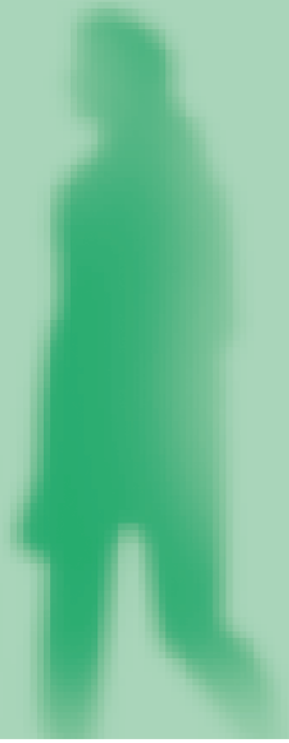
Information for General Practitioners About

Polycystic Kidney Disease (ADPKD)



VSOP

Zeldzame Ziekten

Nierpatiënten Vereniging Nederland

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Contents

Introduction

People with rare, often chronic conditions regularly have frequent contact with one or several healthcare providers over an extended period of time. Medical specialists and general practitioners have their own role in such cases and people with a rare condition have needs that may differ from one healthcare provider to another.[7] One of those needs, of both patient and the general practitioner, is that the GP is familiar with the condition in question. This brochure for general practitioners fulfils that need.
It is therefore written primarily for general practitioners who deal with patients with autosomal dominant polycystic kidney disease (ADPKD) in their practices. However, the information can also be used by other healthcare providers. The relevant information has been gathered together in this brochure, which also includes specific key points for general practitioners. The content focuses primarily on the stage following diagnosis.

The brochure has been carefully prepared using up-to-date information from medical and scientific literature, and expert opinions (see *Accountability*). The centres of expertise have provided us with the most recent information in this field (see *Consultation and referral).* If you have any comments and/or patient-related questions, please contact the treatment specialist or primary physician.

Realisation

This brochure was realised in collaboration with the Dutch Kidney Patients Association (NVN), the Dutch Genetic Alliance (VSOP) and the Dutch College of General Practitioners (NHG). The brochure is part of a series of general practitioner brochures which can be downloaded from www.nhg.org/thema/zeldzame-ziekten (**in Dutch only)** and the VSOP websites www.vsop.nl and www.zichtopzeldzaam.nl/ documenten (**in Dutch only**).

Dutch Kidney Patients Association (NVN)
The NVN is an active association set up for, and in collaboration with, kidney patients. It promotes the interests of all kidney patients. The NVN organises a wide range of activities for its members, provides information, and facilitates contact between patients. For further information, see *Accountability* and www.nvn.nl (**in Dutch only**).

The Dutch Genetic Alliance (VSOP)
The VSOP supports around 70 patient organisations for rare and genetic disorders, and works in collaboration with them to achieve better care for, and prevention of, these conditions. For further information, see Accountability and www.vsop.nl.

The Dutch College of General Practitioners (NHG)
The Dutch College of General Practitioners is the Dutch scientific association of GPs. For further information, see Accountability and www.nhg.org.
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Polycystic Kidney Disease (ADPKD)

Polycystic kidney disease is an umbrella term for chronic and progressive genetic disorders in which cysts develop and grow in the kidneys. This causes a progressive increase in kidney size and, ultimately, deterioration in kidney function. The most common type of polycystic kidney disease is autosomal dominant polycystic kidney disease or ADPKD. There are also other, less common types of polycystic kidney disease. Examples include autosomal recessive polycystic kidney disease (ARPKD) and nephronophthisis. These disorders are often more serious and develop during childhood. This brochure focuses primarily on ADPKD. It also includes an *Appendix* with a brief description of the autosomal recessive type of the disease, ARPKD.

ADPKD is the most common genetic renal disease. The disease accounts for 10% of all patients in Europe who are eligible for renal replacement therapy. In addition to renal cysts, cysts can also develop in other organs, particularly in the liver. The cysts can result in pain, bleeding and infections. Patients with ADPKD also have a greater risk of developing hypertension, cardiovascular disease and intracranial aneurysms.[4,15] Some patients with ADPKD (20 to 30%) never reach the stage of kidney failure for which dialysis or transplant is required. The average age at which patients who do develop kidney failure start renal replacement therapy is 58. [14]

No curative treatment is available at present. It has recently been shown that a vasopressin V2 receptor antagonist (tolvaptan) inhabits the growth of renal cysts in patients with good renal function. This slows down the deterioration of renal function. Once a diagnosis has been made, blood pressure and renal function are checked on a regular basis. Patients are also treated for the various symptoms and complications associated with ADPKD. Most patients ultimately undergo renal replacement therapy. This can consist of dialysis and/or transplantation.

Polycystic kidney disease has lifelong physical and psychological effects that can affect the patient's quality of life and normal functioning. Fatigue and pain are likely to be the symptoms that have the greatest effect on the patient's quality of life.
This brochure aims to inform general practitioners about the background of ADPKD. In addition to medical and nephrological aspects of the disease, general practitioners can play a role when it comes to other important issues such as providing psychosocial support.

A FEW FACTS

Prevention

- **Incidence** No exact incidence figures are known. Recent estimates based on literature suggest an incidence of 1:2500 people.[19] This means that a GP with a standard practice will, on average, received one patient with ADPKD over a period of 30 years. The hereditary character of this condition means that a GP may see more than one patient with this condition from a single family.
- **Age and gender division** The condition affects both men and women from all ethnic groups. ADPKD rarely manifests itself during childhood.

Heredity and aetiology

- **Heredity** ADPKD is caused by a mutation in one of two genes, PKD1 (85%) and PKD2 (15%). Mutations in the PKD1 gene cause a severe type of ADPKD in which kidney failure occurs 20 years earlier, on average, than in patients with PKD2 gene abnormalities. Mutations in the PKD2 gene result in fewer renal cysts, milder kidney failure and the onset of hypertension at a later age.
- **Risk of recurrence** ADPKD is an autosomal dominant disease; this means there is a 50% risk of passing the gene mutation on to a subsequent generation. Carrying the gene mutation irrevocably leads to polycystic kidney disease.

- **Aetiology** Ciliopathy, a disorder of the cellular cilia, develops as a result of the mutations described**.** *PKD1 and PKD2 encode polycystin-1 and polycystin-2 respectively; these proteins are found in the cilia.* Although the exact function of the polycystin proteins is still unclear, there are indications that defects in the cilia play an important role in the development of cysts originating from the renal tubules of both kidneys, and in the extrarenal characteristics of ADPKD. More potentially active medications have been developed in recent years thanks to increased insight into the pathophysiology of the disease.

