Clinical and Experimental Nephrology
https://doi.org/10.1007/s10157-021-02097-6

GUIDELINE

# A digest from evidence-based Clinical Practice Guideline for Polycystic Kidney Disease 2020

**Saori Nishio[1] · Ken Tsuchiya[2] · Shinya Nakatani[3] · Satoru Muto[4] · Toshio Mochizuki[2] · Haruna Kawano[4] · Kazushige Hanaoka[5] · Sumi Hidaka[6] · Daisuke Ichikawa[7] · Eiji Ishikawa[8] · Kiyotaka Uchiyama[9] · Eri Koshi-Ito[10] · Hiroki Hayashi[11] · Shiho Makabe[2] · Soshiro Ogata[11] · Michihiro Mitobe[12] · Akinari Sekine[13] · Tatsuya Suwabe[13] · Hiroshi Kataoka[2] · Hirayasu Kai[14] · Yoshikatsu Kaneko[15] · Mahiro Kurashige[16] · Koichi Seta[17] · Keiji Shimazu[18] · Taketsugu Hama[19] · Kenichiro Miura[20] · Koichi Nakanishi[21] · Shigeo Horie[4] · Kengo Furuichi[22] · Hirokazu Okada[23] · Ichiei Narita[15] · Committee of Clinical Practical Guideline for Polycystic Kidney Disease 2020**

Accepted: 9 June 2021


## List of contributors

### Principal Investigator

Ichiei Narita Niigata University

### Co-Investigator

| | |
|---|---|
| Hirokazu Okada | Saitama Medical University |
| Kengo Furuichi | Kanazawa Medical University |
| Saori Nishio | Hokkaido University |

### Committee chairman

Ken Tsuchiya Tokyo Women's Medical University

### Committee member

| | |
|---|---|
| Satoru Muto | Juntendo University Dept. of Urology and Dept. of Advanced Informatics for Genetic Disease |
| Toshio Mochizuki | Tokyo Women's Medical University |
| Haruna Kawano | Juntendo University and Dept. of Advanced Informatics for Genetic Disease |
| Kazushige Hanaoka | The Jikei University |
| Sumi Hidaka | Shonan Kamakura General Hospital |
| Daisuke Ichikawa | St Marianna University School of Medicine |
| Eiji Ishikawa | Saiseikai Matsusaka General Hospital |
| Kiyotaka Uchiyama | Keio University |
| Eri Koshi-Ito | Komaki City Hospital |
| Hiroki Hayashi | Fujita Health University |
| Shiho Makabe | Tokyo Women's Medical University |
| Soshiro Ogata | Fujita Health University |
| Michihiro Mitobe | Takeda General Hospital |
| Shinya Nakatani | Osaka City University |
| Akinari Sekine | Toranomon Hospital |
| Tatsuya Suwabe | Toranomon Hospital |
| Hiroshi Kataoka | Tokyo Women's Medical University |
| Hirayasu Kai | University of Tsukuba |
| Yoshikatsu Kaneko | Niigata University |
| Mahiro Kurashige | The Jikei University |
| Koichi Seta | National Hospital Organization Kyoto Medical Center |
| Keiji Shimazu | Osaka Saiseikai Nakatsu Hospital |
| Taketsugu Hama | Wakayama Medical University |
| Kenichiro Miura | Tokyo Women's Medical University |
| Koichi Nakanishi | University of the Ryukyus |

In 2020, the Research for Intractable Renal Diseases of the Ministry of Health, Labour and Welfare of Japan established the Committee of Guideline for Polycystic Kidney Disease, which published (A Digest from Evidence-Based Clinical Practice Guideline for Polycystic Kidney Disease 2020) on the website (jin-shogai.jp/policy/index.html). This is the English version of that digest.

✉ Hirokazu Okada
hirookda@saitama-med.ac.jp

Extended author information available on the last page of the article

Published online: 26 September 2021

Shigeo Horie Juntendo University Dept. of Urology and Dept. of Advanced Informatics for Genetic Disease

Levels of Evidence:

A High: It is highly likely that the true effect lies close to the estimate of the effect.
B Moderate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C Low: The true effect may be substantially different from the estimate of the effect.
D Very low: The estimate of the effect is very uncertain and often will be far from the truth.

Grades of Recommendations:

1 "We recommend"
2 "We suggest"
None

## Disease concept and definition of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

### Disease concept

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive incidence and enlargement of bilateral renal cysts, usually accompanied by disorders in other organs. It is the most common hereditary cystic kidney disease. Bilateral cysts increase in size and number with age, even as renal function progressively deteriorates. Approximately half of all patients with ADPKD reach end-stage renal disease (ESRD) by their sixties.

The hereditary form of ADPKD is transmitted through autosomal dominant inheritance, which occurs in both males and females with a mutant allele. However, a new mutation may cause an individual to develop ADPKD, even if neither parent had the disease. PKD1 (16p13.3) and PDK2 (4q21) were identified as the two causative genes. Approximately 80% of all patients develop ADPKD through mutant PKD1 and 15% through a mutant PKD2 gene. In the remaining 5%, pathogenesis may involve a mutation in other genes as no mutation is detected in either PKD1 or PKD2.

