



Autosomal Dominant Polycystic Kidney Disease: Core Curriculum 2016

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease. It is characterized by relentless development of kidney cysts, hypertension, and eventually end-stage renal disease (ESRD). ADPKD is associated with abdominal fullness and pain, cyst hemorrhage, nephrolithiasis, cyst infection, hematuria, and reduced quality of life, among other symptoms. The disease is a consequence of mutations in *PKD1* or *PKD2*, encoding polycystin 1 (PC-1) and polycystin 2 (PC-2), respectively. Many recent advances have been made in understanding and managing ADPKD. This Core Curriculum outlines the different aspects of molecular genetics, pathophysiology, diagnosis, and management of kidney and extrarenal complications in ADPKD.

Additional Readings

- » Chapman AB, Devuyst O, Eckardt K, et al. Autosomal dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2015;88(1):17-27.
- » Ong AC, Devuyst O, Knebelmann B, et al. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet.* 2015;385(9981):1993-2002.

EPIDEMIOLOGY

ADPKD was first described more than 300 years ago. Population-based epidemiologic studies with ascertainment of autopsies have estimated that ADPKD affects 1 in 400 to 1,000 live births, or 12.5 million people worldwide. Other studies based on clinical registry data suggest lower prevalence rates, ranging from 1 in 543 to 1 in 4,000. ADPKD affects both sexes equally and occurs in all ethnicities. It accounts for 5% to 10% of ESRD cases, making it the fourth leading global cause for kidney failure. In the United States, incidence rates of ESRD due to ADPKD are higher in men than in women (8.2 compared to 6.8 per million, respectively). In recent years, some studies

have reported later onset of ESRD; this may be due to reduced cardiovascular mortality of older patients before reaching ESRD or increased access of older patients to kidney replacement therapy.

Additional Readings

- » Reule S, Sexton DJ, Solid CA, Chen SC, Collins AJ, Foley RN. ESRD from autosomal dominant polycystic kidney disease in the United States, 2001-2010. *Am J Kidney Dis.* 2014;64:592-599.
- » Spithoven EM, Kramer A, Meijer E, et al; ERA-EDTA Registry; EuroCYST Consortium; WGIKD. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry. *Nephrol Dial Transplant.* 2014;29(suppl 4):iv15-iv25.

GENETICS

ADPKD is a Mendelian autosomal dominant disorder. Therefore, individuals at risk have a 50% chance of inheriting the disease. It is genetically heterogeneous, with 2 causative genes identified: *PKD1*, which encodes PC-1 and accounts for 85% of cases; and *PKD2*, which encodes PC-2 and accounts for 15% of cases (Fig 1). Population-based studies from Canada and the United States have suggested a higher prevalence of *PKD2*-associated disease, such that mutations in this gene may account for up to one-fourth to one-third of all ADPKD cases. Although some have postulated that there is a third PKD gene, convincing evidence to support this putative gene is lacking.

ADPKD has strikingly high phenotypic variability. Mutations in *PKD2* versus *PKD1* lead to much milder disease, with average ages at ESRD of 79.7 and 58.1 years, respectively (Table 1). Milder disease is also noted in ADPKD cases associated with nontruncating versus truncating mutations of *PKD1* (the latter account for 65% of *PKD1* mutations). The genotype-phenotype relationship in ADPKD is not completely understood. The disease is associated with a variety of phenotypes, from newborn infants with massive cystic kidneys to patients whose kidney function persists at adequate levels well into old age. Key influences determining this variability are the identity of the affected locus (*PKD1* vs *PKD2* mutation), the allelic variant (truncating, nontruncating, or hypomorphic), timing of gene inactivation, mosaicism, and genetic background. Men may have a slightly more severe phenotype. Affected family members

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Received March 3, 2015. Accepted in revised form July 21, 2015. Originally published online October 31, 2015.

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0272-6386

<http://dx.doi.org/10.1053/j.ajkd.2015.07.037>

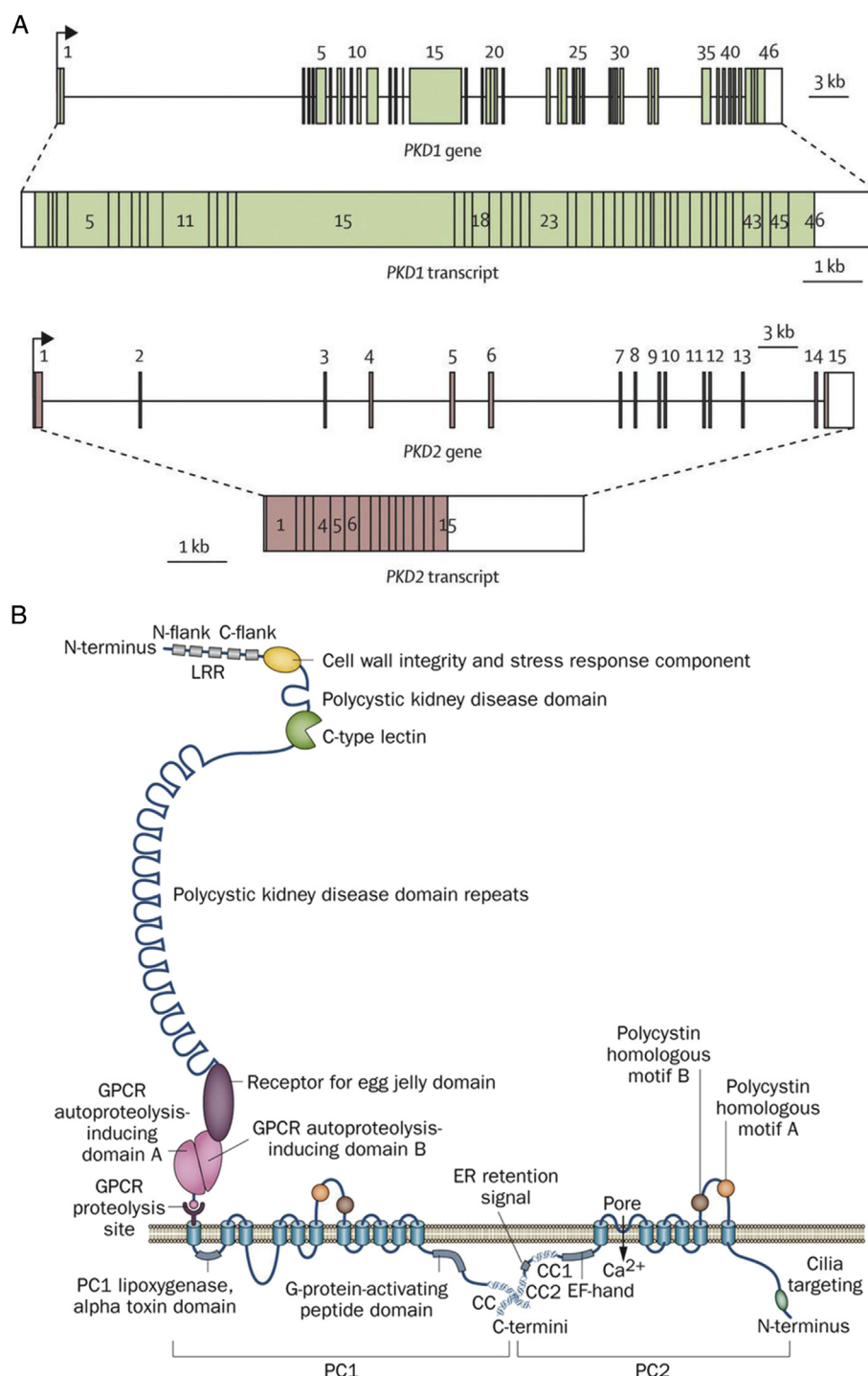


Figure 1. (A) *PKD1* and *PKD2* genes and transcripts. Numbered boxes indicate exons; in total, there are (top) 46 for *PKD1* and (bottom) 15 for *PKD2*. The coding regions are shaded; 5' and 3' untranslated regions are not shaded. Reproduced from Torres et al ("Autosomal dominant polycystic kidney disease." *Lancet*. 2007;369(9569):1287-1301) with permission of Elsevier. (B) Predicted structures of polycystin 1 (PC1) and polycystin 2 (PC2): PC1 is a receptor-like protein with a large ectodomain, 11 transmembrane domains, and a cytoplasmic tail consisting of ~200 amino acids. The last 6 transmembrane domains of PC1 are homologous to the transmembrane region of PC2. PC2 is a transient receptor potential-like calcium channel that has an EF-hand motif and an endoplasmic reticulum (ER) retention signal in the carboxy (C) terminus and a proposed cilia targeting sequence in the amino (N) terminus. PC1 and PC2 physically interact through coiled-coil domains in the cytoplasmic tail of PC1 and in the carboxy-terminal tail of PC2. Reproduced from Chebib et al ("Vasopressin and disruption of calcium signaling in polycystic kidney disease" *Nat. Rev. Nephrol.* 2015;11:451–464) with permission of Nature Publishing Group. Abbreviations: GPCR, G protein-coupled receptor; LLR, leucine rich repeat.

Table 1. *PKD1*- and *PKD2*-Associated ADPKD

	<i>PKD1</i> -Associated ADPKD	<i>PKD2</i> -Associated ADPKD
Gene location	16p13.3	4q21
Protein product	Polycystin 1	Polycystin 2
Year gene discovered	1994	1996
No. of known pathogenic mutations in gene	>1,270	>200
Function of protein product	Receptor, adhesion molecule (not well understood)	Calcium-permeable nonselective cation channel
Proportion of ADPKD cases	64%-85%	15%-36%
No. of cysts	More numerous	Less numerous
Mean age at ESRD incidence, y	58.1	79.7

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease.

may have discordant disease severity, suggesting a role for both genetic and environmental modifiers.

In 10% to 15% of patients with ADPKD, there is no positive family history for the disease. Reasons for such cases include de novo mutations (5% of cases), mild disease from *PKD2* mutations and nontruncating *PKD1* mutations, mosaicism, or unavailability of parental medical records.

Additional Readings

- » Cornec-Le Gall E, Audrezet MP, Chen JM, et al. Type of *PKD1* mutation influences renal outcome in ADPKD. *J Am Soc Nephrol.* 2013;24(6):1006-1013.
- » Harris PC, Hopp K. The mutation, a key determinant of phenotype in ADPKD. *J Am Soc Nephrol.* 2013;24(6):868-870.

