Autosomal Dominant Polycystic Kidney Disease: Core Curriculum 2025

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney failure. Scientific advances have improved the approach to diagnosis, prognosis, and management of renal and extrarenal manifestations. The combination of total kidney volume, kidney function, and the genetic mutation (if known), predicts risk for progression to kidney failure, thereby identifying patients in whom disease modifying therapy is recommended. Currently there is one therapy approved by the US Food and Drug Administration (FDA) for slowing ADPKD progression, the V2 receptor antagonist, tolvaptan. Other therapies are under active investigation for ADPKD. This Core Curriculum discusses diagnosis and management of the renal and extrarenal manifestations seen in ADPKD including acute and chronic pain and cyst infection and polycystic liver disease and intracranial aneurysm. Management of hypertension and women's health and pregnancy management in ADPKD are covered. This review was aligned with the findings of the recently published Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the Evaluation, Management, and Treatment of ADPKD.

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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.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney failure. Decades of scientific advances have led to improvements in the ability to diagnose ADPKD, predict kidney outcomes, and manage renal and extrarenal manifestations, including bringing the first disease-modifying therapy, tolvaptan, to practice. Ongoing work to develop and refine prediction tools to accurately identify patients with more rapidly progressive disease is central to the care of ADPKD. A variety of pharmacologic and dietary interventions are being actively investigated. A major development is the publication of the 2025 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD, which defines nomenclature, summarizes the current evidence for diagnosis and management, and identifies areas for future research. This installment in the *AJKD* Core Curriculum in Nephrology, intended for the clinician, summarizes best practices and commonly encountered questions that arise in managing the ADPKD patient.

Genetic Mutations Underlying the ADPKD Phenotype

Mutations in the *PKD1* and *PKD2* genes (encoding polycystin 1 and 2, respectively) are responsible for the vast majority (~93%) of patients presenting with ADPKD in research populations. In those with ADPKD due to mutations in *PKD1* and *PKD2*, *PKD1* mutations account for most of these (85%) and *PKD2* for ~15% of these (Table 1). Mutation in a single allele of either of these genes usually leads to "typical" or Mayo Imaging Classification (MIC, discussed below) class 1 disease, with bilateral and symmetric cystic kidney enlargement and progressive loss of kidney function leading to kidney failure at a median age of ~55 years for a *PKD1* mutation and ~74 years for *PKD2* mutation. Mutations that result in a truncated *PKD1* protein usually exhibit a more severe phenotype than those that are nontruncating.

The remaining cases are due to mutations in "minor" ADPKD genes, which currently include *ALG5*, *ALG9*, *DNAJB11*, *GANAB*, *IFT140*, or *NEK8*, and an estimated 5% are due to other genes that have yet to be identified (Table 1). Mutations involving the minor PKD genes usually present as "atypical" or MIC class 2 disease, in which there is a smaller number of cysts and less kidney enlargement than with *PKD1* and *PKD2* mutations, asymmetric distribution of cysts (Fig 1), and a slower decline in kidney function, such that many patients do not reach kidney failure. Liver cysts and intracranial aneurysms can occur.

Significant variability in the severity of the kidney disease can exist within a family despite the same germline mutation, which may be due to genetic mosaicism, biallelic involvement, modifier genes, or environmental factors (eg, tobacco use) or other comorbidities (eg, diabetes or obesity).

Autosomal dominant polycystic liver disease (ADPLD) involves genes such as *PRKCSH*

Table 1. Genes Associated With ADPKD Spectrum

Gene	Screened Families	No. of Families[a]	Disease Designation	Kidney Phenotype	Extrarenal Phenotype	Comments
Major ADPKD Genes and Nomenclature for Unknown, Not Screened, and Unresolved Typical Cases						
Unknown, or not screened, or unresolved			ADPKD	Bilateral PKD; kidney enlargement; age-related CKD, may result in KF	Liver cysts including severe PLD; increased risk of ICA	Wide phenotypic range in terms of TKV and KF risk and timing
PKD1	~48%	>3,250	Truncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD; early kidney enlargement; CKD G3, age ~40 y; KF in 50s	Liver cysts including severe PLD; increased risk of ICA	Some disease variability, including a more benign course, sometimes associated with mosaicism
	~19%	>1,750	Nontruncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD, kidney enlargement; age-related CKD; may result in KF	Liver cysts including severe PLD; increased risk of ICA	Phenotype ranges from severe as *PKD1* truncating to mild PKD in old age, partly depending on the degree of residual protein function
PKD2	~15%	>1,000	ADPKD-*PKD2*	Bilateral PKD; milder and later kidney enlargement; CKD G3, age ~55 y; KF in 70s	Liver cysts including severe PLD; increased risk of ICA	Some disease variability, including a more severe or more benign course
Minor ADPKD Genes With Definitive-to-Moderate Evidence of Disease Involvement[b]						
ALG5	<0.5%	<10	ADPKD-*ALG5*	Mild to moderate cyst development with limited kidney enlargement and fibrosis; CKD and some KF in older adults[1]	A few liver cysts in a minority of people	
ALG9	<0.5%	<20	ADPKD-*ALG9*	Mild to moderate cystic disease with significant CKD in older adults[2]	Liver cysts common	Biallelically, associated with the congenital disorder of glycosylation, type IL (CDG1L)
DNAJB11	<0.5%	<30	ADPKD-*DNAJB11*	Bilateral small cysts, limited or no kidney enlargement; progressive fibrosis; limited CKD G3a <55 y, but KF in 70s[3,4]	Liver cysts, usually mild; ICA and vascular risk possible	ADPKD-*DNAJB11* has similarities to ADTKD, because of the small, fibrotic kidneys, but visible cysts are usually present. Biallelically, associated with renal-hepatic- pancreatic dysplasia[5]
GANAB	<0.5%	<20	ADPKD-*GANAB*	Mild cyst development; limited CKD, no KF[6]	Liver cysts, including severe PLD; ICA risk unclear	Can present as ADPLD
IFT140	1-2%	<50	ADPKD-*IFT140*	Few, large bilateral cysts resulting in kidney enlargement with kidney function usually preserved into old age[7]	Liver cysts only rarely seen, with risk of ICA unclear	Biallelically, associated with short-rib thoracic dysplasia (*SRTD9*) and retinitis pigmentosa (*RP80*)
NEK8	<0.5%	<20	ADPKD-*NEK8*	Bilateral PKD, kidney enlargement; KF in childhood, occasionally later in cases of specific alleles or mosaicism[8]	Liver cysts rare	De novo occurrence was reported in 75% of reported cases. Biallelically, associated with renal-hepatic-pancreatic dysplasia and nephronophthisis (*NPHP9*)
Suspected Monoallelic PKD Genes With Limited Evidence of Disease Involvement or Not Assessed[b]						
ALG6	<0.5%	<10	ADPKD (only when phenotype consistent with this diagnosis)	Generally mild with or without persevered kidney function[9]	Liver cysts, including severe PLD	Can present with mainly a liver phenotype. Monoallelic *ALG6* is likely a lower-penetrant phenotype. Biallelically, associated with the congenital disorder of glycosylation, type IC (CDG1C)

(Continued)

Table 1 (Cont'd). Genes Associated With ADPKD Spectrum

Gene	Screened Families	No. of Families[a]	Disease Designation	Kidney Phenotype	Extrarenal Phenotype	Comments
ALG8	~1%	<40[c]	ADPKD (only when phenotype is consistent with this diagnosis)	Generally mild cystic kidney disease with preserved function into old age[10]	Liver cysts, including severe PLD; ICA risk unclear	Can present with mainly a liver phenotype. *ALG8* is likely a low-penetrant genotype.[10,11] Biallelically, associated with congenital disorder of glycosylation, type 1H (CDG1H)
PKHD1	~1%	<50[c]		Generally very mild cystic kidney development with preserved function into old age[12]	Liver cysts common and can be seen without kidney cysts	Biallelic pathogenic variants are associated with ARPKD, which can present with mainly a liver phenotype. Monoallelic *PKHD1* is likely a low-penetrant genotype, including people with no cysts.[11]

The major ADPKD genes are bolded. The chart has been divided into the major genes, the minor genes with a moderate level of evidence, and the possible minor genes with limited evidence. ADPKD is used as the disease designation of the major and well-supported minor genes. Abbreviations: AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; TKV, total kidney volume.

[a]Estimate of number of published families.

[b]Evaluation from ClinGen (https://search.clinicalgenome.org/kb/gene-validity?page1&size25&search).

[c]Additional people with monoallelic loss-of-function variants have been identified but the kidney phenotype is unknown or nonpenetrant.

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12. Gunay-Aygun M, Turkbey BI, Bryant J, et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol Genet Metab*. 2011;104:677-681. doi:10.1016/j.ymgme.2011.09.001

and *SEC63* and others and is classified separately from ADPKD, although there can be significant overlap in ADPKD and ADPLD phenotypes. Mutations associated with ADPLD usually result in predominantly liver cyst disease with a few kidney cysts. Liver cysts are common in ADPKD, and massive polycystic liver disease can occur.

Several other genetically based diseases can present with kidney cysts, but they sometimes can be diagnosed by characteristic renal and extrarenal manifestations that would be unusual for ADPKD. These conditions range from collagen disorders arising from *COL4A3*, *COL4A4*, or *COL4A5* mutations to developmental disorders such as *HNF1β*, among others (Table 2).

When to Perform Genetic Testing

Genetic testing is not required for diagnostic purposes in patients with a family history of ADPKD and typical appearing imaging, nor is it presently required for treatment decisions. Genetic testing can be helpful in the following circumstances: (1) a negative family history, (2) a patient exhibiting a different phenotype or disease course from affected family members, (3) atypical imaging appearance, (4) to enable selection of mutation-free embryos (preimplantation genetic diagnosis), (5) workup of an at-risk potential kidney donor with no kidney cysts on imaging but below the age where an ultrasound can exclude ADPKD with certainty, or (6) clinical manifestations atypical of ADPKD and suggesting another genetic condition (Table 2).