## Diagnosis of ADPKD

### Diagnostic criteria

The ADPKD diagnostic criteria (ADPKD Diagnostic Guidelines, 2nd Edition, published by a Grant-in-Aid for Progressive Renal Diseases Research, Ministry of Health, Labour and Welfare of Japan) are shown in the Table 1. ADPKD transmission occurs through autosomal dominant inheritance, with a patient's offspring having a 50% chance of inheriting the disease. Although genetic diagnosis is important, only family history and bilateral cyst counts serve as functional diagnostic criteria and do not incorporate a genetic diagnosis.

### Diagnostic criteria for ADPKD as an intractable disease

A patient must fulfil either of the following criteria to be diagnosed with ADPKD:

- Red area of the CKD severity classification heat map.
- Total kidney volume (TKV) of 750 ml or more and a TKV increase of ≥ 5% per year.

### Differential diagnosis

Clinical assessment and imaging are used to rule out non-hereditary cystic kidney diseases such as multiple simple renal cysts or acquired cystic kidney disease and hereditary forms such as tuberous sclerosis. In particular, 30% of tuberous sclerosis cases reportedly lack symptoms other than renal cysts, causing some cases to be mistakenly attributed to ADPKD. In addition, diseases such as autosomal dominant tubulointerstitial kidney disease (ADTKD), juvenile nephronophthisis, oral-facial digital syndrome (OFDS), multicystic kidney, multicystic dysplastic kidney (MCDK), and multilocular cysts of the kidney should be ruled out during differential diagnosis.

### Diagnostic imaging

While ultrasound is the standard imaging method for ADPKD diagnosis (Fig. 1), total kidney volume (TKV) is the standard biomarker for evaluating disease progression, with CT (Figs. 2, 4) or MRI (Fig. 3) only recommended for follow-up. A risk/benefit analysis should always precede the use of contrast medium, as it can result in serious adverse events. Subsequent to a definitive diagnosis of ADPKD, plain CT is appropriate for follow-up imaging and should be performed at least annually along with TKV, as the chronological changes of the diseases are part of designation criteria for intractable diseases in Japan.

### Total kidney volume (TKV) measurement

TKV is a standard biomarker for the evaluation of disease progression. Various methods for accurate kidney and TKV measurements have been reported (Fig. 4).

**Table 1** The diagnostic criteria of ADPKD (*ADPKD Diagnostic Guidelines, Second Edition*, published by a Grant-in-Aid for Progressive Renal Diseases Research, Research on intractable disease, from the Ministry of Health, Labour and Welfare of Japan)

| |
|---|
| 1. Confirmation of family history |
| a. Three or more bilaterally-manifested cysts confirmed with ultrasonography |
| b. Five or more bilaterally-manifested cysts confirmed with CT and MRI imaging |
| 2. Non-confirmation of family history |
| a. Patients 15-years old or younger: three or more bilaterally-manifested cysts confirmed with either CT and MRI imaging or ultrasonography |
| b. Patients 16-years old or older: five or more bilaterally-manifested cysts confirmed with either CT and MRI imaging or ultrasonography |
| Diseases to be excluded |
| 1. Multiple simple renal cyst |
| 2. Renal tubular acidosis |
| 3. Multicystic kidney (multicystic dysplastic kidney) |
| 4. Multilocular cysts of the kidney |
| 5. Medullary cystic disease of the kidney (juvenile nephronophthisis) |
| 6. Acquired cystic disease of the kidney |
| 7. Autosomal recessive polycystic kidney disease |

## Genetic diagnosis (including genetic screening)

Although the gene responsible for ADPKD is known, diagnosis is typically performed with diagnostic imaging, which indicates the presence of multiple cysts. Genetic diagnostic tests are not necessary for clinical practice.

## Diagnosis in infants and young adults

Since no effective treatments for ADPKD in infants and young adults have been established, screening imaging tests should be performed with informed consent from both patients and families for non-symptomatic children and young adults with ADPKD.

## Initial symptoms

Most individuals remain asymptomatic until their 30 s or 40 s. Initial subjective symptoms may include abdominal or lower back pain, posttraumatic macroscopic hematuria (through physical impact during sports, for example), or abdominal bloating. Acute pain is often attributed to hemorrhagic cysts, infections, or urinary tract stones. Chronic pain, defined as pain continuing for 4–6 weeks and identified in around