Diagnosis

- **Adults** The condition is usually diagnosed when people from a family of patients with polycystic kidney disease present with symptoms such as abdominal pain, blood in the urine, or when high blood pressure is detected. The diagnosis may also result from findings (including incidental findings) in medical imaging tests. If there is a family history of ADPKD, adults can undergo diagnostic tests before they develop symptoms (presymptomatic testing). Tests are usually conducted using ultrasound. People with a known risk factor of 50% are advised to have their blood pressure and proteinuria levels monitored (see *Disease management*). DNA testing is not usually indicated in adults with a known gene mutation in the family. In 10-15% of cases there is no positive family history of ADPKD, for example because there is a newly-developed mutation, a mild form in the family or an absence of medical data for one or both parents. If there are no indications for a different type of renal disease, ADPKD is the most likely diagnosis in the event of enlarged kidneys and bilateral multiple renal cysts.
- **Children** Newborns or children with renal cysts form a heterogeneous diagnostic group for cystic conditions. The diagnosis is normally not ADPKD as only 1-2% of children with ADPKD develop symptoms before the second year of life. In general, it is not recommended to carry out presymptomatic testing in children who are at risk of ADPKD, but rather to wait until the individual in question is old enough to decide for themselves (or in consultation with a medical specialist) about the diagnostic options available. The ultimate decision regarding whether or not to undergo diagnostic testing is that of the parents once they have been sufficiently informed about the possible benefits and drawbacks.[3] Given the adverse effects of high blood pressure, paediatric nephrologists recommend that children of parents with ADPKD undergo annual blood pressure measurement and proteinuria level tests (see *Disease Management*) . The presence of proteinuria is a reason for referral to a paediatric nephrologist for further diagnosis and treatment.

Differential diagnose In addition to ADPKD, other genetic disorders can also lead to the development of cysts in the kidneys. Generally, these disorders are less common and lead to a syndromic clinical presentation which manifests itself during childhood. Examples of these disorders include: autosomal recessive polycystic kidney disease (ARPKD, see *Appendix*), nephronophthisis, Bardet-Biedl syndrome, Joubert syndrome and Von Hippel-Lindau syndrome. However, there are also exceptions to the rule. For example, mutations in the HNF1B and GANAB genes, and mild mutations in the ARPKD gene, result in a clinical picture that is indistinguishable from that of ADPKD. A mild mutation in PKD1 can also present in a family as a clinical picture compatible with PKD2.

Course of disease and prognosis

The severity and course of this disease is variable. There is variation between different families, but disease progression can also vary within polycystic kidney families. Patients continually develop new renal cysts throughout their entire lives. This causes the kidneys to grow in size by 5-6% every year. Although the development and growth of renal cysts often starts in utero, kidney function is usually maintained until the patient reaches 30 - 40 years of age. The glomerular filtration rate (eGFR) long remains within normal standards because the glomeruli of the unaffected tubules compensate through hyperfiltration.[6] Disease progression and rapid deterioration of kidney function characterised by fibrotic and inflammatory changes occur in later stages of the disease when most of the nephrons have been destroyed. On average, patients with ADPKD need a kidney transplant or dialysis around the age of 65. Most patients with a PKD1 mutation have end-stage kidney failure before they reach the age of 70, while over 50% of PKD2 patients still have adequate kidney function at this age. The main factors in predicting disease progression are:6,12

- A PKD1 mutation
- Male gender
- Age
- Development of hypertension before the age of 35
- first urological events before the age of 35
- kidney function (eGFR)
- Total kidney volume

Cardiovascular disorders are the main cause of death.[15] As a result of the decrease in mortality due to cardiovascular disorders in recent years, the two-year survival rate of patients after starting renal replacement therapy has significantly increased.

SYMPTOMS

General

- **Fatigue** A survey among Dutch patients with ADPKD (n=145) showed that fatigue is the most commonly reported symptom (77%).
- **Pain** Acute or chronic pain is very common. Acute pain can occur due to a cyst bleed, the passage of kidney stones or a cyst infection.[16] Some patients develop chronic pain in the flank.
- **Feeling of fullness and bloating** The enlarged kidneys, liver and growing cysts cause a feeling of fullness and can cause an increase in girth size. Pressure on adjacent organs can also cause symptoms such as shortness of breath and a feeling of abdominal fullness.

Abnormalities of the kidneys and urinary tract

- **Urine** There is a reduced capacity to concentrate urine, even in the early stages of disease. Approximately 60% of children are unable to concentrate urine to the maximum. Plasma vasopressin concentrations are increased.[20] Thanks to the stimulation of water resorption, the increased vasopressin concentration ensures that the urine is nevertheless concentrated as well as possible.
- **Proteinuria** Approximately 25% of adults with ADPKD have a proteinuria level of over 300 mg/day, but never more than 1 gr/day.[3] Proteinuria is associated with a larger total kidney volume, a more rapid decrease in kidney function and earlier onset of kidney failure.
- **Kidney failure** There is a wide variation in the development of kidney failure.[16] Kidney and cyst volume are the main predictors of deteriorating kidney function. The change in renal circulation is also an independent predictor. External factors such as the use of analgesics can also accelerate the progression of chronic kidney failure.
- **Macroscopic haematuria** This is a frequent complication of ADPKD. Haematuria can be caused by a cyst bleed, kidney stones, a cyst infection and, in exceptional cases, by additional causes such as renal cell carcinoma or urothelial carcinoma (having ADPKD does not increase this risk).[3]
- **Cyst bleed** A bleed may be accompanied by acute pain. MRI or CT findings suggest that asymptomatic bleeds are also very common.[16]
- **Urinary tract infections** As is the case in the general population, urinary tract infections are more common in women. Most infections are caused by enterobacteria. Ascending infections can lead to a cyst infection.
- **Cyst infection** Symptoms may include: fever, abdominal pain, macroscopic haematuria and blood tests showing an elevated CRP. Blood and urine cultures may be negative. Infected cysts can show up on a combined PET/CT scan.
- **Nephrolithiasis** Kidney stones and cyst wall calcifications are common in patients with ADPKD (20%).[16] A CT scan is the best diagnostic tool with which to detect stones.[3]

Abnormalities of the liver and bile ducts

- **Polycystic liver disease (PLD) Liver cysts occur in over 80% of adults with ADPKD.** Liver cysts occur more often and are larger in volume in females, particularly if they have had multiple pregnancies or if they use exogenous oestrogen (oral contraceptives or hormonal replacement therapy). Liver cysts are rare in children.[16] The symptoms associated with liver cysts worsen with age. The assessment of patients with ADPKD should include medical imaging tests of the liver in order to determine the severity of the PLD. Approximately 20% of ADPKD patients suffer from liver cysts. Symptoms may occur due to complications of the liver cysts, such as a cyst bleed, infection or occasionally torsion or a rupture. The following symptoms can also occur due to the effect of the mass:
  - A distended, painful abdomen
  - Back pain
  - A rapid feeling of fullness
  - Gastrointestinal reflux
  - Shortness of breath
  - Compression of the inferior vena cava
  - Compression of the portal vein
- **Liver cyst infection** Usually recognised by local pain, fever and blood values indicating an infection. The infection is almost always monobacterial. A PET/CT scan is the most sensitive investigation for detecting infected cysts.
- **Cholangitis** 40% of patients develop mild dilatation of the bile ducts and this is sometimes accompanied by cholangitis.[16] Irregularities in the walls of the dilated ducts make them vulnerable to infection. Typical symptoms of cholangitis are fever, icterus (jaundice) and pain in the upper right abdomen.

