CME

An update on treatments for autosomal dominant polycystic kidney disease

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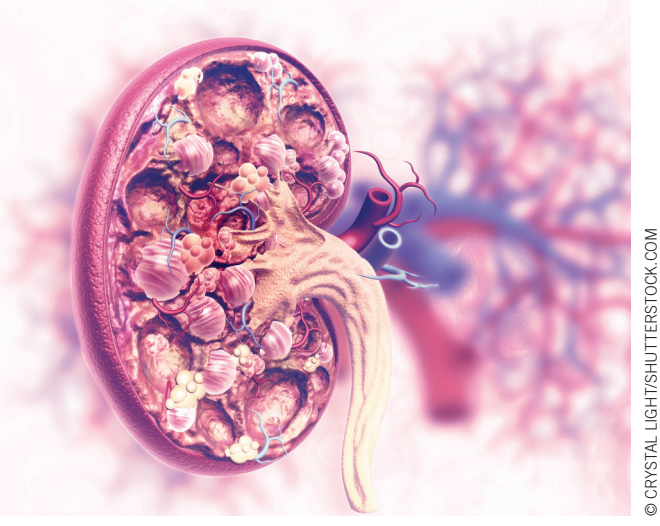
ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is less common than primary hypertension or diabetes but should be considered as a possible cause of end-stage renal disease, especially in young patients without comorbidities. Because of ADPKD's nonspecific symptoms, the diagnosis, treatment, and pertinent patient education may be delayed. This article describes ADPKD and its management, including tolvaptan, a new treatment with the potential to reduce or delay morbidity. However, only a subset of patients qualifies for this expensive treatment.

Keywords: autosomal dominant, polycystic kidney disease, ADPKD, tolvaptan, end-stage renal disease, hypertension

Learning objectives

- Describe the pathophysiology, clinical presentation, differential diagnoses, diagnostic studies, lifestyle modifications, and complications of ADPKD.
- Describe the importance of hypertension management to reduce renal dysfunction and cardiovascular complications associated with ADPKD.
- Outline the indication, mechanism of action, adverse effects, and contraindications of tolvaptan treatment.
- Describe the 10 steps for prescribing tolvaptan to a high-risk patient with ADPKD.



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Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end-stage renal disease (ESRD).[1] Worldwide, an estimated 1:1,000 to 1:2,500 patients have ADPKD.[2] ADPKD is more prevalent than sickle cell disease, Down syndrome, cystic fibrosis, and hemophilia combined.[3] Clinical suspicion for ADPKD often is low because of its nonspecific symptoms.[4] In 2020, about 40% of patients with ADPKD received preemptive transplant or home dialysis.[5]

ADPKD is linked to genetic mutations in the *PKD1* or *PKD2* genes. These mutations are inherited in an autosomal dominant pattern, giving each offspring of a parent with the mutation a 50% probability of having the condition.[4] Cystic kidneys are the hallmark sign of this disease. Other presentations include nephrolithiasis, hematuria, renal failure, hypertension, hepatic cysts, and intracranial aneurysms.[6] The ambiguous symptoms, delayed presentation, and variable penetration can make diagnosis difficult.

Treatment of ADPKD focuses on managing symptoms and preventing complications. Early detection and treatment of hypertension remain crucial in delaying the progression of kidney dysfunction and preventing cardiovascular complications.[7] For a select subset of patients, tolvaptan, the first disease-targeting therapy, may be appropriate. Tolvaptan reduces the rate of kidney function decline in adults with rapidly progressing ADPKD.[8,9] This medication has been proven to delay renal failure and the need for renal replacement therapy (RRT) or transplant, reduce symptom burden, and lower the risk of cardiovascular complications associated with ADPKD.[10] Although tolvaptan is only appropriate for patients who meet specific criteria (discussed later in this article), clinicians should be aware of this therapy so they can refer their patients to nephrology appropriately.

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Key points

- ADPKD is the most common genetic cause of ESRD.
- The hallmark of ADPKD is cystic growth on the kidneys leading to an increase in total kidney volume and CKD.
- Clinical manifestations of ADPKD include hypertension, hematuria, flank pain, nephrolithiasis, kidney or liver cysts, and intracranial aneurysms.
- The standard of treatment for ADPKD focuses on symptomatic management and complication prevention.
- Tolvaptan, a disease-modifying therapy, is a recently approved medication for a subset of patients with ADPKD who meet eligibility criteria.