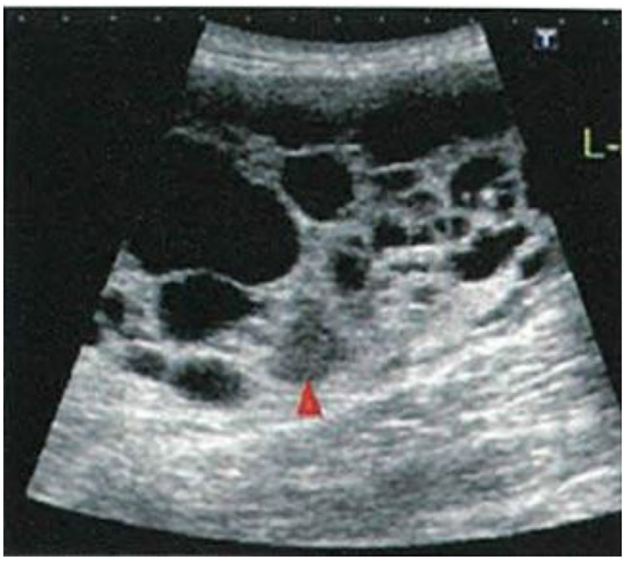

**Fig. 1** Ultrasonic image. Multiple low-echogenic spots resembling black sacs of various sizes are cysts. The non-uniform cyst with slightly high echogenicity, shown by the arrow in the center of the image, may indicate infection or hemorrhage

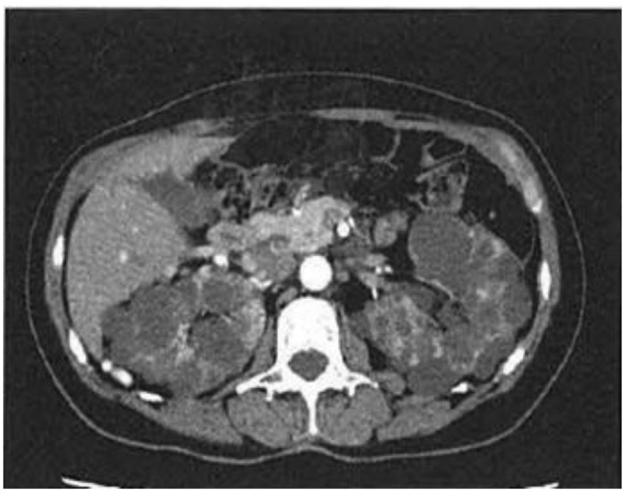

**Fig. 2** Contrast CT image. The spots resembling black low-density areas or sacs are cysts

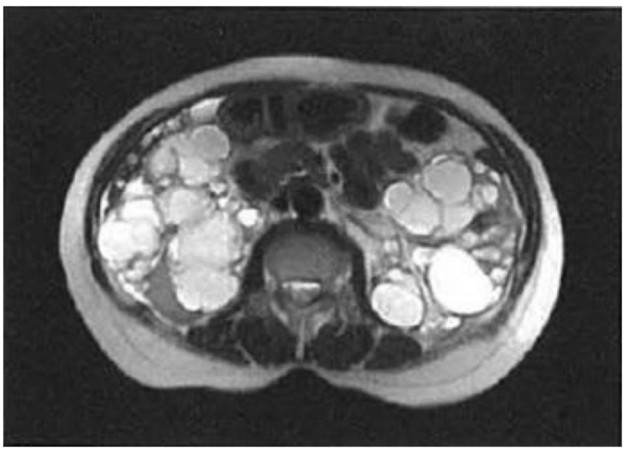

**Fig. 3** MRI T-2 weighted image. The image shows multiple bilateral cysts of varying sizes but uniform hyperintensity

60% of patients with ADPKD, is thought to derive from pressure generated by liver or renal cysts. Macroscopic hematuria occurs in approximately half of all ADPKD cases. Many patients remain asymptomatic until diagnosis during routine physical examinations, when objective symptoms such as hypertension, proteinuria, renal cysts, and/or kidney impairment are identified.

## Risk classification

TKV and height-adjusted TKV (htTKV) are currently the standard biomarkers for objective indication of disease progression. Other known risk factors include causative gene mutations, age, sex, weight, hypertension, and proteinuria. The predicting renal outcomes in ADPKD (PROPKD) score (Table 2) is recognized as a classification tool that includes the Mayo classification (Fig. 5) (age and htTKV), sex, hypertension, renal and urethral complications, and causative gene mutations as variables.

## Prevalence and prognosis

The results of a 1994 epidemiological survey yielded an estimated 31,000 (diagnosed and undiagnosed) patients with ADPKD in Japan, with one in 4033 Japanese citizens estimated to have the disease. However, in a single institution in Japan, the prevalence rate was 137 per 100,000 population, with the estimate that 1 in 730–1471 individuals was an ADPKD patient in fiscal 2017, a clear increase over the earlier report.

Approximately half of all patients with ADPKD reach ESRD by their 60 s. Many deaths are the result of refractory kidney and liver cyst infection, or sepsis resulting from colonic diverticulum rupture. Similarly, many deaths

**Table 2** PROPKD score

| Variable | Points for PROPKD score |
|---|---|
| Male | 1 |
| Hypertension before age 35 yr | 2 |
| ≧1 urologic event before age 35 yr | 2 |
| PKD2 mutation | 0 |
| PKD1 nontruncating | 2 |
| PKD1 truncating | 4 |

