Chapter 4

Diagnosis and Treatment Modalities of Symptomatic Polycystic Kidney Disease

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Abstract

Polycystic kidney disease (PKD) can cause end stage kidney disease with an autosomal dominant inheritance pattern. Besides renal replacement therapy or renal transplantation, there are no other curative therapies. Renal insufficiency, severe pain due to hemorrhagic expansion of the cysts, or infections are the most common clinical presentations. Diagnosis of infected cysts can be quite challenging. In recent years, 18FDG-PET/CT has shown to be the most sensitive and accurate modality for the diagnosis of infected cysts. The majority of these infections respond to systemic antibiotic therapy, but in some cases, percutaneous drainage is indicated. In some cases, the volume of the native polycystic kidneys is so

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extensive that native nephrectomy is necessary to create enough space in the iliac fossa to allow the placement of a renal graft. Tolvaptan, a selective arginine vasopressin V2 receptor antagonist, can be used to reduce the speed of disease progression in selected patients. Trans-arterial embolization has shown to be safe and effective to downsize very large native kidneys and it can be beneficial for patients who are at high risk for surgery or who decline surgery. The aim of our chapter is to present the current literature on the best diagnostic tests for patients with suspected infected or hemorrhagic cysts, and the best treatment modalities for patients with symptomatic polycystic kidneys prior or after renal transplantation.

Key words: Diagnosis; Genetic Mutations; Therapy; Transarterial Embolization; Vasopressin Repressin Antagonists

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) represents the fourth leading cause of end-stage kidney disease (ESKD) in the United States where 33 patients per million initiate dialysis due to progression of their disease every year (1). Mutations of two major genes cause ADPKD by stimulating renal tubule cells to proliferate at increased rates (2). Molecular mechanism and/or defective development and function of the primary cilia are involved in causing cysts to form in the kidneys and in the liver. In the late stages, cysts virtually replace the renal parenchyma (**Figure** 1). Mutated polycystins are expressed in kidney, liver, pancreas, seminal vesicles, brain and endothelium; thus, ADPKD should be considered a systemic disorder (3, 4). Vascular expression of the mutation can be life threatening when it leads to the formation of intracranial and large-vessels aneurysms and cardiac valvular disease (4, 5).

Genetic mutations and molecular abnormalities

PKD can be classified into ADPKD and autosomal recessive PKD (ARPKD) (6). ARPKD is an abnormality of renal tubular development affecting the collecting ducts while ADPKD is an abnormality of the homeostasis of the renal tubules (4). ADPKD is the most common abnormality with an incidence of 1 in 400-1000 individuals and accounts for 5% of patients with ESKD (7) while ARPKD has an incidence of 1 in 20,000-40,000 individuals and tends to manifest early in life (7). ADPKD is due to mutations of Polycystin 1 (PC1) and 2 (PC2), transmembrane glycoproteins found on renal tubular epithelial cells. PC1 and PC2 are the normal proteins that inhibit cell proliferation and mutations of their respective genes are responsible for the development of PKD. Mutations of PKD1 (Chromosome 16) represents 85% of cases while mutations of PKD2 (Chromosome 4) represent the remaining 15%. ARPKD, a rare pediatric form of polycystic kidney disease, is due to mutations of PKHD1 (Chromosome 6), encoding for fibrocystin/polyductin (8). The presence of two completely inactivated PKHD1 alleles results in a more severe clinical outcome associated with perinatal mortality (4) (Table 1).