PATHOGENESIS

During the past few years, understanding of ADPKD pathogenesis has advanced substantially; nonetheless, the function of the polycystins and the molecular mechanisms underlying disease development are still poorly understood. The polycystins constitute a subfamily of protein channels and are thought to regulate intracellular calcium signaling. Polycystins are expressed in many tissues, including renal tubular epithelia, hepatic bile ducts, and pancreatic ducts. PC-1 is localized to the primary cilium and structures involved in cell-cell contacts (eg, tight junctions). PC-1 probably functions as a receptor and/or adhesion molecule, whereas PC-2, a calcium-permeable nonselective cation channel, is found on the primary cilium, endoplasmic reticulum, and possibly the plasma membrane. These polycystins interact to form the PC complex, which localizes to the primary cilia and plays a role in intracellular calcium regulation.

Cystogenesis in ADPKD is not fully understood, although several hypotheses have been evolving. The

somatic second-hit mutation model suggests that cystogenesis starts after a somatic mutation occurs in the unaffected allele, increasing the functional loss of the causative gene from 50% to 100%. In other words, ADPKD is considered recessive at the cellular level. This model is based on multiple observations, including the focal nature of cystogenesis (ie, a minority of the renal epithelial tubular cells become cystic, although the inherited genetic mutation is present in all cells). Additionally, it has been observed that the normal allele of the affected ADPKD gene in cystic cells undergoes loss or mutation. Recent evidence suggests that for cystogenesis to occur, a complete loss of function is not required; rather, functional PC-1 or PC-2 must be reduced to a certain threshold level. Below this critical threshold, PC-1 dosage correlates with disease severity in relation to both rate of cyst initiation and progression.

Mutations in *PKD1* or *PKD2* lead to a reduction in intracellular calcium, an increase in cyclic adenosine monophosphate (cAMP), activation of protein kinase A, and an increase in sensitivity of collecting duct principal cells to the constant tonic effect of vasopressin (Fig 2). The disruption in calcium signaling coupled with enhanced cAMP signaling activate downstream signaling pathways responsible for impaired tubulogenesis, cell proliferation, increased fluid secretion, and interstitial inflammation. Abnormal epithelial chloride secretion occurs through the cAMP-dependent transporter encoded by the *CFTR* gene and plays an important role in generating and maintaining fluid-filled cysts in ADPKD. Other pathogenic pathways may include activation of mTOR, Wnt, or hedgehog signaling; direct effects of PC-1 fragments on gene transcription; and increased aerobic glycolysis.

Additional Readings

- » Antignac C, Calvet JP, Germino GG, et al. The future of polycystic kidney disease research, as seen by the 12 Kaplan Awardees. *J Am Soc Nephrol.* 2015;26(9):2081-2095.
- » Chebib FT, Sussman CR, Wang X, et al. Vasopressin and disruption of calcium signaling in polycystic kidney disease. *Nat Rev Nephrol.* 2015;11:451-464.
- » Hoppé H, Peters DJ. Translational research in ADPKD: lessons from animal models. *Nat Rev Nephrol.* 2014;10(10):587-601.
- » Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease (ADPKD). *J Clin Invest.* 2014;124(6):2315-2324.
- » Torres VE, Harris PC. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J Am Soc Nephrol.* 2014;25(1):18-32.

KIDNEY PATHOLOGY

Kidneys in patients with ADPKD are characterized by cysts that gradually form and grow in number and size. In early disease, the kidney contains few

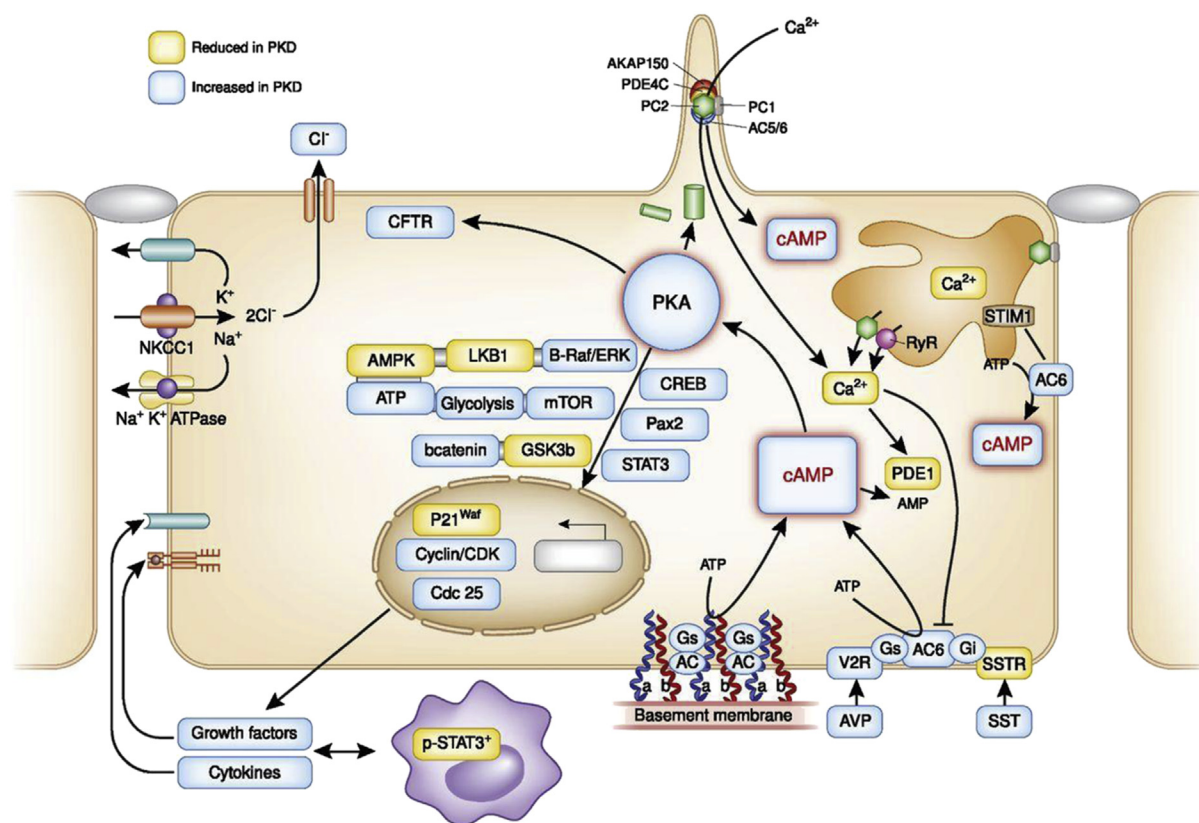


Figure 2. Putative up- or downregulated pathways in polycystic kidney disease. Dysregulation of intracellular Ca^{2+} and increased concentrations of cAMP play a central role. Increased accumulation of cAMP in polycystic kidneys may be explained by the following hypotheses. (1) Reduced Ca^{2+} activates Ca^{2+} -inhibitable AC6, inhibits Ca^{2+} /calmodulin-dependent PDE1 directly, and cGMP-inhibitable PDE3 indirectly. (2) Disruption of a ciliary protein complex (comprising AKAP150, AC5/6, PC2, PDE4C, and PKA), which normally restrains cAMP signaling through inhibition of AC5/6 activity by PC2-mediated Ca^{2+} entry and degradation of cAMP by PDE4C transcriptionally controlled by HNF1 β . (3) Depletion of the ER Ca^{2+} stores that triggers oligomerization and translocation of STIM1 to the plasma membrane, where it recruits and activates AC6. (4) Other contributory factors include disruption of PC1 binding to heterotrimeric G proteins, upregulation of the V2R, and increased levels of circulating vasopressin or accumulation of forskolin, lipo-phosphatidic acid, ATP, or other AC agonists in the cyst fluid. Increased cAMP levels disrupt tubulogenesis, stimulate chloride and fluid secretion, and activate proliferative signaling pathways, including MAPK/ERK (in a Src- and Ras-dependent manner), mTOR, and β -catenin signaling. Activated mTOR transcriptionally stimulates aerobic glycolysis, increasing ATP synthesis and lowering AMP levels, which together with B-Raf-dependent activation of LKB1, inhibits AMPK, further enhancing mTOR activity and CFTR-driven chloride and fluid secretion. PKA signaling also activates a number of transcription factors, including STAT3. Activated STAT3 induces the transcription of cytokines, chemokines, and growth factors that in turn activate STAT3 signaling in interstitial alternatively activated M2 macrophages and result in a feedforward loop between cyst-lining cells and M2 macrophages. Aberrant integrin-extracellular membrane interaction and cAMP signaling within focal adhesion complexes may contribute to the increased adhesion of cyst-derived cells to laminin-322 and collagen. Abbreviations: AC, adenylyl cyclase; AKAP, A-kinase anchoring protein; AMP, adenosine monophosphate; AMPK, AMP kinase; ATP, adenosine triphosphate; B-Raf, B rapidly accelerated fibrosarcoma kinase; cAMP, cyclic AMP; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; ER, endoplasmic reticulum; ERK, extracellularly regulated kinase; HNF1 β , hepatocyte nuclear factor 1 β ; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PC, polycystin; PDE, phosphodiesterase; PKA, protein kinase A; STAT3, signal transducer and activator of transcription 3; STIM1, stromal interaction molecule 1; V2R, vasopressin 2 receptor. Reproduced from Torres and Harris ("Strategies Targeting cAMP Signaling in the Treatment of Polycystic Kidney Disease." *J Am Soc Nephrol*. 2014 Jan;25(1):18-32) with permission of American Society of Nephrology.

fluid-filled cysts and a large amount of well-preserved parenchyma. The cysts originate from the epithelia of only 1% to 5% of nephrons and are bordered by a single layer of tubular cells that proliferate more rapidly and are less differentiated than normal. Cysts arise mostly from the distal nephron and collecting duct; they detach as they expand in volume. The cystic epithelium secretes large amounts of chemokines and cytokines, which likely induce an inflammatory response surrounding the cysts. In advanced

ADPKD, marked enlargement of the kidneys, vascular remodeling, and interstitial fibrosis are present (Fig 3). Benign adenomas are noted in 25% of kidneys of patients affected by ADPKD.

Additional Readings

- » Galarreta CI, Grantham JJ, Forbes MS, et al. Tubular obstruction leads to progressive proximal tubular injury and atubular glomeruli in polycystic kidney disease. *Am J Pathol*. 2014;184(7):1957-1960.