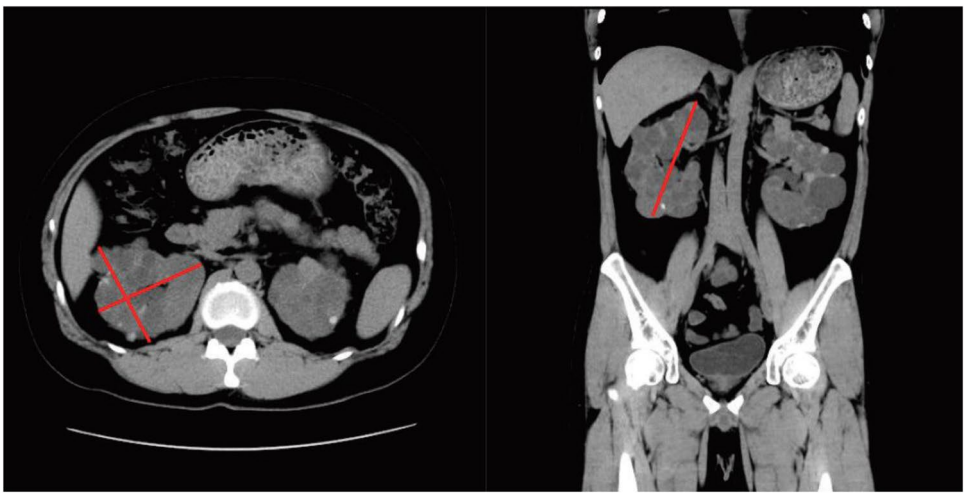

**Fig. 4** TKV measurement. TKV measurement using the ellipsoid method: Tri-directional measurement of each kidney was performed, with calculations assuming the kidney to be an ellipse. Kidney volume = π × 6 × length × width × depth

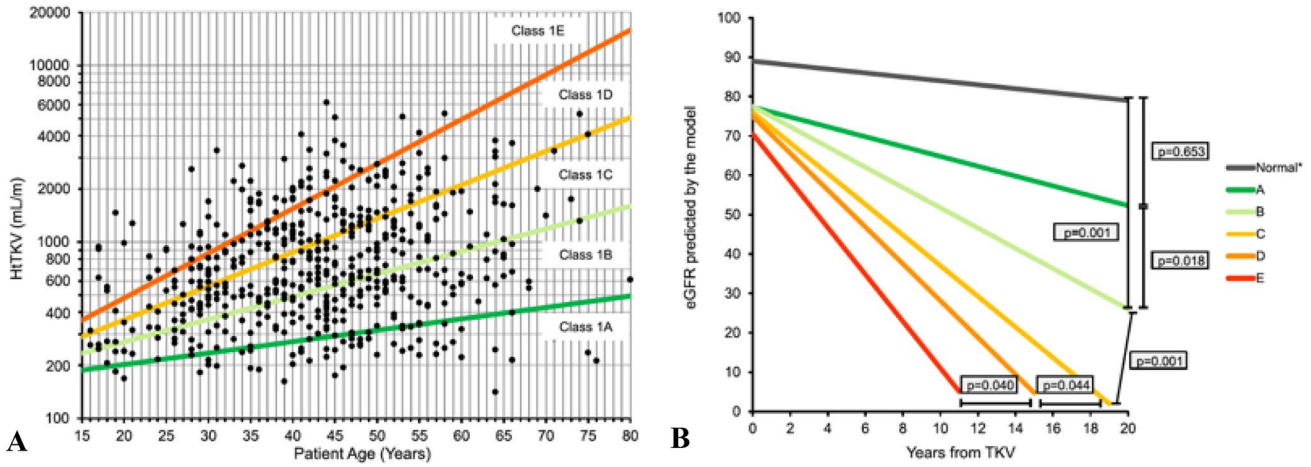


**Fig. 5** Mayo classification. **A** Subclassification of patients with class 1 ADPKD at baseline based on htTKV limits for their age. **B** Prediction of eGFR in patients with class 1 ADPKD

occur due to cardiovascular diseases such as myocardial infarction or congestive heart failure. Among dialysis patients, those with ADPKD tend to have a higher mortality rate from cerebrovascular disease compared with patients with other primary diseases. Among those with cerebrovascular disease, more patients tend to experience a brain hemorrhage associated with hypertension than a subarachnoid hemorrhage from a ruptured cerebral aneurysm.

## Treatment and management of complications

### Treatments inhibiting disease progression

#### Clinical Questions (CQs) addressing treatment

CQ1-1 Should RA system inhibitors be administered to patients with ADPKD with hypertension?

> Recommendation Grade 2C
> As ACE inhibitors and ARBs may have an inhibitory effect on ESRD progression and proteinuria in patients with ADPKD with hypertension, their use is recommended.

CQ 1-2 Is strict antihypertensive therapy (110/75 mmHg) recommended for patients with ADPKD with hypertension?

> Recommendation Grade 2B
> Strict antihypertensive therapy may benefit patients with ADPKD with albuminuria, left ventricular hypertrophy, or increased kidney volume; however, adverse reactions such as lightheadedness are frequent. Rigorous blood pressure control is recommended only for patients with ADPKD aged <50 years with eGFR >60 ml/min/1.73 $m^2$ and tolerance to antihypertensive therapy.

