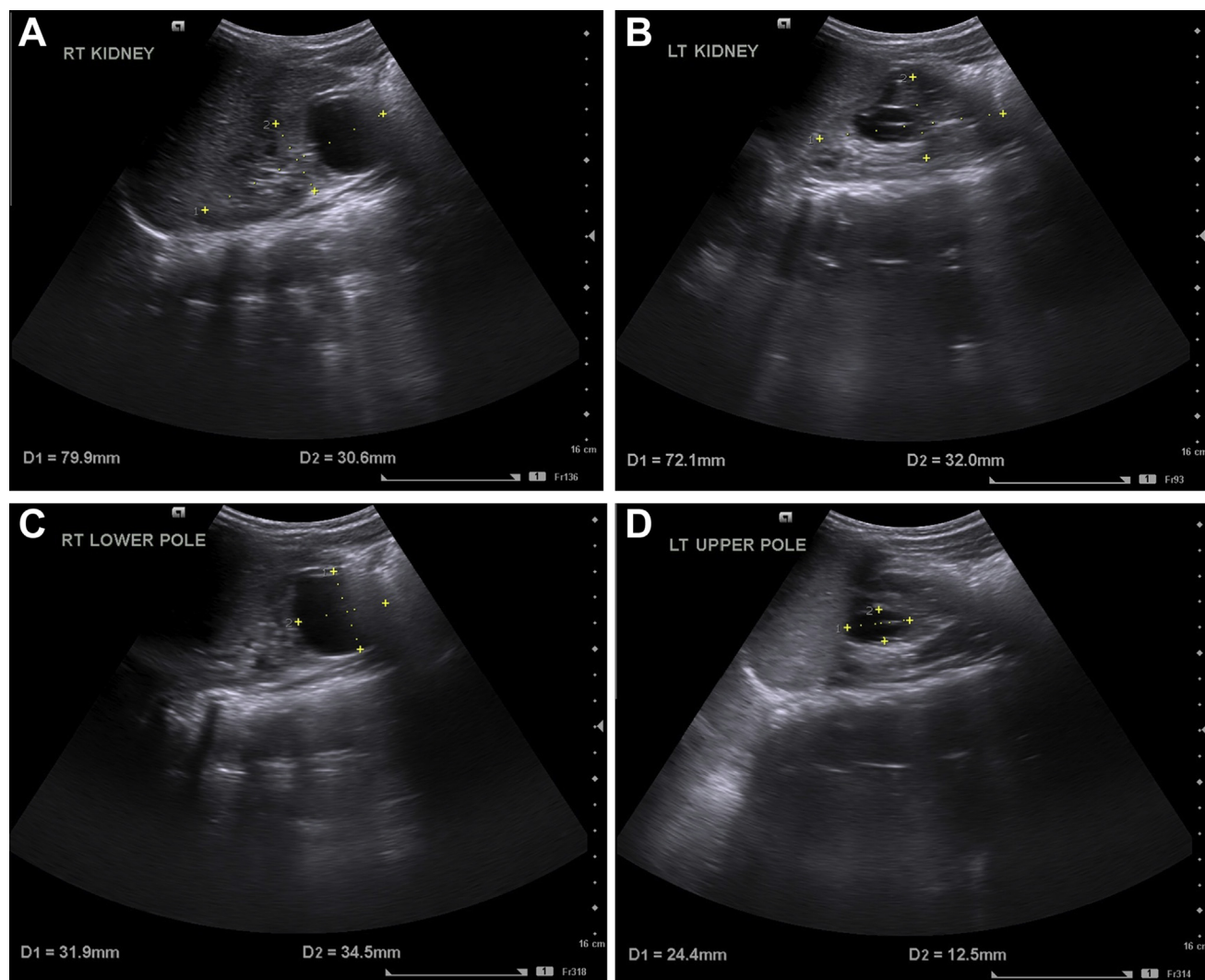


Figure 5. Ultrasonography imaging of a 16-month-old child with a heterozygous mutation in *PKD1* with cysts in both kidneys. Both kidneys were enlarged for age with (A, B) multiple cortical cysts of various sizes, the largest of which measured 34 × 32 mm in the (C) right lower pole and 24 × 12 mm in the (D) left upper pole.

Albuminuria/proteinuria in children with ADPKD have been shown to be an established biomarker of disease progression and a cause of additional tubulointerstitial damage and fibrosis. It is recommended that infants with ADPKD or those at risk should be monitored for albuminuria. If proteinuria is present, ACEIs or ARBs should be used as the primary treatment. Increase in total kidney volume (TKV), which can be quantified by ultrasonography, MRI, or CT scans, has also been demonstrated as a potential biomarker of ADPKD severity and progression.