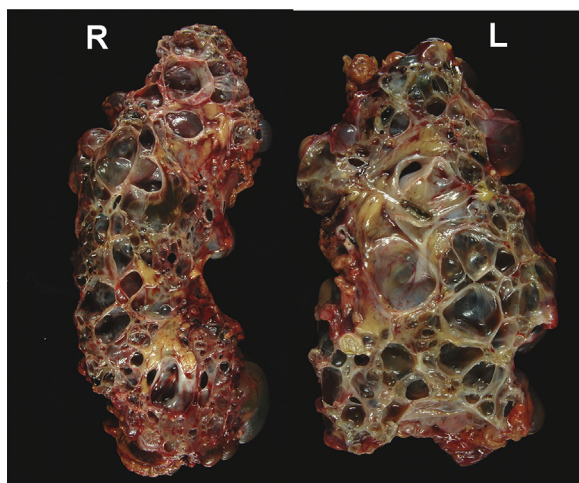


Figure 3. Right (R; 1,830 g) and left (L; 1,040 g) nephrectomy specimens resected from a 51-year-old woman with autosomal polycystic kidney disease 4 months after kidney transplantation.

» Grantham JJ, Mulamalla S, Grantham CJ, et al. Detected renal cysts are tips of the iceberg in adults with ADPKD. *Clin J Am Soc Nephrol.* 2012;7(7):1087-1093.

DIAGNOSIS

Imaging

The diagnosis of ADPKD relies primarily on imaging, although some cases are diagnosed by genetic testing. Typical imaging findings from patients with ADPKD reveal large kidneys with multiple bilateral cysts (Fig 4). Factors important in diagnosing the disease include family history of ADPKD, age of patient, and number of kidney cysts. Given its availability, safety, and low cost, ultrasonography is the imaging modality of choice for presymptomatic diagnosis. Age-dependent ultrasound criteria for both diagnosis and disease exclusion have been established

for patients with a positive family history (Table 2). Specifically, the presence of a total of 3 or more kidney cysts for at-risk individuals aged 15 to 39 years and 2 or more cysts in each kidney for at-risk individuals aged 40 to 59 years are sufficient for a diagnosis of ADPKD. If ultrasonography results are equivocal, magnetic resonance imaging (MRI) or computed tomography (CT) may clarify the diagnosis. Excluding the disease in at-risk individuals also depends on their age, which in turn dictates the imaging modality. For individuals older than 40 years, the absence of kidney cysts on ultrasound excludes ADPKD; in younger individuals (<40 years), MRI is superior to ultrasonography for excluding ADPKD. A recent study of 73 affected and 82 nonaffected individuals suggested that finding fewer than 5 cysts by MRI is sufficient to exclude the diagnosis of ADPKD in potential living related kidney donors. Contrast-enhanced CT with thin slices likely provides similar information, but this has not been ascertained in formal studies.

In the absence of a family history, these imaging-based criteria do not apply. In such situations, multiple factors should be considered, including the age of the patient, the presence of associated manifestations (eg, liver cysts), and findings or family history suggestive of other genetic disorders. ADPKD is the most likely diagnosis in the presence of bilaterally enlarged kidneys and innumerable (>10) cysts in each kidney. Of note, other genetic diseases (eg, tuberous sclerosis, von Hippel-Lindau disease, and autosomal dominant tubulointerstitial kidney disease) can be associated with kidney cysts. When suggestive findings are noted, the differential diagnosis should be broadened (summarized in Table 3).

A practical algorithm for diagnostic evaluation of patients 18 years or older with kidney cysts is shown in Fig 5.

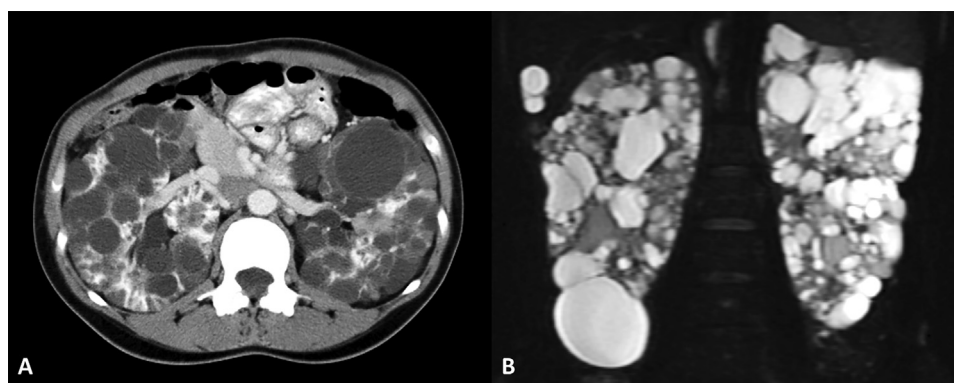


Figure 4. (A) Axial contrast-enhanced computed tomography (CT) image and (B) coronal T2-weighted single-shot fast spin echo magnetic resonance imaging (MRI) in a 39-year-old woman with autosomal polycystic kidney disease. Contrast administration is necessary to differentiate the cystic tissue from preserved parenchyma and detect small cysts using CT, but it is not necessary using MRI.

Table 2. Performance of Ultrasound-Based Unified Criteria for Diagnosis or Exclusion of ADPKD in Patients With a Positive Family History

Diagnostic Purpose	Age, y	Imaging Findings	PKD1	PKD2	Unknown Gene Type
Confirmation	15-29	Total of ≥ 3 cysts ^a	PPV, 100%	PPV, 100%	PPV, 100%
			Sensitivity, 94.3%	Sensitivity, 69.5%	Sensitivity 81.7%
	30-39	Total of ≥ 3 cysts ^a	PPV, 100%	PPV, 100%	PPV, 100%
			Sensitivity, 96.6%	Sensitivity, 94.9%	Sensitivity, 95.5%
	40-59	≥ 2 cysts in each kidney	PPV, 100%	PPV, 100%	PPV, 100%
			Sensitivity, 92.6%	Sensitivity, 88.8%	Sensitivity, 90.0%
Exclusion	15-29	No kidney cyst	NPV, 99.1%	NPV, 83.5%	NPV, 90.8%
			Specificity, 97.6%	Specificity, 96.6%	Specificity, 97.1%
	30-39	No kidney cyst	NPV, 100%	NPV, 96.8%	NPV, 98.3%
			Specificity, 96.0%	Specificity, 93.8%	Specificity, 94.8%
	40-59	No kidney cyst	NPV, 100%	NPV, 100%	NPV, 100%
			Specificity, 93.9%	Specificity 93.7%	Specificity, 93.9%

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; NPV, negative predictive value; PPV, positive predictive value.

^aUnilateral or bilateral.

Adapted from Chapman et al (*Kidney Int.* 2015;88:17-27) with permission of the International Society of Nephrology.

Additional Reading

- » Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 2015;26(3):746-753.

Genetic Testing

Genetic testing is not always required for diagnosis but may be helpful when imaging results are uncertain and/or a firm diagnosis is required, as in identifying living related kidney donors, or in atypical cases (eg, early and severe polycystic kidney disease [PKD], kidney failure without significant enlargement of the kidneys, marked discordant disease within family, marked asymmetry in disease severity between kidneys, or very mild PKD). Genetic testing is also useful in the diagnosis of sporadic PKD with no family history or PKD with syndromic features. Such testing can be helpful in reproductive counseling as well. When effective disease-modifying therapies become available, it will be beneficial to test young patients to confirm the diagnosis prior to starting treatment.

Currently, the most common method used for molecular diagnosis of ADPKD is direct mutation screening by Sanger sequencing of the *PKD1* and *PKD2* genes. This can be followed by multiplex-dependent probe amplification in cases with negative DNA sequencing results. Next-generation sequencing technologies have a potential for high-throughput screening and lower cost. Currently, molecular screening is available commercially but remains expensive and is often difficult to interpret. More than 1,270 and 200 pathogenic mutations have been reported for *PKD1* and *PKD2*, respectively (<http://pkdb.mayo.edu>).

Up to 15% of patients with suspected ADPKD do not have a mutation in these genes despite a comprehensive screen.

Additional Readings

- » Eisenberger T, Decker C, Hiersche M, et al. An efficient and comprehensive strategy for genetic diagnostics of polycystic kidney disease. *PLoS One.* 2015;10(2):e0116680.
- » Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am Soc Nephrol.* 2012;23(5):915-933.
- » Tan AY, Michael A, Liu G, et al. Molecular diagnosis of autosomal dominant polycystic kidney disease using next-generation sequencing. *J Mol Diagn.* 2014;16(2):216-228.

Presymptomatic Screening of Patients at Risk for ADPKD

Presymptomatic screening of ADPKD is not currently recommended for at-risk children. A positive diagnosis might have future implications on a child's career, insurability, and education. A positive diagnosis could cause an emotional burden as well. Prior to testing a child, clinicians should have a discussion with the parents or guardian. Nevertheless, at-risk children should be monitored for early presentations of the disease that require treatment (eg, hypertension). Presymptomatic screening of adults at risk for ADPKD is typically performed by ultrasonography, but MRI can be considered.