#### Summary

ADPKD is often accompanied by hypertension and is frequently identified in juvenile-onset patients before the deterioration of kidney function. ACE inhibitors or ARBs-based antihypertensive therapy may have an inhibitory effect on ESRD and proteinuria. Strict antihypertensive therapy (targeting blood pressure of < 110/75 mmHg) may benefit patients aged < 50 years with eGFR > 60 ml/min/1.73 $m^2$ with albuminuria, left ventricular hypertrophy, and increased kidney volume; however, lightheadedness and dizziness are possible side effects. The concomitant use of ACE inhibitors and ARBs is not beneficial. Based on the

above, administration of RA system inhibitors in patients with ADPKD with hypertension is recommended, while strict antihypertensive therapy targeting a blood pressure of < 110/75 mmHg is only recommended for patients aged < 50 years with eGFR > 60 ml/min/1.73 $m^2$ and tolerance to antihypertensive therapy.

*RA system: renin-angiotensin system.

ACE inhibitor: angiotensin-converting enzyme inhibitor.

ARB: angiotensin receptor blocker.

CQ 2 Is tolvaptan recommended for treatment of ADPKD?

> Recommendation Grade 1A
> The use of tolvaptan to prevent deterioration of kidney function is recommended along with liver function monitoring in adult patients with ADPKD with evident or projected rapid progression of disease under observation for adverse events accompanying diuresis.

**Summary**

In a meta-analysis of double-blind, randomized controlled trials (RCT) of adult patients with ADPKD in early stage disease during which kidney impairment is expected (TEMPO 3:4 trial) and in late-stage disease when kidney impairment has progressed to some degree (REPRISE trial), administration of vasopressin V2 receptor antagonist tolvaptan suppressed the rate of eGFR decline by 0.92 ml/min/1.73 $m^2$/year. Tolvaptan administration is also expected to inhibit the growth of TKV and reduce nephralgia and albuminuria. Tolvaptan has an inhibitory effect on kidney function decline, but the longevity and accumulative characteristic of its medicinal action in long-term administration as well as the results of the open-label TEMPO 4:4 extension trial (following the TEMPO 3:4 trial) indicate the importance of early stage intervention. Tolvaptan use is recommended for the purpose of inhibiting kidney function impairment in cases where available medical information (obtained through follow-up, diagnostic imaging, etc.) has been identified as rapidly progressive with poor prognosis. When tolvaptan is administered, patients should be monitored for adverse events accompanying diuresis and liver impairment.

### Sufficient water intake, dietary protein restriction, and calorie restriction

At the very least, sufficient water intake is key to avoiding dehydration and thirst. While the significance of a protein-restricted diet is not recognized, a balanced diet conforming to CKD guidelines is recommended as a means of preventing complications. A calorie-restricted diet has reportedly inhibited progressive impairment of kidney function and kidney size in animal models, while excessive weight and obesity are inferred to be exacerbating factors in early stage ADPKD in humans.

## Management of complications

### CQs addressing complications

CQ 3 Is intracranial aneurysm screening recommended for patients with ADPKD?

> Recommendation Grade 2C
> There is no evidence indicating that screening for intracranial aneurysms reduces the total mortality rate or prevents intracranial aneurysm rupture, but magnetic resonance angiography (MRA) screening is suggested and particularly recommended for patients with a family history of subarachnoid hemorrhage and/or intracranial aneurysm.

**Summary**

Intracranial aneurysms are well-known extrarenal complications of ADPKD. The prevalence of unruptured intracranial aneurysms is significantly higher in patients with ADPKD than in those without ADPKD. While a ruptured intracranial aneurysm is a fatal complication, there is no evidence from previous reports that screening for intracranial aneurysms reduces the total mortality rate, prevents ruptured intracranial aneurysms, or accelerates referral to a neurosurgeon. However, the 4–7% mortality rate from intracranial aneurysms in patients with ADPKD greatly impacts prognosis, and according to two different decision analyses, screening extends life expectancy by an average of 0.9 years, gaining patients 1.29 quality-adjusted life years with great cost-effectiveness. MRA screening of intracranial aneurysms may be useful in improving prognosis.

CQ 4 Are newer quinolones recommended for the treatment of cyst infection in ADPKD?

> Recommendation Grade 2C
>
> Newer quinolones may be useful in treating cyst infection in patients with ADPKD and may be considered as a treatment option, but caution is required to ensure that they are not abused.

**Summary**

Cyst infection is a frequent and severe complication of ADPKD and is intractable and recurrent. Most pathogenic bacterial cysts originate in the intestines and are gram-negative rods. Newer lipid-soluble and cyst-permeable quinolines are broadly useful against gram-negative bacteria and have thus been recommended for the treatment of cyst infection.

However, some reports do not indicate new quinolines for treatment, as some pathogenic bacteria that cause cyst infections are not responsive to the drug. As *E. coli* and other gram-negative bacteria also exhibit antibiotic resistance with high frequency, care should be taken not to abuse newer quinolines. As complete recovery from cyst infections treated with water-soluble antibacterial agents has often been reported, the use of newer quinolines should be limited to patients such as those with severe cyst infections or infections resistant to early stage treatment.

#### Cyst infection (drainage)

Drainage is required for refractory cyst infections that are resistant to conservative therapy, including intravenous administration of antibacterial drugs. It is recommended at an early stage for massive infectious cysts and recurrent cyst infections.