Which Genetic Test Should Be Performed?

The implications of genetic testing should be discussed including the potential for a negative test despite clinically evident disease, the potential for variants of undetermined significance (VUS), and the potential inability to obtain life, health, or disability insurance if the test reveals an ADPKD mutation. When the genotype is unknown, the recommended initial test is an accredited next-generation

Class, subclass, and term	Description
1. Typical ADPKD	Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV
2. Atypical ADPKD	
A	
Unilateral	Diffuse cystic involvement of one kidney causing marked kidney enlargement with a normal contralateral kidney defined by a normal kidney volume (<275 ml in men; <244 ml in women) and having no or only 1–2 cysts
Segmental	Cystic disease involving only one pole of one or both kidneys and sparing the remaining kidney tissue
Asymmetric	Diffuse cystic involvement of one kidney causing marked kidney enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney defined by a small number of cysts (>2 but <10) and volume accounting for <30% of TKV
Lopsided	Bilateral distribution of kidney cysts with mild replacement of kidney tissue with atypical cysts where ≤5 cysts account for ≥50% TKV (the largest cyst diameter is used to estimate individual cyst volume)
B	
Bilateral presentation with acquired unilateral atrophy	Diffuse cystic involvement of one kidney causing moderate to severe kidney enlargement with contralateral acquired atrophy
Bilateral presentation with bilateral kidney atrophy	Impaired kidney function (serum creatinine ≥1.5 mg/dl [133 μmol/l]) without significant enlargement of the kidneys, defined by an average length <14.5 cm, and replacement of kidney tissue by cysts with atrophy of the parenchyma

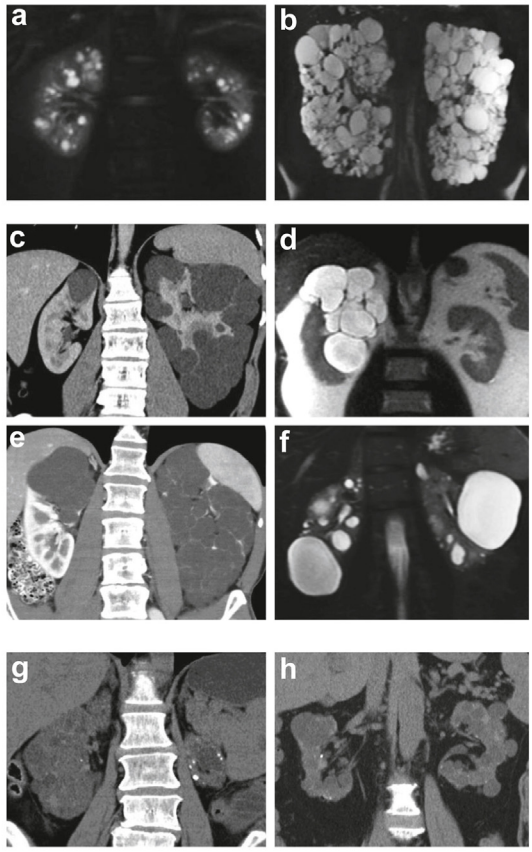

Figure 1. The Mayo Imaging Classification of ADPKD description (left panel) and imaging examples (right panel) with examples (right panel) of (a, b) subclass 1A and 1E, (c-f) subclass 2A, and (g, h) subclass 2B. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; TKV, total kidney volume. Reproduced with permission of the copyright holder (Kidney Disease: Improving Global Outcomes) from Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S):S1-S239. doi:10.1016/j.kint.2024.07.009

Table 2. Genetic Conditions That Can Mimic ADPKD by Presence of Kidney Cysts

Condition	Gene	Inheritance	Differentiating Signs/Symptoms
Alport spectrum	*COL4A1*	AD	Hematuria, retinal arterial tortuosity, brain small vessel disease, muscular contractures.
	COL4A3, *COL4A4*, *COL4A5*	AD and X-linked	Microscopic hematuria; progressive kidney failure in males (X-linked). Occasionally kidney cysts are presenting feature.
Autosomal dominant tubulointerstitial kidney disease	*MUC1*, *REN*, *SEC61A1*, *UMOD*	AD	Interstitial fibrosis; rarely cysts in the corticomedullary junction; slowly progressive kidney failure; small- to normal-sized kidneys. Hyperuricemia, gout are common in ADTKD, *UMOD*, and *REN*.
Autosomal recessive polycystic kidney disease	*PKHD1*	AR	Early in life kidneys are cystic, enlarged, and echogenic. With increasing age, kidneys are smaller with macroscopic cysts, nephrocalcinosis, and/or small medullary calcifications common; oligohydramnios (Potter phenotype) and pulmonary hypoplasia in utero, congenital hepatic fibrosis, Caroli disease.
Tuberous sclerosis	*TSC1-2*	AD	Angiomyolipoma; skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, and Shagreen patch); retinal hamartomas; seizures; intellectual disability; cortical tuber; subependymal giant cell astrocytoma; cardiac rhabdomyoma; lymphangioleiomyomatosis. Contiguous deletion of *PKD1*/*TSC2* results in severe early onset PKD with ESKD typically occurring in the first 2 decades of life.
Von Hippel-Lindau	*VHL*	AD	High risk of renal cell carcinomas; CNS and retinal hemangioblastomas, pancreatic cysts, pancreatic endocrine tumors, pheochromocytoma.
Nephronophthisis	*NPHP1-6*	AR	Normal-sized kidneys with corticomedullary junction cysts; interstitial fibrosis; retinitis pigmentosa; cerebellar vermis aplasia, polydactyly, occipital encephalocele (*NPHP 1-6*); ocular motor apraxia (*NPHP1-2*); liver fibrosis (*NPHP2-3*), situs inversus (*NPHP2*).
Bardet-Biedl syndrome	*BBS1-12*	AR	Retinal degeneration, childhood obesity, intellectual disability, malformations of the urogenital tract, polydactyly.
HNF1-β related kidney disease	*HNF1B*	AD	Congenital kidney and genitourinary tract malformations, hypomagnesemia, hyperuricemia, and elevated liver enzymes; can present as ADPKD alone.

Abbreviations: AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; CKD, chronic kidney disease; CNS, cerebral nervous system; ESKD, end-stage kidney disease; PKD, polycystic kidney disease.
Based on information in Alves M, Fonseca T, de Almeida EAF. Differential Diagnosis of Autosomal Dominant Polycystic Kidney Disease. In: Li X, editor. Polycystic Kidney Disease [Internet]. Brisbane (AU): Codon Publications; 2015 Nov. Chapter 1. doi:10.15586/codon.pkd.2015.ch1

sequencing (NGS)–based multigene kidney (or targeted cystic or ciliopathy) disease panel. The panel of genes should be reviewed to ensure it includes both *PKD1* and *PKD2* or the gene of interest if there is suspicion of a condition other than ADPKD. A negative NGS result test should not be considered to exclude ADPKD because some mutations have yet to be identified. Consequently, a patient with typical ADPKD based on clinical findings but with negative genetic testing should be managed identically to a genetically confirmed case. The Mayo Clinic database of *PKD1* and *PKD2* variants (https://pkdb.mayo.edu) may provide more information about the pathogenicity of a variant that has been classified as a VUS.

When a genetic diagnosis is required (ie, preimplantation genetics or an at-risk potential kidney donor) and a pathogenic mutation is not identified through NGS, whole genome sequencing should be performed. When the ADPKD mutation has been previously identified in a family member, Sanger analysis (sequencing of the pathogenic variant only) can be employed with long-range polymerase chain reaction (PCR) for *PKD1* mutations. One exception would be the individual exhibiting a very different disease course than affected family member(s); in these cases, NGS would be preferred to assess the potential for an additional ADPKD gene(s) or genetic condition other than ADPKD. Consulting a genetics expert is recommended when pursuing further testing after a negative multipanel NGS or for interpreting equivocal results, such as a VUS when the phenotype is highly suggestive.

Additional Readings

➢ Aron AW, Dahl NK. Clinical genetic testing in nephrology: core curriculum 2024. *Am J Kidney Dis.* 2024;84(5):632-645. doi:10.1053/j.ajkd.2024.05.011

➢ Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S): S1-S239. doi:10.1016/j.kint.2024.07.009 ★ESSENTIAL READING

Diagnosis of ADPKD

Case 1: *A 23-year-old man developed abdominal pain while playing football. An ultrasound of the abdomen revealed 5 cysts on his right kidney, and 2 cysts on his left kidney. The liver was normal without cysts. His father required a kidney transplant at 68 years of age, but he does not know whether there was a diagnosis of ADPKD.*

Question 1: Which of the following is true regarding diagnosis?

(a) The absence of liver cysts makes ADPKD unlikely.
(b) Genetic testing is required to make the diagnosis of ADPKD.
(c) The diagnosis of ADPKD is definite whether or not the father has ADPKD.
(d) The diagnosis is confirmed if the father has ADPKD.

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

Imaging Criteria for the Diagnosis of ADPKD

Ultrasound is the recommended initial test to obtain in the patient with a positive family history given its low cost, routine availability, and high diagnostic accuracy. The Pei-Ravine Criteria uses age, number of cysts on ultrasound, and presence of a *PKD1* or *PKD2* mutation (including a category for unknown) to provide thresholds for the number of cysts required at a specific age to enable high diagnostic accuracy for ruling in or ruling out ADPKD in individuals with a family history (Tables 3-5). Diagnostic accuracy for ruling in disease increases with the number of cysts present, and, for ruling out disease, with the absence of cysts. For instance, in a patient aged 15-39 years with a positive family history but unknown genotype, the presence of 3 cysts total is sufficient to make the diagnosis of ADPKD, with a positive predictive value of 100% (Table 3). The sensitivity of this finding ranges from 70% to 94% depending on whether the family has known *PKD1*, *PKD2*, or an unknown genotype. The absence of cysts by age 30 in patients with a positive family history of *PKD1* rules out APDKD with a negative predictive value of 100% (Table 4). In patients with a family history of *PKD2* or unknown genotype, ADPKD cannot be completely ruled out by ultrasound until age 40, at which time, the presence of fewer than 2 cysts has 100% negative predictive value (Table 4).

