

Diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease: attributes and limitations of the current modalities

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Abstract

Cyst infection is a diagnostic challenge in patients with autosomal dominant polycystic kidney disease (ADPKD) because of the lack of specific manifestations and limitations of conventional imaging procedures. Still, recent clinical observations and series have highlighted common criteria for this condition. Cyst infection is diagnosed if confirmed by cyst fluid analysis showing bacteria and neutrophils, and as a probable diagnosis if all four of the following criteria are concomitantly met: temperature of >38°C for >3 days, loin or liver tenderness, C-reactive protein plasma level of >5 mg/dL and no evidence for intracystic bleeding on computed tomography (CT). In addition, the elevation of serum carbohydrate antigen 19-9 (CA19-9) has been proposed as a biomarker for hepatic cyst infection. Positron-emission tomography after intravenous injection of 18-fluorodeoxyglucose, combined with CT, proved superior to radiological imaging techniques for the identification and localization of kidney and liver pyocyst. This review summarizes the attributes and limitations of these recent clinical, biological and imaging advances in the diagnosis of cyst infection in patients with ADPKD.

Keywords: carbohydrate antigen 19-9; cyst infection; polycystic kidney disease; positron-emission computed tomography

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) represents the most common inherited kidney disease [1]. It is characterized by the development of fluid-filled cysts in kidney and liver parenchyma, derived from various renal tubular segments and biliary ducts. Cyst growth causes organ enlargement leading to abdominal and/or loin discomfort. Liver cysts are not associated with

hepatic dysfunction, whereas kidney cysts cause end-stage renal disease (ESRD) in more than 70% of ADPKD patients. In addition, cysts carry significant morbidity, including bleeding and infection.

Cyst infection represents a serious complication of ADPKD. Its incidence has been calculated as 0.01 episode/patient/year, according to an 11-year retrospective monocentric series [2]. Predisposing conditions include age, female gender and recent instrumentation of the urinary tract. In the chronic haemodialysis population, the prevalence of renal infection is significantly higher in ADPKD patients than in controls, and appears even more so in patients with a history of pyocyst before the initiation of dialysis [3]. In the renal transplant recipient (RTR) population, the prevalence of urinary tract infections in patients with ADPKD does not appear to be increased [4]. On the whole, cyst infection accounts for 15% of all causes of hospitalizations of ADPKD patients [2, 5]. Pathogens usually include enteric flora, *Escherichia coli* being the most common agent. The retrograde route via the ureters or the biliary ducts is the presumed mechanism of cyst infection in the kidney and liver, respectively. The identification of the causative germ is lacking in more than half of cases, similar to the rate observed in the general population with severe sepsis. In the study by Sallée *et al.* including 33 patients with 41 kidney ($n=31$) or liver ($n=10$) cyst infections [2], urine and blood cultures were found to be respectively positive in 39 and 24% episodes. Similarly, the bacterial agent could be identified in 53% of our series of 15 episodes of kidney ($n=5$) or liver ($n=10$) cyst infections [5]. Thus, although the identification of the infectious agent is essential for tailoring the antibiotic therapy, its poor yield limits its diagnostic usefulness. Furthermore, it does not reliably distinguish cystic from non-cystic infections.

The diagnosis of cyst infection is not easy because of the various, most often non-specific, clinical

manifestations and the limitations of conventional imaging techniques. Proving the presence of cyst infection requires cyst fluid analysis. However, this is not always possible or indicated, so that diagnosis relies practically on a constellation of concurrent clinical, biological and radiological parameters. Sallée *et al.* [2] proposed criteria commonly used in clinical routine on the basis of an 11-year retrospective series of pyocysts in ADPKD patients:

- Cyst infection is diagnosed when confirmed by cyst aspiration showing neutrophils and bacteria;
- Cyst infection is a probable diagnosis in the concurrent manifestation of four conditions: fever (temperature >38°C for >3 days), abdominal tenderness in the kidney or liver area, increased C-reactive protein levels (CRP, >5 mg/dL) and the absence of computed tomography (CT) augmentation for recent intracystic bleeding suggested by spontaneous intracystic density above 25 Hounsfield units.

None of these criteria *per se* are specific to cyst infection, except pus analysis. They do not allow precise location of the pyocyst and cannot rule out a secondary infection complicating a cyst haemorrhage. In liver cyst infection, the combination of early percutaneous drainage and antimicrobial therapy proved more efficient than antibiotics alone [6]. Therefore, the identification of the pyocyst is important in patients presenting with suspected liver cyst infection. Furthermore, the type and the duration of antibiotic therapy vary according to the infectious site, the causative agent and the patient's medical history [2]. Nephrectomy or partial hepatectomy may be required because of persistent or recurrent cyst infection, *a fortiori* in candidates on the waiting list for kidney transplantation.