#### Cystic hemorrhage and hematuria

Most hemorrhaging is relieved spontaneously or through bed rest. As there are reports of intravenous or oral administration of tranexamic acid achieving quick hemostasis in cases of intractable cystic hemorrhage, such administration may be considered. Renal artery embolization therapy and surgery must be considered for progressive anemia that necessitates blood transfusion.

#### Urolithiasis

Urolithiasis is reportedly a complication in 20–30% of ADPKD cases. Anatomical urinary retention and metabolic disorders are the contributing causal factors. No published studies have addressed preventive measures for urolithiasis in patients with ADPKD, but general recommendations to prevent recurrence, such as increasing water intake, may be helpful.

#### Pain management

Acetaminophen is the first-choice drug therapy for nephralgia. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended if acetaminophen is insufficient to reduce pain. The safety of NSAID usage in CKD patients remains unclear, and no evidence exists regarding its role in the progression of ADPKD. However, patients with renal impairment should not use NSAIDs.

#### Screening for cardiac complications (including valvular heart disease)

Valvular heart diseases among patients with ADPKD commonly include mitral valve prolapse (MVP) and mitral valve regurgitation (MR). MR is the most common heart valvular disease in Japan, affecting 21% of patients with ADPKD.

However, the effect of valvular disease therapy on the prognosis of patients with ADPKD with valvular disease remains unknown.

As non-ADPKD valvular disease patients diagnosed with moderate or severe MR are expected to benefit from improved prognosis through disease assessment and sustained treatment protocols, echocardiography screening for cardiac complications (including valvular disease) is recommended for patients with ADPKD.

## Special treatment of complications

#### Fine-needle aspiration of the renal cysts

Surgery and transcutaneous paracentesis for cyst decompression are promising therapies for patients with ADPKD to help conserve kidney function and relieve hypertension and chronic pain. However, as benefits beyond alleviating chronic pain have yet to be demonstrated, fine-needle aspiration of renal cysts in patients with ADPKD is not recommended for purposes beyond mitigating chronic pain for which analgesics prove insufficient.

#### Transarterial embolization (TAE) for an enlarged polycystic kidney and liver

Renal transarterial embolization (TAE) is reportedly effective in reducing the volume of enlarged kidneys in patients with ADPKD and has become a common global tool for pre-transplantation maintenance of the host site and alleviation of symptoms from enlarged kidneys.

Few reports exist on the effects of hepatic TAE on patients with ADPKD with hepatomegaly, but as those reports suggest some reduction in liver enlargement from hepatic TAE, such treatment may be effective in reducing liver volume in patients with ADPKD.

#### Surgical intervention (drainage, fenestration/partial resection) for an enlarged polycystic liver

Drainage (fine-needle cyst aspiration), fenestration, partial resection, and transplantation are the treatment options for enlarged polycystic liver. Liver failure is rare even in cases of hepatomegaly, and treatment should be considered in light of cyst severity, as determined by subjective symptoms and Gigot classification (Fig. 6). Surgical treatment is not recommended for asymptomatic liver cysts, but is endorsed for enlarged polycystic liver volume reduction to alleviate intense symptoms such as abdominal swelling, gastrointestinal disorders, or restricted physical movement that results to deterioration in ADL, and to improve QOL.

### Kidney replacement therapy for end-stage renal disease

#### Hemodialysis

Treatment generally involves 4-h sessions three times per week. As storage of large quantities of peritoneal dialysate is difficult for patients with ADPKD experiencing enlarged livers and kidneys, hemodialysis is often performed instead of peritoneal dialysis.

#### Peritoneal dialysis

In the case of enlarged kidneys, one or both kidneys may be removed to secure sufficient intraperitoneal space for dialysate.

#### Kidney transplantation

As ADPKD is congenital, it does not recur following kidney transplantation, which is performed as it is in other patients and includes immunosuppressive therapy. Post-transplantation survival is favorable for patients with ADPKD compared with ESRD patients with other primary diseases. As post-transplantation reduction in native kidney volume is typical, nephrectomy of the native kidney is not always required during surgery.

## Autosomal Recessive Polycystic Kidney Disease (ARPKD)

### Disease concept and definition

#### Etiology and pathophysiology

ARPKD is a hereditary cystic kidney disease that is characterized by an autosomal recessive trait. It is characterized by expanded collecting ducts and bile duct dysplasia along with

