Inherited renal cystic disease, of which autosomal-dominant polycystic kidney disease (ADPKD) is the more common form.

Characterised by renal cysts, extrarenal cysts, intracranial aneurysms and dolichoectasias (elongated and distended arteries), aortic root dilation and aneurysms, mitral valve prolapse, and abdominal wall hernias.

Interfamilial and intrafamilial variability is explained to a large extent by its genetic heterogeneity and modifier genes.

Long-term complications include hypertension, increased cardiovascular morbidity and mortality, chronic renal failure, ruptured intracranial aneurysm, and end-stage renal disease (ESRD).

Efforts to slow the progression of the disease and delay the need for renal replacement therapy are being investigated, and in some countries therapies that slow kidney disease are approved for use.
**Definition**

Polycystic kidney disease (PKD) is part of a heterogeneous group of disorders characterised by renal cysts and numerous systemic and extrarenal manifestations. There are 2 types: autosomal-dominant PKD (ADPKD) and autosomal-recessive PKD (ARPKD). This monograph concentrates on ADPKD, the more common form.

**Epidemiology**

Autosomal-dominant PKD (ADPKD) occurs worldwide and in all races. Prevalence in the US is estimated to be between 1 in 400 (including observed and estimated autopsy cases) and 1 in 1000 (clinically diagnosed cases only).\[9\] \[10\] \[11\] \[12\] \[13\] Approximately 600,000 Americans are affected with the disease, with over 2000 patients starting renal replacement therapy reported due to cystic kidney disease every year.\[14\]

In Copenhagen, prevalence is estimated to be 1 in 1000;\[10\] however, lower figures have been reported in France (1 per 1111),\[15\] Wales (1 per 2459),\[16\] and Japan (1 per 4033).\[17\] In the Seychelles, prevalence in the white population was found to be 1 in 544, but the disease was rare in black people.\[18\]

ESRD due to ADPKD is less common among black people than among white people because of the higher incidence of ESRD from other causes in black people. Annual US incidence rates for ESRD caused by ADPKD (1998-2001) was 8.7 million in men and 6.9 million for women; in Europe (1998-1999) the rates for men were 7.8 million and 6 million for women;\[19\] and in Japan, 5.6 million for men (1999-2000) and 4 million women.\[20\] Age-adjusted sex ratios greater than unity (1.2 to 1.3) suggest a more progressive disease in men than in women.

Autosomal-recessive PKD is far less common with an incidence of 1 in 10,000 to 1 in 40,000.\[21\] \[22\]

**Aetiology**

Two genes have been identified in autosomal-dominant PKD (ADPKD): PKD1 (chromosome region 16p13.3), which is found in around 85% of cases and encodes the protein polycystin 1; and PKD2 (4q21), found in around 15% of cases and encodes polycystin 2. The current theory is that a wild-type copy of the gene develops an inactivating somatic mutation in a minority of cells, leading to loss of polycystin function and clonal cyst development.\[23\] The protein products of PKD1 and PKD2, polycystin 1\[24\] \[25\] and polycystin 2\[26\] are membrane proteins that form a functional complex, but so far, no extracellular ligands for polycystin 1 have been identified.\[27\] \[28\] \[29\] \[30\] \[31\] Polycystin 2 is a non-selective cation channel capable of transporting calcium ions.\[32\] \[33\] \[34\] Recent evidence points to a role for the polycystins in the renal tubule primary cilium acting as a mechanosensitive cation channel.\[35\] Polycystin 1, polycystin 2, and the autosomal-recessive PKD (ARPKD) protein have been found in urine in membranous vesicles known as exosomes.\[36\]

**Pathophysiology**

Renal cysts develop and grow over time, leading to compression of the normal renal architecture and intrarenal vasculature, increased renal size, interstitial fibrosis and tubular atrophy, and progressive renal impairment.\[37\] Cysts develop from cells in the tubular portion of the nephron and collecting ducts. Although all cells are programmed with an autosomal-dominant PKD (ADPKD) mutation, only a minority develop cysts.
Based on findings of the landmark Modification of Diet in Renal Disease (MDRD) study, ADPKD patients had the most rapid decline of renal function of all forms of chronic kidney disease.[38] Most patients with PKD1 mutations have renal failure by the age of 70 years, whereas >50% of patients with PKD2 mutations have adequate renal function at the same age. Mean age of onset of ESRD is 54 years with a PKD1 mutation and 74 years with PKD2.[1] Patients with mutations in the 5’ region of PKD1 have more severe disease (18.9% versus 39.7% with adequate renal function at 60 years of age) and are more likely to have intracranial aneurysms and aneurysm ruptures than are patients with 3’ region mutations.[2] [3] No clear correlations have been found with mutation type in PKD1, or with mutation type or position in PKD2.[4]

Additional disease-specific complications and morbidity arise from hepatic involvement, valvular heart disease, intracranial aneurysms, pain, massive kidney enlargement, and diverticular disease, contributing to additional morbidity and mortality.[39]

In autosomal-recessive PKD, renal cysts arise from collecting ducts and congenital hepatic fibrosis is characteristic.[40] [41]

**Classification**

**Autosomal-dominant polycystic kidney disease (ADPKD)**

ADPKD is genetically heterogeneous with 2 genes identified:

- **PKD1** (chromosome region 16p13.3), which is found in around 85% of cases and encodes the protein polycystin 1
- **PKD2** (4q21), which is found in around 15% of cases and encodes polycystin 2.

Most patients with PKD1 mutations have renal failure by the age of 70 years, whereas >50% of patients with PKD2 mutations have adequate renal function at the same age. Mean age of onset of ESRD is 54.3 years with a PKD1 mutation and 74 years with PKD2.[1]

Patients with mutations in the 5’ region of PKD1 have more severe disease (18.9% versus 39.7% with adequate renal function at 60 years of age) and are more likely to have intracranial aneurysms and aneurysm ruptures than are patients with mutations in the 3’ region.[2] [3] No clear correlations have been found with mutation type in PKD1, or with mutation type or position in PKD2.[4]

**Autosomal-recessive polycystic kidney disease (ARPKD)**

Patients with ARPKD often present in the neonatal period with enlarged echogenic kidneys; in these cases there is a high mortality rate in the first year of life, with many requiring ventilation.[5] For patients who survive the neonatal period, the probability of survival to 15 years of age ranges from 50% to 80%, and many of them will not require renal replacement therapy at that stage. This monograph does not deal with ARPKD.
Screening

**General population**

There is no evidence for screening in the general population; however, screening of patients with secondary hypertension, especially patients aged 20 to 34 years, is mandatory with renal ultrasound.[12]

**Asymptomatic members with positive FHx of autosomal-dominant PKD (ADPKD)**

Screening should be considered for asymptomatic patients who have a family history of ADPKD. The patient's right to know, or not to know, should be taken into account. Some patients may not wish to know if they have the disease because there is no proven effective treatment. Instead, if they do not wish to find out, general health screening and maintenance measures can be carried out.

Until effective treatments become available, the adverse effects from presymptomatic diagnosis in children (removal of choice to know or not know; psychological, educational, and career implications; and insurability issues) outweigh the benefits and it is recommended that testing not be done in these patients. There are certain situations when it might be beneficial to intervene if the child of an affected person is at risk (e.g., physical examination reveals kidneys are markedly enlarged), so then precautions can be taken during participation in sport. Children with ADPKD may have undiagnosed hypertension and benefit from detection.

**Screening ADPKD patients for intracranial aneurysms**

Widespread presymptomatic screening for intracranial aneurysms is not justified. Screening is indicated if there is a family history of aneurysm or of subarachnoid haemorrhage, if there is previous aneurysm rupture, if the patient is going for elective surgery (e.g., kidney transplant), in high-risk occupations (e.g., pilots, crane operators), and in patients with extreme anxiety despite adequate information.[42] Most unruptured intracranial aneurysms (UIA) detected by presymptomatic screening in ADPKD patients are small (median <3.5 mm diameter) and in the anterior circulation. Growth and rupture risks are not higher than those of UIAs in the general population.[70]

Risk of enlarging an existing aneurysm in ADPKD patients is very low if the aneurysm is <7 mm detected by presymptomatic screening, but yearly surveillance is recommended.[71] [72] Because the risk of developing a new aneurysm after an initial negative study is approximately 3% at 10 years in patients with a family history of intracranial aneurysm, rescreening is suggested after 5 to 10 years.[73]

Secondary prevention

Consultation for diagnosis with a genetic counsellor or nephrologist with expertise in PKD should be considered to provide counselling, diagnosis, and treatment recommendations.

Diet, smoking cessation, regular exercise, avoiding contact sport, and lipid and BP control are all initial options. Vaccinations recommended include annual influenza and, in those with evidence of chronic kidney disease, pneumococcal vaccination.

Head magnetic resonance angiography should be done in patients with a family history of intracranial aneurysm or subarachnoid haemorrhage at baseline and every 5 to 10 years, or as needed.

Low sodium, restricted protein, and a low-cholesterol diet should be reviewed yearly. Patients should avoid caffeine (minimise daily caffeinated beverage intake and avoid caffeine-containing foods or related drugs, such as theophylline) as it increases levels of cAMP in vitro, which has been shown to exacerbate cyst enlargement.[122]
Patients should be asked about chest pain and, if detected, an ECG, exercise testing, and echocardiogram, as appropriate, should be obtained.

MRI and CT can detect small changes in kidney and cyst volumes over short periods of time.

Antenatal genetic diagnosis is usually not done for autosomal-dominant PKD (ADPKD), as this is not a fatal disease and women do not usually consider termination of pregnancy. Few centres offer this service.

Widespread presymptomatic screening for intracranial aneurysms is not justified. Screening is indicated if there is a family history of aneurysm or subarachnoid haemorrhage, if there is previous aneurysm rupture, if the patient is going for elective surgery (such as kidney transplant), if the patient is in a high-risk occupation (e.g., pilots, crane operators), and for patients with extreme anxiety despite adequate information.[42]
Case history

Case history #1

A 30-year-old woman with a family history (i.e., father, aunt, and grandfather) of polycystic kidney disease (PKD) comes to the renal clinic for evaluation. She denies any history of flank pain, pyelonephritis, or haematuria, but reports having had 2 urinary tract infections (UTIs) over the last year. She is contemplating having a family in the near future. She was recently screened for this disease with an abdominal ultrasound. This showed several small echogenic foci and small cystic changes in the liver. Several bilateral kidney cysts were seen (with the largest measuring 3.2 cm), and an adjacent renal calculus. She denies any history of migraines or headaches. There is no family history of aneurysms or cerebrovascular events. She had an ambulatory blood pressure (BP) monitor study performed prior to her evaluation revealing normal BP. Her examination is completely normal.