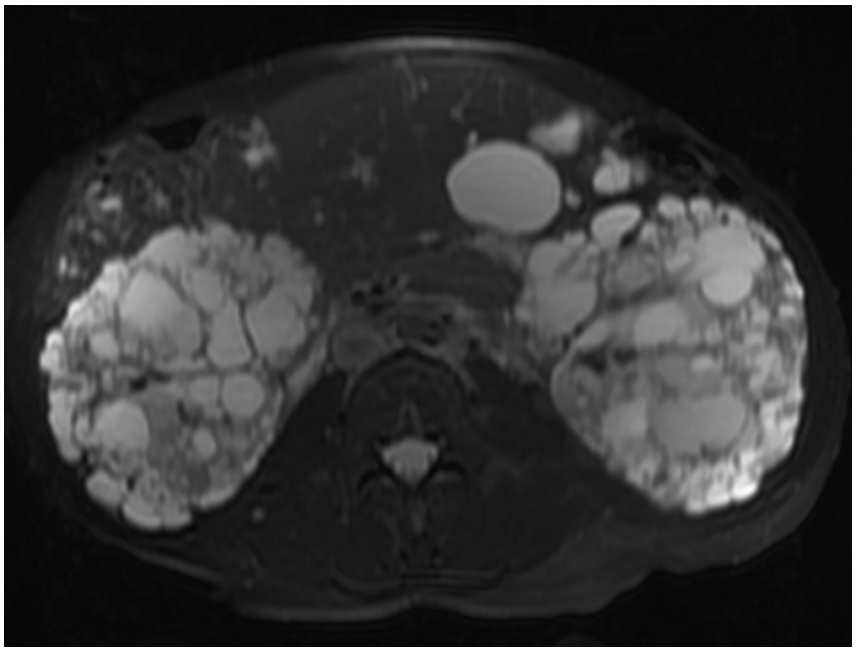

Figure 1. T2 phase MRI of the abdomen and pelvis of a patient affected by autosomal dominant polycystic kidney disease (ADPKD). Both kidneys are affected by multiple cysts of different size. Normal renal parenchyma can be found in the space between the renal cysts. The pressure generated by the fluid that fills the lumen of the cysts progressively compresses normal renal tissue and, over time, 40-50% of patients affected by ADPKD can progress to end stage kidney disease (4). Contrary to autosomal recessive polycystic kidney disease (ARPKD), the renal cysts in ADPKD develop in any part of the nephron and involve the medulla as often as the cortex. Because ADPKD is a progressive disease, most patients are born with normal kidney and a normal ultrasound examination cannot exclude ADPKD until after the age of 35 (5), especially for patients with PKD2 mutations which are associated with later disease onset.

Mutations of PKD1 are associated with more renal cysts and faster progression to renal failure in comparison to mutations of PKD2. Mutations in PKD1 and PKD2 on one allele are not sufficient to cause ADPKD as a second mutation on another allele is necessary to stimulate monoclonal differentiation of tubular cells and development of renal cysts (9). However, despite extensive research efforts, the molecular basis of cyst formation and enlargement remains not completely understood (6).

Table 1. Genetic, clinical and radiological imaging characteristics of autosomal recessive and autosomal dominant polycystic kidney disease

Condition	Genetics	Clinical and Pathologic Features	Imaging Features
ARPKD	PKHD1 (6p12): polyductin-fibrocystin	**Renal**: oliguria, dilated collecting ducts **Pulmonary**: hypoplasia **Liver**: portal hypertension due to congenital hepatic fibrosis, biliary duct dilatation	Echogenic kidneys with tubular cysts, mostly medullary. Hepatic periportal edema and fibrosis, intra and extra-hepatic biliary dilatation
ADPKD	PKD1 (16p13,3): polycystin-1, PKD2 (4q22_ polycystin-2	**Renal**: cortical and medullary cysts **Liver**: hepatic cysts **Other organs**: cysts of other organs (e.g. pancreas), vascular abnormalities (aneurysms)	Initially normal-sized kidneys with a few round cysts. Hepatic and other abdominal organ cysts in adults

PKD1= Polycystic kidney disease 1; PKD2=polycystic kidney disease 2; ADPKD=autosomal-dominant polycystic kidney disease; ARPKD=autosomal recessive polycystic kidney disease.

In 40% of patients affected by PKD, the condition can be diagnosed *in utero* by ultrasound within the 13th-20th week of gestation (7). Contrary to ADPKD where patients are expected to survive for several decades, infants affected by ARPKD often die shortly after birth due to respiratory failure from pulmonary complications due to hypoplasia as the results of oligohydramnios for the insufficient fetal urine output or due to pneumothorax (1, 4). ARPKD is also associated with biliary dysgenesis where the intrahepatic bile ducts increase in number and dilate with subsequent periportal fibrosis and portal hypertension (4, 10) and children who survive to adolescence tend to develop liver and biliary dysfunction later in life that might require liver transplantation (4, 11). Overall, 20-year outcomes after diagnosis of ARPKD depend largely on the age at presentation with 36% survival rate when diagnosis is made at less than 1 year of age, 80% with presentation at 1-20 years of age, and 88% with presentation older than 20 years of age (12).