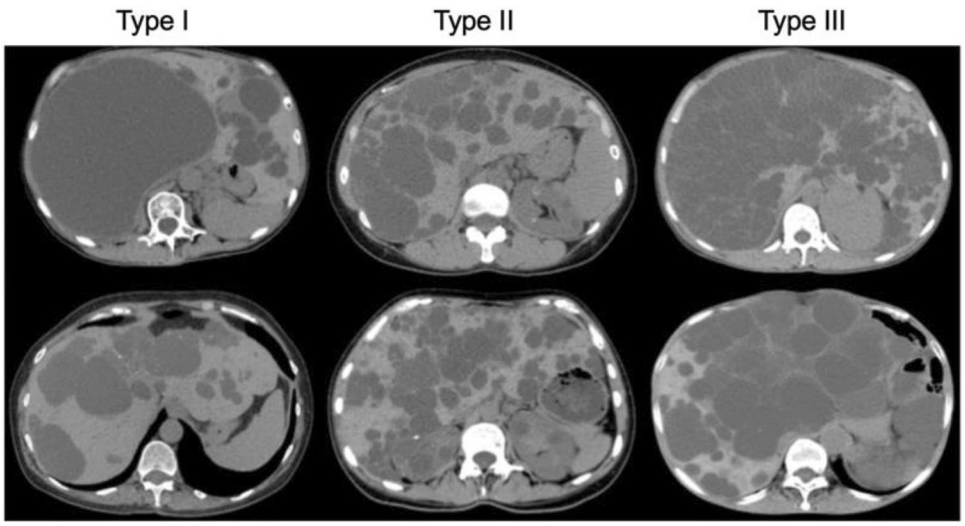


**Fig. 6** Classification of cystic liver. Type I: limited number (< 10) of large cysts (> 10 cm) (Treatment: Drainage and fenestration). Type II: Diffuse involvement of the liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma. (Treatment: Liver resection). Type III: The most severe form of APLD with massive, diffuse involvement of the liver parenchyma by small-and medium-sized liver cysts, with only a few areas of remaining normal liver parenchyma between cysts. (Treatment: Liver transplantation)

hepatic lesions, such as intrahepatic periportal fibrogenesis. In general, ARPKD hepatic lesions are clinically referred to as congenital hepatic fibrosis when present alone and are associated with a histological feature called ductal plate malformation. ARPKD is mainly caused by mutations in the gene PKHD1 on chromosome 6p21.1-p12, despite various clinical manifestations. It is known that in three forms of human PKD, which are PKD1, PKD2, and ARPKD, the causative gene protein plays a role in the function of primary cilia and related structures, and it is assumed that abnormalities and functional disorders in primary cilia induce disease and represent a rationale in the pathophysiology common to ARPKD and ADPKD.

## Diagnosis

### Symptomatology/symptoms/laboratory findings

Ultrasound findings and medical history of a sibling with the disease are important in the diagnosis of ARPKD (Tables 3). ARPKD cysts are typically small and exhibit primarily diffuse dilation, rather than a cell-like shape. Renal ultrasonography indicated enlarged echogenic kidneys, rather than the typically nodulous and low-echogenic kidneys. Ultrasound may reveal ARPKD symptoms during the second trimester of pregnancy, but this has not been clarified until 30 weeks of gestation (Table 4). As many kidney diseases are characterized by cyst formation, differential diagnosis is essential. ADPKD is an important differential diagnosis among hereditary cystic kidney diseases (Table 5). Caution is required for macrocysts, as no collecting duct dilation can be identified in some cases. Differential diagnosis may become difficult as the disease progresses because of morphological similarities. It has long been assumed that symptoms present neonatally in most ARPKD patients, with the disease being discovered in infancy or thereafter due to abdominal distension from kidney enlargement or hepatosplenomegaly.

## Epidemiology and prognosis

### Incidence rate, prevalence, and treatment outcome

ARPKD is inferred to occur in 1 case in 10,000–40,000 births. Long-term survival of all but the most severely affected newborns with lung hypoplasia is known to be possible; however, prognosis assessment remains challenging. Improvements in early stage disease management in infants soon after birth and advancements in ESRD treatments offer promise for further improvements in prognosis.

**Table 3** Diagnostic criteria of ARPKD

| |
|---|
| 1. Ultrasonographic features typical of ARPKD, including enlarged, echogenic kidneys, with poor corticomedullary differentiation |
| 2. One or more of the following: |
| (a) Absence of renal cysts in both parents, particularly if they are at least 30 years old |
| (b) Clinical, laboratory, or radiographic evidence of hepatic fibrosis |
| (c) Hepatic pathology demonstrating characteristic ductal plate abnormalities |
| (d) Previous affected sibling with pathologically or genetically confirmed disease |
| (e) Parental consanguinity suggestive of autosomal recessive inheritance |

**Table 4** Typical sonographic appearance of ARPKD

| | |
|---|---|
| Pattern I | Massive enlargement of the kidneys<br>Increased echogenicity of the entire parenchyma<br>Loss of corticomedullary differentiation<br>Loss of the central echo complex<br>Small macrocysts, below 2 cm in diameter |
| Pattern II | Massive enlargement of the kidneys<br>Increased echogenicity predominantly in the medulla<br>Macrocysts remaining below 2 cm in diameter |
| Pattern III | Moderate enlargement of the kidneys<br>Increased echogenicity confined to the medulla with reversal of normal intrarenal anatomy<br>No macrocysts seen |

In older children, the medullaly location of the cysts (i.e. the hyper echogenicity) is more obvious (patterns II and III)