PATHOPHYSIOLOGY

ADPKD is a genetically heterogeneous disease defined by two common mutations: either the *PKD1* gene (chromosome 16p13.3) or the *PKD2* gene (chromosome 4p21). The *PKD1* mutation accounts for 78% of ADPKD cases and correlates to earlier onset of ESRD.[11] The *PKD2* mutation accounts for 15% of disease and correlates to later onset.[11]

In a normal kidney, the *PKD1* gene encodes for polycystin 1 (PC1), an amino-acid receptor-like transmembrane protein; the *PKD2* gene encodes for polycystin 2 (PC2), a calcium-permeable nonselective cation channel.[1] PC1 and PC2 create a complex that regulates intracellular calcium influx in the primary cilia of renal epithelial cells. Primary cilia sense fluid movement through the tubules, which helps maintain their size and structure.[6]

Mutations of *PKD1* or *PKD2* lead to a decrease in intracellular calcium concentration and an increase in cyclic adenosine monophosphate and cystogenesis through activation of proliferation and secretion pathways.[1,6,11] Patients with the *PKD1* mutation progress to ESRD about 20 years earlier than those with the *PKD2* mutation.[1] Patients with the *PKD1* mutation develop more cysts and a greater height-adjusted total kidney volume (a prognostic marker) compared with patients with the *PKD2* mutation.[1,6,11]

CLINICAL PRESENTATION

Most patients with ADPKD are asymptomatic for many years and are only diagnosed when kidney function is greatly reduced. As the disease silently progresses, patients develop impaired kidney function secondary to cyst burden and enlargement of the kidneys between ages 45 and 60 years (**Figure 1**).[12] The average age of symptom onset depends on the gene mutation. A patient with the *PKD1* mutation can start to experience the effects of kidney function impairment between ages 40 and 50 years; a patient with the *PKD2* mutation typically experiences the effects of impairment between ages 50 and 60 years.[1] Although family history can help guide the diagnosis in certain cases, the clinical presentation often varies depending on patient comorbidities, and ADPKD frequently is mistaken for other diseases.[4]

Hypertension, occurring in 60% of patients, is one of the most common clinical manifestations of ADPKD.[13] Hypertension precedes kidney impairment and leads to the development of cardiovascular complications, including left ventricular hypertrophy, mitral valve prolapse, and/or aortic root dilation.[4] Antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors is recommended to prevent such complications.[7]

The growth of kidney cysts causes flank or abdominal pain from compression or stretching of the kidney capsule.[3] The degree of pain varies with cyst size, which ranges from microscopic to 11 cm (4.3 in). In extreme cases, kidneys can weigh up to 30 lb (13.6 kg) each, leading to tubular atrophy, basement membrane thickening, and interstitial fibrosis.[13]

Cystic growth is not limited to the kidneys. Simple hepatic cysts develop in more than 90% of patients with ADPKD who are age 35 years or older.[6] These patients complain of abdominal pain, early satiety, and gastroesophageal reflux, but hepatic cysts rarely grow large enough to cause obstruction, jaundice, or portal hypertension, so patients rarely develop liver function impairment.[3]

In addition to kidney and hepatic cysts, older patients with the *PKD1* mutation may develop pancreatic cysts.[14] About 10% of patients with ADPKD develop pancreatic cysts, but there is little evidence to suggest that these cysts alter pancreatic function.[14]

Patients with ADPKD also may develop abdominal hernias caused by abdominal distension and decreased extracellular matrix integrity.[14] These hernias can become incarcerated or strangulated and require surgical management. Hernias also can disturb a patient's anatomy, creating complications for those in need of