Case history #2

A 40-year-old man discovered that he had PKD about 15 years ago when he had renal colic. He was found to have bilateral stones at the time and was treated with lithotripsy. A stone was analysed. He thinks it was a uric acid stone but is not sure. He has had no further renal colic or passage of stones since that time. About 10 years ago, he developed hypertension that has been treated since with adequate control, by his account. He denies having had any UTIs. He had repair of a left inguinal hernia when he was a teenager. Recently, he had a bout of gross painless haematuria lasting 3 days and went to the emergency department for evaluation. A computed tomography (CT) scan was performed, which showed no change in his polycystic kidneys compared with findings on a CT scan 1 year prior. Over the last several years, he has experienced increasing abdominal girth and has developed early satiety and dyspnoea on exertion. He denies any mechanical low back pain.

Other presentations

Large population-based studies show that the most frequent presenting symptoms of autosomal-dominant PKD (ADPKD) are hypertension, flank or abdominal pain, renal colic, palpable abdominal mass, and gross haematuria. However, some patients may initially present with subarachnoid haemorrhage or symptoms of renal insufficiency.[6] [7] [8] Hypertension is often a prominent feature in young adults with ADPKD when compared with aged-matched patients aged 20 to 34 years in the general population, where hypertension is uncommon. Additionally, renal function and urinalysis are often normal in this age group.

Step-by-step diagnostic approach

Family physicians and nephrologists are more likely to make the diagnosis than other specialists. Positive family history of autosomal-dominant PKD (ADPKD), with signs and symptoms of renal and/or extrarenal manifestations, is highly suggestive of ADPKD. However, definitive diagnosis is from imaging studies of the kidneys, or genetic testing if imaging is inconclusive. A presumptive diagnosis may be considered in patients without a positive family history, and the presence of renal cysts, with or without hepatic cysts, in the absence of other manifestations is suggestive of a different renal cystic disease. However, genetic testing is required
for a definitive diagnosis in these patients. Approximately 5% of patients with a negative family history will have a new mutation.[43] [44]

History

Family history may include ADPKD, ESRD, intracranial aneurysm, haemorrhagic stroke, or subarachnoid haemorrhage. Common presenting symptoms include flank/abdominal pain, renal colic, gross haematuria, and, less commonly, headaches.[9] [10] [11] Cystitis occurs in 50% to 75% of PKD patients at some time.[43] patients typically present with a history of dysuria, urgency, and suprapubic pain. UTIs involving the renal parenchyma or cysts typically present with flank pain and fever. Patients with kidney stones may present with flank pain, haematuria, dysuria, and fever. Heartburn, reflux, nausea, dyspnoea, early satiety, or increased abdominal girth may occur with severe hepatic disease.

Physical examination

Abdominal examination often reveals a palpable renal or hepatic mass.[9] [10] [11] Hypertension is common and often occurs at a relatively young age. Detection of hypertension before any of the other clinical manifestations is often how the disease is first detected in patients 20 to 34 years of age. There may also be signs or symptoms of renal insufficiency/ESRD. Inguinal, incisional, or paraumbilical hernias, and rectus abdominis diastasis, are often present. A cardiac murmur may be present, suggestive of mitral valve prolapse, mitral regurgitation, aortic regurgitation, or dilated aortic root.

Laboratory tests

Serum electrolytes, blood urea, creatinine, and fasting lipid profile should be ordered initially. Creatinine can be used to estimate GFR. Elevated lipids may be associated with a higher likelihood of progressive renal insufficiency.

Urinalysis should be ordered in all patients to detect presence of increased urinary albumin excretion or proteinuria. If increased urinary albumin excretion or proteinuria are found, this indicates a higher likelihood of progression to chronic kidney disease. Increased urinary albumin excretion also correlates with a high incidence of LVH in patients with ADPKD. Microscopic or macroscopic haematuria is common. Leukocyturia can be seen in these patients, but it does not always indicate UTI, and a urine culture should be obtained in that situation. Urine culture should always be obtained at initial evaluation if there are symptoms of UTI or fever. Urine culture may be negative even with serious urine infection, because cysts do not communicate with the urinary tract. All patients with metabolically active stone disease should have 24-hour urine collection for urine biochemistry (urine volume, pH, oxalate, uric acid, citrate, phosphate, sodium, and calcium, as well as creatinine to assess the completeness of the collection), and supersaturation should be calculated.

Renal imaging

Imaging shows the presence of renal cysts with, or without, hepatic cysts. Benefits of imaging include certainty of diagnosis that could affect family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living-related-donor transplantation. Appropriate counselling should be done before testing.[45] Potential discrimination, in terms of insurability and employment, associated with a positive diagnosis should be discussed.

Ultrasonography is the most common initial test to order because of low cost and safety. Sonographic diagnostic criteria for patients at 50% risk for the disease include at least 2 unilateral or bilateral cysts in people younger than 30 years of age; 2 cysts in each kidney in patients 30 to 59 years of age; and 4
Polycystic kidney disease

Diagnosis

cysts in each kidney in patients 60 years of age or older.[43] Sensitivity of these criteria is nearly 100% for patients 30 years of age or older and for younger patients with PKD1 mutations, but only 67% for patients with PKD2 mutations younger than 30 years of age.[43] [44] CT scan or MRI should therefore be used in the latter group. Large echogenic kidneys (without distinct macroscopic cysts) in a child at 50% risk for the disease are diagnostic. New ultrasound diagnostic criteria for the diagnosis of ADPKD in at-risk people (those from families with ADPKD) have been developed.[46] They should not be applied to MRI or CT scans as that could lead to false-positive results.

Contrast-enhanced CT scan or MRI should be used if ultrasound is equivocal, especially in patients with PKD2 mutations younger than 30 years of age. Because CT and MRI are more sensitive than ultrasonography, the sonographic criteria listed above are not applicable to these techniques. The use of CT needs to be weighed against the radiation dose. A presumptive diagnosis of ADPKD can be considered if, despite no family history, there are >10 cysts in each kidney, and there is no evidence of renal or extrarenal manifestations of another cystic renal disease that could explain the phenotype. CT scan (with and without contrast) can provide helpful information on the severity of renal cyst involvement and relative parenchymal preservation in patients with preserved renal function at the time of the initial evaluation. This will help establish an idea of prognosis and the likelihood of renal function decline. [Fig-2]

An image-based classification system based on total kidney volumes from CT scan has been used to identify potential cases of more rapidly progressive disease. This classification system may optimise patient selection for clinical trial enrolment.[47]

Extrarenal investigations

CT scan may also provide evidence of extrarenal cysts. Hepatic cysts are the most common extrarenal manifestation. Pancreatic cysts (prevalence 9%) are almost always asymptomatic with rare occurrences of recurrent pancreatitis. They may be possibly rarely associated with intraductal papillary mucinous tumour or carcinoma. Additionally, nephrolithiasis will be detected and differentiate stone disease from cyst wall calcification or parenchymal calcifications. About 20% of patients have kidney stones and the composition of these is typically uric acid or calcium oxalate.[48] [49] [50] Low urine citrate and urine pH are the main metabolic factors predisposing to stone formation in ADPKD.[48] KUB and tomograms may be considered to differentiate between uric acid stones (radiolucent) and calcium stones (radiopaque).[49] Dual-energy CT is another useful method to discriminate uric acid stones from other (non-uric acid) renal stones.[49]

Identification of sentinel headaches and prompt diagnosis and treatment of a leaking aneurysm is an important determinant of outcome. Thin-cut non-contrast CT scan of the brain is more sensitive than MRI brain in the detection of acute intracranial bleed. Most aneurysms tend to be in the anterior cerebral circulation and are small. If the CT is negative and index of suspicion remains high, a lumbar puncture or a magnetic resonance angiogram should be obtained. If there is intracranial haemorrhage, a lumbar puncture will reveal red blood cells in cerebrospinal fluid and xanthochromia (a yellow or pink tinge seen after cerebrospinal fluid is centrifuged), which is due to haemoglobin degradation products. If these tests are positive, the patient should be admitted immediately to a neurosurgical ICU for a conventional angiogram and treatment of the leaking intracranial aneurysm.
An ECG should be ordered in patients with cardiac murmurs or suspected left ventricular dysfunction. An echocardiogram may be considered in selected patients with cardiac murmurs to confirm biventricular diastolic dysfunction and aortic root dilation.

**Genetic testing**

Genetic testing can be used in the following cases:

1. The imaging results are equivocal or inconclusive.
2. To confirm a presumed diagnosis in the absence of family history of the disease (conclusive proof of the diagnosis in these patients relies on mutation analysis).
3. When a definite diagnosis is required in a younger patient, such as a potential living related kidney donor.

Antenatal and preimplantation genetic testing is rarely considered for ADPKD.[55] [56] Preimplantation genetic diagnosis (PGD) of embryos after in vitro fertilisation is not routinely available.[57]

Approximately 5% of patients with a negative family history will have a new mutation.[43] [44] Mutations in the PKD1 gene cause more severe disease than those in the PKD2 gene.[58] Genetic testing can be done by linkage or sequence analysis; however, sequence analysis is preferred. Screening of patients with ADPKD using complete gene sequencing detects mutations in up to 91% of cases, and 65% have truncating mutations that can readily be used for diagnostics.[59] All published mutations and other variants are publicly available in the ADPKD mutation database. [PKD Foundation: ADPKD mutation database] However, this mutation analysis is costly and is usually not necessary.[59]

If a mutation is known in one family member, this mutation can be confirmed in other family members at a considerably lower cost. Gene sequencing of PKD1 and PKD2 is helpful in certain situations: living related potential donors younger than 30 years of age, or when the suspicion of PKD2 is high; and in patients (or living related donors) with negative family history and when imaging is non-diagnostic.[60] [61] The large size and complexity of PKD1, and marked allelic heterogeneity, are obstacles to molecular testing by direct DNA analysis.

Linkage analysis uses highly informative microsatellite markers flanking PKD1 and PKD2 and requires accurate diagnosis, availability, and willingness of sufficient affected family members to be tested. Because of these constraints, linkage analysis is suitable in <50% of families. Linkage analysis is often not feasible and detection rates are <100%. In linkage-characterised populations, PKD1 accounts for approximately 85% of cases and PKD2 accounts for most of the remainder. Linkage analysis is rarely performed having been superseded by complete gene sequencing.

Another emerging approach may be whole-exome sequencing but the sensitivity and specificity of this method has not been well characterised in ADPKD populations and is complicated because of the presence of homologous PKD1 genes.