This review summarizes the recent advances in cyst infection diagnosis. Elevated serum levels of the carbohydrate antigen 19-9 (CA19-9) may represent a novel biomarker for liver cyst infection. Positron-emission tomography (PET) after intravenous injection of 18-fluoro-deoxy-glucose (¹⁸FDG), coupled with CT, proved reliable not only in detecting but also in locating kidney and liver pyocyst. Prospective trials are still required to (i) define the gold standard of cyst infection, (ii) establish the sensitivity and specificity of the new diagnostic modalities and (iii) propose a standardized approach for cyst infection in ADPKD patients.

Serum levels of the CA19-9 in liver cyst infection

Liver cysts represent the most common extra-renal manifestation in ADPKD and are associated with significant morbidities. Recent observations using the biomarker of bilio-pancreatic malignancies, CA19-9, showed promising results in the diagnosis of liver cyst infection [7].

CA19-9 is a 36-kDa glycolipid produced by bile duct cells. Its biosynthesis depends on the α -1,4-fucosyltransferase pathway. This enzyme is lacking in rare Lewis blood group-negative individuals, who therefore show undetectable serum levels of CA19-9. In contrast, increased serum CA19-9 levels have been reported in non-

malignant conditions, including biliary obstruction and benign hydronephrosis. High CA19-9 levels have also been measured in non-infected cyst fluid of patients with benign sporadic liver cysts or with polycystic liver disease (PCLD) [8]. The production of CA19-9 probably results from secretion by epithelial cells lining the cysts, as illustrated by immunohistochemistry [7]. Of note, epithelial cells lining renal cysts inconsistently express a low level of cytoplasmic CA19-9. Leakage from liver cysts and/or direct secretion into the circulation cause significantly higher steady-state serum CA19-9 levels in patients with ADPKD or PCLD than in controls [7, 8], which limits the use of standard upper values (<35 U/mL) in this population. The 90th percentile of serum CA19-9 levels in our series of 30 ADPKD patients was 106 U/mL [7]. Such elevation of CA19-9 levels is similar in patients with either ADPKD or PCLD, correlates with cyst fluid levels of CA19-9 and is not influenced by age or gender [8].

Isolated reports showed that CA19-9 levels are further increased in the serum and cyst fluid of patients with infected simple liver cysts. Similarly, serum CA19-9 levels increase in ADPKD patients during liver cyst infection and decrease with resolution of the infection. Moreover, extremely high CA19-9 levels (>100 000 U/mL) have been measured in infected cyst fluids [7]. These observations suggest that liver cyst infection induces CA19-9 secretion in cyst fluid and/or its release into the bloodstream, resulting in elevated serum CA19-9 levels. Such increase in serum CA19-9 levels may thus represent a helpful diagnostic marker of liver cyst infection. However, a CA19-9 cut-off level with acceptable specificity and sensitivity to make diagnosis of a liver cyst infection in ADPKD patients is currently lacking. Because of inter-individual variations, comparison with baseline levels in each ADPKD patient may be more useful for the interpretation of elevated CA19-9 levels in suspected liver cyst infection.

CT and MRI in the diagnosis of kidney and liver cyst infection

Chronic parenchyma injury and cyst growth are associated with profound morphological disorganization of kidney and liver anatomy and with cyst heterogeneity. Consequently, conventional imaging procedures, such as CT and magnetic resonance imaging (MRI), often fail to confidently locate cyst infection. Wall thickening and heterogeneous content are usually suggestive of cyst infection [9] (Figure 1A). However, the presence of intracystic cellular debris, hyperintense on CT, shows a poor specificity to differentiate infected from non-infected cysts in ADPKD patients. In addition, contrast enhancement lining cyst walls can be caused by either inflammation or residual functional parenchyma. In the series of Sallée *et al.* [2], CT and MRI showed contributive images in 18 and 40% of cyst infection cases, respectively, and yielded negative results in more than half of patients with a definite diagnosis of cyst infection. In a prospective series of 10 consecutive patients with suspected cystic infection,