CLINICAL MANIFESTATIONS AND MANAGEMENT

Kidney Manifestations

ADPKD can present with hypertension, pain, hematuria, proteinuria, or decreased glomerular

Table 3. Differential Diagnosis of Other Kidney Cystic Diseases

Disorder	Inheritance	Family History	Clinical Features
Multiple benign simple cysts	Acquired	None	Relatively common in the general population; increase in number and size with age (age < 30 y, uncommon, rarely multiple or bilateral; age 30-59 y, uncommon to have at least 2 cysts in each kidney; age > 60 y, uncommon to have ≥4 cysts in each kidney); kidney ultrasound in family members may be helpful
Acquired kidney cystic disease	Acquired	None	Seen in advanced CKD, particularly in patients receiving RRT; cysts are small, bilateral, and multiple (>4 cysts in each kidney); kidneys are small to normal
Localized kidney cystic disease	Acquired	None	Uncommon, benign, unilateral, not progressive
Autosomal recessive polycystic kidney disease (ARPKD)	Autosomal recessive	25% concordance between siblings	Affects ~1 in 20,000; in neonates, death in 30%, enlarged echogenic kidneys and pulmonary hypoplasia; in older children, biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation) resulting in portal hypertension and cholangitis; collecting duct ectasia and macrocystic changes associated with calcifications, hypertension, and/or decrease in kidney function
Tuberous sclerosis complex (TSC)	Autosomal dominant	Absent in 2/3 of cases	Affects ~1 in 10,000 live births; skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, shagreen patch); >90% have cerebral pathology (cortical tuber, subependymal nodules, giant cell astrocytoma); 90% have kidney manifestations (polycystic kidneys, angiomyolipomas); 50%-70% have retinal hamartomas; 50% have pulmonary lymphangioleiomyomatosis
PKD1-TSC contiguous gene syndrome	Autosomal dominant	Spontaneous presentation frequent	Presentation with polycystic kidneys at an early age, with kidney angiomyolipomas frequently presenting after the first year of life
von Hippel-Lindau syndrome	Autosomal dominant	~20% de novo	Affects ~1 in 36,000, cerebellar and spinal hemangioblastoma, retinal angiomas, serous cystadenomas and neuroendocrine tumors of pancreas, pheochromocytoma, renal cell carcinoma
Medullary sponge kidney (MSK)	Unclear; autosomal dominant in some cases	Familial clustering reported	Affects ~1 in 5,000, tubular dilatation of the collecting ducts giving the appearance of “brush” or linear striations on intravenous pyelogram, medullary nephrocalcinosis, kidney stones, kidney cortex spared on CT or MRI
Medullary cystic kidney disease (MCKD ^a)	Autosomal dominant	Rare	Slowly progressive kidney disease, medullary cysts (but uncommon in families with type 2 MCKD ^a), hyperuricemia and gout (in type 2 MCKD ^a), small to normal-sized kidneys
Renal cysts and diabetes syndrome (RCAD/MODY5/HNF-1B ^b)	Autosomal dominant	Spontaneous mutations (often deletions) in 50%	Kidney cysts or malformation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%
Bilateral parapelvic cysts	Unknown		Lymphatic (not epithelial) cysts, distort the kidney pelvis, infundibula, and calyces

Abbreviations: ADTKD, autosomal dominant tubulointerstitial kidney disease; CKD, chronic kidney disease; CT, computed tomography; ESRD, end-stage renal disease; HNF-1B, hepatocyte nuclear factor 1β; MODY5, maturity-onset diabetes mellitus of the young type 5; MRI, magnetic resonance imaging; MUC1, tumor-associated mucin; PKD1, polycystic kidney disease 1; RRT, renal replacement therapy; UMOD, uromodulin.

^aUse of the term MCKD is discouraged; what was formerly type 1 MCKD should be referred as ADTKD-MUC1 and what was formerly type 2 MCKD should be referred as ADTKD-UMOD.

^bCurrent designation is ADTKD-HNF-1B.

filtration rate (GFR). The age of onset of these manifestations is variable. The clinical manifestations of patients with *PKD1* or *PKD2* mutations are fully overlapping, but the former is associated with larger kidneys, more severe disease, and younger age at ESRD incidence. The different

kidney manifestations in ADPKD are summarized in the first section of [Table 4](#).

Cyst Growth and Disease Monitoring

As noted, ADPKD is characterized by the gradual formation and enlargement of bilateral kidney cysts

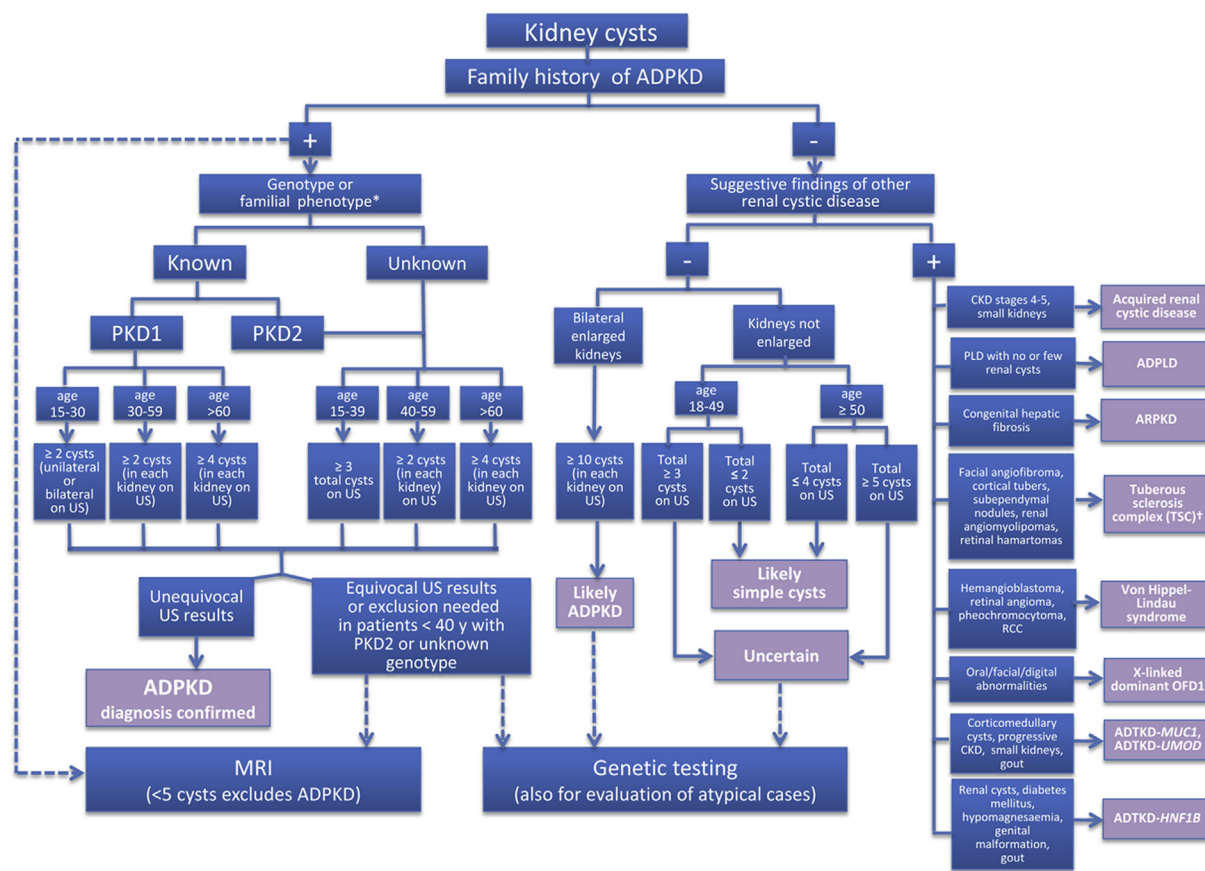


Figure 5. Practical algorithm for diagnostic evaluation of patients 18 years or older with kidney cysts. *At least 1 affected member with ESRD 50 years or younger strongly suggests *PKD1* mutation; at least 1 affected family member without ESRD 70 years or older suggests *PKD2* mutation. †Polycystic kidneys with multiple angiomyolipomas (contiguous *PKD1-TSC2* syndrome). Abbreviations: ADPKD, autosomal polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ADTKD-MUC1, autosomal dominant tubulointerstitial kidney disease—tumor-associated mucin (previously known as medullary cystic kidney disease type 1); ADTKD-UMOD, autosomal dominant tubulointerstitial kidney disease—uromodulin (previously known as medullary cystic kidney disease type 2); ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; MRI, magnetic resonance imaging; OFD1, oral-facial-digital syndrome type 1; PKD1, polycystic kidney disease 1; PKD2, polycystic kidney disease 2; RCC, renal cell carcinoma; US, ultrasound.

during the lifetime of the patient. Until age 40 to 60 years, kidney function may remain within the normal range, making GFR ascertainment less useful in monitoring the disease in its early stages. At the point that GFR decline has started, physical changes in the kidneys are visible on imaging studies: they become notably enlarged with little recognizable parenchyma. At this stage, the average rate of GFR decline is 4.4 to 5.9 mL/min per year.

Total kidney volume (TKV) is a better tool for monitoring and prognosticating in early stages of ADPKD. TKV, measured by MRI or CT, is an accurate estimate of kidney cyst burden and correlates with multiple kidney manifestations in ADPKD, such as pain, hypertension, hematuria, and proteinuria. TKV and cyst volume increase exponentially in all patients with ADPKD, but at variable rates (5%-6% per year on average). Although patients with *PKD1*-related disease have larger kidneys and more cysts

than those with *PKD2* mutations, the rate of growth is not different. However, most regulatory agencies have not yet accepted TKV as a primary end point in clinical trials. Once disease-modifying therapies become available, repeat imaging to follow TKV may be indicated in clinical practice.

A classification of ADPKD has been developed based on age- and height-adjusted TKV. This classification stratifies patients into different classes (class 1A through 1E), which translate into varying rates of decline in GFR (<http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754>). This tool is useful in identifying individuals who are at higher risk for disease progression and for estimating the age at which the patient will reach ESRD (Fig 6). For instance, comparing subclass 1E to 1A, the frequency of reaching ESRD within 10 years is substantially greater (66.9% vs 2.4%). This classification is useful in clinical trial

Table 4. Kidney and Extrarenal Manifestations in ADPKD Patients

PKD Manifestation	Frequency	Comments
Kidney		
Urinary concentration defect	In up to 60% of children	Earliest manifestation
Hypertension	In 50%-70% prior to GFR decline; average age of onset, 30 y	Screen children with family history of ADPKD from age 5 y, then at 3-y intervals if negative
ESRD	Occurs in 50% by age 60 y	Mean age of onset, 58 y
Proteinuria (>300 mg/d)	Associated with GFR decline	Prognostic marker
Abdominal/flank pain	In 60% of adults	Acute, chronic; multiple causes
Nephrolithiasis	In 20%-35% of patients	Uric acid, calcium oxalate composition
Cyst hemorrhage/gross hematuria	In up to 60% of patients	Most resolve within 2-7 d
Urinary tract infection	In 30%-50% of patients	More common in women
Renal cell carcinoma	In <1% of patients	Risk not increased, may present with systemic symptoms
Extrarenal		
Polycystic liver disease	In >80% by age 30 y	Include liver imaging in initial visit
Intracranial aneurysm	In 20%-27% of those with positive family history of intracranial aneurysm; in 9% of those without such family history	Screen if family history of intracranial aneurysm, personal history of intracranial hemorrhage, individuals with high-risk professions, pretransplantation
Arachnoid cysts	In 8%-12%	Possible increased risk for spontaneous subdural hematoma
Mitral valve prolapse	In 25%	Screen if symptoms
Pericardial effusion	In up to 35%	Screen if symptoms
Pancreatic cysts	In 10%	No screening needed
Diverticulosis	In 20%-25% of those with ESRD	No screening needed
Bronchiectasis	In up to 37%	Mild, no screening needed
Congenital hepatic fibrosis	Rare	No screening needed
Seminal vesicle cysts	In up to 40% male patients	No correlation to semen abnormalities
Male infertility	Associated with ADPKD	Abnormal semen parameters reported

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

settings to identify patients with rapid disease progression who might benefit most from therapy, as opposed to patients who progress slowly and might not need therapy. Knowing the patient's classification also may be helpful in the clinical practice setting for counseling and treatment planning.