**Risk factors**
**Strong**

**family history of autosomal-dominant PKD (ADPKD)**

- Obtaining a family history is a simple and inexpensive way to identify people who might be at risk for ADPKD, and thus lead to an earlier diagnosis. The family history may appear to be negative because of failure to recognise the disorder in family members, early death of the parent before the onset of symptoms, or late-onset disease in the affected parent. The incidence of de novo mutations is significant in ADPKD, occurring in about 10% of affected families.
- Family history of ADPKD should prompt earlier hypertension screening.

**family history of cerebrovascular event**

- Intracranial aneurysms occur in 6% of patients with ADPKD without a family history of aneurysms, and in 16% of those with a family history.[42]
- Indications for screening in patients with good life-span expectancy include family history of aneurysm or subarachnoid haemorrhage, previous aneurysm rupture, preparation for major elective surgery, patient anxiety, and high-risk occupations (e.g., pilots, crane operators).
- Widespread screening is not recommended because it yields small aneurysms with a low risk of rupture.

## History & examination factors

### Key diagnostic factors

**family history of autosomal-dominant PKD (ADPKD) or end-stage renal disease (ESRD) (common)**

- The diagnosis is considered to be confirmed if there is a family history of disease in a first-degree relative and imaging criteria are met. The family history may appear to be negative because of failure to recognise the disorder in family members, early death of the parent before the onset of symptoms, or late-onset disease in the affected parent. The incidence of de novo mutations is significant in ADPKD, occurring in about 10% of affected families.
- Family history of ADPKD should prompt earlier hypertension screening.

**family history of cerebrovascular event (common)**

- There is a clear association between autosomal-dominant PKD (ADPKD) and a family history of intracranial aneurysm or subarachnoid haemorrhage.
- Intracranial aneurysms occur in 6% of patients without a family history of aneurysms and in 16% of those with a family history. Most tend to be in the anterior cerebral circulation and are small.[42]

**renal cysts (common)**

- Seen on imaging studies and diagnostic in patients with positive family history.
- Multiple bilateral cysts (>10 per kidney) prompt presumptive diagnosis in patients without family history in absence of other manifestations suggestive of a different renal cystic disease.
- Kidneys progressively enlarge and become distorted with little recognisable parenchyma on imaging studies and when renal function drops below 60 mL/minute/1.73 m². The average rate of decline of renal function is 4.4 to 5.9 mL/minute/year.
- Mutated gene PKD1 versus PKD2, position of the PKD1 mutation, and modifier genes determine clinical course.
• Other unfavourable clinical factors are onset of haematuria before age 30, onset of hypertension before 35 years of age, hyperlipidaemia, black race, low HDL, and sickle cell trait.

**hypertension (common)**

• Common presenting symptom. Hypertension will affect nearly all patients and is often present before renal function abnormalities.
• Often presents at a relatively young age. Detection of hypertension before any of the other clinical manifestations is often how the disease is first detected in patients 20 to 34 years of age.[12]
• Can often occur in the absence of abnormal renal function or abnormal urinalysis.[12]
• Additionally, hypertension in autosomal-dominant PKD (ADPKD) patients is associated with a high incidence of left ventricular hypertrophy, leading to increased cardiovascular morbidity and mortality, which is also the leading cause of death in this patient group.[62]

**abdominal/flank pain (common)**

• Common presenting symptom.
• Underlying cause sought, including nephrolithiasis, infection, or haemorrhage. Urinary tract infections (UTIs) involving the renal parenchyma or cysts typically present with flank pain.
• May also be caused by hepatic enlargement.
• Chronic pain may be due to traction on kidney pedicle.
• Colonic diverticulosis is common and diverticulitis is more common, especially in ESRD patients with autosomal-dominant PKD (ADPKD).

**haematuria (common)**

• Both microscopic and macroscopic haematuria is common.
• History of gross haematuria is associated with worse renal function at a given age.[58]

**palpable kidneys/abdominal mass (common)**

• Abdominal examination often reveals a palpable renal or hepatic mass.[9] [10] [11]
• Highly suggestive of autosomal-dominant PKD (ADPKD) in the setting of an appropriate family history or confirmatory imaging.

**headaches (common)**

• May be symptom of cerebrovascular event.
• Atypical or new onset of headaches or a change in the character of the headaches should be investigated.

**dysuria, urgency, suprapubic pain, fever (common)**

• In their lifetime, 50% to 75% of all patients will experience at least 1 clinical UTI, with the majority occurring in women.
• Urinary tract instrumentation with a bladder catheter or cystoscope is a frequent precipitating factor.[63]
• UTIs involving the renal parenchyma or cysts typically present with fever.

**Other diagnostic factors**

**cardiac murmur (common)**

• Mitral valve prolapse, mitral regurgitation, aortic regurgitation, and dilated aortic root are the most common cardiac abnormalities.
abdominal hernia or rectus abdominis diastasis (common)

- Inguinal, incisional, and paraumbilical hernias, and rectus abdominis diastasis, are common presentations.
- Usually present with a visible swelling and are detected before the renal disease is detected.

hepatomegaly (common)

- Polycystic liver disease is typically asymptomatic. Abdominal examination often reveals a palpable hepatic mass.[9] [10] [11] Highly suggestive of autosomal-dominant PKD (ADPKD) if positive family history and confirmatory imaging.
- Frequency increases with age.
- More prevalent, and liver cyst volume is larger in women than in men. Women who have had multiple pregnancies, have used contraceptive drugs, or were using oestrogen replacement therapy have worse disease. Oestrogen receptors are expressed in the epithelial lining of hepatic cysts and stimulate hepatic cyst cell proliferation.
- Significant symptoms or complications from liver involvement can occur in up to 20% of cases.
- More patients are living long enough to experience symptoms from polycystic liver disease due to more effective treatment of renal disease. Heartburn, GORD, early satiety, nausea, increased abdominal girth, or dyspnoea may occur in patients due to hepatic enlargement.

diagnostic tests

1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>renal ultrasound</td>
<td>&lt;30 years of age: at least 2 unilateral or bilateral cysts; 30 to 59 years of age: 2 cysts in each kidney; &gt;60 years of age: 4 cysts in each kidney</td>
</tr>
<tr>
<td></td>
<td>Test is performed when diagnosis is suspected.</td>
</tr>
<tr>
<td></td>
<td>Diagnostic result criteria are for patients at 50% risk for the disease.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis confirmed when there is family history and patient meets result criteria.</td>
</tr>
<tr>
<td></td>
<td>Non-invasive, safe, relatively inexpensive, and widely available, but lacks sensitivity.</td>
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<tr>
<td></td>
<td>Large echogenic kidneys (without distinct macroscopic cysts) in a child at 50% risk for the disease are diagnostic.</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<td>--------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CT scan of abdomen/pelvis</strong></td>
<td>absence of FHx: &gt;10 cysts in each kidney; presence of FHx: &lt;30 years of age - at least 2 unilateral or bilateral cysts; 30 to 59 years of age: 2 cysts in each kidney; &gt;60 years of age: 4 cysts in each kidney</td>
</tr>
<tr>
<td>• Considered if ultrasound is equivocal, especially in patients with PKD2 mutations &lt;30 years of age. [Fig-2]</td>
<td></td>
</tr>
<tr>
<td>• In the absence of a family history of autosomal-dominant PKD (ADPKD), considered presumptive diagnosis if &gt;10 cysts in each kidney. Often there is bilateral renal enlargement. There should be no evidence supporting an alternative cystic renal disease.</td>
<td></td>
</tr>
<tr>
<td>• In the presence of a family history of ADPKD (for people at a risk of 50% or more of developing the disease), at least 2 unilateral or bilateral cysts in patients &lt;30 years of age; 2 cysts in each kidney in patients 30 to 59 years of age; and 4 cysts in each kidney in patients 60 years of age or older. [43]</td>
<td></td>
</tr>
<tr>
<td>• These criteria are established for ultrasound because CT (and MRI) is more sensitive than ultrasound. Today’s CT scanners use a much lower dose of radiation than was the case even 5 years ago. This is in part a result of recent concerted efforts to decrease the radiation doses associated with CT imaging. Radiation doses associated with a CT examination (1 mSv-14 mSv) depend on the specific equipment and examination type. CT of abdomen/pelvis is usually associated with a dose of 5 mSv-12 mSv. This range is comparable to the annual dose (about 3 mSv) from naturally occurring sources of radiation, such as radon and cosmic radiation.</td>
<td></td>
</tr>
<tr>
<td>• If a CT scan is available it can permit disease classification that provides important prognostic information.</td>
<td></td>
</tr>
<tr>
<td><strong>MRI of abdomen/pelvis</strong></td>
<td>&gt;10 cysts in each kidney</td>
</tr>
<tr>
<td>• Considered if ultrasound is equivocal, especially in patients with PKD2 mutations &lt;30 years of age. [Fig-3]</td>
<td></td>
</tr>
<tr>
<td>• Test of choice in patients intolerant of iodine, or if renal function precludes use of iodine.</td>
<td></td>
</tr>
<tr>
<td>• In the absence of a family history, considered presumptive diagnosis if &gt;10 cysts in each kidney and there is no evidence supporting alternative cystic renal disease.</td>
<td></td>
</tr>
<tr>
<td>• Use of gadolinium contrast should be avoided in patients with advanced kidney disease (GFR &lt;30 mL/minute/1.73 m²).</td>
<td></td>
</tr>
<tr>
<td><strong>urinalysis/Gram stain and urine culture</strong></td>
<td>significant bacteriuria in setting of urinary tract infection (UTI), microscopic haematuria, proteinuria, increased urinary albumin excretion</td>
</tr>
<tr>
<td>• Ordered in all patients to detect presence of increased urinary albumin excretion or proteinuria.</td>
<td></td>
</tr>
<tr>
<td>• Increased urinary albumin excretion or proteinuria indicate a higher likelihood of progression to chronic kidney disease.</td>
<td></td>
</tr>
<tr>
<td>• Increased urinary albumin excretion also correlates with a high incidence of left ventricular hypertrophy (LVH) in patients with autosomal-dominant PKD (ADPKD).</td>
<td></td>
</tr>
<tr>
<td>• Microscopic or macroscopic haematuria are common.</td>
<td></td>
</tr>
<tr>
<td>• Leukocyturia does not always indicate UTI, and a urine culture should be obtained in this situation.</td>
<td></td>
</tr>
<tr>
<td>• Urine culture is always obtained at initial evaluation if there are symptoms of UTI or fever.</td>
<td></td>
</tr>
<tr>
<td>• Urine culture may be negative, even with serious urine infection, because cysts do not communicate with the urinary tract.</td>
<td></td>
</tr>
</tbody>
</table>
**Polycystic kidney disease**

## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serum electrolytes, urea, creatinine</strong></td>
<td>normal or elevated</td>
</tr>
<tr>
<td>• Not a sensitive test. Creatinine is often normal in these patients but can be used to estimate GFR.</td>
<td></td>
</tr>
<tr>
<td>[VIDEO: Glomerular Filtration Rate Estimate by the IDMS-Traceable MDRD Study Equation ]</td>
<td></td>
</tr>
<tr>
<td>• Electrolytes should be followed in patients on ACE inhibitors or diuretics.</td>
<td></td>
</tr>
<tr>
<td>• End-stage renal disease develops in approximately 50% of affected patients by 53 years of age and is rare in patients &lt;30 years of age.[64] [65] In most people renal function remains in the normal range, despite cyst growth, until the fourth to sixth decade of life.</td>
<td></td>
</tr>
<tr>
<td><strong>fasting lipid profile</strong></td>
<td>normal or elevated (prognostic marker)</td>
</tr>
<tr>
<td>• Elevated total and LDL cholesterol and low HDL levels have been associated with increased risk of renal insufficiency and should be treated appropriately.</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>LVH changes in setting of cardiovascular complications</td>
</tr>
<tr>
<td>• Ordered in patients with cardiac murmurs or suspected left ventricular dysfunction.</td>
<td></td>
</tr>
<tr>
<td><strong>CT scan of brain</strong></td>
<td>positive for intracranial bleed in setting of ruptured intracranial aneurysm</td>
</tr>
<tr>
<td>• Used for initial evaluation of sudden-onset, severe, or unusual headache.</td>
<td></td>
</tr>
<tr>
<td>• Thin-cut non-contrast CT is more sensitive than MRI in the detection of acute intracranial bleed.</td>
<td></td>
</tr>
</tbody>
</table>

**Other tests to consider**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>genetic testing</strong></td>
<td>PKD1 or PKD2 mutation</td>
</tr>
<tr>
<td>• Genetic testing (linkage analysis or gene sequencing) should be considered when imaging studies are inconclusive, to confirm a presumed diagnosis in the absence of family history of the disease, or in rare cases for antenatal diagnosis or possibly for preimplantation genetic diagnosis.</td>
<td></td>
</tr>
<tr>
<td>• Complete gene sequencing is commercially available in the US through Athena Diagnostics (Worcester, MA) and research testing is also possible. It is reported to identify the mutation in up to 89% of cases; the clinical test is commercially available but usually reserved for special situations due to cost.[59] It is the preferred genetic test.</td>
<td></td>
</tr>
<tr>
<td>• Linkage analysis is often not feasible, and detection rates are &lt;100%. In linkage-characterised populations, PKD1 accounts for approximately 85% of cases and PKD2 accounts for most of the remainder.</td>
<td></td>
</tr>
<tr>
<td><strong>echocardiogram</strong></td>
<td>mitral valve prolapse, aortic root dilation, diastolic dysfunction, or LVH in setting of cardiovascular complications</td>
</tr>
<tr>
<td>• Considered in selected patients with cardiac murmurs to evaluate valvular heart disease, aortic root dilation, and biventricular diastolic dysfunction.</td>
<td></td>
</tr>
</tbody>
</table>
## Polycystic kidney disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24-hour urine collection</strong></td>
<td>low citrate, high uric acid, or oxalate in setting of stones, proteinuria</td>
</tr>
<tr>
<td>• All patients with metabolically active stone disease should have 24-hour urine collection for urine biochemistry (urine volume, pH, oxalate, uric acid, citrate, phosphate, sodium, calcium, and creatinine) to assess the completeness of the collection, and urinary supersaturation should be calculated.</td>
<td></td>
</tr>
<tr>
<td>• Low urine citrate is consistent with distal renal tubular acidosis; high urine uric acid or oxalate may be found.</td>
<td></td>
</tr>
<tr>
<td>• Proteinuria is quantified. Increased urinary albumin excretion or proteinuria indicate a higher likelihood of progression to chronic kidney disease. Increased urinary albumin excretion also correlates with a high incidence of LVH in patients with autosomal-dominant PKD (ADPKD).</td>
<td></td>
</tr>
<tr>
<td><strong>kidney, ureters, bladder (KUB) x-ray and tomogram</strong></td>
<td>radiopaque stones seen on KUB; radiolucent identified on tomogram</td>
</tr>
<tr>
<td>• Stone disease and renal calcification will be evaluated at baseline and can be followed. Obstructing stones can be identified.</td>
<td></td>
</tr>
<tr>
<td>• KUB and tomograms should be considered when CT urography is not available in order to differentiate between uric acid stones (radiolucent) and calcium stones (radiopaque), or to avoid the larger radiation dose needed for CT urography.[49]</td>
<td></td>
</tr>
<tr>
<td>• Provides information about calcification, the majority of calculi, and, occasionally, renal size.</td>
<td></td>
</tr>
<tr>
<td><strong>dual-energy CT</strong></td>
<td>differences in attenuation values differentiate between stones if present</td>
</tr>
<tr>
<td>• Dual-energy CT is another useful method to discriminate uric acid stones from other (non-uric acid) renal stones.</td>
<td></td>
</tr>
<tr>
<td>• Differences in attenuation values are usually higher in stones containing no uric acid.</td>
<td></td>
</tr>
<tr>
<td><strong>lumbar puncture and cerebrospinal fluid analysis</strong></td>
<td>elevated cerebrospinal fluid pressure or xanthochromia in setting of ruptured intracranial aneurysm</td>
</tr>
<tr>
<td>• If the CT scan is negative and index of suspicion of intracranial bleed remains high, a lumbar puncture is obtained. If xanthochromia is present this result is highly suggestive of intracranial haemorrhage.</td>
<td></td>
</tr>
<tr>
<td>• Considered only in selected patients where intracranial aneurysm is a concern.</td>
<td></td>
</tr>
<tr>
<td><strong>magnetic resonance angiogram of brain</strong></td>
<td>bleeding vessel or intracranial aneurysm identified</td>
</tr>
<tr>
<td>• If the brain CT scan is negative and index of suspicion of intracranial bleed remains high (e.g., new-onset cerebrovascular accident, severe headache), a magnetic resonance angiogram is obtained.</td>
<td></td>
</tr>
<tr>
<td>• Considered only in selected patients for screening where intracranial aneurysm is a concern.</td>
<td></td>
</tr>
<tr>
<td>• Widespread presymptomatic screening for intracranial aneurysms is not justified but magnetic resonance angiogram should be considered in patients with a family history of intracranial aneurysms or subarachnoid haemorrhage, before major elective surgeries with potential for haemodynamic instability and in patients with high-risk occupations.</td>
<td></td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
<td>&gt;5 mg/dL suggests infection</td>
</tr>
<tr>
<td>• Useful in diagnosis of infected renal or hepatic cyst(s). In one study, cyst infection was probable if all 4 of the following criteria were met: temperature of &gt;38°C (100.4°F) for &gt;3 days, loin or liver tenderness, C-reactive protein plasma level of &gt;5 mg/dL, and no CT evidence for intracystic bleeding.[66]</td>
<td></td>
</tr>
</tbody>
</table>
### Polycystic kidney disease

#### Diagnosis

**Test** | **Result**
--- | ---
PET scan | increased uptake suggests infection

- PET/CT is useful to confirm and locate cyst infection in autosomal-dominant PKD (ADPKD) patients.[66]

---

#### Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acquired cystic kidney disease</strong></td>
<td>• Clinical history is the most helpful discriminator. • Occurs in the setting of pre-existing renal disease.</td>
<td>• Kidney size and cysts are usually small, as opposed to enlarged kidneys usually seen in autosomal-dominant PKD (ADPKD); however, kidneys may increase in size and resemble those of ADPKD. • Haemorrhage often seen on imaging.</td>
</tr>
<tr>
<td><strong>Simple cyst</strong></td>
<td>• Common in adults. Incidence increases with age; tend to be uncommon in people &lt;40 years of age. • Absence of family history and not meeting the Ravine’s criteria is helpful.[43] • Rarely leads to significant pain, rupture, or infection.</td>
<td>• Diagnosis made on ultrasound. Criteria include absence of internal echoes; strong, sharply defined distant wall with smooth distinct margins; acoustic enhancement; and a spherical or slightly ovoid shape. • Bosniak’s classification is used to classify renal cysts and defines appropriate management.[67] [68]</td>
</tr>
<tr>
<td><strong>Tuberous sclerosis complex</strong></td>
<td>• Facial angiofibromas, forehead patches, shagreen patches, subungual fibromas, hypomelanotic macules, cortical tubers, subependymal nodules, giant cell astrocytomas, cardiac rhabdomyomas, and pulmonary lymphangioleiomyomatosis.</td>
<td>• TSC1 and TSC2 gene mutation analysis. • Commercial testing is available. • Most frequent renal findings are angiomyolipomas, renal cysts, and renal cell carcinomas.</td>
</tr>
<tr>
<td><strong>von Hippel-Lindau syndrome (VHL)</strong></td>
<td>• Renal cell carcinoma, retinal and/or central nervous system haemangioblastomas, phaeochromocytomas, pancreatic cysts, and epididymal cystadenoma.</td>
<td>• VHL gene mutation analysis. • Commercial testing is available.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Maturity-onset diabetes of the young type 5</td>
<td>• Type 2 diabetes mellitus, renal cysts, and genital tract abnormalities.[69]</td>
<td>• HNF1-beta gene mutation analysis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Commercial testing is available.</td>
</tr>
<tr>
<td>Medullary cystic kidney disease/uromodulin-associated kidney diseases</td>
<td>• Chronic tubulointerstitial disease and frequent gout, with renal cysts at the corticomedullary junction.</td>
<td>• MRI of kidneys reveals renal cysts typically at the corticomedullary junction.</td>
</tr>
<tr>
<td></td>
<td>• Family history of chronic kidney disease of unknown cause.</td>
<td>• Magnetic resonance urography shows a medullary nephrogram or a ring-shaped contrast enhancement along the base of the papillae. Thin-cut CT may also be helpful.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UMOD gene mutation analysis (MCKD2), if positive, confirms diagnosis. However, there is a second disease locus for the MCKD1 (MUC1) locus; therefore, mutation analysis will not completely exclude medullary cystic kidney disease if negative.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Commercial testing is available.</td>
</tr>
<tr>
<td>Orofacial digital syndrome type 1</td>
<td>• PKD occurs in &lt;50% of patients with orofacial digital syndrome type 1 (OFD1), which is a sex-linked disorder.</td>
<td>• OFD1 gene mutation analysis.</td>
</tr>
<tr>
<td></td>
<td>• Renal cysts can develop from tubules and glomeruli.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Age of onset is most often in adulthood, but renal cysts in children have been described.</td>
<td></td>
</tr>
<tr>
<td>Medullary sponge kidney</td>
<td>• Characterised by tubular dilation of the collecting ducts confined to the medullary pyramids.</td>
<td>• Sparing of the cortex on CT or MRI.</td>
</tr>
<tr>
<td>Localised cystic disease</td>
<td>• Small cysts localised to one portion of the kidney.</td>
<td>• Cystic disease is always unilateral.</td>
</tr>
<tr>
<td></td>
<td>• Not a genetic disease. Family history is always absent.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not associated with renal failure.</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic criteria

Modified Ravine criteria[46]

New ultrasound diagnostic criteria for the diagnosis of autosomal-dominant PKD (ADPKD) in at-risk people (those from families with ADPKD) have been developed.[46] Note that these criteria, if applied to MRI or CT, will result in false-positive diagnoses. The presence of at least one affected family member who developed end-stage renal disease (ESRD) at age 55 years or younger was highly predictive of a PKD1 mutation (positive predictive value 100%; sensitivity 72%). In contrast, the presence of at least one affected family member who continued to have sufficient renal function or developed ESRD at age >70 was highly predictive of a PKD2 mutation (positive predictive value 100%; sensitivity 74%).