Infants with ADPKD may suffer from severely decreased GFR and require support through dialysis in the form of peritoneal dialysis or dialysis as a bridging therapy for kidney transplantation. Routine monitoring of cyst growth by ultrasonography in ADPKD patients is also advised, to monitor disease progression; however, routine monitoring should not be performed too frequently in asymptomatic

Box 5. Indications for Genetic Testing in ADPKD

- To determine whether a young relative who may be a potential kidney donor for a patient with ADPKD is genetically affected.
- To obtain a definitive diagnosis or test for mosaicism in individuals with negative family history.
- To assess recurrence risk and aid family planning when there is no family history and the origin of the ADPKD is unclear.
- To identify biallelic disease or other complex genetic syndromes in patients who have very early-onset disease.
- To establish a definitive diagnosis prior to treatment and to assess likelihood of rapid progression for patients being considered for a clinical trial.
- To offer all patients with ADPKD the opportunity for a definitive diagnosis and prognostic information.

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease. Based on information from Bergmann et al (Polycystic kidney disease. *Nat Rev Dis Primers*. 2018;4(1):50).

ADPKD patients due to the psychological impact of cyst monitoring and its low probability of influencing clinical management decisions.

Beyond these current treatment options, other novel therapies such as somatostatin analogs, tyrosine kinase inhibitors, and cyclic AMP inhibitors have continued to emerge for use in ADPKD patients. However, there are no well-defined studies that have examined these potential therapeutics in infants. Tolvaptan, a highly selective vasopressin 2 receptor antagonist (Fig 6), was reported as a possible treatment for severe neonatal ADPKD in a case report. In that study, a female infant diagnosed with ADPKD presented with massive kidney enlargement and respiratory failure. After she was treated with tolvaptan, she had increased urine output, resolution of hyponatremia without an increase in kidney size, and a decrease in plasma creatinine levels with a sustained GFR of 60 mL/min/1.73 m². Although that report showed benefit from treatment, larger scale studies are warranted to determine the efficacy of tolvaptan in the management of infants with ADPKD. Also, tolvaptan has not yet been approved by the US Food and Drug Administration (FDA) for use in children. Overall, although novel therapies are currently being developed and explored, the development of therapies for this population has been shown to be quite challenging due to a variety of factors including the young patient age, developmental effects, issues with monitoring therapeutic effect, and presentation of significant disease at birth.

The answer for question 3 is therefore (d).

Essential Reading

- Cadnapaphornchai MA. Autosomal dominant polycystic kidney disease in children. *Curr Opin Pediatr*. 2015;27(2):193–200.
- 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: 713–726.

Nephronophthisis (NPHP)

Question 4: Which among the following is true for infantile nephronophthisis (NPHP)?

- a. Antenatal presentation with fetal oliguria and oligohydramnios
- b. Individuals with rapid deterioration of kidney function, eventually leading to kidney failure
- c. Hypertension, situs inversus, and ventricular-septal defect might be associated extrarenal features
- d. Infantile NPHP usually differs from later-onset NPHP due to absence of medullary cysts and tubular basement membranes and the presence of cortical microcysts
- e. All of the above

For the answer to the question, see the following text.

Infantile nephronophthisis (NPHP), also known as type 2 NPHP, is very rare due to its severe phenotype, with kidney failure typically occurring prior to 4 years of age. In NPHP, there may be prenatal presentations of oligohydramnios and bilaterally enlarged cystic kidneys. Additionally, NPHP patients often present with extrarenal ciliopathy features, such as hypertension, ventricular-septal defects, and situs inversus. This condition is most commonly caused by recessive mutations in NPHP2/INVS and NPHP3, with mutations in NPHP9/NEK8 and ZNF423/NPHP14, and ANKS6/NPHP16 reported less commonly. Infantile NPHP, in contrast to other forms of NPHP, presents with enlarged cystic kidneys on kidney ultrasound and histologically lacks the tubular basement membrane changes (Fig 7). Additionally, features of infantile NPHP, such as interstitial fibrosis and tubular atrophy, overlap and show resemblance to PKD. Currently, there are no specific or effective treatments available, although management includes supportive treatment for those in the early stages of CKD. For patients with kidney failure, transplantation has been reported as the preferred treatment, as the tubular injury does not recur in the transplanted kidney. The potential use of vasopressin V₂ receptor antagonists (eg, OPC31260) is currently being evaluated as they have shown to be effective in inhibiting the development and potentially reversing the kidney cystic phenotype of a mouse model with mutation of *pcy*, which corresponds to the human NPHP3 gene. Currently, studies are evaluating the use of rapamycin and a mechanistic target of rapamycin (mTOR) inhibitor as possible therapeutic options.