Diagnosis of PKD

ADPKD is characterized by the development of bilateral tubular ectasias of the collecting ducts (renal cysts), kidney pain, hypertension and progressive loss of renal function. Although ADPKD cannot be differentiated from ARPKD only on the basis of utrasonographic findings, the presence of renal cysts in a fetus, favours ADPKD since ultrasound in neonates with ARPKD usually reveal massively-enlarged, smooth, hyperechogenic kidneys with lack of normal corticomedullary differentiation but rarely well-formed cysts (4, 13). The single most reliable means of differentiating between these two hereditary cystic diseases is to perform renal ultrasound in the parents. The diagnosis of ARPKD is favoured if neither parent has the characteristic findings of ADPKD. When the diagnosis of PKD is uncertain, molecular testing can be obtained by

gene sequencing of PKHD1 or by linkage analysis (14). Direct molecular genetic tests have an accuracy of only 80% since it cannot detect all mutations responsible for ARPKD (15,16). Despite this limitation, one of the strengths of molecular test is that it is the only one able to provide predictive information about ARPKD before the clinical signs and symptoms develop.

One of the greatest challenges of ADPKD is to make the diagnosis in patients younger than 30 years and without a positive family history since the formation of renal cysts is age dependent and the disease may be caused by new mutations in up to 15% of cases (17). In fact, unlike patients with ARPKD, most patients with ADPKD are born with normal kidneys and present with renal insufficiency or hypertension in adulthood, when much of their kidneys have been replaced by cysts (4). Currently, molecular testing is recommended for individuals under the age of 30 at risk of being affected by PKD and with less than 3 renal cysts on ultrasound (18, 19).

Ultrasonography is the most cost-effective radiological modality for the diagnosis of PKD (1) while MRI should be used when ultrasound is inconclusive (20). The following diagnostic criteria are used for patients suspected with PKD according to their age:

- For patients aged 15-39 years the presence of 3 or more unilateral or bilateral cysts has a sensitivity of 0.7 and specificity of 1, positive predictive value of 1 and negative predictive value of 0.7.
- For patients aged 40-59 the presence of 2 or more unilateral or bilateral cysts has a sensitivity of 1, specificity of 0.9, positive predictive value of 0.9 and negative predictive value of 1.
- For patients aged 60 years or older the presence of 4 or more cysts in each kidney has a sensitivity of 1 and specificity of 1.

Natural history of ADPKD

The rate of disease progression is quite variable and the expected increase in total kidney volume can range from 1-10% per year (21). Approximately 50% of patients with ADPKD will develop ESKD in their fourth to sixth decades of life. However, many factors modify the course and severity of ADPKD and its natural history still remains poorly understood (6). Even among members of the same family with the same germline mutation, there is marked variability in disease severity (6). Interval assessment of the radiological changes in kidney volume is the best method of monitoring patients with ADPKD. The factors that are associated with worse renal outcome include PKD1 mutation in contrast to PKD2, male gender, African origin, sickle cell disease, earlier age of presentation, presence of hypertension, episodes of gross hematuria, recurrent urinary tract infections and low HDL(2, 5, 9, 22-24).

Table 2. Manifestations of Autosomal Dominant Polycystic Kidney Disease

Renal Manifestations	Extra-renal Manifestations
Renal Cysts	**Gastrointestinal**
Renal Adenomas	Hepatic cysts
Renal cell carcinoma	Pancreatic cysts
Hypertension	Diverticulosis
Hematuria / Hemorrhage	Congenital hepatic fibrosis (rare)
Acute and chronic pain	Cholangiocarcinoma (rare)
Urinary tract infections	**Cardiovascular**
Nephrolithiasis	Valvular abnormalities
Nephromegaly	Intracranial aneurysm
Renal failure	Thoracic and abdominal aneurysm
	Other Systems
	Ovarian cysts
	Arachynoid cysts (rare)
	Pineal cysts (rare)
	Splenic cysts (rare)

Symptoms of ADPKD

Unilateral or bilateral lumbar pain is a common symptom of ADPKD that can lower patients' quality of life (QOL). Rarely, patients require narcotics to control their symptoms. Other common manifestations associated with ADPKD are abdominal distension and early satiety due to the compression of surrounding gastrointestinal organs, hematuria, urinary tract infections, infections of the renal cysts and nephrolithiasis (Table 2).