Cardiovascular abnormalities

- **Hypertension** People with ADPKD have an increased risk of developing hypertension and other cardiovascular disorders. Over 60% of patients develop hypertension before there is a quantifiable decrease in kidney function. Half of those in this group of patients are between 20 and 40 years of age.[12] Several factors play a role here, including abnormalities in the renin-angiotensin-aldosterone system (RAAS). *Children:* The prevalence of hypertension in children is between 5 and 44%.[16]

- **Intracranial aneurysm (ICA)** Five to 10% of patients with ADPKD develop an ICA. This percentage is 4-5 times higher than for the general population.[18] It is caused by changes in the circulatory system resulting directly from mutations in PKD1 or PKD2. There are no clear risk factors except a positive family history of ruptured ICA. The average age at which a rupture first occurs is lower than in the general population (41 instead of 51 years). Most patients have normal kidney function and up to 29% have a normal blood pressure at the time of the rupture.[16] The number of ruptures is generally no higher than for the general population. Comprehensive presymptomatic testing for ICAs is not useful in most cases. They aneurysms are usually small with a low risk of rupture. Intervention is generally considered a risk. Indications for presymptomatic testing using MRI are:
  - Good life expectancy and a family history of ICA or subarachnoid haemorrhage.
  - Previous ICS rupture
  - Professions with a high risk due to responsibility for many people (e.g. pilot).
  - Patient is anxious despite being well informed. It is important that the nephrologist discusses with the patient the fact that tests can sometimes reveal asymptomatic abnormalities for which a watchful waiting policy is initially recommended. The nephrologist may choose to refer the patient to a neurologist for consultation.
  - **Mitral valve prolapse** This is the most common valve defect in patients with APKPD.[16]
- **Other vascular abnormalities** Other vascular disorders can occur less frequently such as coronary artery aneurysms, thoracic aortic dissection, and dilated aortic root. Aortic insufficiency can occur in combination with a dilated aortic root.[16] Valve replacement is not usually necessary. Tests are only needed if there is a heart murmur or if a first-degree relative has had a thoracic aortic dissection or dilated aortic root.

Psychosocial aspects and psychiatric problems

- **Quality of life** ADPKD has lifelong physical and psychological effects that can affect the patient's quality of life, wellbeing and normal functioning. Fatigue and pain are likely to be the symptoms that have the greatest effect on the patient's quality of life. In the later stages of disease, renal replacement therapy has a significant impact on the patient's daily life.
- **Impact** The condition often has a far-reaching emotional impact with feelings of:
  - Loss of future, function, self-image and favourite activities.
  - Insecurity about when and how severe the certain deterioration will be
  - Anxiety, about issues such as dialysis, transplantation or a ruptured aneurysm
  - Guilt if the patient wants to have children and risks potentially passing the condition on to the next generation

  Together, these aspects often result in anxiety or depression.[18] Anxiety and depression are highly prevalent in patients with chronic kidney disease. ADPKD can also adversely affect various other aspects of life such as taking out health insurance, life insurance or a mortgage. It can also affect a patient's wish to have children. In many cases the condition results in patients having to take sick leave or becoming incapacitated for work (partially or fully). Healthcare professionals and other professionals involved often underestimate the impact of ADPKD on patients and their families.[18]

DISEASE MANAGEMENT

General

· **Treatment** Despite progress and new insights, there is as yet no curative treatment for ADPKD. Treatment focuses on minimising symptoms and complications, and maintaining kidney function for as long as possible with a view to improving the quality of life, and prolonging life.[3]
Important aspects to consider in the treatment of ADPKD are:
- Adapting lifestyle
- Slowing down associated kidney damage
– Treating hypertension and renal/extrarenal complications
- Renal replacement therapy

· **Care coordination** The internist/nephrologist is the main treatment specialist. The nephrologist consults with other disciplines depending on the situation. These disciplines can include: urology and gastroenterology, anaesthesia (pain team), neurology, clinical genetics, radiology and pathology. The patient, the main treatment specialist and the general practitioner can make agreements about the coordination of care (e.g. about the role of the GP in acute situations, and with respect to psychosocial support).

Management of nephrological problems

· **Lifestyle advice** Some lifestyle changes can, to a greater or lesser extent, have a positive effect on the course of the disease (see *NHG-Zorgmodules Leefstijl*). The nephrologist discusses this lifestyle advice with the patient:[18]
- Increased water intake can protect kidney function.
- A low-salt diet can help to keep blood pressure under control and may help to protect the kidneys.
- A low-protein diet helps patients with severely reduced kidney function (eGFR <30) in preventing metabolic waste products from collecting in the blood.
- Reducing high caffeine intake prevents a potential increase in cyst growth caused by caffeine.
- A healthy, varied diet and sufficient physical exercise can help achieve and maintain a healthy body weight.
- Smoking exacerbates kidney damage. The nephrologist will urgently advise smokers to stop smoking and if necessary offer support by coaching the patient or referring them to support programmes (see *NHG Standaard Stoppen met roken*).

· **Kidney failure** It has recently been shown that a vasopressin V2 receptor antagonist (tolvaptan) inhabits the growth of renal cysts in patients with good renal function. This slows down the deterioration of renal function. Negotiations regarding remuneration for this medication are currently underway; doctors may therefore be able to prescribe tolvaptan in clinical practice in the near future. The main side-effect of tolvaptan is increased diuresis, sometimes up to 5/6 litres a day. This is associated with a risk of dehydration. Another possible side-effect is liver toxicity, and regular liver function monitoring is therefore important. To date, these abnormalities have been shown to be reversible following the cessation of tolvaptan in all patients with impaired liver function. The use of tolvaptan is not a replacement for other types of treatment and should be regarded as supplementary to the standard care currently applicable.