Revised unified criteria for diagnosis of ADPKD

- Age 15-29, 3 or more cysts (unilateral or bilateral):
  - For PKD1, positive predictive value (PPV) 100%; sensitivity 94.3%
  - For PKD2, PPV 100%; sensitivity 69.5%
  - For unknown ADPKD gene type, PPV 100%; sensitivity 81.7%

- Age 30-39, 3 or more cysts (unilateral or bilateral):
  - For PKD1, PPV 100%; sensitivity 96.6%
  - For PKD2, PPV 100%; sensitivity 94.9%
  - For unknown ADPKD gene type, PPV 100%; sensitivity 95.5%

- Age 40-59, 2 or more cysts in each kidney):
  - For PKD1, PPV 100%; sensitivity 92.6%
  - For PKD2, PPV 100%; sensitivity 88.8%
  - For unknown ADPKD gene type, PPV 100%; sensitivity 90.0%

Revised ultrasound criteria for exclusion of ADPKD

- Age 15-29, 1 cyst or more
  - For PKD1, negative predictive value (NPV) 99.1%; specificity 97.6%
  - For PKD2, NPV 83.5%; specificity 96.6%
  - For unknown ADPKD gene type, NPV 90.8%; specificity 97.1%

- Age 30-39, 1 cyst or more
  - For PKD1, NPV 100%; specificity 96.0%
  - For PKD2, NPV 96.8%; specificity 93.8%
  - For unknown ADPKD gene type, NPV 98.3%; specificity 94.8%

- Age 40-59, 1 cyst or more
  - For PKD1, NPV 100%; specificity 93.9%
  - For PKD2, NPV 100%; specificity 93.7%
• For unknown ADPKD gene type, NPV 100%; specificity 93.9%
Step-by-step treatment approach

The goals of treatment are to prolong life, prolong time to development of renal failure, and manage disease complications.

Many manifestations of the disease are directly related to cyst growth and enlargement. Kidney and cyst volumes increase exponentially over time. Mean total kidney volume increases 5.3% per year, and baseline kidney volume predicts the subsequent rate of increase in kidney volume and is associated with declining glomerular filtration rate (GFR) in patients with total kidney volume >1500 mL.

Mutated gene PKD1 versus PKD2, position of the PKD1 mutation, and modifier genes determine clinical course. Other unfavourable clinical factors are gross haematuria, onset before 30 years of age, onset of hypertension before 35 years of age, hyperlipidaemia, black race, low high-density lipoprotein (HDL), male sex, and sickle cell trait.

Hypertension

Target blood pressure (BP) should be guided by the HALT polycystic kidney disease trials, which examined BP control in early and late autosomal-dominant PKD (ADPKD) in 2 separate randomised controlled trials.[74] [75]

One of the studies compared rigorous BP control (i.e., 95/60 mmHg to 110/75 mmHg) with standard BP control (i.e., 120/70 mmHg to 130/80 mmHg) using an ACE inhibitor and/or angiotensin-II receptor antagonist in patients with ADPKD aged 15 to 49 years who were at risk of progressing to end-stage renal disease. The study found that the annual percentage increase in total kidney volume was lower in the rigorous BP control group (i.e., 95/60 mmHg to 110/75 mmHg). The rate of change in estimated GFR was similar in both groups. Left-ventricular-mass index and urinary albumin excretion was reduced in the rigorous BP control group.[74]

Combination therapy with an ACE inhibitor and angiotensin-II receptor antagonist did not show benefit in regard to change in total kidney volume or estimated GFR in this study. Therefore, first-line drug therapy should be with either an ACE inhibitor or an angiotensin-II receptor antagonist. Use of these drug classes increases renal plasma flow in these patients[76] [77] and offers cardioprotective and renoprotective effects in early ADPKD. The safety of both dual blockade and rigorous BP control is considered to be excellent.[74] In patients with more advanced chronic kidney disease (i.e., GFR 25-60 mL/minute), monotherapy with an ACE inhibitor is associated with good BP control in most patients. The addition of an angiotensin-II receptor antagonist did not alter the decline in estimated GFR.[75]

Choice of drug therapy should also be tailored to comorbidities. Beta-blockers (useful in patients with hypertension and coronary artery disease, or in those with hypertension and cardiac arrhythmias), combined alpha- and beta-blockers (useful in patients with cardiac failure and ADPKD), and diuretics (useful in ADPKD patients with volume overload) are all good second-line options. Non-cardioselective beta-blockers with selective alpha-blocking properties (e.g., labetalol or carvedilol) are preferred over beta-blockers. Beta-blockers may be the first choice in the patient with an abdominal aortic aneurysm. In most cases diuretics are not needed to control hypertension in this patient group. Calcium-channel blockers are not considered antihypertensives of choice.
**Urinary tract infections**

Urinary tract infections have increased morbidity in patients with ADPKD; therefore, they should all be treated promptly according to cultures and current treatment guidelines. If the infection relapses after completing antibiotics, complications such as obstruction, cyst infection, or infected stone need to be excluded. If none is found, several months of continued antibiotic treatment may be needed to eradicate the infection. When unavoidable, urinary tract instrumentation should be done under prophylactic antibiotic coverage before, and for 24 hours after, the procedure.

**Infected renal cysts**

Infected renal cysts should be treated with antibiotics first line. Quinolones accumulate in cysts and are considered the antibiotics of choice. Trimethoprim/sulfamethoxazole also has good cyst penetration and may be a second-line option. Chloramphenicol is reserved for special cases. Treatment can fail because of poor antibiotic penetration into cysts. Percutaneous or surgical cyst drainage should be considered if there is no prompt response to treatment with antibiotics or presence of large cyst >5 cm where there is high index of suspicion of cyst infection.[78] A longer course of antibiotics may be needed to adequately treat these patients, for up to 6 weeks. Persistent or recurrent cyst infections are an indication for pre-transplant removal of polycystic kidneys.

**Renal pain**

Abdominal discomfort and flank pain occur in up to 60% of patients and may have varying aetiology.[11] Cyst haemorrhage, renal infection, nephrolithiasis, and tumours are causes of renal pain and should be excluded before treatment is initiated. A stepwise approach to pain management is recommended in patients where no reversible cause can be found, such as cyst rupture or haemorrhage.

First-line therapy for all causes of pain is bed rest. Long-term administration of nephrotoxic drugs should be avoided. The second-line option is analgesic therapy including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), or opioid analgesics for acute or severe pain. Despite the risk of nephrotoxicity, NSAIDs may be used for short periods of time to treat acute pain in patients with good renal function. Adjuvant therapies including tricyclic antidepressants, gabapentin or pregabalin, nerve blockade with local anaesthesia, or splanchnic nerve blockade may also be tried.

Pain related to cyst rupture tends to be localised. Surgery can be considered for the management of cyst complications when conservative measures fail. Cysts are aspirated under CT guidance, with sclerosing drugs used in some patients to prevent fluid reaccumulation. If there are multiple cysts, laparoscopic or surgical cyst fenestration or decortication may be used.[79] Despite a potential role in blood pressure management, cyst decortication has not been definitively shown to alleviate hypertension in patients with ADPKD. Renal function also does not appear to improve following surgery. Patients with compromised baseline renal function appear to be at an increased risk of further deterioration in renal function after cyst decortication. Improvement in pain symptoms appears to be transient, lasting only weeks to months. Therefore, repeat procedures or alternative approaches may be necessary.[80] Laparoscopic or thoracoscopic renal denervation is considered in rare situations, especially in patients with polycystic kidneys without large cysts; however, only a few cases have been reported.[81] [82] [83] [84]

Cyst haemorrhage is usually self-limiting and responds to conservative measures in an outpatient setting. Patients should be hospitalised if there is a serious episode of cyst haemorrhage from a renal or
hepatic cyst. Haemoglobin should be monitored and, if haematocrit drops, transfusion, CT angiogram, or embolisation may be required.

Laparoscopic or retroperitoneoscopic unilateral or bilateral nephrectomy is used very rarely; it is an option reserved for patients with renal pain who have end-stage renal disease (ESRD) or in preparation for patients who meet criteria for renal transplant.

Gross haematuria is alarming to patients and they should be reassured. The patients should be advised to stay off work, drink large volumes of fluid, and avoid physical activity. If haematuria persists they should be medically evaluated. New onset of painless gross haematuria in older people may require additional evaluation to rule out other pathologies.

**Nephrolithiasis**

Stone type influences management, but potassium citrate is indicated for 3 types of stones seen in ADPKD: uric acid stones, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects.[85] Urology evaluation may be necessary for symptomatic stones. Extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy can often be performed without a greatly increased risk of complications. The passage of stone fragments may be impaired in ADPKD patients following lithotripsy. Retrograde endoscopy or manipulation may also be considered. Adequate fluid intake is recommended for prophylaxis of stones.

**Polycystic liver disease**

Most patients will have liver cysts, but only a minority will be symptomatic. Most cases do not require treatment. Patients should avoid oestrogens and compounds that lead to cAMP accumulation. Symptomatic patients may need interventions to reduce cyst volume and liver size (e.g., cyst drainage, liver resection with cyst fenestration). Choice of procedure is dictated by anatomy and cyst distribution. Antibiotics are required in patients with infected cysts (diagnosis of hepatic cyst infection may be aided by PET scan[66]); long-term suppression therapy may be required in selected patients. Patients with severe disease should be referred to a specialty centre for liver resection or transplant.

**Intracranial aneurysm**

Size, location, morphology, age of the patient, and their general health will determine management. Recommendation to intervene depends on size, site, and morphology; history of subarachnoid haemorrhage from other aneurysm; and feasibility to coil or clip.[86] Conservative management is usually recommended small aneurysms (<7 mm) identified in asymptomatic patients, especially if the location is the anterior circulation.