Therapy of ADPKD and management of symptomatic polycystic kidneys

Dialysis or renal transplantation, are the only treatment options for patients with ADPKD that has progressed to ESKD. Recent studies have shown that selective arginine vasopressin V2 receptor antagonists may be beneficial for patients with early renal dysfunction. Among them, Tolvaptan has been the most promising to delay progression of the disease in patients with a modest degree of renal insufficiency. For the rest of the patients with ADPKD, treatment options are limited to palliation of their symptoms. Anti-inflammatory medications and narcotics are used to control severe abdominal or back pain,

broad spectrum antibiotics, specifically floxacins, for the treatment of infections of the urinary system and of the renal cysts, and embolization of renal arteries for the treatment of macroscopic hematuria. In recent years, arterial embolization has been accepted as an effective technique to decrease the volume of large and symptomatic polycystic kidneys as an alternative to the more traditional surgical approach (25).

Treatment with Tolvaptan

Tolvaptan is orally active, has a half-life of about 12 hours and it is approved for the treatment of hyponatremia. Tolvaptan has received approval for the treatment of ADPKD in Canada, Great Britain, Europe and Japan. Patients taking Tolvaptan must drink volumes of water reaching 4 to 5 liters per day; consequently, its use is associated with aquaretic side effects (polyuria, nocturia, and rarely, hypernatremia). Hepatotoxicity, manifested by elevated liver enzymes has been observed, but is reversible upon withdrawal of the drug. Elevated plasma uric acid concentrations and gout may also be encountered. Therefore, the benefits of Tolvaptan must be carefully weighed against the associated risks for each individual patient.

Recent evidence has highlighted the beneficial effect of Tolvaptan on delaying the progression of ADPKD. The TEMPO 2:4 trial examined long-term (3 years) safety, tolerability and efficacy of Tolvaptan in a multicenter open-label study (26, 27). Overall 96% of patients taking a daily dose of 60 mg tolerated the treatment well and had an annual total kidney volume change of 1.7 + 3.5% compared to 5.8% + 4.3% for the control group ($p<0.01$). These findings were confirmed by a subsequent randomized phase III multicenter double blind placebo controlled trial TEMPO 3:4 (28). The benefits of Tolvaptan appeared enhanced in patients older than 35 years, with hypertension or total kidney volume of 1500 ml or higher at baseline. Limited data of the effect of Tolvaptan are available for patients with more advanced ADPKD. Expert opinion and the results of these randomized studies indicate that any intervention in later stages of ADPKD is likely to be futile in slowing the progression of the disease and therefore the routine use of Tolvaptan is not recommended without the additional evidence from large clinical trials.

Trans-arterial embolization

ADPKD can produce severe, often intractable abdominal pain and flank pain, which is attributed to progressive cyst dilation and displacement of renal parenchyma. This process is responsible for nerve irritation within the renal parenchyma, the intrarenal collecting system and renal capsule. In ADPKD with ESKD, nephrectomy is one of the treatment options for pain relief. However, nephrectomy of patients with very large renal volumes can be technically challenging and associated with risks of bleeding, incisional hernias, superficial and deep infections and intestinal perforation (29). In addition to the morbidity of the surgical intervention, patients might be exposed to blood products with the

subsequent formation of allo-antibodies that decrease their chances of human leukocyte antigens (HLA) matching for future renal transplants. Some studies have shown that surgical decompression of cysts is safe and effective for patients with intractable pain when a dominant cyst is suspected to be the main cause of symptoms (30). If a few cysts are present, another suitable option is percutaneous aspiration with chemical ablation of the cysts. However, when the cysts are numerous, this approach is ineffective since it is technically very difficult to drain and ablate all the potential cysts that might be responsible for the symptoms.