The answer for question 4 is therefore (e).

Essential Reading

- Gagnadoux MF, Bacri JL, Broyer M, Habib R. Infantile chronic tubule-interstitial nephritis with cortical microcysts: variant of nephronophthisis or new disease entity? *Pediatr Nephrol*. 1989; 3(1):50–5.
- Salomon R, Saunier S, Niaudet P. Nephronophthisis. *Pediatr Nephrol*. 2009;24(12):2333–2344.

Bardet-Biedl Syndrome (BBS)

BBS is a heterogeneous ciliopathic disorder with multi-system involvement. BBS has an approximate incidence of 1:100,000 in North America and Europe (Table S1). It is an autosomal recessive disorder, although oligogenic inheritance has been anecdotally reported in a few cases. More than 20 genes (BBS1 to BBS21) have been identified and account for more than 95% of clinically diagnosed BBS cases, with the largest share of mutations occurring in BBS1 (23.2%) and BBS10 (20%). Kidney ultrasonography shows that BBS is characterized by a range of variable abnormalities including unilateral or bilateral cysts; persistent fetal lobulation; urinary tract malformation; absence of corticomedullary differentiation; presence of ectopic, duplex, or horseshoe kidneys; or absence of kidneys (Fig 8). Prenatal ultrasonography most commonly shows

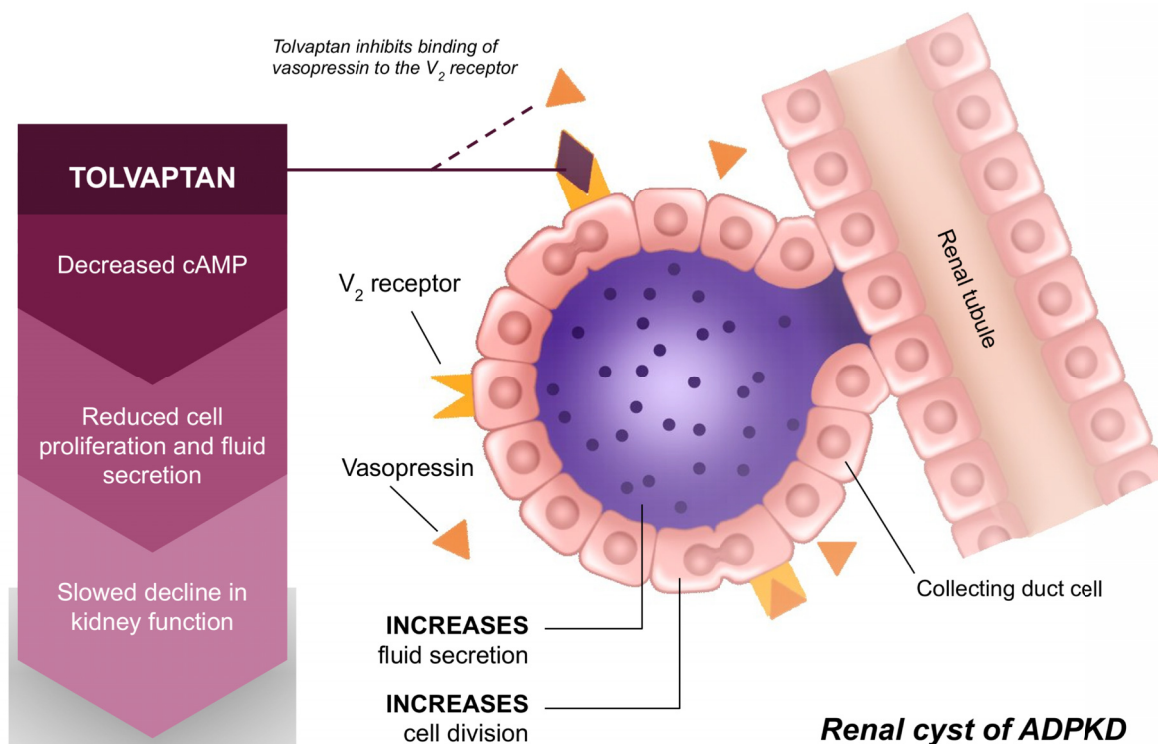


Figure 6. Mechanism of action of a highly selective vasopressin 2 receptor antagonist, tolvaptan, on a renal cyst of ADPKD. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; cAMP, cyclic adenosine monophosphate; V₂, vasopressin 2. Graphic created by Joshua Colina based on information in Devuyst and Torres (Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. *Curr Opin Nephrol Hypertens.* 2013;22(4):459-70).

enlarged hyperechoic kidneys without corticomedullary differentiation. However, kidney ultrasonography is nonspecific, as the kidney phenotype may resemble PKD or nephronophthisis later in life. Thus, the BBS cannot be diagnosed solely by kidney imaging, and genetic analysis should be performed.