When it is critical to exclude ADPKD with 100% certainty, such as in an at-risk individual being considered as a kidney donor, more sensitive imaging techniques such as magnetic resonance imaging (MRI) or contrast-enhanced computerized tomography (CT), or genetic testing can be performed. There are no established imaging-based criteria for diagnosis in the absence of family history, but KDIGO suggests a threshold of greater than 10 cysts per kidney by ultrasound. This lacks sensitivity for younger patients without a *PKD1* mutation and with more mild disease, in whom imaging should be repeated periodically or a more sensitive imaging study or genetic testing can be performed.

Other Imaging Modalities

CT and MRI have higher a sensitivity than ultrasound for detecting kidney cysts. In a single center study, MRI revealed more than 20 cysts in 99% of 73 individuals between the ages of 16-40 with known *PKD1* or *PKD2* mutations. Only 1 of 37 patients (2.7%) with a family history of ADPKD but negative genetic testing for *PKD1* and *PKD2* mutations had more than 3 cysts; the remainder had no cysts on MRI. The presence of >10 total cysts by MRI in individuals with a positive family history between 16 and 40 years of age had 100% sensitivity and positive predictive value for diagnosing ADPKD; the presence of <5 cysts had 100% specificity and negative predictive

Table 3. Performance Characteristics of Ultrasound for the Diagnosis and Exclusion of ADPKD in Patients With Positive Family History

		ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown Gene Type	
Age, y	No. of Cysts[a]	Predictive Value Based on a Positive Test	Sensitivity	Predictive Value Based on a Positive Test	Sensitivity	Predictive Value Based on a Positive Test	Sensitivity
15-29	≥3 total	100%	94%	100%	70%	100%	82%
30-39	≥3 total	100%	97%	100%	95%	100%	96%
40-59	≥2 in each kidney	100%	93%	100%	89%	100%	90%
60+	≥4 in each kidney	100%	100%	100%	100%	ND	ND

Ultrasound criteria by age group to diagnose ADPKD when there is a positive family history.
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ND, not determined.
[a]Test criterion based on number of cysts.
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Table 4. Performance Characteristics of Ultrasound for the Diagnosis and Exclusion of ADPKD in Patients With a Positive Family History: Ultrasound Criteria by Age Group to Exclude ADPKD

		ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown Gene Type	
Age, y	No. of Cysts[a]	Predictive Value Based on a Negative Test	Specificity	Predictive Value Based on a Negative Test	Specificity	Predictive Value Based on a Negative Test	Specificity
15-29	≥1 total	99%	98%	84%	97%	91%	97%
30-39	≥1 total	100%	96%	97%	94%	98%	95%
40-59	≥2 total	100%	98%	100%	98%	100%	98%

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.
[a]Test criterion based on number of cysts.
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value for excluding ADPKD (Table 5). However, many transplant centers perform genetic testing despite <5 cysts by MRI in a potential kidney donor with a family history of ADPKD.

Returning to question 1, the best answer is (d): with a positive family history, 7 cysts by ultrasound would be diagnostic of ADPKD in a 23-year-old. The other answers are incorrect because more than 10 cysts (by ultrasound) would be required to diagnose ADPKD in the absence of family history. Genetic testing is not required in most cases because imaging has high diagnostic accuracy when the threshold for number of cysts at a given age and family history (presence/absence) to include or exclude disease are considered. Although liver cysts are common and increase in number with age, their absence does not exclude the diagnosis.

Additional Readings

- Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S):S1-S239. doi:10.1016/j.kint.2024.07.009
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Assessing Progression of Disease

Predicting Rapid Progression of Disease

Case 2: *A 28-year-old man presents for evaluation of ADPKD. The diagnosis was made by ultrasound 10 years ago after he had experienced sharp flank pain and hematuria. His father is 56 years old and has kidney failure from ADPKD. A recent ultrasound demonstrated diffusely enlarged, cystic kidneys measuring 15.2 cm (right) and 14.7 cm (left). His blood pressure is 138/71 mm Hg, and laboratory testing reveals an estimated glomerular filtration rate (eGFR) of 91 mL/min/1.73 m^2, and spot urinary albumin-creatinine ratio of 0.02 g/g.*

Question 2: Which of the following is the best next step to determine his risk for rapid progression?

(a) Repeat an ultrasound in 5 years.
(b) Measure eGFR and spot urine albumin in 1 year.
(c) Obtain an MRI or CT.
(d) Perform genetic testing.

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

After diagnosing ADPKD, the patient's risk for rapid progression should be determined to guide decisions about disease-modifying therapy or participation in clinical trials. Unlike most other forms of chronic kidney disease (CKD), proteinuria is not a typical feature of ADPKD, except in advanced disease. The eGFR generally

Table 5. Performance Characteristics of MRI for the Diagnosis and Exclusion of ADPKD in Patients With a Positive Family History: MRI Criteria for Ages 16-40 Years

		Based on a Positive Test		Based on a Negative Test	
Age, y	No. of Cysts[a]	Predictive Value	Sensitivity	Predictive Value	Sensitivity
16-29	≥10 cysts	100%	100%		
30-40		100%	100%		
16-29	≥5 cysts			100%	98.3%
30-40				100%	100%

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; MRI, magnetic resonance imaging.
[a]Test criterion based on number of cysts.
Reproduced with permission of the copyright holder (Kidney Disease: Improving Global Outcomes) from: Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S):S1-S239.

remains normal early in disease, despite significant cystic kidney enlargement and histological evidence of inflammation and scarring. Total kidney volume (TKV) has been qualified by the FDA as a prognostic biomarker based on studies showing it to be a stronger predictor of future GFR decline than age or baseline GFR.

In practice settings, TKV is most often determined based on the calculation for the volume of an ellipsoid ($\pi/6 \times$ Length $\times$ Depth $\times$ Width) with kidney dimensions measured from CT or MRI images. Alternate methods for determining TKV including stereology or the application of deep-learning algorithms to automate kidney segmentation, although these are at present not widely available. The sum of the volume of the 2 kidneys constitutes the TKV, which is standardized for patient height (htTKV). When MRI or CT is not available, kidney length >16.5 cm on ultrasound in patients aged 15-46 years with creatinine clearance > 70 mL/min is considered to define rapid progression.

The Mayo Imaging Classification (MIC) is a validated and free prediction tool that utilizes age, height, and TKV (by CT or MRI) to predict progression in patients with typical or MIC class 1 disease: bilateral, diffuse, and symmetrically distributed kidney cysts. It is not intended for use in MIC class 2 disease: atypical disease including unilateral, asymmetric, segmental, or lopsided cyst distribution or the presence of parenchymal atrophy (Fig 1). Class 2 generally follows a slower disease course than MIC class 1 disease. The calculator (www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754) yields an MIC class of 1A through E. Each increase in class corresponds to an increase in htTKV growth (for a given age) and a faster rate of GFR decline (Fig 2).

Per the 2025 KDIGO ADPKD guideline, the risk of rapid progression is defined as MIC classes 1C-1E or a historical eGFR decline of ≥3 mL/min/1.73 m^2 per year. For patients with MIC results at the border between classes 1B and 1C, other factors predicting the disease course, such as age of kidney failure in first-degree relatives, known truncating *PKD1* mutation, personal history of hypertension at age <35 years, or reduced eGFR without other explanation should be considered.

A patient with MIC class 1B but with other risk factors for rapid progression could be treated with tolvaptan. Conversely, a patient with MIC class 1C but few risk factors for progression might defer treatment. Because the rate of TKV growth for an individual is consistent over time, serial imaging to recalculate the MIC is generally not required.

Genetics and Other Information to Assess Disease Progression

The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score is another prognostication tool that requires genotype but not TKV. It is calculated as the sum of the weighted factors of *PKD1* mutation type (*PKD2* = 0, *PKD1* nontruncating = 1, *PKD1* truncating = 4), patient sex (female = 0; male = 1), and onset of hypertension (no = 0; yes = 2) or first urologic event before 35 years (n = 0; yes = 2). The score is divided into 3 levels of low (0-3), intermediate (4-6), and high (>6) risk, with 1 study finding excellent discrimination of the PROPKD in predicting risk, with a median age of onset of kidney failure of 71 years in the low-risk group to 49 years in the high-risk group.

Returning to Question 2, the best answer is (c): TKV and MIC can be determined from MRI or CT and used to determine the risk of rapid progression. If eGFR was declining at a rate of ≥3 mL/min/1.72 m^2 per year, this would meet the definition for fast progression, but it is unlikely at this patient's young age except in the most severe cases; because it takes more than a year to determine the rate of GFR decline, treatment would be delayed. Risk of progression can be defined by a single TKV and does not require serial imaging in 5 years. The use of genetic testing alone to determine risk of rapid progression is not currently a standard approach.