· **Renal replacement therapy** The nephrologist will usually start this therapy if kidney function is around 10% and/or if the patient is showing symptoms and/or complications of kidney failure. There are two types of renal replacement therapy: kidney transplantation and dialysis.
- *Transplantation:*
If possible, transplantation is preferable to dialysis because it results in improved quality of life and longevity. Donation by living donors, preferably when renal replacement therapy is not yet required (pre-emptive transplantation), is likely to have the best chance of success. Timely preparation reduces the risk of a patient first having to undergo dialysis before they are eligible for a transplant. The kidneys should, preferably, not be removed as a matter of course immediately before the transplant because this is often associated with a certain morbidity and mortality. The urologist may, in consultation with the patient, consider nephrectomy in the event of certain physical symptoms caused by the affected kidneys (such as recurrent infections, bleeds or kidney stones), or if there is a lack of intra-abdominal space prior to the transplant. Immunosuppression is required following transplantation in order to prevent rejection. The risk of post-transplant complications is no greater than for other transplant recipients.
- *Dialysis:*
If a kidney transplant is not an option or if the patient is awaiting transplantation, haemodialysis or peritoneal dialysis can offer a suitable solution. Dialysis does not replace kidney function entirely but ensures that waste products are removed from the blood.

· **Urinary tract infections** An ascending urinary tract infection can lead to a cyst infection in patients with polycystic kidneys. It is therefore important to treat urinary tract infections with antibiotics early and in many cases for longer than usual.

A urine culture is recommended before starting antibiotic treatment. If a complicated kidney cyst infection should develop, the culture results will be an important factor in determining the ultimate antibiotic treatment policy. Treatment can be determined in accordance with the *NHG-Standaard Urineweginfecties* for risk groups, and should include a pre-treatment urine culture. If in any doubt about policy, consult with the nephrologist.

- **Cyst infection** These are often difficult to treat. The treatment consists of antimicrobial substances such as fluoroquinolones and trimethoprim-sulfamethoxazole, as these probably permeate the cysts better. The duration of the treatment is not yet clear. In general, a longer treatment is required, ranging from 3 to 6 weeks, depending on clinical findings and CRP response. If fever continues after 1 to 2 weeks of adequate antibiotic treatment, cyst drainage is indicated. In the event of terminal kidney failure, the nephrologist may, in consultation with the patient and the urologist, consider nephrectomy. Despite adequate antibiotic treatment, cyst infections may recur. If a cyst infection is suspected, consult with the nephrologist regarding treatment or consider a referral (urgent if necessary).
- **Cyst bleeds** Episodes of bleeding cysts are usually self-limiting and repair spontaneously within 2-7 days. Hospital admission may be required in exceptional cases when bleeding persists, sometimes accompanied by extensive subcapsular or retroperitoneal haematomas. Temporary cessation of ACE inhibitors and/or diuretics during this type of episode may help prevent acute kidney damage.[3] If you suspect a cyst bleed, consult with the nephrologist regarding the treatment policy.
- **Nephrolithiasis** Adequate analgesia is important in acute situations, for example using 10mg morphine administered intramuscularly or subcutaneously. Avoid NSAIDs if at all possible. Extracorporeal shock therapy, flexible ureterorenoscopy and percutaneous removal of the kidney stones are safe treatment methods for most patients. Consultation with the nephrologist is recommended with respect to the treatment policy for ADPKD patients with suspected kidney stones. The treatment policy for these patients differs from that recommended in the *NHGStandaard Urinesteenlijden* (**in Dutch only**).

Treatment policy for disorders of the bile ducts and liver

- **Polycystic liver disorders** Treatment is not required if the liver cysts do not cause symptoms. Women with a significant number of liver cysts should avoid exogenous oestrogen (e.g. contraceptives).
  There are several therapeutic options for the symptomatic cysts:
  - ultrasound-guided aspiration of cyst fluid followed immediately by ethanol injection, after which the cyst shrinks (sclerotherapy)
  - cyst fenestration
  - partial or segmental hepatectomy
  - liver transplant

  Specialists are currently prescribing experimental somatostatin analogues in order to discover whether this stabilises or reduces liver volume in patients with polycystic liver disorders.
- **Liver cyst infections** Treatment consist of broad-spectrum antibiotics from the fluoroquinolones group (e.g. ciprofloxacin). If the infection does not respond to antibiotic treatment, percutaneous cyst drainage may offer a solution. Liver cyst infections frequently recur. If you suspect a liver cyst infection, discuss the treatment policy to be adopted with the nephrologist or hepatologist.
- **Cholangitis** Patients with cholangitis are usually very ill and need to be admitted to hospital. The treatment consists of intravenous administration of antibiotics usually followed by an ERCP to clear the bile duct obstruction. If you suspect cholangitis, consult with the hepatologist regarding treatment and possible referral (urgent if necessary).

Treatment policy for cardiovascular disease

- **Hypertension** Treatment comprises lifestyle changes and medication. Blood pressure should ideally be 130/80 mmHg or less. A recent study showed that even stricter blood regulation may be better still. When determining individual target values and choice of medication, the nephrologist will take comorbidity into account.[3] An ACE inhibitor (or A2 antagonist) combined with a low-sodium diet usually provides the best results. Other risk factors, such as high cholesterol levels, should also be taken into consideration (see *NHG-Standaard Cardiovasculair risicomanagement*). Despite their extreme importance, cardiovascular risk factors are often controlled insufficiently.[18]
  Children: It is recommended that children of parents with ADPKD are screened for hypertension and proteinuria or haematuria. If appropriate, consult with the paediatric nephrologist regarding the frequency of screening and the age at which it should begin. In the event of hypertension or proteinuria, the paediatric nephrologist will suggest further diagnosis using ultrasound and blood/urine tests. An ACE inhibitor is the medication of choice for treating hypertension or proteinuria[3] in patients with ADPKD.

- **Intracranial aneurysm (ICA)** Small, intact ICAs often do not require treatment, and regular re-evaluation by the neurologist is sufficient. The frequency of the check-ups is determined for each patient individually. Patients should be urgently advised to stop smoking. It is also important to minimise other cardiovascular risk factors. Patients with ADPKD and no identified ICAs but a positive family history of these should visit the neurologist every 5 to 10 years for presymptomatic testing. A patient with ADPKD or suspected ADPKD who experiences an acute severe headache may be suffering an intracerebral haemorrhage and should therefore be referred to a neurologist urgently.

Management of psychosocial and psychiatric problems

- **Anxiety and depression** The impact of ADPKD on a patient's physical and psychological well-being means that it is important for physicians to listen and deal with their psychological and emotional needs. If a patient is suffering from anxiety and/or depression, GPs should follow treatment recommendation as described in the *NHG-Standaard Depressie*.