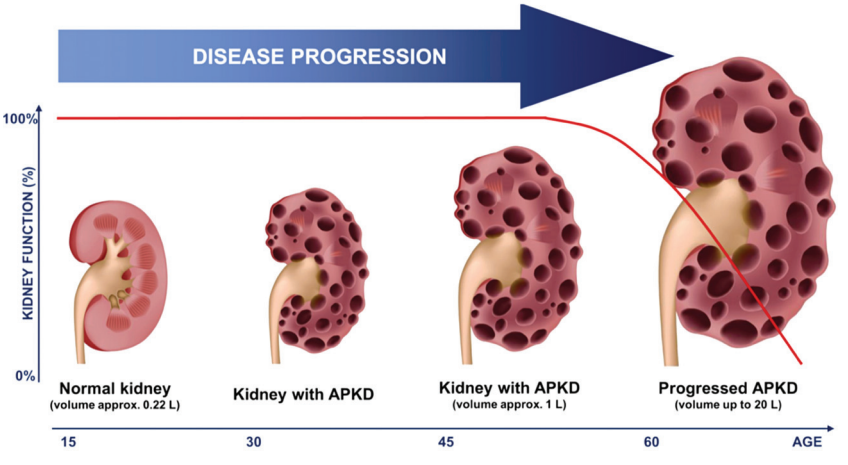

FIGURE 1. ADPKD disease progression
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peritoneal dialysis.[14]

Nephrolithiasis occurs in about 20% of all patients with ADPKD.[3] Uric acid or calcium oxalate stones are more common due to increased calcium and urate accumulation in the kidneys.[3] Patients also are at a higher risk for recurrent stones because of lower urinary volumes and increasing total kidney volumes.[3] Gross and recurrent hematuria from cyst rupture, nephrolithiasis, or urinary tract infection is another common symptom.[3]

Patients with ADPKD have a fourfold increased risk for intracranial aneurysms.[3,6] These aneurysms are one of the most lethal presentations of ADPKD because rupture can lead to subarachnoid hemorrhage and death.[3] Screening with magnetic resonance angiography is recommended if a patient has a family history of aneurysms or aneurysm rupture.[6]

DIAGNOSTIC STUDIES

The diagnosis of ADPKD is largely guided by imaging. Most often, ADPKD is an incidental diagnosis when patients present with other symptoms, such as abdominal pain, nephrolithiasis, hematuria, or pregnancy.[13] If ADPKD is suspected, renal ultrasound is the initial screening modality because it is safe and inexpensive. Ultrasonography is user-dependent and is less sensitive in younger patients because they typically have fewer, smaller cysts.[3] T2-weighted MRI and CT with contrast can identify cysts that are 2 to 3 mm in diameter; ultrasound detects cysts greater than 10 mm.[6] The Ravine criteria can be used to establish the diagnosis of ADPKD if a patient has evidence of cysts on ultrasound and a documented *PKD1* mutation.[3]

For at-risk patients (those with a family history of ADPKD), MRI is the preferred imaging modality. If more than 10 cysts are detected on MRI for an at-risk patient who is age 40 years or younger, the results are considered diagnostically 100% specific and sensitive for ADPKD.[6] Fewer than five cysts on MRI excludes the disease.[6] If family history is negative but there is evidence of disease or the patient needs a kidney transplant, genetic testing is an option to confirm the diagnosis.[3] With the growth of genetic research, clinicians should have confidence that resources exist for their patients. Clinicians can refer patients to genetic testing centers, or genetic testing kits can be mailed to laboratories if testing is not available locally.

DIFFERENTIAL DIAGNOSIS

Several genetic diseases are associated with kidney cysts.[6,15] A family history of cystic disease or kidney enlargement is useful information to differentiate ADPKD from nonhereditary conditions. The presence of extrarenal manifestations, results of imaging studies, and patient age at disease presentation also provide helpful information.

TABLE 1. ProPKD score[10,21,28]

Variable	Points
Male sex	1
Hypertension before age 35 years	2
First urologic event before age 35 years	2
PKD2 mutation	0
Nontruncating *PKD1* mutation	2
Truncating *PKD1* mutation	4

Scoring: 0 to 3, low risk of progression to ESRD; 4 to 6, intermediate risk; 7 to 9, high risk

Mutations in two different genes, *GANAB* and *DNAJB11*, produce ADPKD-like phenotypes.[6,16,17] A mutation in the *GANAB* gene leads to cystogenesis because of a defect in PC1 protein maturation. However, unlike in ADPKD, a patient with the *GANAB* gene mutation has preserved kidney function.[16] Consider the *DNAJB11* gene mutation if a patient presents with multiple small cysts bilaterally with normal-sized or atrophic kidneys.[17]