Additional Readings

- Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27(3):942-951. doi:10.1681/ASN.2015010016
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- Jdiaa SS, Mustafa RA, Yu ASL. Treatment of autosomal-dominant polycystic kidney disease. *Am J Kidney Dis*. 2025;85(4):491-500. doi:10.1053/j.ajkd.2024.08.008 ★ESSENTIAL READING

Management of ADPKD

Disease Modifying Pharmacotherapy for ADPKD

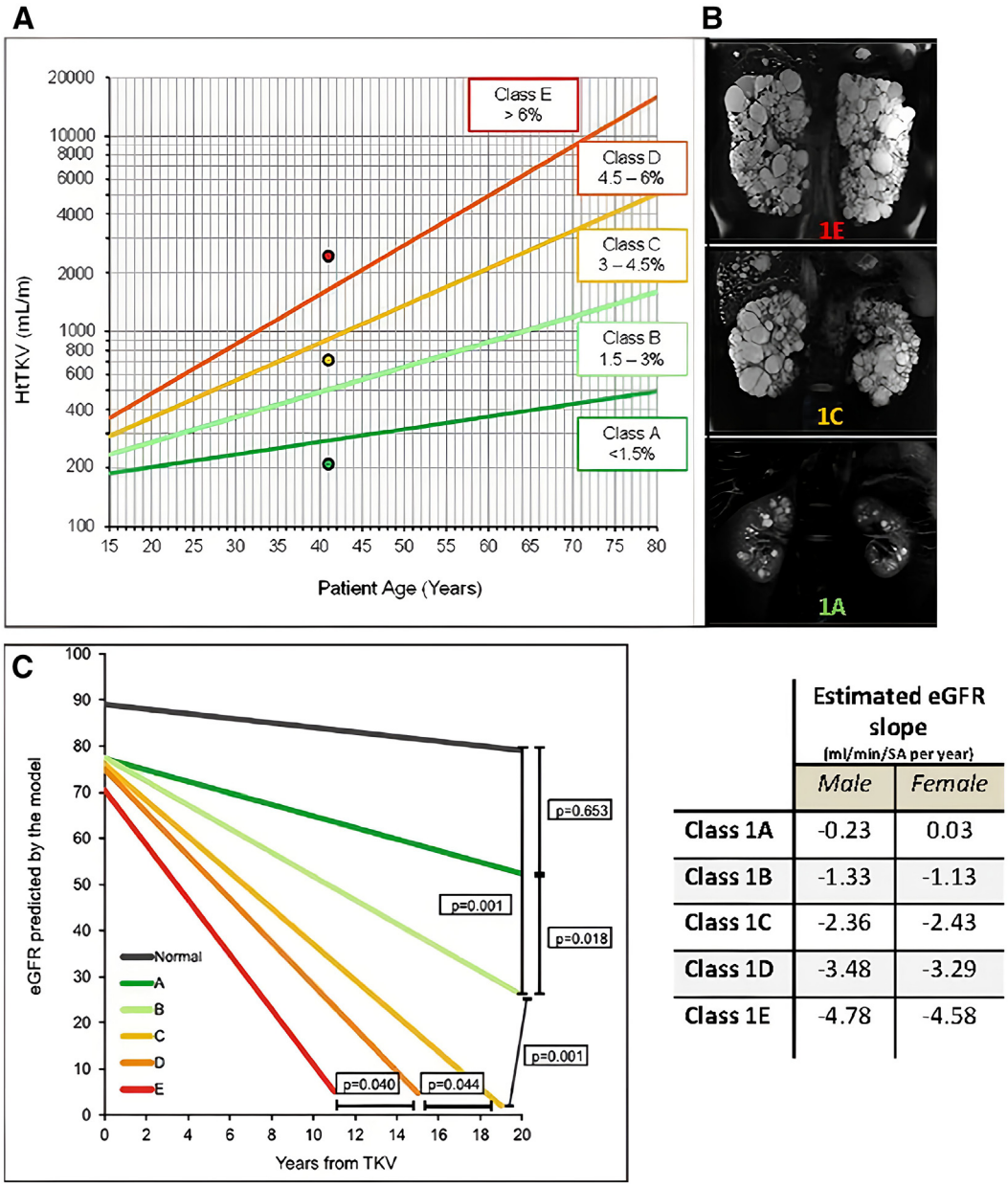
Case 3: *A 26-year-old woman with ADPKD and a family history of early kidney failure is seen at the clinic. She has had no complications of ADPKD except for hypertension which has been well-controlled with an angiotensin receptor blocker. Her eGFR is 96 mL/min/1.73 m^2. MRI reveals htTKV of 628 mL/m consistent with MIC class 1D. Her baseline liver biochemical tests are normal.*

Question 3: Which of the following is the best next step in management?

(a) Tolvaptan now
(b) Tolvaptan when her eGFR declines
(c) No treatment necessary
(d) Sodium/glucose cotransporter 2 (SGLT2) inhibitor

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

A major advance since the last Core Curriculum was the FDA's approval in 2018 of the V2R antagonist, tolvaptan



	Estimated eGFR slope (ml/min/SA per year)	
	Male	*Female*
Class 1A	-0.23	0.03
Class 1B	-1.33	-1.13
Class 1C	-2.36	-2.43
Class 1D	-3.48	-3.29
Class 1E	-4.78	-4.58

Figure 2. The Mayo Imaging Classification and projected rates of GFR decline. This imaging classification predicts the change in eGFR over time in patients with typical, bilateral, and diffuse distribution of cysts. (A) The A–E classification is on the basis of htTKV and age at the time of imaging, assuming kidney growth rates of <1.5%, 1.5%–3%, 3%–3.5%, 4.5%–6%, or >6% per year and a theoretical initial htTKV of 150 mL/m; the dots correspond to the patients in (B). (B) Magnetic resonance imaging studies corresponding to three 41-year-old patients in classes A (bottom), C (middle), and E (top). (C) The eGFR slopes in a cohort of 376 patients stratified by imaging class (−0.23, −1.33, −2.63, −3.48, and −4.78 mL/min/1.73 m^2 per year for classes A–E, respectively). Average eGFR at baseline (75 mL/min per 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. The table shows the estimated eGFR slopes for each class by sex. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, patient height total kidney volume; TKV, total kidney volume; SA, surface area. Reproduced with permission of the copyright holder (Wolters Kluwer) from Chebib FT, Perrone RD, Chapman AB, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. *J Am Soc Nephrol.* 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590

for patients at risk for rapidly progressive disease. Two pivotal randomized clinical trials, the TEMPO 3:4 study involving individuals with early disease (18-50 years of age with TKV > 750 mL) and the REPRISE study involving individuals with moderately advanced disease (18-55 years of age with eGFR 25-65 mL/min/1.73 m^2 and 56-65 years

of age with eGFR 25-44 mL/min/1.73 m^2), demonstrated the efficacy of tolvaptan. TEMPO 3:4 demonstrated a 50% reduction in the primary outcome of TKV growth, which averaged 2.8% in the tolvaptan arm versus 5.5% per year in the placebo arm, and a reduction in the rate eGFR decline of ~ 1 mL/min/1.73 m^2. REPRISE found a 30% to 35% reduction in eGFR decline, which averaged 2.34 mL/min/1.73 m^2 in the tolvaptan arm and 3.61 mL/min/1.73 m^2 in the placebo arm, for an absolute difference of 1.27 mL/min/ 1.73 m^2 over 1 year. Tolvaptan also reduced the incidence of several secondary outcomes including nephrolithiasis, cyst infection, and acute pain episodes.

Tolvaptan causes polyuria, nocturia, and polydipsia because it blocks the V2R. Patients should be educated about these symptoms and anticipate the need for frequent micturition, which may require planning or special accommodations during the commute or at the workplace. Tolvaptan should be started on a day that is not a workday because the polyuria is more significant upon initiation and tends to lessen somewhat with continued use. Tolvaptan is dosed twice daily with a starting dose of 45 mg upon awakening and 15 mg 8 hours later (Fig 3). Dosing should be increased to 60/30 mg and ideally to 90/30 mg if tolerated.

Patients should be advised to take the first dose of tolvaptan as early as possible in the morning to allow the second dose to be given at midafternoon to lessen nocturia. Reducing dietary osmolar load (sodium and protein) in the evening can partially alleviate the nocturia. Patients should stop tolvaptan in the event of a volume-depleting illness or lack of access to water. Patients should also be informed that initial levels of polyuria will recur with a restart of tolvaptan after stopping it for more than a few doses.

Tolvaptan is contraindicated in pregnancy and during breastfeeding as well as in individuals with an inability to perceive or respond to thirst, urinary tract obstruction, chronic elevation in liver transaminases, and the concomitant use of strong CYP3A inhibitors (Fig 3). Severe liver toxicity is a rare but serious adverse effect of tolvaptan use in ADPKD. Initially identified in the TEMPO 3:4 trial, elevation of transaminases to >3 times the upper limit of normal occurred in 4.4% of the tolvaptan-treated group and 1% of the placebo group. Three tolvaptan-treated patients met Hy's criteria for severe drug-induced liver toxicity. The transaminitis was reversible over 1-4 months with a decrease in dose or discontinuation of drug. In the REPRISE trial (1 year in duration) elevation in transaminases to >3 times the upper limit of normal was seen in 5.6% of the tolvaptan arm and 1.2% of the placebo arm, but there were no cases of severe liver toxicity.