INFORMATION ON HEREDITY AND PREGNANCY

Diagnosis of family members

- **Family testing/ presymptomatic diagnosis** Hereditary aspects of this disease are discussed with the patient and their partner, first by the treatment nephrologist and subsequently in more detail by the clinical geneticist. It is also recommended that patients inform their first-degree relatives of the fact that they too have an increased risk of ADPKD. The risk is 50% due to the autosomal dominant inheritance pattern. The GP can refer the patient's relatives to a clinical geneticist for presymptomatic diagnostic testing (ultrasound or DNA test) (see *Consultation and referral*). The benefits of early diagnosis are:[16]
  - Certainty, which may influence issues such as family planning
  - Early detection at a relatively mild stage of the disease; early treatment of the disease and any complications
  - Selection of family members who might be suitable kidney donors

  However, there are also disadvantages, such as financial considerations when taking out insurance or with respect to work.
- **Presymptomatic diagnosis in children and youngsters** Where children are concerned, the advantages of knowing don't generally outweigh the disadvantages (such as not being able to decide for oneself, the emotional burden, problems taking out insurance). There is currently no treatment that can influence the progress of the disease (other than good control of hypertension). This may change, certainly in adolescents, due to the advent of medications such as tolvaptan (and possible somatostatin analogues), which may slow down the progress of the condition. The diagnosis can sometimes be made by chance at a young age through medical imaging (including imaging carried out for different reasons). Caution should therefore be used with respect to abdominal imaging in first-degree relatives. If symptoms do warrant abdominal medical imaging tests, however, prior discussion with a paediatric nephrologist is recommended.
- **Right of self-determination** All patients (and the parents of children) have the right to self-determination. It is important to thoroughly discuss the desirability and/or consequences of presymptomatic testing and to give patients the opportunity to carefully consider whether they wish to undergo presymptomatic testing. The clinical geneticist will discuss this with the patient. As well as the right to know, patients and family members also have the right *not* to know. The wishes of the person concerned (patient or authorised person) therefore determine whether or not the patient undergoes genetic testing.
- **Informing family members** Dutch privacy legislation states that clinical geneticists/consultants are not permitted to inform family members directly about the existence of a hereditary disease in their family. Only the patient himself/herself can, with the help of letters to the family drawn up by the clinical geneticist, inform family members. The patient should be made aware of the importance of informing family members, and of their moral obligation to do so.

Family planning/antenatal diagnosis

- **Family planning** A parent with ADPKD has a 50% chance of passing the disease on to their children. Both ADPKD patients and first-degree relatives who wish to have children are advised to seek advice before considering a pregnancy. The nephrologist will inform patients who are considering pregnancy that referral to a clinical geneticist is an option. The clinical geneticist can tell them about the options available to prevent the condition arising in a subsequent generation. If a couple wishes to have a child, they themselves will have to make a suitable choice.

A clinical geneticist can provide support with this decision-making process (see *Consultation and referral*).
The choices available are:
- A natural pregnancy that carries the risk of a child with ADPKD
- preimplantation genetic diagnosis (PGD)
- IVF with egg cell donation
- artificial insemination with donor sperm (AI)
- adoption
- remaining childless

· **Preimplantation genetic diagnosis (PGD)** This is an IVF/ICSI procedure in which a cell is removed and examined for the relevant genetic mutation before the embryo is reimplanted. Only non-affected embryos are reimplanted. PGD is a relatively new option and has been carried out on a small group of parent couples with ADPKD (see *Consultation and referral*). PGD is only possible if the causative mutation is known (in the family).

Fertility in men

· Fertility is generally normal in men with ADPKD. Infertility associated with the disease may occur in highly exceptional cases. The possible causes are cysts in the seminal vesicles and reduced sperm motility.[16]

Pregnancy and birth

· **Pregnancy** In general, women with normal blood pressure and kidney function[3] can have a normal pregnancy. Pre-eclampsia is more common than usual, with the risk increasing proportionally with the decline in renal function. Pre-eclampsia is a known risk for the future development of kidney failure in the general population, and probably leads to worsening kidney function in patients with ADPKD.
· **Antenatal care** A gynaecologist provides antenatal care, together with the nephrologist. In general, extra foetal monitoring is not required and regular antenatal check-ups will suffice.
· **Medication** It is important that the nephrologist, in consultation with the gynaecologist, decides which medication the patient may continue to use during pregnancy. From the moment a female patient tries to become pregnant, she must stop taking RAAS inhibitors due to their teratogenic effects and the increased risk of acute kidney failure in the developing foetus. The use of tolvaptan may have adverse effects on the foetus. The use of this medication during pregnancy is contraindicated.
· **Breastfeeding** When breastfeeding, it is important that the nephrologist, in consultation with the gynaecologist or paediatrician, discusses with the patient which medications may be used. The use of tolvaptan in this period is contraindicated. In consultation with the patient, the nephrologist will decide whether or not it is advisable to further postpone treatment with tolvaptan.

KEY POINTS FOR GENERAL PRACTITIONERS

General key points

A survey conducted among general practitioners on people with rare muscle diseases raised certain key points that also apply in general practice with respect to patients with rare diseases such as ADPKD.[5,8]

· Approach the patient actively and promptly, as soon as the diagnosis has been made.
· If necessary, ask how they felt about the general practitioner's approach during the phase before the diagnosis was made. Then ask how that approach, or the GP's attitude, affected the doctor-patient relationship.
· Ask about the extent to which the patient and his/her family have been able to process and accept the diagnosis. Ask this question regularly throughout the course of the illness to find out whether, and how, the patient is able to deal with changes, particularly if their condition deteriorates.
· Ask what agreements have made with the patient regarding the division of tasks among the treatment specialists, and about the coordination of care.
· Discuss what the patient expects from their GP. Is the communication between the patient and GP satisfactory, and what can the GP offer the patient? Adapt expectations where necessary.
· Ask whether a primary physician has been appointed. Patients with certain rare disorders have a primary physician who works proactively and coordinates/keeps track of the disease management. For adults, this may be one of the various specialists. The main treatment specialist is sometimes the primary physician, but not always.[2]
· Agree on a treatment policy (and continue to adapt this as required) with the main treatment specialist/primary physician (and other treating physicians); preferably use the *HASP-Richtlijn*[1] (**in Dutch only).**
· Tell the patient that you are the first point of contact, unless otherwise agreed with the main treatment specialist/primary physician.
· Make sure that the duty physician (including the GP out-of-hours service) is able to access the patient's details, in particular the special characteristics and circumstances), recorded in their medical file (see *Key points for GPs, Specific key points*).
· If the patient has medical symptoms and problems without specific disease-related risks, treat/coach/refer the patient

to the main treatment specialist/primary physician unless otherwise agreed. If the relationship between the symptoms and the condition is unclear, contact the main treatment specialist/primary physician.
- Make sure that you know the effects of the condition on other symptoms or treatments (see *Key points for GPs, Specific key points*). If in doubt, discuss with the treatment specialist.
- Be aware of the extra disease-related risks and warn the patient about these (see *Key points for GPs, Specific key points*).
- If complications arise, refer the patient to the appropriate healthcare providers, preferably after consulting with the main treatment specialist/ primary physician.