Recognizing each disease's unique presentation is key to differentiating the various autosomal dominant kidney diseases. For example, patients with autosomal dominant

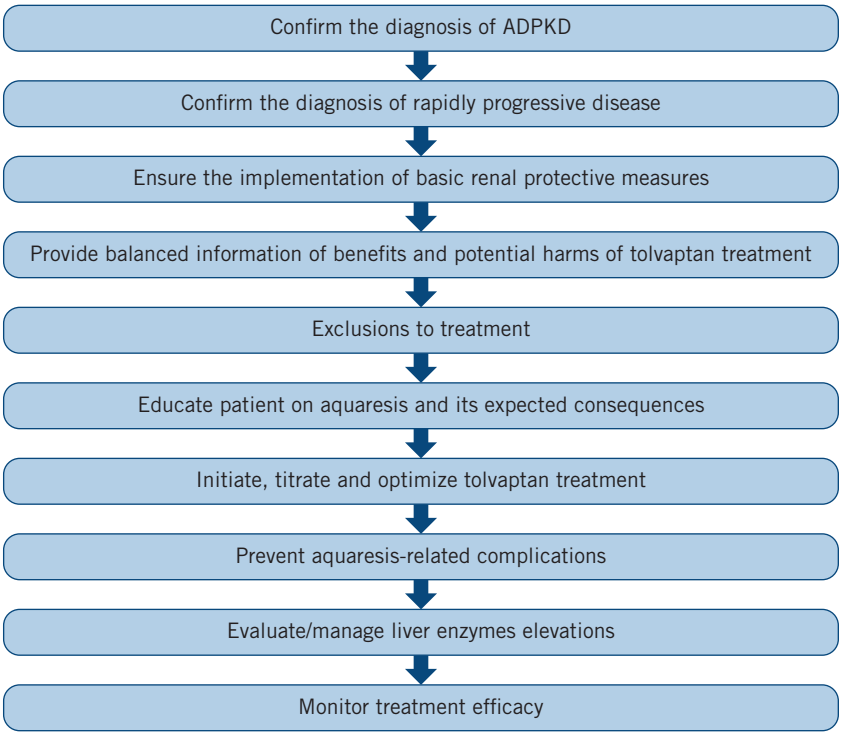

FIGURE 2. Stepwise approach to evaluate and manage patients with ADPKD for tolvaptan treatment

Reproduced with permission 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.

TABLE 2. Potential benefits and harms of tolvaptan therapy[10]

Benefits
- Slows the growth of cysts in the kidneys
- Slows eGFR decline
- May delay need for RRT
- Reduces pain, hematuria, kidney stones, and urinary tract infections
- Slight BP reduction

Harms
- Polyuria, pollakiuria, and nocturia
- Aquaresis
- Thirst and fatigue
- Uric acid elevations (rarely, gout)
- Transaminase elevations and risk for severe hepatocellular toxicity
- Need for frequent liver function monitoring
- Possible interactions with CYP3A inhibitor drugs
- Financial burden

polycystic liver disease (ADPLD) typically present with hepatomegaly, portal hypertension, ascites, jaundice, early satiety, gastroesophageal reflux, and only a few bilateral kidney cysts versus the heavier kidney cyst burden seen in patients with ADPKD.[6,11] In the case of autosomal dominant tubulointerstitial kidney disease (ADTKD), interstitial fibrosis is the hallmark; cystogenesis is the hallmark of ADPKD.[18] Autosomal recessive polycystic kidney disease (ARPKD) is diagnosed prenatally or during early infancy, unlike ADPKD, which is diagnosed during adulthood.[6] Understanding these differences prevents the misdiagnosis of ADPKD and these other diseases.

PROGNOSIS

After patients are diagnosed with ADPKD, disease progression can be projected by identifying the gene mutation. Compared with patients with the *PKD2* mutation, patients with the *PKD1* mutation progress to ESRD about 20 years earlier and present with hypertension about 10 years earlier.[19] Recognizing patients with early-onset ESRD or hypertension is useful in terms of planning the best and most appropriate treatment.