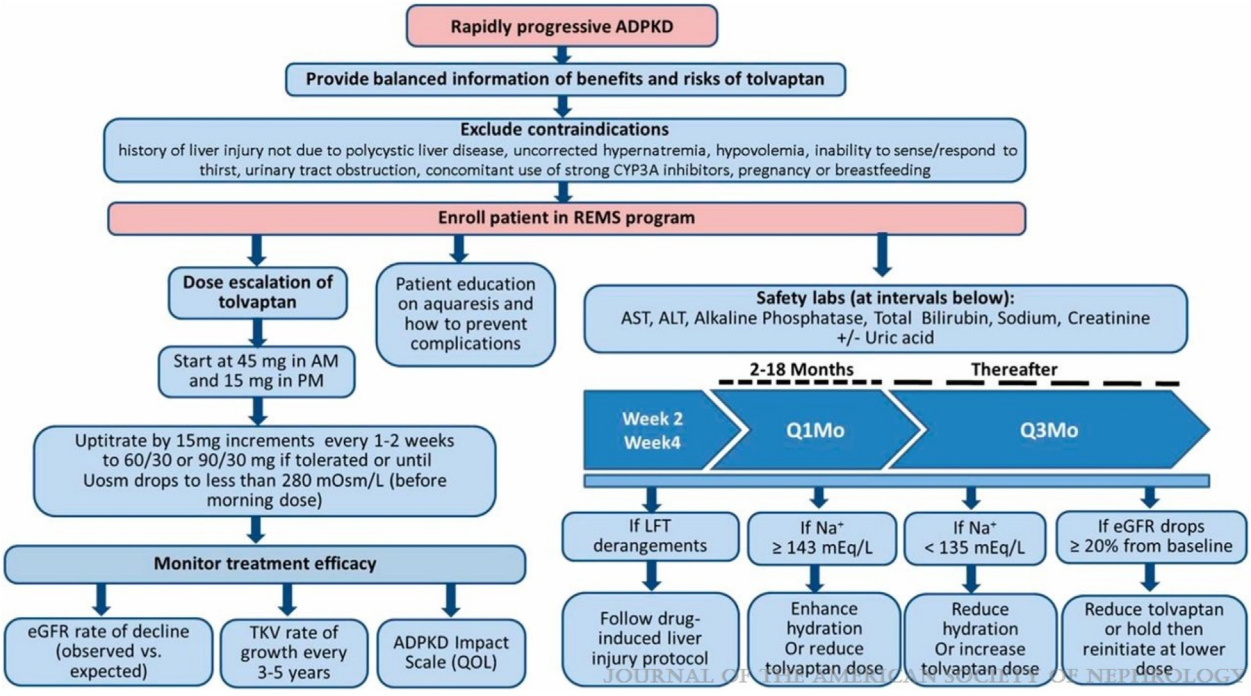


Figure 3. Algorithm for the use of tolvaptan. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, patient height total kidney volume; LFT, liver function tests; Na^+, sodium; Q1Mo, every 1 month; Q3Mo, every 3 months; QOL, quality of life; REMS, risk evaluation and mitigation strategy; TKV, total kidney volume. Reproduced with permission of the copyright holder (Wolters Kluwer) from: Chebib FT, Perrone RD, Chapman AB, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. *J Am Soc Nephrol.* 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590.

Tolvaptan was approved under a REMS (Risk Evaluation and Management Strategy) program, which requires monitoring of transaminases and bilirubin at a frequency of every 2 weeks for a month, every month for 18 months (when most cases of transaminitis were observed in clinical trials), followed by quarterly indefinitely while taking the drug. Increases in transaminase levels or bilirubin to >2 times the upper limit of normal (or 2 times baseline for those with low baseline transaminase levels) should prompt immediate discontinuation and an investigation for other causes of acute hepatitis (Fig 4). Liver function tests should be repeated in 48 to 72 hours. If transaminases normalize, tolvaptan can be restarted with a higher frequency of monitoring than the monthly requirement for REMS; but if they increase again, it should be stopped permanently. Tolvaptan should be stopped and not restarted if transaminase elevation exceeds 3 times the upper limit of normal unless another explanation for the transaminase elevation exists. A case of fulminant hepatic failure requiring liver transplant occurred in 1 patient in Japan.

Tolvaptan use should be prioritized to patients in whom the potential benefits outweigh the risks of hepatotoxicity and aquaretic side effects, which are those with MIC classes 1C-1E or declining eGFR. PROPKD score of >6 may be another potential indication. Starting tolvaptan early, before there is substantial cyst growth and loss of GFR, provides the best opportunity to modify the disease course. The time to reaching kidney failure is projected (based on trial results) to be delayed by 7.5 years if tolvaptan is initiated at an eGFR 90 mL/min/1.73 m^2 compared with 2.3 years if started at a GFR of 30 mL/min/1.73 m^2.

The benefit of tolvaptan in older adults has not been established. The REPRISE trial allowed enrollment of individuals aged 56-65 if the eGFR was between 25 and 44 mL/min/1.73 m^2. A subgroup analysis found a slower eGFR decline in the 56-65 versus ≤55 years age group (2.34 vs 4.60 mL/min/1.73 m^2 per year in the respective placebo arms), and the effect on GFR decline with tolvaptan was not statistically significant in the older subgroup. Tolvaptan should not be initiated in individuals older than 55 unless there is evidence of rapid progression unrelated to other causes.

The lower eGFR limit for inclusion in the clinical trials of ADPKD was 25 mL/min/1.73 m^2, and many experts use this value as the lower limit for starting tolvaptan. Tolvaptan was not discontinued when eGFR declined to <25 mL/min/1.73 m^2 in the trials, and most experts continue it until the start of dialysis or transplant. In a matched analysis that included pooled data from the REPRISE trial and its open-label extension, initiating or continuing tolvaptan therapy in persons with baseline eGFR 15 to 24 and 25 to 29 mL/min/1.73 m^2 was associated with a similar reduction in the rate of eGFR decline to treatment at higher eGFR.

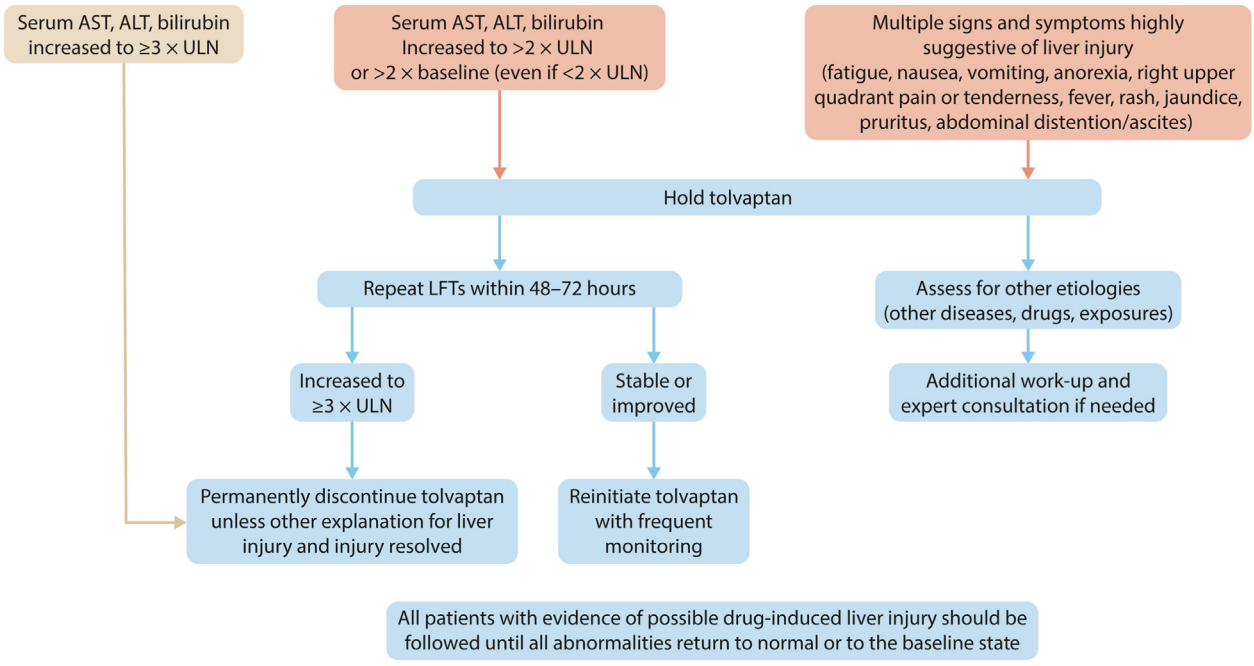


Figure 4. Algorithm of evaluation and management of potential tolvaptan-induced liver injury. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal. Reproduced with permission of the copyright holder (Wolters Kluwer) from: Chebib FT, Perrone RD, Chapman AB, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590.

Other Pharmacologic Agents Under Investigation in ADPKD

Several additional pharmacologic agents have been studied in ADPKD although none to date has shown efficacy in slowing eGFR decline. Although somatostatin analogues can be used for severe polycystic liver disease (as discussed later) and may reduce the growth of kidney cysts, they have not been shown to slow the rate of GFR decline and are not recommended for the purpose of slowing CKD progression in ADPKD. Statins have been investigated in pediatric populations with ADPKD, but not in adults. The results of an ongoing phase 3 study repurposing metformin for ADPKD as well as early phase studies of several other novel treatments for ADPKD are awaited.

SGLT2 inhibitors are not currently recommended in ADPKD outside of investigational settings given that patients with ADPKD were not studied in the major trials of SGLT2 inhibitors and animal models suggest enhanced cyst growth, possibly due to increased vasopressin levels from osmotic diuresis and volume depletion. Randomized trials are currently underway.

Returning to the case, even with the patient's normal eGFR, she is at risk of rapid progression due to the presence of MIC class 1D disease and is a candidate for tolvaptan, so answer (a) is correct. There is no reason to delay tolvaptan until the GFR declines, and the currently normal eGFR is not reassuring about her future prognosis. The efficacy and safety of SGLT2 inhibitors remains to be proven.

Additional Readings

- Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590 ★ESSENTIAL READING
- Chebib FT, Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for disease-modifying therapy. *Am J Kidney Dis*. 2021;78(2):282-292. doi:10.1053/j.ajkd.2020.12.020 ★ESSENTIAL READING
- Jdiaa SS, Mustafa RA, Yu ASL. Treatment of autosomal-dominant polycystic kidney disease. *Am J Kidney Dis*. 2025;85(4):491-500. doi:10.1053/j.ajkd.2024.08.008
- Zhou JX, Torres VE. Autosomal dominant polycystic kidney disease therapies on the horizon. *Adv Kidney Dis Health*. 2023;30(3):245-260. doi:10.1053/j.akdh.2023.01.003

Diet and Lifestyle Management in ADPKD

Case 4: *A 37-year-old man with ADPKD also has persistent elevation of liver function tests. He is evaluated by hepatology, and metabolic dysfunction-associated steatohepatitis (MASH) is diagnosed. His body mass index (BMI) is 36 kg/m². His blood pressure is 138/72 mm Hg. His eGFR is 67 mL/min/1.73 m² and htTKV by MRI is 618 mL/m (MIC class 1C). His alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are 85 IU/L (<40) and 67 IU/L (<40), respectively.*

Question 4: What is the most appropriate next step in management?