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- » Torres VE, Grantham JJ, Chapman AB, et al. Potentially modifiable factors affecting the progression of autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(3):640-647.

Early Manifestations

Impaired urinary concentrating capacity is an early sign of ADPKD. This symptom precedes kidney cyst

formation and is present in up to 60% of children with the disease. In cross-sectional studies and prospective studies, respectively, severity of PKD and the rate of disease progression correlate with plasma copeptin levels, a surrogate of vasopressin.

Additional Reading

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Hypertension

Hypertension (blood pressure [BP] > 140/90 mm Hg) is the most common manifestation of ADPKD. It occurs in 50% to 70% of cases prior to any significant decline in kidney function, with an average age of onset of 30 years. Elevated BP may be detected in a small but significant percentage of children with ADPKD. Increased BP in patients with ADPKD has been attributed to several causes, including activation of the

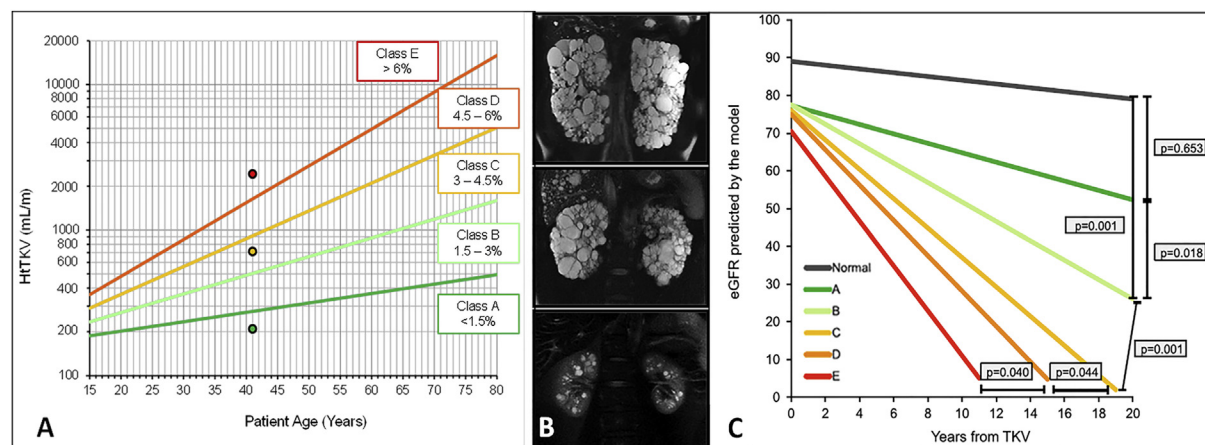


Figure 6. An imaging classification of autosomal polycystic kidney disease predicts the change in estimated glomerular filtration rate (eGFR) over time in patients with typical, bilateral, and diffuse distribution of cysts. (A) The A through E classification is based on height-adjusted total kidney volume (htTKV) and age at the time of imaging, assuming kidney growth rates of $<1.5\%$, 1.5% to 3% , 3% to 4.5% , 4.5% to 6% , or $>6\%$ per year and a theoretic initial htTKV of 150 mL/m ; the dots correspond to the patients in panel B. (B) Magnetic resonance imaging studies corresponding to three 41-year-old patients in classes A (bottom), C (middle), and E (top), respectively. (C) Estimated glomerular filtration rate (eGFR) slopes in a cohort of 376 patients stratified by imaging class (-0.23 , -1.33 , -2.63 , -3.48 , and $-4.78 \text{ mL/min/1.73 m}^2$ per year for classes A through E, respectively); average eGFR at baseline ($75 \text{ mL/min/1.73 m}^2$) and average age at baseline (44 years) for all patients were used for the model; values for normal slope were obtained from a population of healthy kidney donors; eGFR slopes were significantly different among the classes, and all but class A were significantly different from the control population of healthy kidney donors. (A, B) Courtesy of M.V. Irazabal; (C) reproduced from Irazabal MV et al ("Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials." *J Am Soc Nephrol.* 2015;26(1):160-172) with permission of American Society of Nephrology.

renin-angiotensin-aldosterone system (RAAS), increase in sympathetic tone, and primary vascular dysfunction. The most essential factor is activation of the intrarenal RAAS, possibly caused by stretching and compression of the vascular tree by cyst expansion, leading to ischemia. RAAS activation has a potential mitogenic effect on kidney cysts, supported by studies in animals. The Halt Progression of Polycystic Kidney Disease (HALT-PKD) study is a recent randomized, double-blind, placebo-controlled clinical trial that examined the role of RAAS blockade in patients with early and advanced stages of ADPKD. Monotherapy with angiotensin-converting enzyme (ACE) inhibitors was found to be associated with good BP control in the majority of patients. In patients with early (aged 15-49 years; $\text{GFR} > 60 \text{ mL/min/1.73 m}^2$) versus later stage ADPKD, rigorous BP control (BP target range, $95\text{-}110/60\text{-}75 \text{ mm Hg}$) was associated with a slower increase in TKV; more rapid decline in estimated GFR (eGFR) during the first 4 months of treatment, with a slower decline thereafter (an overall eGFR effect was absent); a smaller increase in renal vascular resistance; and a greater decline in left ventricular mass index. Dual RAAS blockade with lisinopril and telmisartan had no beneficial effect compared to lisinopril alone in these patients or in patients with more advanced ADPKD (aged 18-64 years; GFRs , $25\text{-}60 \text{ mL/min/1.73 m}^2$).

In patients with ADPKD, hypertension is associated with progression to ESRD and cardiovascular morbidity

and mortality. The diagnosis of hypertension is often made late. Children with ADPKD with high or borderline-high BP have been found to have attenuated nocturnal dipping, exaggerated BP response to exercise, and higher left ventricular mass indexes. This suggests that target-organ damage develops early in ADPKD. Early detection and treatment of hypertension, particularly in children and young adults, is indicated. Screening of children with a family history of ADPKD from age 5 years onward, with rescreening every 3 years when no hypertension is found, seems prudent.

In adults, home BP monitoring is advised and results in better adherence to treatment. Twenty-four-hour ambulatory BP measurement can identify "nondippers" who would benefit from intensified regimens and evening dosing. The target BP is $\leq 140/90 \text{ mm Hg}$, but should be individualized and lowered to $\leq 130/80 \text{ mm Hg}$ in patients with left ventricular dysfunction, intracranial aneurysm (ICA), diabetes, or proteinuria. In young patients with ADPKD with chronic kidney disease (CKD) stages 1 to 2, tight BP control (BP target, $95\text{-}110/60\text{-}75 \text{ mm Hg}$) may be advantageous. Studies have shown that in recent decades, patients with ADPKD have experienced lower cardiovascular mortality, which could be attributable to improved BP control.

Lifestyle modification and medical treatment can help control BP. It is beneficial to encourage a healthy lifestyle in families with a history of ADPKD through exercise programs, low salt intake ($\leq 2 \text{ g/d}$), and

maintenance of healthy weight (body mass index, 20–25 kg/m²). Salt restriction should be emphasized because patients with ADPKD are usually overloaded with sodium and have sodium-sensitive hypertension. ACE inhibitors or angiotensin receptor blockers, which are equally effective for RAAS blockade, should be a first-line therapy. Of note, coadministration of these drugs does not confer additional benefit. Caution should be used when prescribing ACE inhibitors or angiotensin receptor blockers to women of child-bearing age given their teratogenic risk. It is not clear which antihypertensive drug class should be used as second line. Beta-blockers or α -blockers are preferred for patients with comorbid conditions such as angina or benign prostatic hyperplasia. Calcium channel blockers and diuretics can also be used, but cautiously: in ADPKD, such drugs might play a role in worsening kidney disease progression.

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Proteinuria

Proteinuria (protein excretion > 300 mg/d) is present in almost 25% of adults with ADPKD, but rarely exceeds 1 g/d. Proteinuria has prognostic value because its presence and degree correlate with severity of the disease (eg, larger TKV, more rapid loss of GFR, and earlier onset of ESRD). Nephrotic syndrome in ADPKD is rarely reported and usually reflects a superimposed glomerular process. Proteinuria should be monitored in patients with ADPKD. It is uncertain whether reduction of proteinuria with ACE inhibitors or angiotensin receptor blockers will slow the progression of the disease.

Pain

Abdominal and flank pain are reported in 60% of adults with ADPKD. Acute pain is often associated with kidney cyst hemorrhage, infection, or stones. Pain due to kidney cyst infection is usually diffuse, unilateral, and nonradiating as compared to point tenderness in cyst hemorrhage. Different causes of

acute pain are discussed in diagnosis of and therapies for the following sections.

Pain can also be chronic and in some cases debilitating. Such pain is usually due to cyst enlargement that causes kidney capsule stretching or is musculoskeletal in origin. It is typically a steady discomfort exacerbated by walking or prolonged standing. Patients can frequently localize the pain in an abdominal location with one finger. Mechanical (musculoskeletal) back pain is commonly associated with marked enlargement of the kidneys and/or liver and is insidious and progressive. It is important to recognize the pattern of pain and pursue a differential diagnosis with a multidisciplinary approach. Managing chronic pain can be challenging, and strategies used in standard pain clinics should be applied to patients with ADPKD. These strategies include physical interventions such as ice massage or heating pads, use of support garments or the Alexander technique, and physical therapy. Pain medications should include nonopioid analgesics such as acetaminophen, tramadol, and clonidine. Nonsteroidal anti-inflammatory drugs should be avoided in elderly patients and should not be used beyond 5 to 7 days. Opioids should be dose modified for GFR when needed to treat moderate to severe pain. In cases of disabling pain, cyst sclerosis and laparoscopic cyst fenestration can be attempted. Percutaneous cyst aspiration can be a useful diagnostic and therapeutic trial prior to more permanent and invasive procedures. Other alternatives for pain control that have been tried successfully in small series include celiac plexus blockade, radiofrequency ablation, spinal cord stimulation, thoracoscopic sympathectomy, laparoscopic kidney denervation, and percutaneous transluminal catheter-bases denervation. Success with transluminal catheter-bases denervation has been described in recent case reports and is currently undergoing clinical trials in patients with ADPKD.