In recent years, there have been an increasing number of observational studies reporting good outcomes with trans-arterial embolization (TAE) of the affected kidneys. TAE has been extensively used for treating renal tumors, intrarenal aneurysms and hematuria due to trauma or renal biopsies and most of the interventional radiologists are proficient with the procedure that is usually performed using Seldinger's technique with intravenous sedation in combination with local anesthesia at the arterial puncture site. TAE produces a reduction in renal volume because the volume expansion of cysts is the results of an active and complex cellular process requiring energy and involving the development of an extensive capillary network in the cyst wall secondary to an increase in the level of vascular endothelial growth factor (VEGF) (2, 31). After accessing the femoral artery, renal artery occlusion is usually obtained by infusing microspheres of polyvinyl alcohol under fluoroscopic guidance initially into intrarenal branches using small particles (diameter, 100-300 μm) and then with larger particles (diameter, 300-500 μm) whenever necessary. Using this technique, Cornelis et al. (25) were able to treat 25 patients waiting for a renal transplantation and reduce the volume of their native kidneys so that the patients did not have to undergo pre-transplantation nephrectomies to allow implantation of the grafts in the iliac fossa. In their experience, the mean reduction in volume was 42% at 3 months and 54% at 6 months and TAE was successful in 85% of cases. One patient required additional cyst sclerosis to reach the objective and the absence of sufficient volume reduction in the remaining cases was due to an excessive basal renal volume, missed accessory artery and or renal artery revascularization.

Nephrectomy

The rate of nephrectomy in patients with ADPKD has steadily declined over the past decade due to significant improvements in conservative therapy. Initially, bilateral native nephrectomy for complicated ADPKD was associated with significant complications and 3% mortality (32). Although more modern series including minimally invasive approaches show much lower morbidity and mortality rates (33, 34), there is consensus that most of the ADPKD patients do not require native nephrectomy to facilitate kidney transplantation (35). Therefore, modern management of patients with ADPKD tends to avoid pre-transplant bilateral native nephrectomy to preserve endogenous erythropoietin production, and to maintain better quality of life by sustained urine production. Nevertheless, for

patients who are symptomatic or who have native kidneys that occupy the iliac fossa preventing renal transplantation due to lack of space, native kidneys nephrectomy is necessary. Yet, the timing of nephrectomy (before or during transplantation), and whether it should be performed bilaterally or unilaterally or by open or laparoscopic approach, have been a subject of much debate (22, 35, 36). Since Elashry et al. (37) first described a laparoscopic approach for removing a polycystic kidney, multiple studies have shown the feasibility of this approach with some describing laparoscopic simultaneous bilateral native nephrectomies (38, 39). Benefits of the laparoscopic approach include shorter hospital stays, decreased morbidity and quicker recovery (40). Additionally, when performed as a combined procedure with a simultaneous renal transplant, the laparoscopic approach offers similar morbidity to renal transplantation alone, without graft compromise and with the convenience of a single operation (33). However, some ADPKD kidneys can be severely enlarged, essentially filling the abdominal cavity and often crossing the midline. Laparoscopy in such cases can be daunting, and some have advocated the open approach for these particularly challenging cases where the renal volume for each kidney is more than 2,5 – 3 liters (41).

Native nephrectomy can be performed prior, during or following transplantation. An alternative method is the so called "sandwich technique" where the most severely affected native kidney is removed prior or during transplantation, and the other native kidney is removed subsequently to avoid possible complications due to infections, haemorrhage or pain caused by the native PKD. The advantage of performing unilateral native nephrectomy before transplantation is that the patient can be scheduled for the operation in an elective fashion, the removal of the enlarged kidney facilitates future renal transplantation and patients might experience significant improvement in their quality of life due to decreased abdominal distension and pain. The disadvantage of this approach is that patients require at least two operations: one for the native nephrectomy and another one for the renal transplantation. In addition, some patients will need a third operation to excise the contralateral native kidney if it becomes symptomatic. Neef et al. reported that contralateral native nephrectomy was necessary in 26% of patients who underwent renal transplantation and simultaneous unilateral native nephrectomy due to various reasons including suspected malignancy, infections or bleeding (42). This observation was supported by recent data indicating that more than 40% of patients with ADPKD with a native kidney left in situ after transplantation require nephrectomy due to complications if followed long enough (43). Another important consideration is that some patients might require blood transfusions during or after native nephrectomy and their risk of developing allo-antibodies increases with consequent decrease of their chance of matching with a potential donor. On the other hand, Neef et al. (42) reported that complications rates and graft losses were highest among patients without pre-transplant nephrectomy in comparison to the control group due to ongoing hematuria and recurrent infections after kidney engrafting. Several other studies have also shown better graft function and post-operative survival in patients treated with unilateral or bilateral nephrectomy before

transplantation compared to patients without this additional procedure (36, 44) since the most common cause for adverse outcomes impacting both patient and graft survival were septic complications directly related to the retained polycystic kidneys (36, 44-46).