Specific key points

- **Support** ADPKD is a progressive disease which ultimately requires the patient to undergo renal replacement therapy. It is therefore extremely important to support and advise these patients and their relatives. Care is usually provided by the treatment specialist, but GPs may also be faced with questions regarding the clinical presentation and the approach to symptoms.
- **Accident and emergency department** Patients frequently find that doctors in accident and emergency departments or GP out-of-hours services have very limited knowledge of ADPKD. Patients often feel that healthcare providers fail to take into account - or examine - the relationship between the symptoms the patient presents with and polycystic kidney disease. When referring a patient to the accident and emergency department, clearly indicate that they have polycystic kidney disease. A clear indication of the diagnosis in the patient's electronic patient health record can also be helpful when a locum GP sees the patient during a consultation.
- **Medical passport** Advise patients with ADPKD to carry their medical data with them. This medical passport states that the patient has polycystic kidney disease and includes a list of medications used by the patient.
- **Heredity** Given the autosomal dominant inheritance of ADPKD, it is advisable to discuss with family members (of a patient with ADPKD) presenting with symptoms typical of ADPKD the possibility of a referral to a nephrologist for information and, if appropriate, diagnosis. Do take into account, however, the potentially adverse social effects of presymptomatic diagnosis, particularly if the patient only has mild/vague symptoms. Symptoms indicative of ADPKD are hypertension, abdominal pain, recurrent urinary tract infections and haematuria.
- **Pain relief** Patients may experience several episodes of acute and/or chronic pain. In addition to dialysis, pain is the main limiting factor in people with ADPKD. Pain relief is therefore a common reason for seeking medical advice. Eliminate causes that require intervention (infection, kidney stones) when patients present with pain. Psychological counselling and an understanding, supportive attitude are essential in reducing the risk of drug dependency in patients with chronic pain.[16] Lifestyle changes, avoiding activities that cause fatigue, tricyclic antidepressants or pain clinic interventions may help to alleviate the symptoms.

  Drug treatment options:

  Consult the *NHG-Standaard Pijn* for the options available. In addition to drug treatment, the following advice applies for patients with ADPKD:

  - In principle, no NSAIDs.
  - Tricyclic antidepressants can have a beneficial effect on the pain and may be prescribed for a trial period.
  - Opiates may be prescribed for acute pain that does not respond adequately to medication. Avoid using these substances in patients with chronic pain due to the risk of dependence.

  Non-drug treatment options:

  If medicinal treatment does not control symptoms adequately, other options are available such as: ultrasound-guided or CT-guided aspiration of large cysts in combination with sclerotherapy, cyst fenestration, nerve blocks or renal denervation. Surgical interventions do not generally advance or slow down the process of decline in kidney function. If necessary, discuss pain management options with the treatment specialist. The UMC Groningen has developed a protocol that focuses specifically on pain relief in patients with ADPKD. If necessary, the patient can be referred by the treatment specialist.
- **Lifestyle advice** Some lifestyle changes can have a positive effect on the course of the disease. The physician or GP supports the patient in making these lifestyle changes and may find the *NHG-Zorgmodules Leefstijl* useful in this respect:
  - Increased water intake can protect kidney function.
  - A low-salt diet can help to keep blood pressure under control and may help to protect the kidneys.
  - A low-protein diet helps patients with severely reduced kidney function (eGFR <30) in preventing metabolic waste products from accumulating in the blood.

- Reducing caffeine intake may help to prevent a caffeine-induced increase in cyst growth.
- Weight control Advise patients to eat a healthy, varied diet and to take physical exercise (see *NHG-Standaard Obesitas,* in Dutch only).
- Smoking exacerbates kidney damage. Urgently advise patients who are smokers to stop smoking and, if necessary, offer support by counselling the patient or suggesting support programmes (see *NHG-Standaard Stoppen met roken).*

- **Female sex hormones** Oestrogens and progestogens may possibly encourage the growth of liver cysts. Providing extra patient guidance through good advice, information and monitoring is therefore necessary for all women of reproductive age[3] who have polycystic liver conditions.
- **Flu vaccination** Determining whether or not the patient is eligible for the annual flu vaccination depends on their individual circumstances. Flu vaccination is indicated, for example, in patients with severe renal insufficiency and following renal transplant.
- **Urinary tract infection** The main symptoms are dysuria, polyuria, haematuria and sometimes fever. Treat urinary tract infections in accordance with the *NHG-Standaard Urineweginfecties*. It is advisable to do a urine culture before commencing treatment with antibiotics. If in doubt, discuss the preferred treatment policy with the nephrologist.
- **Renal cyst infection** The main symptoms are haematuria and fever. Treatment consists of antibiotics, preferably fluoroquinolones or trimethoprim-sulfamethoxazole. It also important to do a blood culture to determine the subsequent antibiotic treatment to be given. If you suspect a renal cyst infection, discuss the treatment policy with the nephrologist, or refer the patient to the nephrologist (urgently of necessary).
- **Renal cyst bleed** The main symptom is haematuria. Bleeds are usually self-limiting and recovery takes 2-7 days. Hospital admission may be necessary if bleeding persists. Temporary cessation of ACR inhibitors and/or diuretics during such an episode may help prevent acute kidney damage. If you suspect a renal cyst bleed, discuss the policy to be adopted with the nephrologist.
- **Kidney stones** The main symptoms are flank pain, the urge to move, and haematuria. In acute situations, give 10mg morphine subcutaneously or intramuscularly. If you suspect kidney stones, discuss the policy to be adopted with the nephrologist or a urologist. The treatment policy for kidney stones is different for ADPKD patients than that recommended in the *NHG-Standaard Urinesteenlijden*.
- **Liver cyst infection** The main symptoms are localised pain, fever and blood values indicating an infection. The patient is usually unwell. Treatment comprises broad-spectrum antibiotics from the fluoroquinolones group. If you suspect a liver cyst infection, discuss the treatment policy to be adopted with the nephrologist or hepatologist.
- **Acute cholangitis** The main symptoms are fever, icterus (jaundice) and pain in the upper right abdomen. Patients are usually very ill. Discuss with the hepatologist regarding a possible hospital admission for treatment.
- **Acute headache** Refer patients with ADPKD (or suspected ADPKD) who experience an acute, severe headache urgently to the neurologist for analysis as there may be a risk of intracerebral haemorrhage.
- **Complications arising from tolvaptan use** If you suspect problems due to the use of tolvaptan, discuss this with the nephrologist. Known complications resulting from the use of tolvaptan are:
  - ***Dehydration*** *There is an increased risk of dehydration when tolvaptan users experience periods of vomiting and/or diarrhoea.* In this event, the physician/GP, in consultation with nephrologist, should advise a temporary dose reduction or cessation of tolvaptan. Good rehydration is also essential.
  - ***Increase in liver enzymes*** *Tolvaptan affects the liver enzymes.* During treatment with this drug, the nephrologist checks the liver enzymes on a regular basis (every month for the first 18 months, after that 4 times a year). If an interim check-up shows an increase in the liver enzymes, discuss this with the nephrologist.
- **Signs of rejection** Counselling for the patient and their families following a transplant is very important. In many cases the GP is the first point of contact in the event of symptoms, questions and psychosocial problems. Individual patients recover very differently following a transplant. Even after a successful transplant, the patient may experience physical limitations such as fatigue and lowered resistance due to the lifelong use of immunosuppression. Be specifically aware of signs of rejection of the donor kidney. Rejection may manifest itself as a fever and a general feeling of being ill. However, sometimes there are no symptoms at all. If you suspect rejection of the donor kidney, contact the transplant centre immediately.