Nephrologists often measure total kidney volume as a marker of disease progression. Gradual expansion of cysts leads to bilateral kidney enlargement, which in turn causes increased total kidney volume.[20] The association between height-adjusted total kidney volume and estimated glomerular filtration rate (eGFR) can be assessed using MRI or CT. A patient's eGFR alone is not a sufficient predictor of chronic kidney disease (CKD) because progressive nephron loss occurs years before GFR decreases.[20] Height-adjusted total kidney volume is preferred over baseline age, serum creatinine, blood urea nitrogen (BUN), and urinary albumin to provide adequate sensitivity and specificity in determining patient risk for developing stage 3 CKD within 8 years.[20]

Clinicians can use the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) Score (**Table 1**) to predict a patient's risk for progression to ESRD.[21] This prognostic algorithm incorporates genetic factors and clinical data and divides the *PKD1* mutation into two categories: truncating and nontruncating mutations.[21] The prognostic score predicts kidney outcomes and lets clinicians individualize therapy.[6,21] For example, patients with a score greater than 6 have rapid disease progression and can be initiated on tolvaptan.[22]

GENERAL MANAGEMENT

Treatment for ADPKD focuses on symptom management and preventing complications. Acetaminophen or opioids may be used for pain management; avoid nonsteroidal anti-inflammatory drugs (NSAIDs), which disrupt kidney function. Surgical management is an option for patients with higher cyst burden or high total kidney volume.[23] Kidney stones that will not pass spontaneously are treated with extracorporeal shock wave lithotripsy or ureteroscopy.

Lifestyle modifications increase quality of life in patients with ADPKD while preventing further harm. General management includes BP control, cholesterol management, sodium restriction, maintenance of normal body mass index (BMI) through caloric restriction, and moderate protein restriction.[10] High dietary sodium intake affects vascular structure and function, cardiovascular morbidity and mortality, and kidney disease progression. Therefore, reducing sodium intake improves BP. Sodium also can blunt the therapeutic effect of ACE inhibitors.[24] Smoking is thought to increase cystic growth, so tobacco cessation counseling is vital.[24]

Hypertension management is crucial to prevent cardiovascular and renal complications of ADPKD. In 2017, the HALT-PKD trial outcomes confirmed that optimal BP control with an ACE inhibitor leads to a significant reduction in left ventricular hypertrophy, proteinuria, and renal vascular resistance.[7] Although strict BP management continues to be essential, some patients may require additional support through RRT or transplantation.

If a patient progresses to ESRD, kidney transplantation is the gold standard.[3] Hemodialysis or peritoneal dialysis often are bridging therapies for patients awaiting transplant. Although the cost of peritoneal dialysis is about 10% lower than hemodialysis, patients are treated more often with hemodialysis. In terms of overall survival rate, peritoneal dialysis is equivalent to hemodialysis; however, hospitalization rates related to peritoneal dialysis are higher than for hemodialysis.[25]

During this stage of disease, patients should be undergoing pretransplant evaluation to assess the need for a pretransplant native nephrectomy. Indications include insufficient space for graft placement, recurrent cyst infection or hemorrhage, symptomatic and recurrent nephrolithiasis, chronic pain requiring opioids, symptoms from increased intra-abdominal pressure, or suspected malignancy.[3] Pretransplant nephrectomy is not recommended

in the absence of these indications because the native kidneys regress in volume after transplantation.

ADVANCES IN TREATMENT

For a select subset of patients with ADPKD, tolvaptan, approved in 2018, can target the disease process.[8,9] Tolvaptan is a selective vasopressin V_2-receptor antagonist that reduces the rate of kidney function decline. In turn, this reduction delays the need for RRT or transplant and reduces symptoms and complications in patients with rapidly advancing ADPKD.[10] The most common adverse reactions include aquaresis (excretion of water without electrolyte loss), thirst, polyuria, nocturia, polydipsia, and nonspecific elevated liver enzymes.[26]

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial provided evidence that tolvaptan slowed increase of total kidney volume to 2.8% per year, compared with the placebo group at 5.5% per year.[8] Over a 3-year period, the treatment group showed lower rates of worsening kidney function and flank pain compared with the placebo group. The treatment group reported fewer ADPKD adverse reactions but had a higher discontinuation rate from hepatic adverse reactions unrelated to ADPKD and aquaresis.[8]

The Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial compared the efficacy of tolvaptan with placebo in reducing annualized change in eGFR from pretreatment baseline to posttreatment follow-up.[9] The tolvaptan treatment group revealed a decrease in GFR by 2.34 mL/min/1.73 m^2 compared with the placebo group's decrease of 3.61 mL/min/1.73 m^2.[9] This trial also examined the adverse reactions of liver enzyme and bilirubin elevations and concluded that the elevations were not severe enough to stop treatment during the 1-year trial.[9] Discontinuing tolvaptan resulted in the reversal of elevations in patients' aminotransferase levels.