Ruptured cerebral aneurysms result in subarachnoid haemorrhage (SAH) and require emergency treatment and early referral to the intensive care unit (ICU).[87] [88] An urgent neurosurgical/interventional neuroradiologist referral should be made. Oral nimodipine reduces risk of poor outcome and secondary ischaemia after aneurysmal SAH from vasospasm and should be started on admission.[89]

**Renal failure**

Patients who reach chronic kidney disease stage 3 should be carefully monitored for hypertension with close attention focused on detection of early disease complications at each visit. Hypertension and hyperlipidaemia, if present, should be optimally controlled (i.e., BP <130/80 mmHg; LDL <2.59 mmol/L [100 mg/dL]).
As patients reach chronic kidney disease stage 4 (estimated GFR <30 mL/minute/1.73 m²), they should be prepared for renal replacement therapy. Renal transplantation is the treatment of choice in patients with ADPKD.

Living donor transplant is the preferred transplant option over cadaveric donor transplant. There is no difference in patient or graft survival between these patients with this disease and other disease cohorts in the ESRD population, and complications are no greater than in the general population.[90] It is not usually necessary to remove native polycystic kidneys before transplant. However, pre-transplant nephrectomy may be required for repeated cyst-related complications or frequent bleeding, and rarely for size reasons (permitting future allograft implants).[91] Post-transplant nephrectomy may be needed for similar reasons in some patients. Laparoscopic nephrectomy in patients with ADPKD and ESRD is an effective alternative to open nephrectomy. Benefits are decreased intraoperative blood loss, decreased postoperative pain, shorter hospital stay, and a more rapid convalescence.[92]

Dialysis is a second-line option. Patients should have a functioning permanent access at the time of dialysis therapy initiation, and vascular mapping should be completed in all patients before placement of vascular access. These patients tend to do better on dialysis than patients with ESRD due to other causes,[93] which may be because patients with ADPKD typically have higher haematocrits at presentation than do patients with other causes of ESRD. Haemodialysis is preferred over peritoneal dialysis in this patient group, as large kidney size will not permit adequate volumes of dialysis fluid instills, and risk of peritonitis and inguinal or umbilical hernias is increased. However, cyst infections can occur in haemodialysis patients as a result of haematogenous seeding.

### Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

<table>
<thead>
<tr>
<th>Presumptive</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
<td><strong>Treatment</strong></td>
</tr>
</tbody>
</table>
| intracranial haemorrhage | 1st | urgent neurosurgical appraisal + supportive care  
plus | nimodipine |

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
</tr>
</tbody>
</table>
| hypertension | 1st | antihypertensive therapy  
adjunct | lifestyle modifications |
<p>| urinary tract infections | 1st | antibiotic therapy |</p>
<table>
<thead>
<tr>
<th>Polycystic kidney disease</th>
<th>Treatment</th>
</tr>
</thead>
</table>

### Acute (summary)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>infected renal cyst</td>
<td>antibiotic therapy</td>
<td>cyst drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nephrectomy</td>
</tr>
<tr>
<td>renal pain</td>
<td>treatment of underlying cause</td>
<td>supportive care</td>
</tr>
<tr>
<td></td>
<td>plus supportive care</td>
<td>analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>surgical intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nephrectomy</td>
</tr>
<tr>
<td>nephrolithiasis</td>
<td>lifestyle measures + urinary alkalinisation</td>
<td>analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>surgery</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>observation and avoidance of specific drugs</td>
<td></td>
</tr>
<tr>
<td>symptomatic: infected cysts</td>
<td>antibiotic therapy</td>
<td></td>
</tr>
<tr>
<td>symptomatic: non-infected cysts</td>
<td>surgery</td>
<td></td>
</tr>
<tr>
<td>cerebral aneurysm</td>
<td>observation or coil/clip</td>
<td></td>
</tr>
</tbody>
</table>

### Ongoing (summary)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>end-stage renal disease</td>
<td>1st</td>
<td>renal transplant</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>dialysis</td>
</tr>
</tbody>
</table>
**Treatment options**

<table>
<thead>
<tr>
<th>Presumptive</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>intracranial haemorrhage</td>
<td>1st</td>
<td><strong>urgent neurosurgical appraisal + supportive care</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Subarachnoid haemorrhage (SAH) requires emergency treatment and early referral to the intensive care unit (ICU). [87] [88]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» An urgent neurosurgical/interventional neuroradiologist referral should be made. Options include neurosurgical clipping or coil embolisation of ruptured aneurysm. Size, location, morphology, age of the patient, and the patient's general health will determine management.</td>
</tr>
<tr>
<td></td>
<td>plus</td>
<td>nimodipine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Oral nimodipine reduces risk of poor outcome and secondary ischaemia after aneurysmal SAH from vasospasm and should be started on admission. [89]</td>
</tr>
</tbody>
</table>

**Primary options**

» **nimodipine**: 60 mg orally every 4 hours for 21 days

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>hypertension</td>
<td>1st</td>
<td><strong>antihypertensive therapy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Target blood pressure (BP) should be guided by the HALT polycystic kidney disease trials, which examined BP control in early and late autosomal-dominant PKD (ADPKD) in 2 separate randomised controlled trials. [74] [75]</td>
</tr>
</tbody>
</table>
| | | » One of the studies compared rigorous BP control (i.e., 95/60 mmHg to 110/75 mmHg) with standard BP control (i.e., 120/70 mmHg to 130/80 mmHg) using an ACE inhibitor and/or angiotensin-II receptor antagonist in patients with ADPKD aged 15 to 49 years who were at risk of progressing to end-stage renal disease. The study found that the annual percentage increase in total kidney volume was lower in the...
### Treatment

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
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<tbody>
<tr>
<td>Acute</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

Rigorous BP control group (i.e., 95/60 mmHg to 110/75 mmHg). The rate of change in estimated glomerular filtration rate (GFR) was similar in both groups. Left-ventricular-mass index and urinary albumin excretion was reduced in the rigorous BP control group.[74]

- Combination therapy with an ACE inhibitor and angiotensin-II receptor antagonist did not show benefit in regard to change in total kidney volume or estimated GFR in this study. Therefore, first-line drug therapy should be with either an ACE inhibitor or an angiotensin-II receptor antagonist. Use of these drug classes increases renal plasma flow in these patients,[76] [77] and offers cardioprotective and renoprotective effects in early ADPKD. The safety of both dual blockade and rigorous BP control is considered to be excellent.[74]

- In patients with more advanced chronic kidney disease (i.e., GFR 25-60 mL/minute), monotherapy with an ACE inhibitor is associated with good BP control in most patients. The addition of an angiotensin-II antagonist did not alter the decline in estimated GFR.[75]

- Calcium-channel blockers are not considered antihypertensives of choice.

- Choice of drug therapy should also be tailored to any specific comorbidity. Non-cardioselective beta-blockers with selective alpha-blocking properties (e.g., labetalol or carvedilol) are usually effective. Beta-blockers may be the first choice in a patient with aortic aneurysms, coronary heart disease, or cardiac arrhythmias.

- In most cases, diuretics are not needed to control hypertension in ADPKD; however, diuretics may be needed in patients with congestive heart failure and volume overload or resistant hypertension.

- Treatment is lifelong.

- Dose should be started low and increased gradually according to response.

**Primary options**

- **captopril**: 12.5 to 150 mg orally three times daily

OR
## Polycystic kidney disease

### Treatment
#### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td>» enalapril: 10-40 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» perindopril: 4-8 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» ramipril: 2.5 to 10 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» benazepril: 5-80 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» losartan: 25-100 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» candesartan: 4-32 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» valsartan: 40-320 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» irbesartan: 150-300 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» telmisartan: 20-80 mg orally once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Primary options</td>
<td>» olmesartan: 20-40 mg orally once daily</td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Secondary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>labetalol</em>: 100-400 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
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<tr>
<td></td>
<td></td>
<td><strong>Secondary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>carvedilol</em>: 6.25 to 25 mg twice daily</td>
</tr>
<tr>
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<td>OR</td>
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<tr>
<td></td>
<td></td>
<td><strong>Tertiary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>metoprolol</em>: 100-400 mg/day orally given in 1-2 divided doses</td>
</tr>
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<td>OR</td>
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<tr>
<td></td>
<td></td>
<td><strong>Tertiary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>nebivolol</em>: 5-40 mg orally once daily</td>
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<tr>
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<td>OR</td>
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<tr>
<td></td>
<td></td>
<td><strong>Tertiary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>hydrochlorothiazide</em>: 12.5-25 mg orally once daily</td>
</tr>
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<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Tertiary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <em>furosemide</em>: 20-40 mg orally once daily</td>
</tr>
</tbody>
</table>

**adjunct lifestyle modifications**

» Target BP is <130/80 mmHg. [94]

» Non-pharmacological therapies should be initiated including lifelong adherence to dietary salt restriction.

» Exercise and maintenance of healthy body weight should be encouraged.

» Attention should be paid to the dialytic management of extracellular fluid volume in patients who are on renal replacement therapy.

---

**urinary tract infections**

**1st antibiotic therapy**

» Urinary tract infections have increased morbidity in patients with autosomal-dominant PKD (ADPKD). They should be treated promptly according to cultures and current treatment
Polycystic kidney disease

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>guidelines (e.g., levofloxacin, trimethoprim/sulfamethoxazole). Therapy should be for a minimum of 10 days to avoid cyst infection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» If the infection relapses after completing antibiotics, complications such as obstruction, cyst infection, or infected stones need to be excluded. If none is found, several months of continued antibiotic treatment may be needed to eradicate the infection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» When indicated, urinary tract instrumentation should be done under prophylactic antibiotic coverage before, and for 24 hours after, the procedure.</td>
<td></td>
</tr>
</tbody>
</table>

Infected renal cyst

1st antibiotic therapy

» Infected renal cysts should be treated with antibiotics first line.

» Quinolones accumulate in cysts and are considered the antibiotics of choice. Tissue penetration is very good and intravenous therapy is only indicated if oral therapy cannot be tolerated (e.g., because of nausea). Chloramphenicol is reserved for special cases (e.g., management of serious infections due to resistant organisms).

» Treatment course is usually 4 to 6 weeks. However, chloramphenicol has major toxicity associated with its use; therefore, prolonged or repeated courses of this drug are not recommended.