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Nephrolithiasis

Nephrolithiasis occurs in 20% to 35% of patients with ADPKD, with two-thirds of cases being symptomatic. Stones are usually composed of uric acid and/or calcium oxalate. CT is more sensitive than ultrasonography in detecting stones. Dual-energy CT can distinguish between the 2 types of stones

(Fig 7C and D). Increased frequency of nephrolithiasis is attributed to increased urinary stasis and metabolic factors, which include low urinary pH, low citrate concentration, and decreased ammonia excretion. It often is challenging to distinguish between stones and cyst wall or parenchymal calcifications. Medical treatment for nephrolithiasis prevention is similar to the general population. Potassium citrate is a treatment of choice in most cases. Management of obstructing stones is more difficult in patients with ADPKD. Extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy in patients with early disease and normal kidney function are not contraindicated and have been used successfully without increased complications. Flexible ureterorenoscopy with laser fragmentation also can be considered.

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- » Yili L, Yongzhi L, Ning L, et al. Flexible ureteroscopy and holmium laser lithotripsy for treatment of upper urinary tract calculi in patients with autosomal dominant polycystic kidney disease. *Urol Res.* 2012;40(1):87-91.

Hematuria

Cyst hemorrhage is common in ADPKD. High-density cysts are frequently seen on imaging and likely represent cyst hemorrhage, but can also be indicative of proteinaceous content (Fig 7A and B). Cyst hemorrhage can be associated with fever and is often challenging to differentiate from cyst infection. Gross hematuria may be associated with cyst hemorrhage, infection, passage of kidney stone(s), or kidney/urinary neoplasm. Hemorrhages typically resolve within 2 to 7 days. Tests to exclude neoplasm

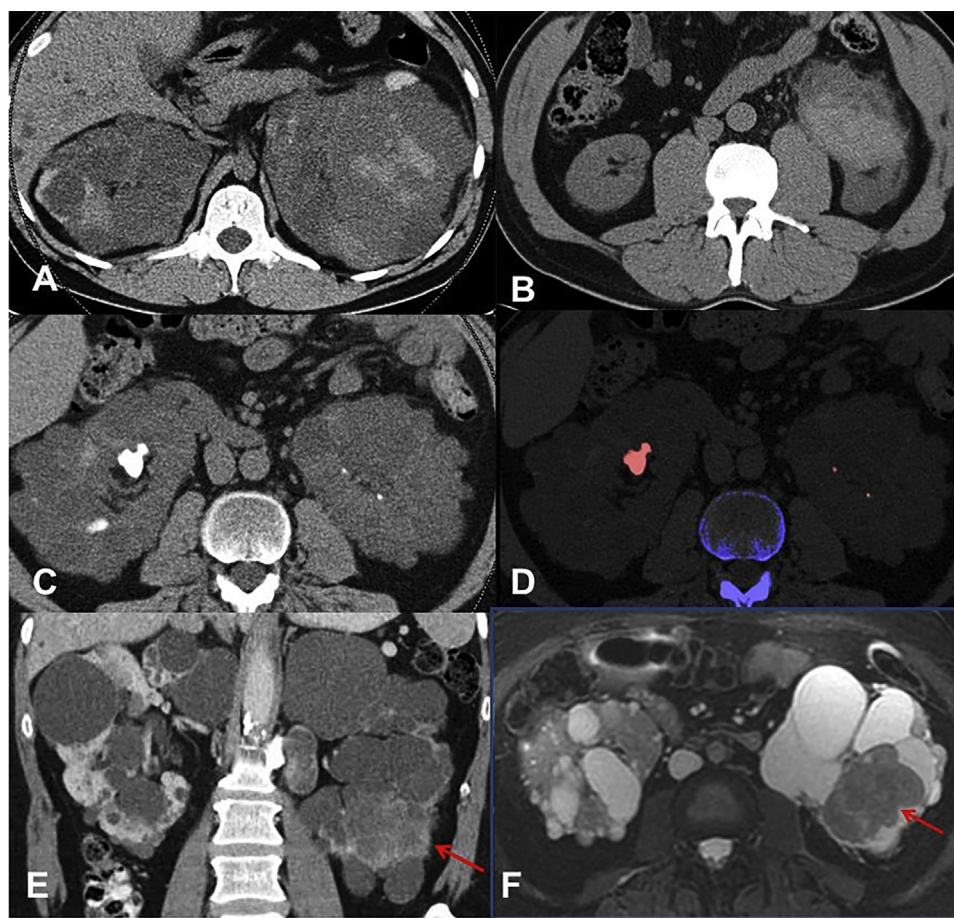


Figure 7. Axial unenhanced computed tomography (CT) scans show (A, B) hyperdense lesions in the left kidney due to cyst and parenchymal hemorrhage and (C) a small staghorn calculus in a right polycystic kidney (D) containing uric acid on a dual-energy CT. (E) Coronal T1-weighted and (F) axial T2-weighted images show an irregular mass (red arrows) in the lower pole of a left polycystic kidney proved to be a renal cell carcinoma.

should be completed if symptoms last longer than 1 week or it is the patient's first hemorrhagic episode and he or she is older than 50 years. Rare complications of cyst hemorrhage include extensive subcapsular or retroperitoneal hematomas. Management of gross hematuria is mostly conservative, with rest, hydration, and avoidance or temporary discontinuation of medications that facilitate bleeding (eg, warfarin, aspirin, or clopidogrel), if feasible. In severe cases of cyst hemorrhage, temporary discontinuation of RAAS inhibitors may be indicated to prevent acute kidney injury. Blood transfusion should be used with caution to prevent sensitization in potential future kidney recipients. Based on a successful experience in a small cohort of patients, the antifibrinolytic agent tranexamic acid can be considered when conservative therapy fails.

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Urinary Tract Infections

Urinary tract infections can occur in 30% to 50% of patients with ADPKD during their lifetime. Cystitis and urethritis are more common in women and are typically caused by Gram-negative enteric organisms. Treatment of lower urinary tract infections should be initiated promptly and is not different from treatment in the general population.

Cyst infection and acute pyelonephritis are the most common causes of upper urinary tract infection. Abdominal or flank pain and fever are common symptoms on presentation and should raise suspicion for cyst infection when concurrent with elevated erythrocyte sedimentation rate or C-reactive protein values. Urinalysis, urine culture with antimicrobial

susceptibility testing, blood culture, and imaging with CT or MRI should be part of the initial evaluation. Fludeoxyglucose positron emission tomography (FDG-PET) scan is more sensitive than CT or MRI in cyst infection detection (Fig 8). If imaging reveals features of a complex cyst, aspiration of cyst fluid should be considered if clinically feasible and sent for microbiology studies. If pain or unabated fever persists for more than 72 hours, repeat imaging should be obtained to exclude complications that may require intervention (eg, perinephric abscess or urinary tract obstruction), and aspiration of cyst fluid should be considered for microbiological studies if not performed initially.

Treatment should include intravenous broad-spectrum antibiotics while the patient has systemic symptoms, with transition to oral antibiotics that have good cyst penetration, such as ciprofloxacin or other quinolones. Therapy will be tailored according to microbial susceptibility when available. For cases of isolated acute pyelonephritis, the total duration of antibiotic therapy should be a minimum of 10 to 14 days. The duration should be extended to a minimum of 4 weeks and up to 6 weeks in the case of an infected cyst using an oral quinolone or sulfamethoxazole/trimethoprim as a reasonable alternative. Perinephric abscess requires prolonged intravenous antibiotic therapy with consideration for drainage. The efficacy of antibiotic treatment and infection eradication is defined by resolution of fever, normalization of C-reactive protein level, and documentation of at least 2 negative blood and/or urine cultures. Infected cysts > 5 cm may be resistant to antibiotic therapy and require percutaneous or surgical drainage. Nephrectomy is rarely needed, but is considered in cases of perinephric abscess or emphysematous pyelonephritis that is resistant to antibiotic therapy.

Additional Readings

- » Jouret F, Lhommel R, Devuyst O, et al. Diagnosis of cyst infection in patients with autosomal dominant polycystic

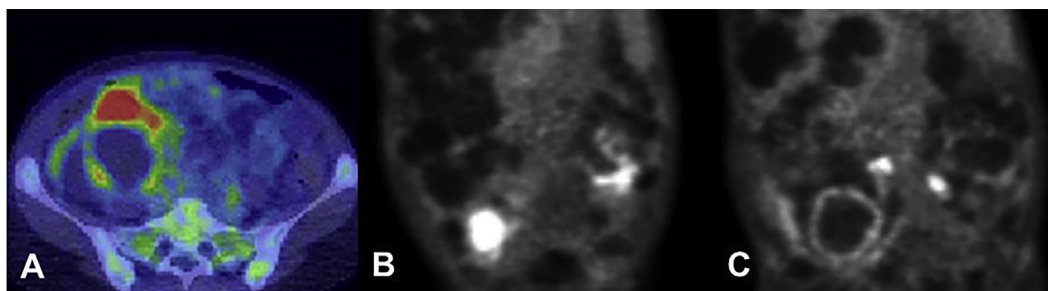


Figure 8. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan in a 45-year-old woman with a 1-month history of malaise and low-grade fever. The scan shows a 6- to 7-cm cyst within the most inferior aspect of the right polycystic kidney with (A, B) an intense focus of hypermetabolism along its anterior margin and (A, C) more moderate hypermetabolism about the periphery of the remainder of the cyst. Other activity seen within both kidneys represents activity within remnant functioning renal parenchyma and excreted activity within the collecting systems.

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Renal Cell Carcinoma

Renal cell carcinoma (RCC) is not frequent in ADPKD (occurs in <1% of cases) and does not occur more commonly in patients with ADPKD than in those with other kidney diseases. Nevertheless, RCC can arise at an earlier age in patients with ADPKD than in the general population and is often bilateral, multicentric, and sarcomatoid in type. Fever and systemic symptoms (anorexia, fatigue, and weight loss) are common presenting symptoms. In the setting of ADPKD, RCC is a rare cause of pain and challenging to diagnose (Fig 7E and F). Potential signs of a carcinoma include rapid growth of a complex cyst, a solid mass detected by ultrasonography, speckled calcifications visible by CT, and contrast enhancement, regional lymphadenopathies, and tumor thrombus on CT or MRI. Screening for RCC in patients with ADPKD is not currently warranted.