(a) Begin tolvaptan.
(b) Start sodium bicarbonate.
(c) Increase water intake to 3-7 L.
(d) Recommend weight loss through diet and exercise.

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

Dietary and Lifestyle Approaches

A wide range of dietary and lifestyle interventions have been recommended in ADPKD based on preclinical and clinical evidence. Consuming at least 2-3 liters of water daily may reduce antidiuretic hormone (ADH) levels and cyclic adenosine monophosphate (cAMP)–driven cyst growth, approximating the effects of tolvaptan. PREVENT-ADPKD, a randomized trial involving 184 patients with MIC classes 1B-1E and eGFR > 30 mL/min/1.73 m², did not show a benefit of prescribed over standard water intake on TKV or eGFR decline over 3 years. However, there was less separation between the treatment arms in daily water intake than expected (3.0 vs 2.4 L, respectively) and in mean urine osmolality (328 vs 419 mOsm/L, respectively), with only 50% of participants in the prescribed group achieving the targeted urine osmolality. Thus, the efficacy of high water intake for reducing ADPKD progression remains uncertain. That patients in the prescribed water intake arm could not drink the required water volume to achieve adequate ADH suppression also suggests it may not be an effective therapeutic strategy. Nevertheless, most ADPKD experts recommend at least 2-3 L of water intake daily to patients who cannot take tolvaptan, given limited harm (9% in the prescribed water intake group developed mild hyponatremia generally in the 130-135 mEq/L range) and the potential benefit of reducing the risk of nephrolithiasis. Importantly, substantially higher volumes of water (>3-7 L/day) may be required to avoid dehydration induced by aquaresis in patients taking tolvaptan.

Dietary sodium intake should be restricted to <2 grams daily (<5 g salt/day). This is based on secondary analyses of the HALT-PKD, CRISP, and DIPAK study populations in which higher 24-hour urine sodium excretion was associated with greater TKV growth and decline in eGFR. This effect appears to be mediated through increases in ADH and not simply via hypertension. Dietary protein should be maintained in the 0.8-1.0 g/kg range; additional protein restriction offered no benefit in the subgroup of ADPKD patients in the MDRD study or in the CRISP and DIPAK studies. Although laboratory studies indicate that caffeine increases cAMP levels with potential downstream increases

in cyst growth, observational studies have not demonstrated an association. Nevertheless, excessive caffeine intake (>400 mg per day) should be avoided.

Management of Obesity in ADPKD

Dysregulated cellular metabolism, with a switch from mitochondrial oxidation to aerobic glycolysis (the Warburg effect), is observed in tubular epithelial cells with PKD mutations and may play a role in the pathogenesis of cyst growth. Studies in animal models have demonstrated slower cyst growth with daily caloric restriction, time-restricted feeding, ketogenic diet, or supplementation with ketones. Data in humans are limited. Observational data have demonstrated a more rapid TKV increase and eGFR decline in patients who are overweight (BMI 25.0-29.9 kg/m^2) or obese (BMI > 30.0 kg/m^2) as compared with normal weight (BMI < 25 kg/m^2).

A 12-month pilot study of 29 people with ADPKD randomized to either daily caloric restriction (1773 ± 253 kcals/day) or intermittent fasting (532 ± 73 kcals on fasting days) demonstrated a stabilization of TKV with >5% loss of body weight. Short-term tolerability and a lack of change in TKV and eGFR were observed in a 3-month study of a ketogenic diet. The potential risks, which depend on the diet, include hyperlipidemia, hyperuricemia, increased cardiovascular risk, nephrolithiasis, and others. Longer term efficacy, tolerability and safety have yet to be established.

Patients who are overweight or obese should be encouraged and supported to lose weight given the benefits of reduced blood pressure, cardiovascular disease, metabolic syndrome, and musculoskeletal disease. The safety and efficacy of pharmacologic or surgical treatments of obesity in ADPKD have not been assessed at the present time.

Returning to the case, the best answer to Question 4 is (d): in pilot studies of weight loss interventions, achieving a weight loss of >5% has been associated with stabilization of TKV and eGFR, and it would be beneficial for this patient's MASH as well. Tolvaptan with this level of baseline transaminase elevation is contraindicated. Increasing water intake to 3-7 L daily has not been shown to be effective in slowing progression and may not be achievable for many patients. Sodium bicarbonate has not been tested for slowing progression of ADPKD.

Additional Readings

- Chebib FT, Nowak KL, Chonchol MB, et al. Polycystic kidney disease diet: what is known and what is safe. *Clin J Am Soc Nephrol*. 2024;19(5):664-682. doi:10.2215/CJN.0000000000000326 ★ESSENTIAL READING
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Blood Pressure Management

The blood pressure target for individuals with ADPKD aged 18-49 years with GFR > 60 mL/min/1.73 m^2 is a home measurement of <110/75 mm Hg; for all others affected by ADPKD, it is an office measurement of 120/80 mm Hg. The basis for the lower target in younger patients is the HALT-PKD study, which found a statistically significant (14%) reduction in TKV growth with treating to <110/75 versus 120-130/70-80 mm Hg. The 120/80 mm Hg target for the remainder of patients is based on the SPRINT trial, which found a 35% reduction in major cardiovascular events and cardiovascular-related mortality with the treatment of patients at high cardiovascular risk to a target of 120/80 mm Hg versus 140/90 mm Hg.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are considered first-line agents partly because they have a well-established role in CKD but also based on the theory that cysts impinging surrounding microvasculature stimulate the renin angiotensin system. Most other antihypertensive classes can be used, but the concomitant use of diuretics in tolvaptan-treated patients has not been established and is generally avoided given increased risk for volume depletion.

Additional Reading

- Frederic F. Rahbari-Oskoui. Management of hypertension and associated cardiovascular disease in autosomal dominant polycystic kidney disease. *Adv Kidney Dis Health*. 2023;30(5):417-428. doi:10.1053/j.akdh.2023.03.004

Renal Complications of ADPKD

Acute Pain and Hemorrhage

Acute pain in ADPKD may be due to cyst hemorrhage (with or without rupture), infection, or nephrolithiasis. Pain from cyst hemorrhage is usually a self-limited process, generally subsiding over 1-2 weeks, and is managed with pain control and hydration. Interventions such as percutaneous embolization or nephrectomy are rarely needed to manage uncontrolled hemorrhage. Although medical treatment of recurrent kidney stones is the same in ADPKD patients as in the general population, procedural stone management should be performed in centers with experience because a large cyst burden can make procedures such as lithotripsy more difficult.

Chronic Pain Management

Chronic pain affects up to 60% of patients with ADPKD and has several potential etiologies, including compression of extrarenal tissue, stretching of the renal capsule, or the enlarged kidney pulling on the hilum. Back pain can be due to paraspinal muscle sprain, disc herniation, or radiculopathy from increased abdominal girth and loss of lumbar lordosis. Kidney size correlates with abdominal fullness symptoms but not with pain. A single large cyst in

a patient with an otherwise small cyst burden may be quite disabling depending on its location relative to surrounding structures.

Tolvaptan treatment may impact the incidence and severity of pain in ADPKD. Acute pain episodes declined by 36% with tolvaptan compared with placebo in the TEMPO 3:4 trial. The impact of tolvaptan on chronic pain has not been studied, so it should not be prescribed as a treatment for chronic pain, but this may be an additional benefit to its use.

Medical management of chronic pain

General principles for medical management of chronic pain entail a stepwise approach, starting with nonpharmacologic measures (heating pad, massage, acupuncture, transcutaneous nerve stimulation) and nonopioid medications (such as acetaminophen, topical capsaicin, or diclofenac) and ending with opioids. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used sparingly or avoided.

Opioids are reserved for when interventional procedures are unsuccessful, anatomy is not conducive to intervention, or the patient declines intervention. Patients should be informed of risks, including dependence and the lowest dose, and the shortest duration that alleviates pain should be prescribed. Cannabinoid products have not been tested in ADPKD, but data in the general population suggest that currently available regulated compounds (chiefly dronabinol) do not provide the same level of analgesia as opioids, and the side effects are more substantial.

Surgical/procedural management of chronic pain

If the pain is focal and corresponds to the location of a single (or few) dominant cyst(s), percutaneous aspiration with sclerotherapy provides a longer duration of pain relief than cyst aspiration alone. Sclerotherapy using detergent foam is less painful than sclerotherapy using alcohol and appears to be equally effective. Patients should be informed that fluid can reaccumulate, irrespective of the drainage procedure used; repeat procedures are often required. The surgical options include laparoscopic cystectomy or fenestration as well as partial or total nephrectomy. Procedures that will result in parenchymal loss should be reserved for only the most debilitating cases or patients already treated with kidney replacement therapy.

More complex pain syndromes may require additional interventions. Because pain fibers travel via the sympathetic nervous system, sympathectomy has been shown to be effective in alleviating pain. Determining whether pain is arising from the kidney or liver is critical because the procedure for performing sympathectomy differs. Celiac plexus blockade via radioablation through a percutaneously placed catheter is effective for pain of hepatic origin because the liver is supplied by nerves running in the celiac plexus. The nerve supply to the kidney travels within the lesser splanchnic nerve along the renal arteries, which can be accessed (for radioablation) via a catheter placed at the distal end of the renal artery, the same procedure used for treatment of resistant hypertension.

Transcatheter arterial embolization of the renal artery is a minimally invasive approach that can alleviate pain and reduce kidney size, the latter of benefit for patients experiencing mass effects, but it will result in loss of GFR. Typically, this procedure is reserved for highly symptomatic patients treated with dialysis or have had a transplant but are poor surgical candidates. Decisions about which procedure to perform should be made at centers with interdisciplinary technical expertise and experience in managing chronic pain in ADPKD.