Primary options

» ciprofloxacin: 250-500 mg orally twice daily; 200-400 mg intravenously twice daily

OR

Primary options

» levofloxacin: 500-750 mg orally/intravenously once daily

OR

Secondary options

» trimethoprim/sulfamethoxazole: 160/800 mg orally twice daily
### TREATMENT

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Tertiary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» chloramphenicol: 50-100 mg/kg/day orally/intravenously given in divided doses every 6 hours, maximum 4000 mg/day</td>
</tr>
<tr>
<td></td>
<td>adjunct cyst drainage</td>
<td>» Percutaneous or surgical cyst drainage should be considered if there is no prompt response to treatment with antibiotics. Drainage of large infected cysts should also be considered if there is fever (&gt;38.5°C [100.4°F] for &gt;3 days), abdominal pain (particularly a palpable area of renal pain), increased C-reactive protein (CRP; &gt;50 mg/L), and the absence of any significant recent intracystic bleeding (based on the results of a CT scan) or other causes of fever.[78]</td>
</tr>
<tr>
<td></td>
<td>2nd nephrectomy</td>
<td>» Persistent or recurrent cyst infections are an indication for pre-transplant removal of polycystic kidneys.</td>
</tr>
<tr>
<td>renal pain</td>
<td>1st treatment of underlying cause</td>
<td>» Cyst haemorrhage, renal infection, stones, or tumours cause renal pain and should be excluded before initiating treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Underlying causes (e.g., infection, haemorrhage) should be investigated and treated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» A stepwise approach to pain management is recommended in patients where no reversible cause can be found.</td>
</tr>
<tr>
<td></td>
<td>plus supportive care</td>
<td>» Bed rest is often helpful.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Long-term administration of nephrotoxic drugs should be avoided.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Patients with haematuria should be advised to drink large volumes of fluid and avoid physical activity.</td>
</tr>
</tbody>
</table>
| | 2nd analgesia | » Second-line option is analgesics, including paracetamol, or opioid analgesics for acute or
## Polycystic Kidney Disease

### Treatment

#### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Treatment</strong></td>
<td>severe pain. Non-steroidal anti-inflammatory drugs (NSAIDs) should generally be avoided but may be used for short periods of time to treat acute pain in patients with good renal function.</td>
</tr>
<tr>
<td></td>
<td>» <strong>Paracetamol</strong> may be used in combination with other analgesics. Tramadol is useful for moderate pain. Oxycodone should not be used for prolonged daily use, but reserved for rescue treatment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» <strong>Adjuvant therapies</strong> including tricyclic antidepressants, gabapentin or pregabalin, nerve blockade with local anaesthesia, or splanchnic nerve blockade may also be tried, but only under consultant guidance.</td>
<td></td>
</tr>
</tbody>
</table>

#### Primary options

- **paracetamol**: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

#### Primary options

- **ibuprofen**: 300-400 mg every 4-6 hours when required, maximum 2400 mg/day

#### Primary options

- **naproxen**: 250-500 mg every 12 hours when required, maximum 1250 mg/day

#### Secondary options

- **tramadol**: 50-100 mg orally every 4-6 hours when required, maximum 400 mg/day

#### Tertiary options

- **oxycodone**: 2.5 to 5 mg orally (immediate-release) every 6 hours when required

**plus** **supportive care**

- Bed rest is often helpful.
- Long-term administration of nephrotoxic drugs should be avoided.
## Treatment

### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>» Patients with haematuria should be advised to drink large volumes of fluid and avoid physical activity.</td>
</tr>
</tbody>
</table>

### 3rd Surgical intervention

» Considered for the management of cyst complications when conservative measures fail. Cysts are aspirated under CT guidance, with sclerosing drugs used in some patients to prevent fluid reaccumulation. If there are multiple cysts, laparoscopic or surgical cyst fenestration or decortication may be used.[79] Despite a potential role in blood pressure management, cyst decortication has not been definitively shown to alleviate hypertension in patients with ADPKD. Renal function also does not appear to improve following surgery. Patients with compromised baseline renal function appear to be at an increased risk of further deterioration in renal function after cyst decortication. Improvement in pain symptoms appears to be transient, lasting only weeks to months. Therefore, repeat procedures or alternative approaches may be necessary.[80]

» Laparoscopic or thoracoscopic renal denervation is considered in rare situations, especially in patients with polycystic kidneys without large cysts; however, only a few cases have been reported.[81] [82] [83] [84]

» Patients with cyst haemorrhage and a decrease in haematocrit may require transfusion and, if bleeding persists, angiography with embolisation.

### 4th Nephrectomy

» In very rare situations, laparoscopic or retroperitoneoscopic unilateral or bilateral nephrectomy is a last-resort option reserved for patients with renal pain who have ESRD, or in preparation for patients who meet criteria for renal transplant.

### Nephrolithiasis

#### 1st Lifestyle measures + urinary alkalinisation + analgesia

» Diet should be changed (e.g., low sodium, restricted protein, low cholesterol). Adequate fluid intake is also advised. Hospitalisation and administration of intravenous fluids may be appropriate.
Polycystic kidney disease

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td></td>
<td>» Stone type influences management, but potassium citrate is indicated for 3 types of stones seen in autosomal-dominant PKD (ADPKD): uric acid stones, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects.[85]</td>
</tr>
</tbody>
</table>

» Appropriate analgesia should be considered.

» Urology evaluation may be necessary for symptomatic stones.

2nd surgery

» Extracorporeal shock wave lithotripsy and percutaneous nephrolitholotomy can often be performed without a greatly increased risk of complications.

» Lithotripsy is indicated in obstructing ureteric calculus, severe pain, and patient inability to maintain hydration. The passage of stone fragments may be impaired in autosomal-dominant PKD (ADPKD) patients following lithotripsy.

» Retrograde endoscopy or manipulation may also be considered.

### Asymptomatic

1st observation and avoidance of specific drugs

» Most patients will have liver cysts, but only a minority will be symptomatic. Most cases do not require treatment.

» Patients should avoid oestrogens and compounds that lead to cAMP accumulation (e.g., limit caffeine intake).

### Symptomatic: Infected Cysts

1st antibiotic therapy

» Antibiotics are required in patients with infected cysts. Long-term prophylactic therapy may be required in selected patients (i.e., patients with relapses or recurrences after appropriate course of antibiotics). Monthly rotation of 3 or more antibiotics (listed below) can be used for patients with frequent recurrences.

**Primary options**

» **ciprofloxacin**: 250 mg orally twice daily

OR
### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>symptomatic: non-infected cysts</strong></td>
<td>1st</td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>levofloxacin:</strong> 250 mg orally once daily</td>
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<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>trimethoprim/sulfamethoxazole:</strong> 160/800 mg orally once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Secondary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>doxycycline:</strong> 100 mg orally once daily</td>
</tr>
</tbody>
</table>

**cerebral aneurysm** 1st | **observation or coil/clip** |
| | » Size, location, morphology, age of the patient, and their general health will determine management. |
| | » Recommendation to intervene depends on size, site, and morphology; history of subarachnoid haemorrhage from other aneurysm; and feasibility of coiling or clipping.\[95\] |
| | » Conservative management is usually recommended for small aneurysms (<7 mm) identified in asymptomatic patients, especially if the location is the anterior circulation. |
| | » Patients should be referred for neurosurgical assessment. |
## Treatment

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient group</td>
<td>end-stage renal disease</td>
<td>1st renal transplant</td>
</tr>
</tbody>
</table>

- Renal transplantation is the treatment of choice for end-stage renal disease (ESRD) in autosomal-dominant PKD (ADPKD). Living donor transplant is the preferred option. Cadaveric donor transplant is a second-line option. [European Renal Best Practice Guidelines]  Current United Network for Organ Sharing rules permit listing on deceased donor renal transplant lists for medically fit individuals with GFR <20 mL/minute. [United Network for Organ Sharing]

- Sirolimus immunosuppression has been shown to decrease native kidney and liver volumes in a small study of ADPKD patients who had undergone kidney transplant.[96] These observations are too preliminary for recommendation of sirolimus immunosuppression in ADPKD patients.

| 2nd dialysis | |

- Dialysis is a second-line option in patients with autosomal-dominant PKD (ADPKD) and ESRD. Patients should have a functioning permanent access at the time of dialysis therapy initiation, and vascular mapping should be completed in all patients before placement of vascular access. [Kidney Disease Outcomes Quality Initiative] [European Renal Best Practice Guidelines]

- Haemodialysis is preferred over peritoneal dialysis in this patient group, as large kidney size will not permit adequate volumes of dialysis fluid instills, and risk of peritonitis and inguinal or umbilical hernias is increased. However, cyst infections can occur in haemodialysis patients as a result of haematogenous seeding.

- The outcome of maintenance haemodialysis in patients with ADPKD is similar to other patient groups, although prevalence of renal pain, haematuria, and renal infection is higher in ADPKD patients. These patients tend to do better on dialysis than patients with ESRD due to other causes.[93]
Emerging

Tolvaptan

Tolvaptan, a vasopressin V2 receptor antagonist, lowers cAMP concentrations in the distal nephron and collecting duct, the major site of cyst development in autosomal-dominant PKD (ADPKD), and inhibits the development of PKD in animal models orthologous to the human disease.[97] In a large randomised trial, tolvaptan slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in individuals with early-stage ADPKD compared with placebo, but was associated with a higher discontinuation rate owing to adverse events.[98] Tolvaptan also resulted in a slower decline in estimated glomerular filtration rate (GFR) than placebo in patients with later-stage ADPKD.[99] Tolvaptan has not been approved for the treatment of ADPKD by the US Food and Drug Administration but has been approved for use in several countries, including Japan and Canada, and the European Medicines Agency has recommended granting a marketing authorisation for the drug with an indication for slowing the progression of cyst development and failing kidney function in adults with normal to moderately reduced kidney function who have rapidly progressing ADPKD. High water intake alone may be protective through suppression of vasopressin and should be encouraged in individuals with preserved renal function. These drugs have no effect on liver cysts.