Currently, there is no specific treatment for BBS, although a multidisciplinary approach can be used for effective management. Blood pressure should be measured every 6 months, or more frequently in case of hypertension. Additionally, all patients should have at least 1 baseline kidney ultrasound and undergo weight management and ophthalmological (ie, electroretinogram, although not earlier than at 5 years of age) and endocrinological assessments to avoid BBS-associated morbidity and mortality.

Essential Reading

- Forsythe E, Kenny J, Bacchelli C, Beales PL. Managing Bardet-Biedl Syndrome—now and in the future. *Front Pediatr.* 2018; 6:23
- Bergmann C. Educational paper: ciliopathies. *Eur J Pediatr.* 2012;171(9):1285-1300.

Meckel-Gruber Syndrome (MKS)

MKS is a rare autosomal recessive congenital anomaly disorder caused by mutations in genes involved in the architecture and functionality of the primary cilium. This syndrome has a worldwide incidence of up to 1 in 13,250 births and an even higher incidence of up to 1 in 3,500 births in endogamous populations (eg, Gujarati Indians, Hutterites, and the Finish population). MKS is reported to be the severest form of ciliopathy and is characterized by posterior fossa abnormalities (such as occipital encephalocele), bilaterally enlarged cystic kidneys, defects in hepatic system development, and polydactyly. Kidney cystic dysplasia is the most characteristic feature of MKS, with kidneys often being grossly enlarged, leading to massive swelling of the abdomen. In an MKS pregnancy, oligohydramnios is a common complication due to abnormal fetal kidney function. Fetal anomalies can be detected using transabdominal ultrasonography at 10-14 weeks' gestation in both high- and low-risk pregnancies. Additionally, fetal MRI is a valuable complement to ultrasonography if ultrasonography findings are inconclusive or there is presence of

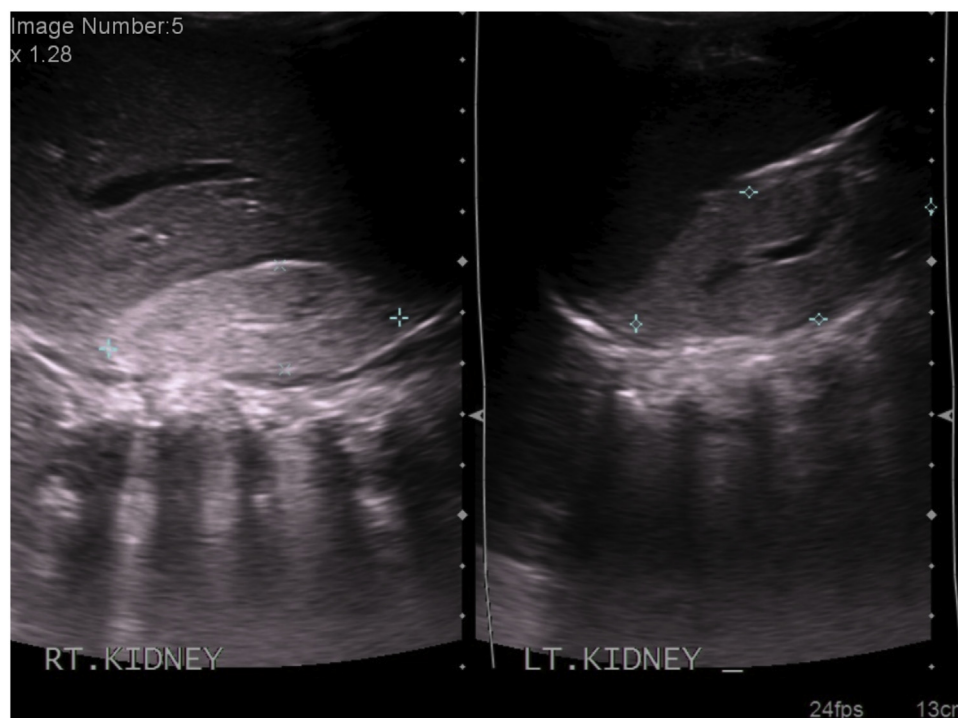


Figure 7. Kidney ultrasonography of a boy with nephronophthisis-related-ciliopathy phenotype. Both kidneys are normal in size for age and show increased cortical echogenicity. Corticomedullary differentiation is lost. There is no evidence of calculi, cysts, or nephrocalcinosis.

oligohydramnios. Genetic testing using NGS and pre-natal genetic diagnosis by chorionic villus sampling may provide a definitive diagnosis. Parents who already have an affected child or with a history of MKS should be provided genetic counseling due to the autosomal recessive inheritance pattern of MKS. Currently, there are no curative treatments available for MKS, and it often leads to mortality in utero or

immediately after birth due to pulmonary hypoplasia, kidney failure, and the frequently occurring occipital encephalocele.