Additional Readings

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End-Stage Renal Disease

Most patients with ADPKD reach ESRD, although its onset varies between individuals. Almost 50% of patients with ADPKD reach ESRD by age 60 years, with a mean age of ESRD onset of 58.1 years in patients with *PKD1*-associated disease. Patients with ADPKD represent 9.8% and 5% of prevalent patients with ESRD in Europe and the United States, respectively. The lower prevalence in the United States is explained by the dilution effect of higher diabetes prevalence there compared to Europe. Patients with ADPKD have an overall favorable prognosis compared to the general ESRD population. Kidney transplantation is the optimal renal replacement therapy. Preemptive transplantation can be planned given the natural course of the disease and has been associated with better outcomes. In our opinion, patients with ADPKD preparing for kidney transplantation should be screened for ICAs by brain magnetic resonance angiogram (MRA). Nephrectomy prior to transplantation for space considerations varies widely between practices and is performed in 20% to 25% of patients. Other indications for nephrectomy include

recurrent and/or severe infection, bleeding, intractable pain, symptomatic nephrolithiasis, and suspicion for kidney malignancy. Nephrectomy is associated with perioperative morbidity, mortality, and risk for sensitization due to the need for blood transfusion. The hand-assisted laparoscopic approach is less invasive. Timing of the nephrectomy can also be concurrent with the transplantation surgery or post-transplantation. Some posttransplantation complications may be more frequent in patients with ADPKD, such as new-onset diabetes mellitus, diverticulitis, and thromboembolic events.

The second option for renal replacement therapy is either hemodialysis or peritoneal dialysis. ADPKD is not a contraindication for peritoneal dialysis therapy, but this modality is less common: patients with ADPKD experience challenges in accommodating large volumes of peritoneal dialysate and have an increased risk for abdominal wall hernias and peritonitis secondary to cyst infection. Patients with ADPKD who receive hemodialysis have higher survival compared with patients without ADPKD undergoing the same treatment. Higher hemoglobin levels also have been noted in patients with ADPKD treated by hemodialysis. Patients with ADPKD who have received renal replacement therapy do not appear to be at higher risk for developing RCC compared with patients with other kidney diseases.

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- » Jung Y, Irazabal MV, Chebib FT, et al. Volume regression of native polycystic kidneys after renal transplantation [published online ahead of print June 4, 2015]. *Nephrol Dial Transplant*. <http://dx.doi.org/10.1093/ndt/gfv227>.
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Conventional Strategies for Renoprotection

Families at risk for ADPKD are advised to implement a healthy lifestyle for all family members. Some interventions could be theoretically beneficial based on the current understanding of the disease pathogenesis, particularly early detection and strict control of hypertension. Other interventions include drinking water

throughout the day to inhibit release of antidiuretic hormone for a goal urine osmolality of 250 mOsm/kg, low sodium intake (≤ 2 g/d), healthy weight and lifestyle with regular exercise, a low threshold to initiate statins for hyperlipidemia, and avoiding high caffeine intake in order to prevent cAMP accumulation. Lowering daily protein intake to 0.8 g per kilogram of body weight when eGFR is <30 mL/min/1.73 m² is recommended and should be done through a renal dietitian to monitor for malnutrition. Moderation in alcohol intake is recommended as well. Hard contact sports such as rugby or American football should be avoided, but individual risk assessment is advised. Patients should be assessed for cardiovascular risk factors and treated aggressively. If applicable, patients should be strongly advised and counseled for smoking cessation.

Novel Strategies for Nephroprotection

Novel therapies have been proposed and tested based on the improved understanding of ADPKD pathophysiology. However, the role of these novel therapies in treating ADPKD has not yet been established. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3:4 trial evaluated the effect of tolvaptan, a vasopressin V2 receptor antagonist, on ADPKD disease progression. Treatment with tolvaptan in patients with ADPKD with GFRs > 60 mL/min and TKVs ≥ 750 mL showed significant effect on the rate of growth of TKV (-48%) and the rate of eGFR decline (-26%). In Japan (March 2014), Canada (February 2015), and the European Union (May 2015), tolvaptan has been approved to delay the progression of ADPKD in patients with a rapid increase in TKV. In the United States, US Food and Drug Administration approval has been deferred until further data are available on potential benefits and risks.

Sirolimus and everolimus, mTOR-inhibiting rapamycin analogues, failed to show benefit in clinical trials despite encouraging results in animal models of PKD; this was likely because therapeutic levels could not be reached without inducing systemic toxicity. The A Long-Acting somatostatin on Disease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN) study randomly assigned patients with ADPKD to the somatostatin analogue octreotide or placebo and noted a favorable trend in halting TKV increase. However, statistical significance was not reached in the study, leading the investigators to call for larger trials. DIPAK1 (Developing Interventions to Halt Progression of ADPKD 1) and LIPS (Lanreotide in Polycystic Kidney Disease Study) are ongoing clinical trials evaluating the effect of the somatostatin analogue lanreotide on disease progression

in patients with ADPKD with CKD stage 3 or CKD stages 2 to 3, respectively. Pravastatin, an HMG-CoA reductase inhibitor, has shown promising results on disease progression in a small randomized clinical trial in children with ADPKD. Larger and longer studies in adults are needed to confirm these results.

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Extrarenal Manifestations

ADPKD is a systemic disease and is associated with several extrarenal manifestations that have implications on mortality, morbidity, and quality of life. The different extrarenal manifestations in ADPKD are summarized in the second half of [Table 4](#).

Hepatic cysts

Liver cysts are the most common extrarenal manifestation of ADPKD. By 30 years of age, 80% of patients show evidence of liver cysts on MRI. The burden of liver cysts increases with age and is worse in women. It is estimated that 20% of patients eventually develop symptoms due to polycystic liver disease. Risk factors for severe polycystic liver disease include multiple pregnancies and prolonged use of estrogens. Symptoms may arise from compression of organs caused by massive liver enlargement. Those symptoms include abdominal pain and distension, back pain, early satiety, gastroesophageal reflux, inferior vena cava or hepatic venous-outflow obstruction, and dyspnea. Liver cysts can be complicated by infections, rupture, or hemorrhage. Most patients are asymptomatic and managed conservatively, and liver dysfunction is unusual.

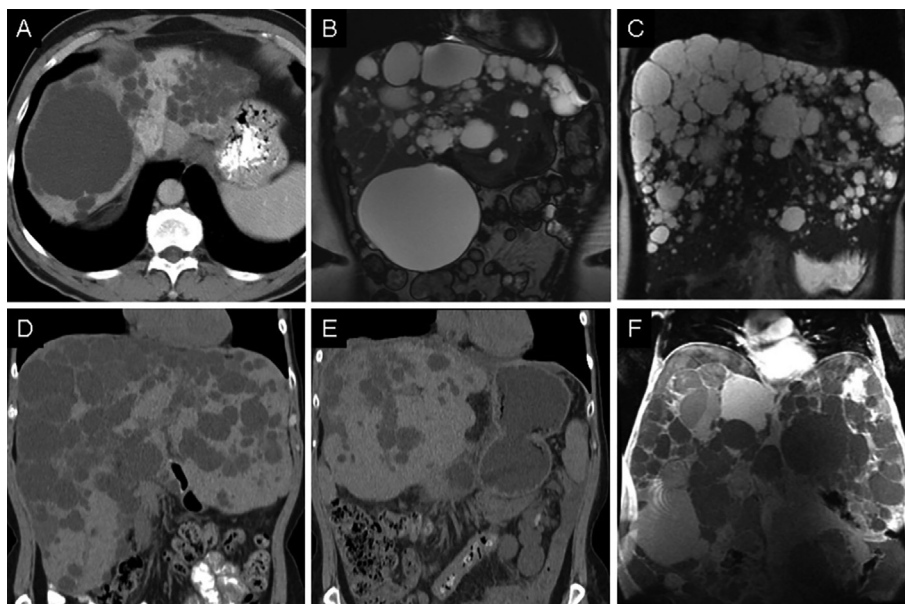


Figure 9. (A) Deep-seated large cyst in the right hepatic lobe best treated by cyst aspiration and alcohol sclerosis. (B) Superficial large cyst arising from the right lobe of the liver suited for laparoscopic fenestration. (C) Polycystic liver disease involving both lobes, more severely segments VII and VIII; this patient is not a good candidate for combined liver resection and cyst fenestration because of the distribution of the cysts and involvement of the less severely affected segments by many small cysts with further potential for growth. This patient might benefit from embolization of hepatic artery branches supplying segments VII and VIII that have no recognizable hepatic parenchyma. (D, E) Polycystic liver (D) before and (E) after combined right lobectomy and cyst fenestration (note compensatory hypertrophy of the left lobe after surgery). (F) Massive polycystic liver without relative preservation of any liver segment; the only feasible treatment in this patient is liver transplantation. Reproduced from Torres ("Treatment of polycystic liver disease: one size does not fit all." *Am J Kidney Dis.* 2007;49(6):725-728) with permission of Elsevier.

Liver imaging should be included in the initial evaluation of patients with ADPKD. Women with severe polycystic liver disease should be advised to avoid exogenous hormones or hormone-containing contraceptives.

Medical or surgical interventions should aim to alleviate symptoms and improve quality of life. Options include percutaneous aspiration and sclerotherapy with ethanol or other agents, deroofing of cysts surgically or laparoscopically, and partial liver resection (Fig 9). The latter procedure should be reserved for patients with severe symptomatic polycystic liver disease and liver anatomy that allows preservation of at least 2 contiguous liver segments with adequate hepatic venous drainage. Patients fitting these criteria should be referred to centers with substantial expertise in this surgery. Partial resection provides significant and sustained symptom relief. As a last resort, liver transplantation is considered for patients who are not candidates for partial liver resection. Patients with polycystic liver disease typically have low priority on the transplant waiting list due to their low MELD (Model for End-Stage Liver Disease) score (international normalized ratio and albumin level are usually normal). The somatostatin analogues octreotide and lanreotide have been tested in clinical trials and have been shown to be associated with a significant

reduction in liver cyst volume. Benefit is mostly seen during the first year of their use, and the treatment effect is greater in women younger than 48 years. Currently, somatostatin analogues are not approved for use to slow polycystic liver disease progression and should be reserved for use in research studies. Such drugs have been prescribed in rare cases for compassionate use in patients with very severe polycystic liver disease without other options.