One of the benefits of performing simultaneous unilateral native nephrectomy and renal transplantation is that patients undergo one operation that can be performed using an extended Gibson incision, it reduces overall hospital stay and it is cosmetically attractive as patients will have only one surgical scar. Unilateral nephrectomy accomplished via an extension of the Gibson incision, increases the operative time of only 20-45 minutes (42) versus bilateral simultaneous nephrectomy, which is usually performed via a transperitoneal access and lengthens the operation time by 180 minutes (47). Drawbacks of this method is that the transplant operation is significantly longer and technically more challenging especially when performed during cadaveric transplantation after regular hours and the postoperative management of these patients is more complex as perioperative fluid shift is more extensive.

The option of performing simultaneous bilateral native nephrectomies and renal transplantation appears attractive as it is the most expeditious way of dealing with the potential risk of post-transplant complications due to the presence of polycystic kidneys. Tyson et al. (48) used the Nationwide Inpatient Sample (NIS) registry to assess the outcome of patients with PKD who underwent simultaneous renal transplantation and bilateral native nephrectomy and patients who underwent bilateral native nephrectomy alone. These authors found that among 2,368 patients who satisfied the inclusion criteria, 271 (11.4%) underwent simultaneous renal transplantation and developed higher rates of intraoperative haemorrhage, blood transfusion and urological complications in comparison to the control group. However, in-hospital mortality was lower in patients undergoing simultaneous bilateral nephrectomy and renal transplantation. Several other groups noted acceptable results and argued that simultaneous nephrectomy and transplantation are the preferred strategy because it avoids the negative effects of being anephric as well as the toll of 2 operations (34, 49).

Infections

The estimated incidence of infections of renal cysts in patients with ADPKD is 1 episode per 100 patients per year (50). Known predisposing factors include advanced age, female gender and instrumentation of the urinary tract (51) as the presumed mechanism of the infection is the retrograde migration of bacteria trough the ureters while hematogenous seeding is less likely (51).

The diagnosis of cystic infections is usually based on clinical grounds when patients develop systemic symptoms such as fever, weight loss and malaise often in combination

with abdominal or back pain (52). The diagnosis can be quite straightforward when symptoms are combined with elevation of laboratory markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen but there are no established cut off values for these parameters. On the other hand, to prove that a patient is indeed affected by infection of a renal cyst is quite difficult as the gold standard requires the analysis of the content of the responsible cyst. This is often not feasible nor recommended especially when there is no clear identification of which cyst is infected.

Common pathogens include *E. coli* (74% of positive cultures) (50) and other enteric flora and cyst infections accounts for 10-15% of all causes of hospitalizations of ADPKD patients (50, 51). These infections can have serious consequences (51), and patients who are waiting for a renal transplant should be put on hold until their infection is resolved since bacteremia and sepsis can result in graft loss or perioperative death. Similarly, patients who are immunosuppressed after renal transplantation can develop serious infections in the native polycystic kidneys cysts that can be responsible for systemic complications due to their attenuated immune response (51). Sallee et al. (50) have proposed clinical criteria for the diagnosis of infected cysts in patients with ADPKD. These criteria are: 1) presence of neutrophils and bacteria in the fluid aspirate from the suspected cyst; or alternatively, 2) the concurrent manifestation of fever (temperature >38 C for > 3 days), abdominal tenderness in the area of the polycystic kidney, increased serum C-reactive protein levels (CRP, >5 mg/dL) and the absence of computed tomography (CT) findings suggestive for recent intracystic bleeding (intracystic density < 25 Hounsfield units).

Although these criteria are important to initiate and direct the duration of systemic antibiotic therapy (53), they are not helpful for the identification of which cysts are infected. Currently, there is no diagnostic imaging gold standard (54) and conventional cross sectional imaging modalities, including ultrasounds (US), CT and magnetic resonance scans (MRI) are only valuable in discriminating between non-complicated and complicated cyst and are unable to discriminate between bleeding, infection or early neoplasia (23).

In addition, the diagnostic accuracy of these tests is further limited by the fact that contrast agents cannot be used in the presence of renal dysfunction in patients with ADPKD (2). Recently, there has been some enthusiasm around the use of scintigraphy with indium- or gallium-labelled leukocytes as some investigators have reported promising results in localizing infected cysts (55). However, one of the limitations of this technique is the fact that it is not universally available, it is quite costly and provides a relatively poor spatial discrimination when patients have severe anatomical distortion of their native kidneys (56, 57).