Essential Reading

- Hartill V, Szymanska K, Sharif SM, Wheway G, Johnson CA. Meckel-Gruber syndrome: an update on diagnosis,

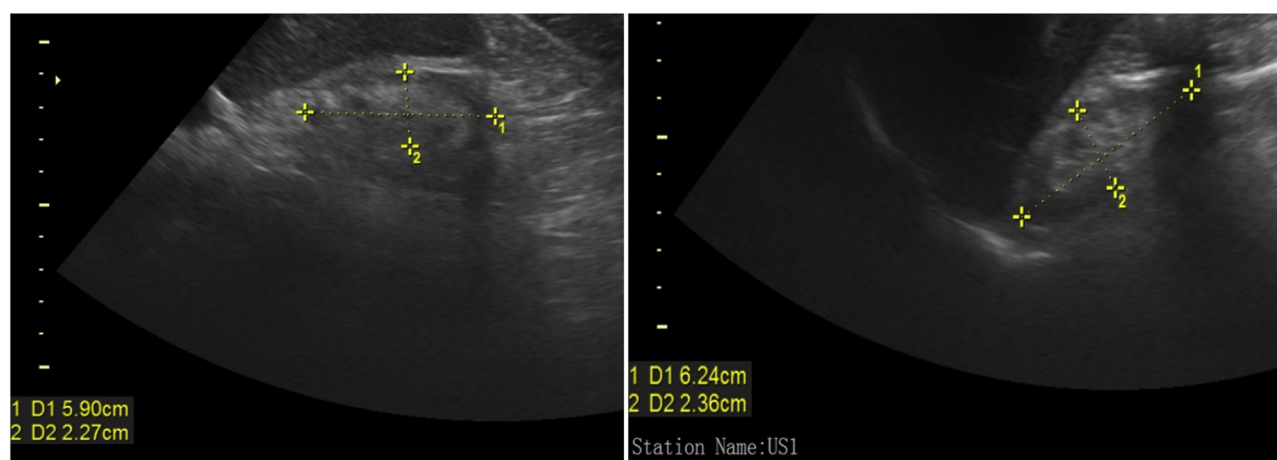


Figure 8. Kidney ultrasonography of a boy with suspected Bardet-Biedl syndrome. This child was receiving maintenance hemodialysis and presented with obesity, polydactyly, and bilateral optic atrophy with blindness. Ultrasonography imaging showed bilateral, small echogenic kidneys with loss of corticomedullary differentiation.

clinical management, and research advances. *Front Pediatr.* 2017;5:244.

- Bergmann C, Frank V, Salonen R. Clinical utility gene card for: Meckel syndrome— update 2016. *Eur J Hum Genet.* 2016;24(8).

Conclusions

Recent clinical and basic science discoveries have helped identify the pathogenesis of genetic and sporadic RCDs occurring in the newborn and thus have greatly enhanced our ability to diagnose and manage them. Modern newborn intensive care and kidney replacement therapy modalities have improved prognosis in terms of survival and quality of life. Additionally, families now have the option to use genetic testing to improve outcomes and explore preimplantation genetic diagnosis for early diagnosis in affected families. Routine monitoring and proactive management of RCDs have allowed patients to have an enhanced quality of life. Currently, curative measures are being explored in the infant population and future therapies will likely leverage multiple agents and modalities to target specific pathways at different stages of kidney disease.

Supplementary Material

Supplementary File (PDF)

Table S1: Descriptions of renal cystic diseases and associated syndromes.

Article Information

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Support: Dr Bergmann is an employee of Limbach Genetics and holds a part-time faculty appointment at the University of Freiburg. His research laboratory receives support from the Deutsche Forschungsgemeinschaft (DFG) (BE 3910/8-1, BE 3910/9-1, and Project ID 431984000 - Collaborative Research Centre [SFB] 1453) and the Federal Ministry of Education and Research (BMBF, 01GM1903I and 01GM1903G).

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

Peer Review: Received May 20, 2020 in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form October 24, 2020.