**Table 5** Differential clinical features of PKD

| |
|---|
| Major clinical features of both ARPKD and ADPKD |
| Enlarged kidneys |
| Systemic hypertension |
| Renal concentrating defect |
| Sterile pyuria |
| Clinical features suggesting ARPKD rather than ADPKD |
| Neonatal presentation |
| Progression to end-stage renal disease as a child |
| Hepatosplenomegaly |
| Portal hypertension and esophageal varices |
| Bacterial cholangitis |
| No evidence of ADPKD in parents or grandparents |
| Clinical features suggesting ADPKD rather than ARPKD |
| Family history of ADPKD |
| Extrarenal cysts (liver, ovary, pancreas, spleen) |
| Cerebral aneurysms |
| Asymptomatic presentation |
| Unilateral renal presentation |
| Hematuria |
| Urinary tract infection |

### Genetic diagnosis

ARPKD is a monogenetic disease for which genetic diagnosis is appropriate, but does not typically require genetic analysis. Such analysis may help yield accurate results in mild or atypical cases in which diagnosis can be difficult. As genetic analysis is essential in prenatal diagnosis and preimplantation, in a typical family case in which a sibling is diagnosed with ARPKD, creating an environment for the option of genetic diagnosis is desirable.

### Prenatal diagnosis

In ARPKD, as serious symptoms often appear in early infancy, prenatal screening is helpful for subsequent disease management. In a broad sense, prenatal screening includes fetal ultrasound and MRI. There is a great clinical significance in implementing these as needed in current perinatal care. However, there is low accuracy in ultrasound and other forms of diagnostic imaging, as ARPKD cysts usually do not clearly manifest until 30 weeks of gestation. Genetic analysis of ARPKD in prenatal screening is technologically established and may be considered as a tool for diagnosing ARPKD in the cells of siblings' future children.

## Treatment

Hypertension is often exhibited during infancy and is treated with antihypertensive therapies, primarily with ACE inhibitors and ARBs. Multidrug therapy is often required. If the child experiences ESRD, suitable treatment is chosen from among the available renal replacement therapies (hemodialysis, peritoneal dialysis, or kidney transplantation). During peritoneal dialysis, unilateral or bilateral nephrectomy may be necessary to improve the respiratory status or secure intraperitoneal capacity for nutrient intake and dialysis. In terms of quality of life and development, kidney transplantation is the recommended choice, with the evaluation of liver complications being critically important in determining the treatment strategy. In ESRD with serious complications (including uncontrollable hemorrhaging in the esophageal varices, refractory ascites, and hepatopulmonary syndrome) from recurrent cholangitis or portal hypertension, liver and kidney transplantation may be a suitable option.

**Acknowledgements** This study was supported in part by a Grant-in-Aid for Intractable Renal Diseases Research, Research on Rare and Intractable Diseases, and Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan.

## Authors and Affilations

**Saori Nishio[1] · Ken Tsuchiya[2] · Shinya Nakatani[3] · Satoru Muto[4] · Toshio Mochizuki[2] · Haruna Kawano[4] · Kazushige Hanaoka[5] · Sumi Hidaka[6] · Daisuke Ichikawa[7] · Eiji Ishikawa[8] · Kiyotaka Uchiyama[9] · Eri Koshi-Ito[10] · Hiroki Hayashi[11] · Shiho Makabe[2] · Soshiro Ogata[11] · Michihiro Mitobe[12] · Akinari Sekine[13] · Tatsuya Suwabe[13] · Hiroshi Kataoka[2] · Hirayasu Kai[14] · Yoshikatsu Kaneko[15] · Mahiro Kurashige[16] · Koichi Seta[17] · Keiji Shimazu[18] · Taketsugu Hama[19] · Kenichiro Miura[20] · Koichi Nakanishi[21] · Shigeo Horie[4] · Kengo Furuichi[22] · Hirokazu Okada[23] · Ichiei Narita[15] · Committee of Clinical Practical Guideline for Polycystic Kidney Disease 2020**

1 Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

2 Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan

3 Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

4 Departments of Urology and Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan

5 Department of General Internal Medicine, The Jikei University, Tokyo, Japan

6 Kidney Disease and Transplant Center, Shonan Kamakura General Hospital, Kanagawa, Japan

7 Department of Nephrology and Hypertension, St Marianna University School of Medicine, Kanagawa, Japan

8 Department of Internal Medicine, Saiseikai Matsusaka General Hospital, Mie, Japan

9 Division of Endocrinology, Metabolism and Nephrology Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

10 Department of Nephrology, Internal Medicine, Nagoya University Graduate School of Medicine, Aichi, Japan

11 Department of Nephrology, Fujita Health University School of Medicine, Aichi, Japan

12 Department of Nephrology, Takeda General Hospital, Fukushima, Japan

13 Department of Nephrology, Toranomon Hospital, Tokyo, Japan

14 Pathophysiology of Renal Diseases, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan

15 Niigata University, Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan

16 Nephrology & Hypertension, Department of Internal Medicine, The Jikei University, Tokyo, Japan

17 Department of Nephrology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

18 Department of Nephrology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

19 Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

20 Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan

21 Department of Child Health and Welfare (Pediatrics), Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

22 Department of Nephrology, Kanazawa Medical University, Ishikawa, Japan

23 Department of Nephrology, Saitama Medical University, Saitama, Japan