Additional Readings

- Casteleijn NF, van Gastel MD, Blankestijn PJ, et al. Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease. *Kidney Int*. 2017;91(4):972-981. doi:10.1016/j.kint.2016.12.007
- Hogan MC, Norby SM. Evaluation and management of pain in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis*. 2010;17(3):e1-e16. doi:10.1053/j.ackd.2010.01.005

Kidney Infections in ADPKD

Cyst infection in ADPKD

Case 5: *A 45-year-old woman with ADPKD presents with fever, dysuria, and flank pain. She had a similar episode 2 months ago, which was treated with intravenous antibiotics for 3 days followed by 2 weeks of trimethoprim-sulfamethoxazole. Examination reveals temperature of 38.7°C and tenderness over her left kidney. The urinalysis shows the presence of leukocyte esterase and white blood cells (WBC). The WBC count is 16.5 × 10^9/L, and C-reactive protein is 85 mg/L (normal <10 mg/L). A CT scan demonstrates enlarged cystic kidneys bilaterally. A large left upper pole cyst exhibits a thickened cyst wall and pericystic inflammation. Intravenous ceftriaxone is started. Her urine culture subsequently demonstrated >100,000 units of Proteus mirabilis, similar to prior culture results.*

Question 5: Which of the following is most appropriate next step in management?

(a) Perform a WBC scan.
(b) Treat for 10-14 days with trimethoprim-sulfamethoxazole.
(c) Arrange for percutaneous drainage of the left upper pole cyst.
(d) Treat for 4-6 weeks with fluoroquinolone for suspected kidney cyst infection.

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

Distinguishing pyelonephritis from a kidney cyst infection can be difficult. Diagnostic criteria using common clinical and laboratory characteristics have been developed (Fig 5) but are imperfect in distinguishing cyst

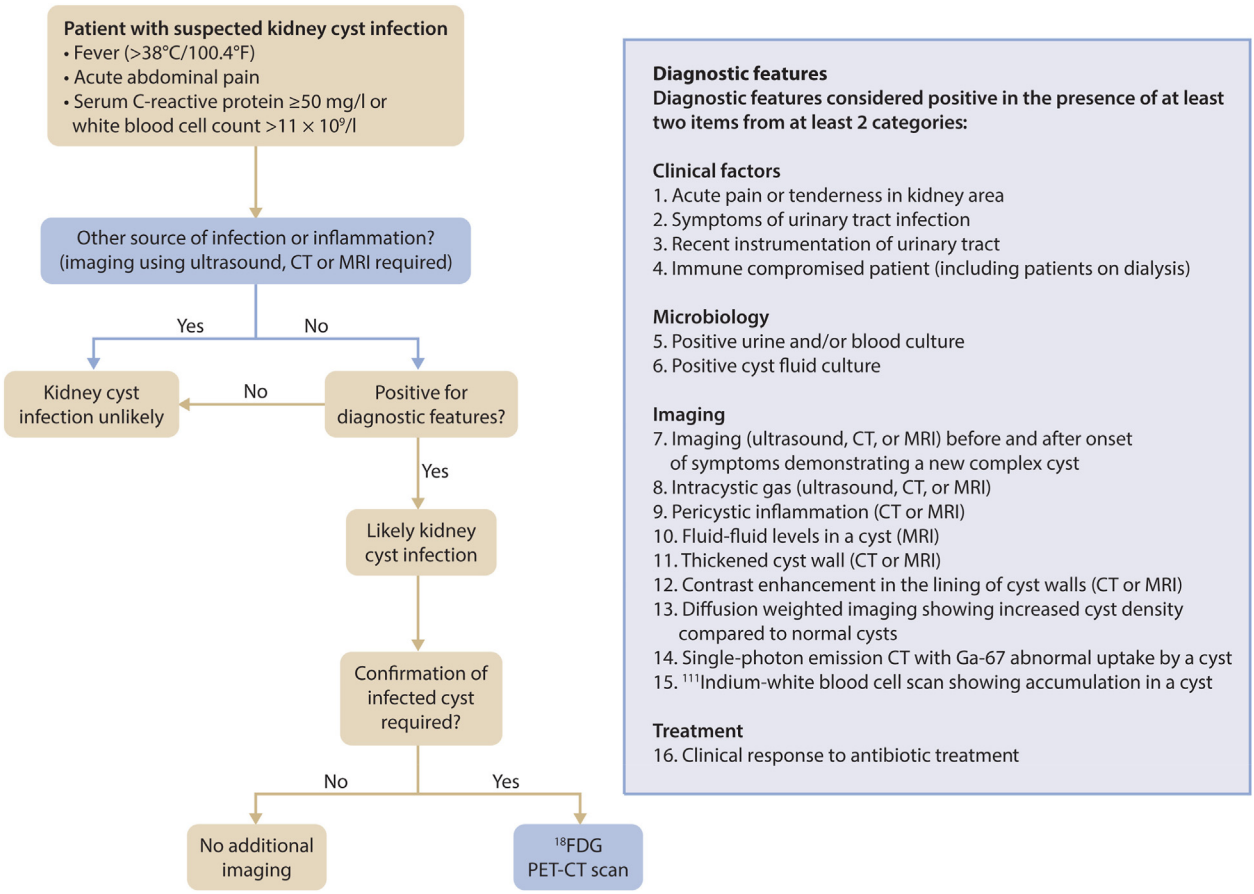

Figure 5. Diagnostic algorithm for an infected kidney cyst in ADPKD. Abbreviations: CT, computerized tomography; MRI, magnetic resonance imaging; FDG-PET, ^{18}F-fluorodeoxyglucose–positron emission tomography.Reproduced with permission of the copyright holder (Kidney Disease: Improving Global Outcomes) from: Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S):S1-S239.

infection from other conditions. Cyst hemorrhage often presents with acute pain similar to a kidney cyst infection but often lacks the laboratory, radiographic, or physical examination features seen with cyst infection. The presence of macroscopic hematuria is more characteristic of cyst hemorrhage whereas high fever is more suggestive of infection. Importantly, a negative urinalysis or urine culture does not preclude a cyst infection because most cysts do not connect to the urinary collecting system.

Cross-sectional imaging studies may show fat stranding, thickened walls, and cyst debris, but none of these are diagnostic for infection. CT or MRI perform better than ultrasound in detecting cyst infection but they require contrast enhancement. ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scans have better performance characteristics for identifying infected cysts in the kidneys and liver compared with other imaging modalities due to their assessment of metabolic activity. Due to their higher cost, PET/CT should be reserved for when there is a lack of clinical response to appropriate antibiotics and to guide the decision of which cyst to drain when the suspicion of cyst infection is high and other imaging modalities are negative.

Treatment of uncomplicated cystitis in ADPKD is identical to the general population. When a cyst infection is suspected, lipophilic antibiotics with robust cyst penetration such as fluoroquinolones or trimethoprim-sulfamethoxazole should be chosen in the absence of other contraindications. Cyst infections require a prolonged 4- to 6-week antibiotic course. Cyst drainage is only required for resistant or recurrent cyst infections when the appropriate antimicrobial therapy has been unsuccessful. Rarely, patients may require native nephrectomy before transplantation or dialysis; this should be limited to those with continued infection despite a prolonged course of appropriate antibiotics and/or cyst drainage procedures, with an anatomical issue that precludes successful treatment (eg, staghorn calculus), or in the setting of high rates of recurrent infections.

Returning to the case, the best answer is (d), treatment of a suspected cyst infection with a 4- to 6-week course of lipophilic antibiotics that penetrate cyst walls (Fig 5). A

10- to 14-day course of antibiotics is too short for treatment of cyst infection. Performing a WBC scan or percutaneous drainage would be considered only when there is a lack of response to antibiotics, which has not been demonstrated in this patient.

Additional Reading

➢ Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S):S1-S239. doi:10.1016/j.kint.2024.07.009

Extrarenal Complications in ADPKD

Polycystic Liver Disease

Polycystic liver disease (PLD) is defined as the presence of >10 liver cysts and can be seen in ADPKD. Most patients with ADPKD will have at least 1 hepatic cyst, and the incidence increases with age. Risk factors for more severe PLD include female sex and exposure to exogenous estrogen therapy. Rarely, men also can be affected with severe PLD. Non-estrogen-containing contraception is recommended for women with severe PLD or with a family history of severe PLD and may be appropriate for any young women or adolescent at risk of or with known ADPKD irrespective of the knowledge of the presence of PLD.

Patients who develop acute abdominal pain should be assessed for kidney or liver cyst infection, cyst hemorrhage, or alternative etiologies of abdominal pain unrelated to PLD, usually via contrast-enhanced CT or MRI. The probability of liver cyst infection increases in the presence of fever, elevated C-reactive peptide, positive blood cultures for enteric Gram-negative bacilli as well as by radiographic findings suggestive of cyst infection. PET-CT may have a higher sensitivity and specificity for detecting liver cyst infection than other imaging modalities; however, as with kidney cyst infections, they should be reserved for situations where the clinical course suggests cyst infection but diagnostic uncertainty persists after a contrast-enhanced CT and/or MRI, particularly when identification of the infected cyst is required for a drainage procedure.

Management of liver cyst infection is similar to kidney cyst infection with the use of 4-6 weeks of lipophilic antibiotics that penetrate into cysts. Early drainage procedures may be indicated in immunocompromised patients and in hemodynamically unstable patients. Other indications for drainage of a potentially infected liver cyst include patients who are not responding to appropriate antibiotic therapy or to confirm the diagnosis when uncertainty exists after a diagnostic workup.