Psychosocial aspects

- **Acceptance** In the initial stage, but also during the further course of the disease, it is important to take into consideration the psychosocial and social aspects of ADPKD. After the diagnosis has been made, the patient may experience feelings of anger, sadness and despair. Patients and/or family members suddenly have to deal with the prospect of an entirely different future. It is necessary to adapt, also emotionally, because the physical possibilities change. Choices relating to career, partner, children and parenting take on a different perspective. The division of tasks and roles within the family also usually demand a rethink.
- **Recognition** The often invisible physical symptoms can make the patient feel they have to fight for recognition of their disease. Patients may face a lack of understanding from society because at first glance nothing appears to be wrong with them, but patients clearly do experience limitations. It is important that healthcare providers recognise the physical, functional and economic consequences experienced by patients and their families as a result of the disease.[20] Regularly evaluate these consequences during consultations. Support patients and family members in dealing with this burden.
- **Contact with peers** Patients can get in touch with peers through the Dutch Kidney Patients Association (NVN) (see *Consultation and referral*). GPs can inform patients about this patient association.
- **Labour participation** Worsening symptoms as the disease progresses (fatigue and pain) may affect the patient's everyday activities and those carried out for work. It may therefore be advisable or necessary to adapt the type or amount of work the patient carries out. GPs can inform patients about the expertise of an occupational health physician. The Dutch Kidney Patients Association also has a support and advice desk (in Dutch: STAP) for questions and problems relating to work and benefits.

CONSULTATION AND REFERRAL

· **Diagnosis** A diagnosis of ADPKD is usually made by an internist or a nephrologist. The multidisciplinary specialised teams in university medical centres and the clinics that work with them have the most up-to-date knowledge available in the field of ADPKD.

· **Treatment and counselling** Treatment usually takes place in a specialist ADPKD medical centre with a multidisciplinary team working under the direction of a nephrologist or paediatric nephrologist.

· **Centres of expertise** In 2015, the Dutch Minister of Health, Welfare and Sport gave three centres of expertise recognition in the field of ADPKD:
- UMCG-Expertise Center for Polycystic Kidney Diseases in Groningen.
- LUMC-Center for Inherited Kidney Disease in Leiden.
- Radboudumc (Radboud Center Renal Disorders). The Radboud University Medical Centre Liver Cyst Centre in Nijmegen is also a recognised centre of expertise in the field of liver cysts. These centres coordinate the treatment and counselling of patients with ADPKD. Patient treatment can also be carried out in other hospitals. For up-to-date information about centres of expertise, see www.zichtopzeldzaam.nl/expertisecentra .

· **Heredity** Information is provided, and patients and relatives are diagnosed, at a University Medical Centre department of clinical genetics (sometimes through the outpatient department of a peripheral hospital). There is a specialised outpatient department for pre-conception advice and policy on pregnancy in kidney patients at the UMC Utrecht.

Patient representation

· **Dutch Kidney Patients Association (NVN)**
The mission of the NVN is to help maintain and/or improve quality of life and healthcare for people with chronic kidney diseases.

· **Nierstichting (NSN)**
Nierstichting (Dutch Kidney Foundation) promotes fundraising among the entire Dutch population for areas such as research, innovation and prevention in the field of kidney disease.

· **Nefrovisie**
This is a support agency for quality systems in nephrology.

· **MEE**
MEE provides information, advice and practical support for people with a mental or physical handicap and/or chronic illness. The support is for parents with children, but also for adults.

· **Ieder(in)**

· Ieder(in) is an umbrella organisation that provides information and support for people with a physical handicap, intellectual disability or chronic illness.

· ***Background information***

· Guidelines:
- Extensive information about ADPKD (and related genetics)

· NHG standards (**in Dutch only**): - M05 Urineweginfecties - M44 Depressie
- M84 Cardiovasculair risicomanagement
- M85 Stoppen met roken
- M95 Obesitas
- M106 Pijn
- NHG-Zorgmodules Leefstijl

· Brochures:
- NVN-brochure erfelijkheid en nierziekten

Relevant websites

- Dutch Kidney Patients Association (NVN): www.nvn.nl
- De Nierstichting: www.nierstichting.nl
- Vereniging Klinische Genetica Nederland: www.vkgn.org
- Nefrovisie: www.nefrovisie.nl
- MEE: www.mee.nl
- Ieder(in): www.iederin.nl
- Information about Preimplantation Genetic Diagnosis: www.pgdnederland.nl
- Website – under the direction of the VSOP – about rare conditions, with short descriptions, relevant documentation, addresses of patient organisations and information about centres of expertise: www.zichtopzeldzaam.nl
- Information about heredity and inherited diseases: www.huisartsengenetica.nl www.erfelijkheid.nl
- Information about heredity and inherited diseases (and insurability): www.erfelijkheid.nl/special/verzekeren

Dutch website for children, with information about inherited diseases: www.ikhebdat.nl

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Appendix:

ARPKD

Autosomal recessive polycystic kidney disease (ARPKD) is a recessive, transmissible disorder characterised by cystic enlargement of the kidneys' collecting ducts and abnormal development of the intrahepatic bile ducts which can cause congenital liver fibrosis.[11] ARPKD often manifests itself around the time of birth or during early childhood and the course of the disease is worse than in ADPKD.