Liver cyst infections are a common complication of polycystic liver disease. Fever, right upper-quadrant tenderness, and elevated levels of inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) should raise clinical suspicion. MRI and CT findings are not specific for infected cyst identification. FDG-PET is more sensitive. Treatment of liver cyst infections entails a prolonged course of parenteral broad-spectrum antibiotics followed by oral antibiotics. Therapy should be guided by culture, antimicrobial susceptibility, and good cyst penetration capability (such as possessed by quinolones).

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Intracranial Aneurysms

ICAs occur more frequently in patients with ADPKD than in the general population: asymptomatic ICA is detected by MRA in 9% to 12% and 2% to 3% of patients with ADPKD and the general population, respectively. Family history of ICA is an important risk factor for the condition; if family history is positive, prevalence increases from 6% to 20%-27%. ICA can occur in both *PKD1*- and *PKD2*-associated disease. ICA rupture is associated with a mortality rate of up to 50%. In patients with ADPKD, the average age at ICA rupture is 40 years, younger than that in the general population. Rupture usually presents as sudden onset of a severe headache described as a thunder clap headache. Increased size, posterior location, family history of ICA, and personal history of subarachnoid hemorrhage are potential risks for rupture. The location of ICA in ADPKD is typically the anterior circle of Willis (80%-90% of cases). The majority of aneurysms that are detected by presymptomatic screening are found to be <7 mm in size. Indication, timing, and frequency of screening are not well defined. Screening for asymptomatic ICA is reasonable for patients with ADPKD who also have a family history of ICA or a personal history of intracranial hemorrhage. Individuals in high-risk professions (eg, pilots) should be screened as well. Routine and long-standing headaches are not an indication for screening. MRA without gadolinium or CT angiography can be used for screening, but MRA is preferable to avoid exposure to iodinated contrast agent. Patients with a positive family history and negative results on screening should undergo rescanning in 5 to 10 years.

Conservative management is advised for patients with ADPKD with small (<7 mm) anterior circulation asymptomatic ICAs detected by presymptomatic screening (Fig 10). Management of unruptured ICAs > 7 mm or in the posterior circulation should involve a multidisciplinary team of neurologists, neurosurgeons, and interventional neuroradiologists. Endovascular approach with coil embolization is more favorable than surgical procedures. Risk for growth and rupture of small asymptomatic ICAs is generally low. Serial imaging is reasonable, starting at 6-month intervals. Later, screens should be performed

yearly and then every 2 to 3 years when stability is established. Modifiable risk factors of ICA growth have been identified in the general population and should be addressed in patients with ADPKD. These factors include smoking cessation, BP control, limited alcohol intake, and control of cardiovascular risk factors.

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Additional Extrarenal Manifestations

Other organs are involved in ADPKD. Most manifestations are asymptomatic and screening is not recommended. Mitral valve prolapse occurs in 25% of patients. Pericardial effusions also are common (prevalence of 35%), but are typically small with no hemodynamic significance. Idiopathic dilated cardiomyopathy and left ventricular noncompaction have been rarely associated with ADPKD. Screening echocardiography is only recommended if a murmur or cardiovascular symptoms are noted. Patients with ADPKD may be predisposed to a vascular phenotype. Cases of aneurysms of large arteries, such as the ascending aorta, popliteal, coronary, and splenic arteries, have been reported. Arachnoid membrane cysts occur in 8% to 12% of patients and are typically asymptomatic, but may slightly increase the risk for subdural hematoma. Spinal meningeal cysts are found in 1.7% of patients with ADPKD and may rarely cause intracranial hypotension that presents with orthostatic headache. Pancreatic cysts are observed in 10% of cases and are almost always asymptomatic. Diverticulosis occurrence is increased in patients with ADPKD who have reached ESRD. Abdominal wall hernias have been noted more frequently in patients with ADPKD as compared with patients with ESRD without ADPKD. Seminal vesicle cysts are found in 40% of men with ADPKD without correlation to semen abnormalities. Some studies have linked ADPKD with reproductive issues (infertility and sperm abnormalities) in men, but not in women. Bronchiectasis

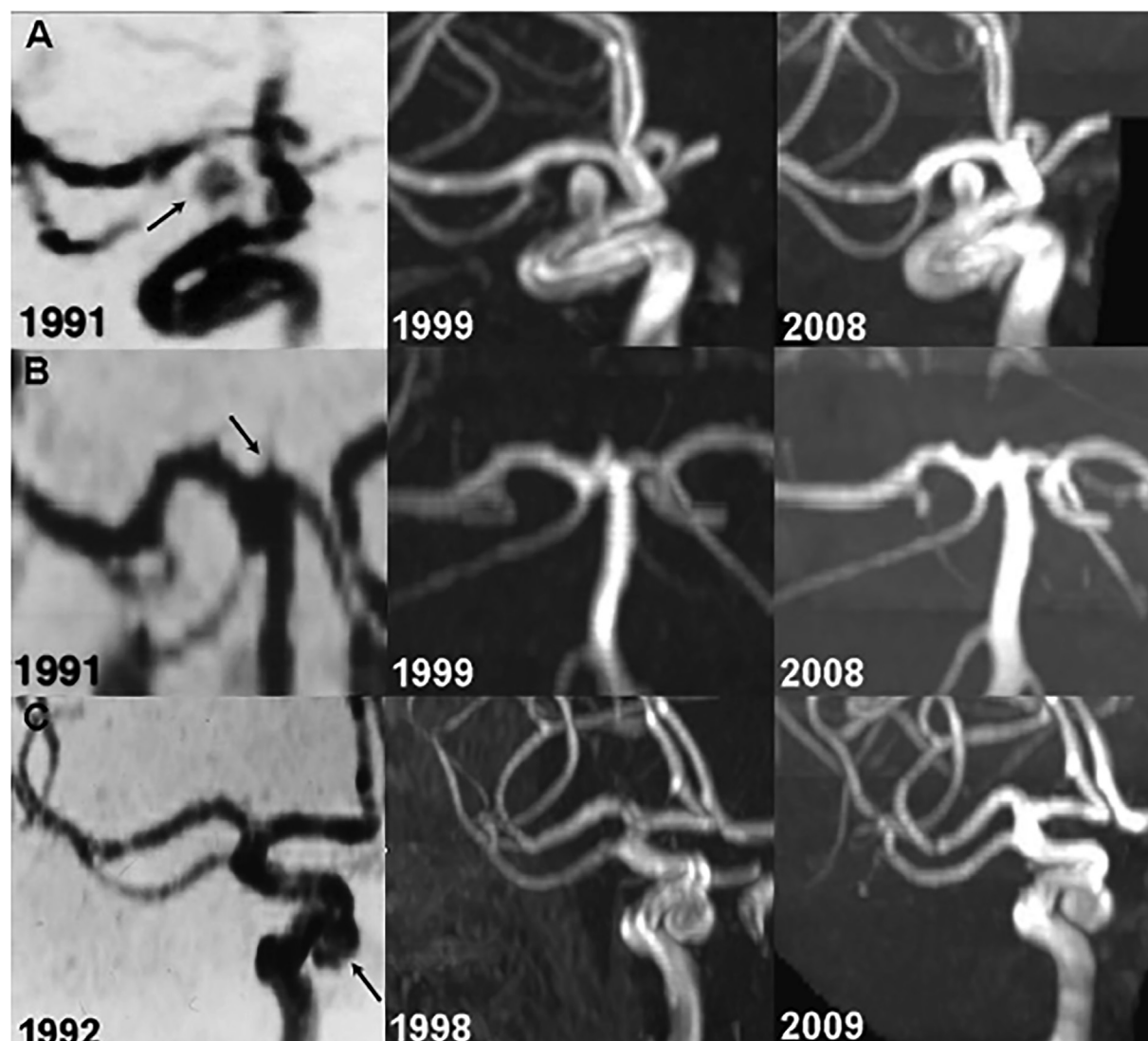


Figure 10. Magnetic resonance angiography follow-up illustrates the stability of small intracranial aneurysms detected by presymptomatic screening in patients with ADPKD. (A) A 59-year-old woman was found to have a 4.0-mm right carotid siphon aneurysm in 1991 that was unchanged during 17 years of follow-up. (B) A 45-year-old woman was found to have a 2.0-mm basilar tip aneurysm that was unchanged between 1991 and 2008. (C) A 49-year-old woman was found to have a 6.0-mm right carotid siphon aneurysm in 1992 that also was unchanged over 17 years of follow-up. Reproduced from Irazabal et al ("Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease." *Clin J Am Soc Nephrol.* 2011;6(6):1274-1285) with permission of American Society of Nephrology.

may occur in up to 37% of patients with ADPKD, but typically is mild. Congenital hepatic fibrosis complicated by portal hypertension is rare in ADPKD, relative to autosomal recessive PKD. Clinical suspicion should be raised if patients have increased liver echogenicity on ultrasound, enlarged left lobe of the liver, thrombocytopenia, or splenomegaly.

Additional Readings

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COUNSELING, PREGNANCY, AND REPRODUCTIVE ISSUES

Family planning should be discussed with patients, and options should be reviewed. Both parents should be counseled about the risk for passing the disease to their offspring, as well as the risk to the fetus and the mother during pregnancy. Women of reproductive age with ADPKD, particularly those with severe polycystic liver disease, should be advised about the potential worsening of their liver disease when exposed to estrogen or progesterone. Multiple pregnancies (>3) have been associated with a greater rate

of GFR decline in ADPKD. Preimplantation genetic diagnosis has been used in ADPKD to select and implant healthy embryos created by in vitro fertilization. If available, this option should be part of the reproductive choices and counseling.

Antihypertensive treatment should be reviewed and adjusted for safety during pregnancy. RAAS inhibitors should be discontinued preemptively. Women with ADPKD and normal BP and kidney function have a favorable course during pregnancy, but are at slightly higher risk for developing pregnancy-induced hypertension and preeclampsia. Similar to women with CKD, pregnant women with ADPKD and reduced kidney function are at higher risk for early fetal loss, accelerated loss of kidney function, and difficulty controlling BP. Referral to an obstetrician with expertise in treating women with high-risk pregnancies is recommended.

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ACKNOWLEDGEMENTS

Support: Supported by National Institute of Diabetes and Digestive and Kidney Diseases grant DK044863 and by the Mayo Clinic Translational PKD Center (DK090728).

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