Somatostatin SST2 inhibitors

A small prospective clinical trial demonstrated that octreotide attenuated the increase in kidney volume in patients with ADPKD. Somatostatin acts on the SST2 receptors to inhibit cAMP accumulation in both the kidneys and liver. Somatostatin analogue therapy (e.g., octreotide, lanreotide) has been shown in 3 clinical trials to be effective in decreasing liver cyst volume.[100] [101] [102] It was also shown to be effective in decreasing mean total kidney volumes at 1- and 3-year intervals in a study that evaluated the effects of octreotide on kidney disease.[103] The drugs are administered intramuscularly on a monthly basis. Safety and efficacy data are limited by the short study duration (6-36 months) and the small patient numbers. Longer and larger trials will be necessary to establish long-term safety and efficacy.[100] [101] [102] [103]

mTOR inhibitors

These agents inhibit the mTOR pathway, which is involved in PKD pathogenesis. In early chronic kidney disease, 18 months of sirolimus therapy failed to halt kidney growth.[104] In the everolimus study, 2 years of treatment slowed the increase in total kidney volume, but did not slow the decline in renal function.[105] In another study, sirolimus halted cyst growth and increased parenchymal volume (compared with no appreciable changes in kidney parenchyma in the control group),[106] although only 15 of 21 patients managed to complete the study, owing to side effects and losses to follow up. Sirolimus therapy was also associated with a marginal increase in proteinuria and also appeared to reduce native kidney and liver volumes in patients with ADPKD following renal transplant. However, it does not seem to slow down the decrease of GFR.[107] Another study combining everolimus with octreotide failed to show an augmentation of positive effects on liver volume reduction.[108] The EXIST 1 and 2 studies in individuals with tuberous sclerosis, which is associated with constitutive activation of mTOR, showed that everolimus was effective in achieving a 50% reduction in total volume of target renal angiomyolipomas relative to baseline in 42% of individuals, and also induced regression in growth of subependymal giant cell astrocytomas.[109] [110] Therefore, despite the conflicting evidence and negative trials, mTOR inhibitors continue not to be recommended as an effective treatment for ADPKD.[111]

Inhibitors of Erb-B1, Erb-B2 tyrosine kinase, Src kinase or MEK

Clinical data are encouraging, but no human data are available in ADPKD yet. Pre-clinical trials are in progress with these agents and clinical trials are in progress with Src kinase inhibitors.[112] [113]

Roscovitine

Roscovitine is a cyclin-dependent kinase inhibitor shown to be effective in animal models of PKD.[114]
ACE inhibitors/angiotensin-II receptor antagonist combinations

The HALT-PKD study (an ongoing NIH-funded prospective study) is designed to determine whether treatment with an ACE inhibitor versus an ACE inhibitor/angiotensin-II receptor antagonist combination is superior in slowing the progression of renal cystic disease in patients with stage 1 or 2 chronic kidney disease, or is effective in slowing the GFR decline in patients with stage 3 disease. The study will also address whether lowering the blood pressure to a target <110/75 mmHg is better than the current standard target of <130/80 mmHg.
Recommendations

Monitoring

Early detection and treatment of complications of autosomal-dominant PKD (ADPKD) are likely to improve quality of life and life expectancy in patients affected by ADPKD. Particular attention should be paid to cardiovascular complications, which are the most common cause of morbidity and mortality in ADPKD.

Patients with hypertension should be followed up every 6 to 12 months to ensure blood pressure (BP) is controlled to a target of <130/80 mmHg. BP monitor should be checked against clinic BP monitor annually. Patients with early or mild disease without hypertension are followed up every 1 to 3 years: instructions regarding BP monitoring are provided; a healthy diet is recommended, including advice on avoidance of excessive salt or protein; cardiovascular risk factors (such as hyperlipidaemia) are corrected; and lifestyle modifications, if appropriate, (such as smoking cessation) are discussed. Close monitoring of renal function is recommended as antihypertensive doses may need to be adjusted if renal function declines.

Frequency of follow-up of patients should be adjusted to their comorbidities. If metabolically active nephrolithiasis (i.e., actively forming stones) is present, these patients need to be followed up every 6 to 12 months to monitor their metabolic activity. CT imaging of the kidneys may be indicated.

The patient should be referred to a nephrologist if renal function is impaired to monitor closely the rate of renal function decline, adjust diet and antihypertensive medications, prepare for renal replacement therapy, and manage metabolic abnormalities associated with chronic kidney disease progression. Erythropoiesis-stimulating agents should be started to maintain target haemoglobin of 100 to 110 g/L (10-11 g/dL).

Pain control issues may require more frequent visits and adequate analgesia should be provided. Given the high prevalence of depression, and its significant impact on morbidity and mortality, screening should be considered.

Early referral to a nephrologist is likely to lead to an improvement in glomerular filtration rate[118] and longer duration of regular nephrology care in the non-end-stage renal disease period is associated with decreased hospitalisation and better long-term survival once commenced on dialysis.[119] [120]

Patient instructions

Information should be provided to patients about the variable course and disease manifestations of autosomal-dominant PKD (ADPKD), and the importance of early detection and modification of risk factors, both for the patient and for them to discuss with potentially affected relatives.

Early detection and treatment will help avoid unnecessary tests and minimise patient anxiety. The following complications specifically should be mentioned: hypertension, haematuria, flank pain, nephrolithiasis, mitral valve prolapse, intracranial aneurysms, and renal failure. Patients should be taught the significance of systolic and diastolic BP readings, how to take their BP themselves, and the targets of BP-lowering therapies. Diet guidelines for 0.8 g/kg protein of ideal body weight per day should be provided. Patients should avoid or limit foods or medications containing caffeine, which increases cAMP. Patients with hypertension or hypercholesterolaemia should be advised to restrict sodium to 90 mmol/L (90 mEq/day) and to follow a low-cholesterol (<200 mg/day) diet.
Patients should be advised that presymptomatic imaging for intracranial aneurysms is recommended in patients with a strong family history of intracranial aneurysmal rupture in high-risk occupations such as pilots, if major elective surgery is planned with anticipated haemodynamic instability, and in people with no unusual risk factors but who want to be screened because of anxiety.

Reproductive counselling may be considered for couples considering having a family. Options are not having children, preimplantation genetic diagnosis, amniocentesis or chorionic villus sampling in the first 10 to 16 weeks of pregnancy, and gamete donation from an unaffected donor depending on which parent is affected. Preimplantation genetic diagnosis is offered in a few specialised centres and there are few reports of its application to ADPKD.

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Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiac complications</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>gastro-oesophageal reflux disease (GORD)</td>
<td>long term</td>
<td>low</td>
</tr>
<tr>
<td>ruptured intracranial aneurysm</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>sepsis</td>
<td>variable</td>
<td>low</td>
</tr>
</tbody>
</table>

As cardiovascular disease is the main cause of mortality in this patient population, this should be a major focus of disease management.

Nearly half of hypertensive patients with autosomal-dominant PKD (ADPKD) have left ventricular hypertrophy (LVH) before end-stage renal disease. LVH is a clinical factor known to be associated with increased risk of major cardiovascular events.

The following are more common in ADPKD: biventricular diastolic dysfunction; aortic root dilation; mitral valve prolapse; mitral regurgitation; aortic incompetence; tricuspid incompetence or prolapse; pericardial effusion.

Increased left ventricular mass and LVH have been found in early stages of ADPKD.

Only rarely do they require valve replacement.

Screening echocardiography is not required unless a murmur is detected on examination.

H2 antagonists and proton pump inhibitors may be considered to treat the symptoms of GORD in patients with hepatomegaly.

Severe or unusual headaches should always be investigated in autosomal-dominant PKD (ADPKD).

Likelihood is higher in patients with previous aneurysm or family history of intracranial aneurysm.
In a bacteraemic patient with negative urine cultures, and with the source of the infection being uncertain, the clinical differential of infected renal cyst or hepatic cysts should be considered.

Imaging should be performed whenever there is concern for a complicated urinary tract infection.

CT is best to identify stones, perinephric abscess, complicated pyelonephritis, or cyst infection. Indium leukocyte scan may be helpful in localising the infected cyst.[115]

Fluid is aspirated whenever possible if a cyst is seen that is suspected to be infected.

<table>
<thead>
<tr>
<th>complications during pregnancy</th>
<th>variable</th>
<th>low</th>
</tr>
</thead>
</table>
Maternal and fetal complications are higher in autosomal-dominant PKD (ADPKD) pregnancies.

Gestational hypertension, oedema, and pre-eclampsia occur more commonly in women with ADPKD than in unaffected pregnant women. These women are also more likely to develop chronic hypertension.

Approximately 16% of women develop new-onset hypertension during pregnancy and up to 25% will have a hypertensive complication during pregnancy.

Women with hypertension are at increased risk of adverse fetal and maternal outcomes.[116]

Women with pre-pregnancy serum creatinine of 106 micromols/L or more (1.2 mg/dL or more) have higher risk of fetal or maternal complications.

Antenatal diagnosis is usually not done for ADPKD because it is not usually a fatal disease and women do not usually choose termination of pregnancy if ADPKD is diagnosed.[117]

**Prognosis**

Assessment of prognosis is determined based on family history, extent of disease seen on renal imaging, and control of secondary risk factors. For patients with stage IV kidney disease, the best prognosis is attained by pre-emptive kidney transplantation from a living kidney donor.
### Diagnostic guidelines

#### International

**Autosomal-dominant polycystic kidney disease (ADPKD): executive summary**

*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2015

#### Oceania

**KHA-CARI autosomal dominant polycystic kidney disease guidelines**

*Published by:* Kidney Health Australia - Caring for Australasians with Renal Impairment  
*Last published:* 2015

### Treatment guidelines

#### Europe

**Laparoscopic deroofing of simple renal cysts**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2007

#### International

**Autosomal-dominant polycystic kidney disease (ADPKD): executive summary**

*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2015

#### Oceania

**KHA-CARI autosomal dominant polycystic kidney disease guidelines**

*Published by:* Kidney Health Australia - Caring for Australasians with Renal Impairment  
*Last published:* 2015

**Cystine stones**

*Published by:* Kidney Health Australia - Caring for Australasians with Renal Impairment  
*Last published:* 2007
## Online resources

1. PKD Foundation: ADPKD mutation database ([external link](#))
2. European Renal Best Practice Guidelines ([external link](#))
3. United Network for Organ Sharing ([external link](#))
4. Kidney Disease Outcomes Quality Initiative ([external link](#))
5. Polycystic Kidney Disease Foundation ([external link](#))
6. GeneReviews ([external link](#))
7. PKD International ([external link](#))
8. PKD Charity (UK) ([external link](#))
9. PKD Foundation of Australia ([external link](#))


**Key articles**


- Eighth Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 8), US. The 2014 JNC 8 and 2017 AHA/ACA guidelines for management of high blood pressure in adults. 2018 [internet publication]. [Full text](#)


**References**


57. Tuffs A. Court allows preimplantation genetic diagnosis in Germany. BMJ. 2010 Jul 12;341:c3741. Abstract


94. Eighth Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 8), US. The 2014 JNC 8 and 2017 AHA/ACA guidelines for management of high blood pressure in adults. 2018 [internet publication]. Full text


**Figure 1: Gross pathology of polycystic kidneys**

Adapted from Dr Edwin P. Ewing, Jr., Public Health Image Library, CDC (1972)
Figure 2: CT scan of abdomen and pelvis of patient with mild disease

From collection of Dr M. Hogan

Figure 3: MRI of abdomen and pelvis of patient with symptomatic polycystic kidney disease

From collection of Dr M. Hogan
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