Severe PLD can lead to additional complications of chronic abdominal pain, early satiety, gastroesophageal reflux, malnutrition, sarcopenia, and lower extremity edema from obstruction of the inferior vena cava. Management depends on patient symptoms, the distribution of the cyst burden, and the size of individual cysts (Fig 6). A single large symptomatic hepatic cyst can be treated with aspiration sclerotherapy, which is preferred over cyst aspiration alone due to lower rates of recurrence. Patients with severe cyst involvement in 1 sector of the liver with normal parenchyma elsewhere can undergo cyst fenestration or partial hepatectomy. By contrast, patients with a diffuse cyst burden throughout the entire liver may benefit from medical therapy with somatostatin analogues such as octreotide. Those with massive PLD and experiencing malnutrition and sarcopenia may require liver transplantation. Complex cases should be managed by a multidisciplinary team at a center with a high volume of PLD cases.

Additional Readings

➢ Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int.* 2025;107(suppl 2S): S1-S239. doi:10.1016/j.kint.2024.07.009

➢ European Association for the Study of the Liver. EASL clinical practice guidelines on the management of cystic liver diseases. *J Hepatol.* 2022;77(4):1083-1108. doi:10.1016/j.jhep.2022.06.002

Intracranial Aneurysms and Vascular Complications of ADPKD

Rupture of an intracranial aneurysm (ICA) leading to subarachnoid hemorrhage (SAH) is a devastating complication and major concern for both patients with ADPKD and their clinicians. The presence of unruptured ICA in ADPKD is estimated to be 4-fold higher than in the general population, with prevalence estimates ranging from 9% to 19%. ICA can occur in patients with *PKD1* or *PKD2* and the minor ADPKD gene mutations. Screening for ICA and SAH risk is thus a major consideration in the management of patients with ADPKD.

The approach to screening varies, but most guidelines and experts recommend screening patients with a personal or family history of ICA or SAH or a family history of unexplained sudden death. Other indications include a high-risk occupation where SAH would be dangerous to the patient or others, limited or no available family history, and patients who wish to evaluate their personal risk of ICA. Additionally, many kidney transplant programs require ICA screening as part of the assessment of transplant candidacy. The risk-benefit balance of screening for ICA in asymptomatic individuals without a family history of ICA remains uncertain because the incidence is lower than the higher risk groups and studies to date have not demonstrated lower rates of morbidity or mortality with

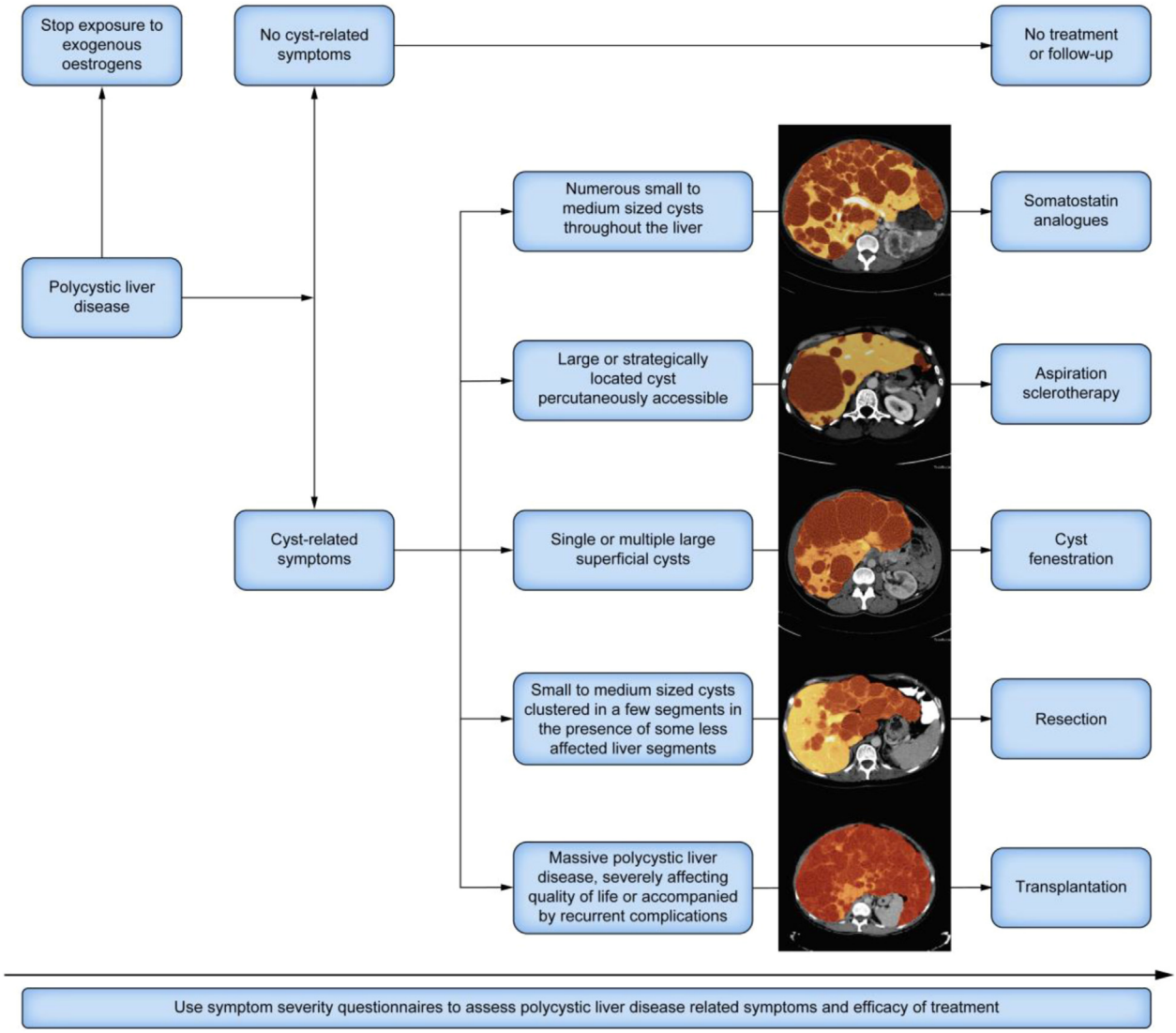

Figure 6. An approach to the management of symptomatic polycystic liver disease. Reproduced with permission of the copyright holder (Elsevier) from: European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of cystic liver diseases. *J Hepatol*. 2022;77(4):1083-1108. doi:10.1016/j.jhep.2022.06.002

screening. In addition to screening, modifiable risk factors for ICA rupture such as hypertension and tobacco use should be addressed.

The preferred modality for screening is time-of-flight magnetic resonance angiography (MRA) using a 3-tesla scanner. This study does not require gadolinium contrast. CT angiography, which requires iodinated contrast dye, is reserved for patients with a contraindication to MRA. The optimal duration for rescreening in those with a negative initial test is unknown, but the KDIGO guidelines suggest repeating MRAs in 5- to 10-year intervals for those at high risk of ICA.

Management of an ICA detected on MRA should be undertaken at experienced centers to avoid unnecessary procedures and their potential risks. Most ICAs detected by screening MRA are small (<5 mm) and are in the anterior circulation of the circle of Willis, both of which are associated with a lower likelihood of rupture. Up to 20% of patients will have multiple ICA. Larger ICA, rapid change in size, location in the posterior circulation, or with anatomic features conveying a higher risk of rupture are more likely to require intervention.

The decision about using endovascular or surgical approaches depends on the size, shape, and location of the ICA as well as center-specific expertise. Management approaches should be made by multidisciplinary teams in centers with a high volume of ICA cases to ensure high levels of experience with these decisions and the related procedures. The frequency for repeating MRA to monitor known ICA is uncertain, but most experts and KDIGO recommend initially retesting at 6-month intervals for the first year, and later increasing to every 1-2 years.

Additional Readings

- Gulati A, Watnick T. Vascular complications in autosomal dominant polycystic kidney disease: perspectives, paradigms, and current state of play. *Adv Kidney Dis Health*. 2023;30(5):429-439. doi:10.1053/j.akdh.2023.09.004
- Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int*. 2025;107(suppl 2S): S1-S239. doi:10.1016/j.kint.2024.07.009

Pregnancy, Women's Health, and ADPKD

Pregnancy outcomes in women with ADPKD and preserved eGFR are generally favorable. The effect of pregnancy on kidney cyst growth is uncertain. With each of hypertension, proteinuria, and reduced eGFR, the risk of preeclampsia, small-for-gestational-age births, and preterm labor increase. Given the increased risk for preeclampsia, all patients with ADPKD should be treated with 81 mg of aspirin from 12 to 36 weeks of pregnancy unless there is a contraindication.

Urinary stasis, a result of elevated progesterone and ureteral compression by the gravid uterus, increases the risk for cystitis, a risk that is already increased in ADPKD patients. Asymptomatic bacteriuria should be treated promptly because cystitis can trigger preterm labor or develop into more serious kidney cyst infections, which can be difficult to treat because antibiotics that can penetrate into cysts are generally avoided during pregnancy.

Patients should be counseled about the option of preimplantation genetic diagnosis, which requires identification of the parental pathogenic ADPKD mutation and in vitro fertilization (IVF). The risks of IVF include liver cyst growth from high estrogen exposure and acute kidney injury from ovarian hyperstimulation syndrome. Because pregnancy may increase liver cyst burden, women with pre-existing severe PLD should be counseled about the additive risk of pregnancy.

Additional Reading

- Al Sayyab M, Chapman A. Pregnancy in autosomal dominant polycystic kidney disease. *Adv Kidney Dis Health*. 2023;30(5):454-460. doi:10.1053/j.akdh.2023.10.006

Conclusion

It is an exciting time for ADPKD. Fundamental scientific and clinical research have advanced the approach to diagnosis, prognostication, and management of all aspects of ADPKD since the previous Core Curriculum. The KDIGO guideline on ADPKD is further evidence of the progress made to date. Several therapeutics are in the pipeline, and we eagerly anticipate ongoing discoveries.

Article Information

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