Despite these positive trial outcomes, some prominent nephrologists remain critical of the drug's cost-benefit ratio. On the one hand, tolvaptan delays ESRD onset by a median of 6.5 years and increases life expectancy by 2.6 years.[27] On the other hand, the drug costs $5,760 per month, which equates to $744,100 per quality-adjusted life-years gained compared with standard care.[27] Some experts argue that the high cost of tolvaptan surpasses the averted costs associated with ESRD, and therefore, they question the overall benefits.[27]

Patient selection The European Renal Association (ERA) Working Group on Inherited Kidney Disorders (WGIKD) published an algorithm in 2021 to define rapid disease progression in order to target tolvaptan therapy appropriately to patients with ADPKD.[22] Tolvaptan is recommended specifically in patients ages 18 to 55 years who have or are at risk for developing rapid disease progression, which is evaluated using markers such as total kidney volume and loss of kidney function.[22] A confirmed annual eGFR decline of more than 3 mL/min/1.73 m^2 is considered rapid disease progression. Identifying the source of eGFR decline is essential: eGFR decline can be caused by comorbidities such as hypertension and diabetes, and in these patients, clinicians need to consider initiating tolvaptan.

In addition to these guidelines, clinicians can follow a 10-step guide before and after prescribing tolvaptan to ensure that treatment is implemented safely and effectively (**Figure 2**).[10] After a diagnosis of rapidly progressive disease has been established, implement basic kidney protective measures, such as BP target goals and lifestyle modifications. Contraindications to tolvaptan include pregnancy, lactation, uncorrected hyponatremia, history of liver injury, hypovolemia, and urinary tract obstructions.[10] The ERA recommends that tolvaptan be discontinued in patients who approach kidney failure and need RRT.[22]

Eligible high-risk patients should be counseled on potential benefits and harms of tolvaptan treatment (**Table 2**).[10] Adverse reactions include aquaresis, which results in significant polyuria and reversible reduction of eGFR due to the increase in afferent arteriolar constriction and lowering intraglomerular pressure. Adequate hydration is necessary to avoid dehydration until patients can tolerate aquaresis.[10] Plasma sodium, serum creatinine, BUN, and body weight need to be checked regularly.[22]

To achieve safety and efficacy, the medication must be initiated by a nephrologist, titrated, and optimized over time. To minimize liver injury, obtain liver function tests (LFTs) before starting treatment and monitor these levels at 2 and 4 weeks, and then monthly for 18 months and every 3 months thereafter. Signs of liver toxicity secondary to tolvaptan are a contraindication to reinitiating therapy. Clinicians can monitor tolvaptan efficacy by measuring the rate of eGFR decline and by MRI or CT scan measuring height-adjusted total kidney volume every 3 to 5 years.[10,26]

CONCLUSION

ADPKD continues to be the leading genetic cause of ESRD in the United States. Patients often require RRT or kidney transplantation at a young age. To assess disease progression, guide treatment, and provide patient education, clinicians must understand the phenotypic manifestations. Treatment of ADPKD has and continues to focus on symptom management, prevention of complications, and lifestyle modifications. Optimal BP control is pivotal for all patients with ADPKD. More recently, treatment has expanded to include tolvaptan, a drug that delays kidney failure, reduces symptom burden, and lowers the risk of complications. Limitations to tolvaptan include adverse reactions, eligibility criteria, and cost. Tolvaptan also is not indicated in patients with kidney failure who are treated with RRT or transplant. Given the complexities of ADPKD, clinicians and patients should have a thorough and thought-

ful discussion of treatment options that align with individual patient goals. **JAAPA**

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