Positron Emission Tomography (PET) using 18-Fluorodeoxyglucose (18FDG) has shown some promising role for the accurate diagnosis and localization of suspected infected renal cysts (51, 58). One of the advantages of 18FDG is that it is not nephrotoxic and can be

successfully used in patients with ESKD (59). In addition, when associated with CT scanning, 18FDG-PET/CT has good spatial discrimination, which may allow the guiding of percutaneous procedures or the study of the adjacent tissues (60). Lantinga et al. (61) evaluated the diagnostic criteria in renal and hepatic cyst infection and found that 18FDG-PET/CT identified 100% of definitive and 93% of probable cyst infection cases. Another group (59) also reported that 18FDG-PET/CT yielded positive results in 87% of cases of infected cysts. Jouret et al. (59) reported that in their experience 18FDG-PET was able to identify distinct non-cystic infectious conditions such as ischemic colitis, diverticulitis, retroperitoneal abscesses, prostatitis, pyelonephritis, and infected abdominal aorta aneurysm and that18FDG-PET changed the management of 26% of patients who were initially diagnosed with suspected infected renal cysts. The excellent sensitivity of 18FDG-PET and the spatial discrimination obtained by combining 18FDG-PET with CT reported by Lantiga et al. (61) and more recently by Jouret et al. (59) should be explored further by other well-designed studies to determine the exact diagnostic sensitivity and specificity of 18FDG-PET/CT across a wide spectrum of disease presentations. In fact, the diagnostic performance of 18FDG-PET has not been fully evaluated for intracystic bleeding that is the main differential diagnosis of cyst infection in ADPKD patients and accumulation of 18FDG has been described in the setting of hematomas outside the renal parenchyma (62). Therefore, the specificity of 18FDG-PET/CT for renal cyst infections remains unknown at this point. Another important drawback of this diagnostic modality is that although preliminary data indicate that 18FDG-PET/CT is a promising tool for the diagnosis and follow-up of infected renal cysts, the low availability and its high costs that are similar to scintigraphy with labeled white blood cells will limit its wider use.

The main treatment for suspected infected renal cysts is systemic antibiotic therapy for 3 to 6 weeks (50). The selection of the type of antibiotic is usually empirical as the results of blood and urine cultures lag behind the clinical presentation. Despite this limitation, in a large cohort of patients treated in the United Kingdom, the clinical efficacy of the initial antibiotic therapy was observed in 71% of infections (50). Fluoroquinolones and third-generation cephalosporins are the most common choice as they cover the majority of the common Gram-negative bacteria responsible for the infections and they have a relative good passive diffusion profile that allow them to accumulate in the lumen of renal cysts (50). Fluoroquinolones are usually favored because of their superior lipophilic properties in comparison to ß-lactamines, mainly penicillins and cephalosporins that are known to have poor penetration in larger renal cysts. In selected patients with good renal function or on haemodialysis, aminoglycosides can be used as monotherapy or in combination with other antibiotics when other antibiotics fail (22, 53).

The majority of patients respond to antibiotic therapy without the need for any other intervention. However, for a small group, percutaneous drainage of suspected large (>5 cm) infected cysts may be beneficial as antibiotics often do not have the ability to reach the concentration necessary to sterilize the cystic fluid (50, 63).

Conclusion and perspective

Approximately 40-50% of patients affected by PKD are symptomatic and clinicians should be familiar with all the possible modalities that are currently available to care for these challenging patients. Tolvaptan, a selective arginine vasopressin V2 receptor antagonist, has been shown to reduce the speed of disease progression in selected patients. Diagnosis of infected cysts can be quite challenging and 18FDG-PET/CT has shown to be the most sensitive and accurate imaging modality. The majority of these infections respond to systemic antibiotic therapy, but in some cases, percutaneous drainage is necessary. The identification of the infectious agent by blood and urine cultures is essential in tailoring the type and duration of the antibiotic therapy. Surgical excision of native polycystic kidneys is necessary when patients are symptomatic and fail other modalities. Surgical therapy is also indicated to remove large volume native kidney that occupy the iliac fossa of patients in need of renal transplantation. In recent years, TAE has shown to be safe and effective to downsize very large native kidneys and it can be beneficial for patients who are at high risk or who decline surgery.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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