- **Prevention The incidence of ARPKD is 1: 20,000 live births.[7] The majority are recognized due to the seriousness of the illness.** The incidence is equally divided among boys and girls.
- **Heredity** This disease is caused by homozygote or compound heterozygote mutations in the PKHD1 gene. This abnormality is autosomal recessive, which means that the disease only occurs if both parents have inherited the gene mutation. The risk of recurrence of ARPKD in a subsequent pregnancy is 25%. Antenatal diagnosis is possible using DNA analysis or ultrasound. With ARPKD, exaggerated kidney growth may occur late in the pregnancy, after the 24th week. DNA testing is therefore preferable. DNA testing in a subsequent pregnancy is only possible if the causal mutation(s) is/are known. Antenatal genetic diagnosis is an option in this case.
- **Aetiology** ARPKD is caused PKHD1 gene mutations encoded for fibrocyctin (also called polyductin). The function of fibrocystin is at present unknown. It is thought that loss of fibrocystin influences the function of the cilia and the terminal differentiation of the collection ducts in the kidney and the biliary system.[13]
- **Differential diagnosis** This is extensive in cases of polycystic kidney disease in foetuses and newborns, and making the correct diagnosis is extremely important for both the prognosis and with respect to giving advice on heredity.[13] As it can be very difficult to distinguish polycystic kidney disease caused by ADPKD, the parents should regularly undergo ultrasound of the kidneys in order to rule out the possibility of ADPKD.
- **Course of the disease** The course of this type of polycystic kidney disease is more severe than in ADPKD, with early manifestation of cysts in the kidneys and biliary ducts during childhood. In most cases, the condition presents during antenatal ultrasound examination with the foetus showing enlarged, echogenic kidneys. As a result of poor kidney function, little or no amniotic fluid is produced. This creates a lack of freedom of movement and can lead to a wide range of abnormalities, such as incomplete development of the lungs. Approximately 30% of the neonates affected die shortly after birth as a result of pulmonary hypoplasia. However, the degree of cyst formation in the kidneys is variable and if there is adequate urine production, the abnormalities described above do not occur and the child can be born alive. In children who survive the neonatal period, kidney failure often develops during the first decade of life and 60% of the children require renal replacement therapy by the age of 10. Approximately 10% of the children require a liver transplant due to recurrent cholangitis and cirrhosis.[10] Patients who survive the first months have more than an 80% chance of surviving for longer than 15 years. Death results primarily from systemic hypertension, kidney failure and liver fibrosis resulting in oesophageal varices.
- **Symptoms** The clinical presentation varies depending on the time at which the first symptoms develop and the degree of involvement of the kidneys and the liver.
  - Children that present with symptoms during breastfeeding usually have severe kidney problems and a poor chance of survival. In addition to respiratory problems, feeding problems are also frequent due to renal insufficiency. This can also result in retarded growth.
  - In children who survive the neonatal period, kidney function may improve over the first few years as a result of kidney development. This is followed by progressive deterioration due to increased cyst formation and the development of interstitial fibrosis. The following symptoms may also develop:
    - **Polyuria and polydipsia** These develop due to the kidneys' reduced ability to concentrate urine.
    - **Hypertension** Two-thirds of these children develop hypertension in the first months of life. This usually precedes deterioration in kidney function. The hypertension is often severe and difficult to treat.[10]
    - **Hyponatremia** This is often seen in infants with early kidney problems. The renin-angiotensin-aldosterone system and vasopressin probably play a role in this respect.[10]
    - **Recurrent urinary tract infections** This occurs in 20-50% of the children, more often in girls than in boys.[10]
    - **Kidney failure** Over half of the patients with ARPKD require renal replacement therapy before the age of 10 due to kidney failure.

- **Congenital liver fibrosis** This is almost always present histologically, but may not be clinically detectable in infants. The fibrosis is progressive and may ultimately lead to severe portal hypertension.[10] Liver enzymes usually remain within the normal range of values.
- **Hepatobiliary manifestations** These are associated with portal hypertension resulting from the liver fibrosis: splenomegaly, ascites and oesophageal varices which can cause gastrointestinal bleeds.
- **Cholangitis** Acute bacterial cholangitis is accompanied by dilatation of the bile ducts during the first months of life. The characteristics are fever and increased liver function test levels (in particular bilirubin and gamma GT). Patients who are diagnosed during adolescence or adulthood typically present with symptoms relating to congenital liver fibrosis (hepatomegaly, portal hypertension).[11]

Treatment policy No curative treatment is available. The main treatment specialist is a paediatric nephrologist, who coordinates the care delivered by a multidisciplinary team in a university medical centre. The care comprises management of the clinical complications resulting directly or indirectly from the disease (such as hypertension and recurrent cholangitis) and ultimately renal replacement therapy. The treatment of choice in this respect is a pre-emptive transplant. The approach needed to treat the extrarenal problems is complex; there is little scientific evidence and the problems are often difficult to treat.[2] An individual, tailor-made approach is therefore needed for each patient. The decision regarding whether or not to carry out a procedure requires thorough analysis based on the results of presymptomatic testing and extensive consultation with the parents.

Accountability

This brochure was realised in collaboration with the Dutch Kidney Patients Association (NVN), the Dutch Genetic Alliance (VSOP) and the Dutch College of General Practitioners (NHG). This brochure is part of a series of GP brochures that can be downloaded/consulted at www.nhg.org/thema/ zeldzame-ziekten (**in Dutch only**) and the VSOP (Dutch Genetic Alliance) websites www.vsop.nl and www.zichtopzeldzaam.nl/documenten (both **in Dutch only**).

Dutch Kidney Patients Association (NVN)
The NVN is an active association for kidney patients. The NVN organises a wide range of activities for its members, provides information and facilitates contact between patients. The association also represents the interests of all kidney patients in the Netherlands, for example by lobbying national politics and consulting with healthcare providers.
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The Dutch Genetic Alliance (VSOP)
The VSOP is an umbrella organisation with a membership of approximately 70 patient organisations for rare, hereditary and congenital diseases. The organisations work together towards providing better care for, and prevention of, these diseases through activities including stimulating genetic and biomedical research, and creating awareness on genetic issues.
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The Dutch College of General Practitioners (NHG) The Dutch College of General Practitioners is the Dutch scientific association of GPs. The NHG's objective is to promote scientifically sound professional practice by general practitioners. The NHG contributes towards the further professionalisation of this field of work by translating science into general practice. The NHG's core activities are developing HNG standards and other guidelines, training and products to support GPs in their general practice, such as patient information (www.thuisarts.nl) (**in Dutch only**).

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