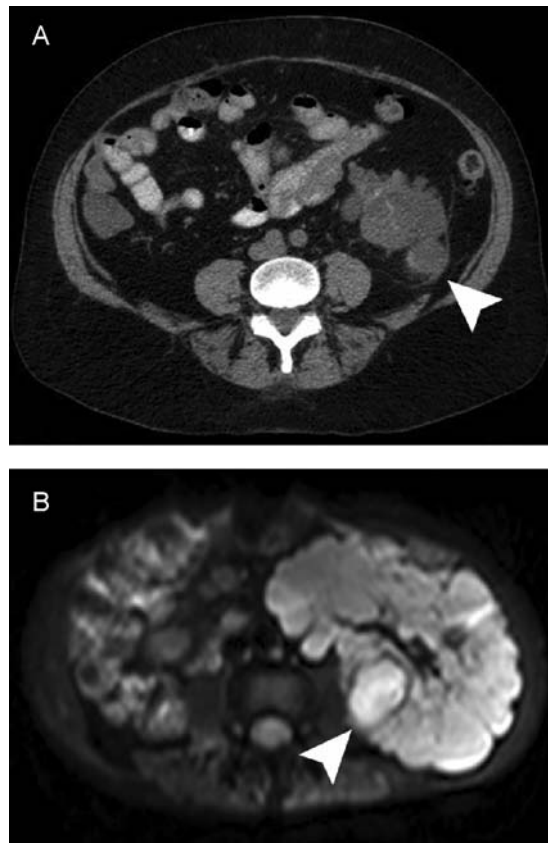


Fig. 1. Representative CT and MRI of cyst infection in patients with ADPKD. (A) CT without intravenous administration of contrast agent shows a heterogeneous peripheral cyst of the lower pole of the left kidney surrounded by oedematous adipose tissue and a thickened renal fascia (arrowhead), in a female RTR with ADPKD presenting with fever, abdominal pain and increased plasma CRP levels. Blood culture grew *Escherichia coli*. Right nephrectomy had been performed before renal transplantation for recurrent cyst infections. (B) Diffusion-weighted MRI shows a heterogeneous cyst with thick wall and hyperintense signal on diffusion (β -value = 20 s/mm²) in the lower internal pole of the left kidney (arrowhead) in a male RTR with ADPKD presenting with fever, left loin tenderness and increased plasma CRP. Blood and urine cultures grew *Escherichia coli*. Right nephrectomy had been performed at the time of renal transplantation.

the independent revision of CT images acquired during PET/CT was unable to locate any of the infected cysts [10]. This study included six patients with ADPKD and four patients with multiple kidney cysts.

An additional limitation of CT in ADPKD patients with chronic kidney disease (CKD) is the relative or absolute contraindication for the use of intravenous radiological contrast medium. Administration of contrast agent was achieved only in 25% of cases reported by Piccoli *et al.* [10]. Similarly, in our series of 27 suspicions of abdominal infection, injection of contrast agent was performed in 30% of cases [5]. CT yielded contributive results in five cases, including one liver cyst infection, one kidney cyst infection, one diverticulitis and two intracystic bleedings. However, CT failed to detect the pyocyst in 85% of cases. Such limited information gained by CT

after administration of contrast material does most often not outweigh its potential harm, which further questions its use in clinical routine.

The accuracy of MRI, with or without gadolinium injection, in cyst infection diagnosis remains largely unknown. Findings of infected cysts using T1- and T2-weighted MRI may mimic those of normal cysts. Intravenous injection of Gd³⁺ before MRI is associated with a parietal enhancement highly suggestive of cyst infection [6, 11]. However, the association between nephrogenic systemic fibrosis (NSF) and exposure to Gd³⁺-based contrast agents has greatly affected the use of MRI in patients with CKD. Current recommendations advocate that a patient should be considered to be at risk of NSF with a glomerular filtration rate (GFR) of <30 mL/min/1.73 m². Efforts have been made to develop both lower risk Gd³⁺-based contrast agents and the contribution of Gd³⁺-free MRI. Hence, diffusion-weighted MRI may help distinguish infected from non-complicated cysts in ADPKD patients on the basis of a decreased apparent diffusion coefficient value [12] (Figure 1B). These encouraging preliminary observations need further prospective investigations.

Radiolabelled-leucocyte scintigraphy in the diagnosis of kidney and liver cyst infection

To complement radiological procedures in the work-up of infectious site localization, techniques using radiolabelled leucocytes have been developed. Particularly, ¹¹¹In-leucocyte scanning allowed the identification of renal cyst infection in ADPKD patients in whom other non-invasive imaging procedures had failed [13]. In a retrospective series of liver cyst infections combining five cases from the Mayo Clinic institution and nine case reports from the literature, ¹¹¹In-leucocyte scans were positive in all four ADPKD patients in whom they were performed [6]. ¹¹¹In-leucocyte scanning requires the handling of blood derivatives and the *ex temporane in vitro* labelling process, as well a 24-h delay before imaging. ¹¹¹In scintigraphy is characterized by poor spatial resolution, low sensitivity, high radiation activity and significant inter-observer variability. Moreover, the use of ¹¹¹In-leucocyte scanning in febrile RTR raises concerns because of unspecific accumulation of white blood cells (WBC) in renal and pulmonary parenchymae [14].

Hexamethylpropylene amine oxime (HMPAO) represents an alternative lipophilic chelator for efficient labelling of leucocytes with ^{99m}Tc-Technetium (^{99m}Tc). Radiation characteristics of ^{99m}Tc-HMPAO are more favourable for imaging than those of ¹¹¹In, particularly for single-photon emission computed tomography (SPECT). Furthermore, the dual modality technique combining CT with SPECT using radiolabelled WBC has been associated with a diagnostic yield of 85% of cases with abdominal infections [15]. The relevance of SPECT/CT to cyst infection diagnosis in ADPKD patients is currently unknown.

¹⁸FDG-PET/CT in the diagnosis of kidney and liver cyst infection

In the general population, ¹⁸FDG-PET/CT imaging represents a reliable tool for the detection of tissue infection on the basis of the high metabolic activity and increased uptake of the radiolabelled glucose analogue, ¹⁸FDG, by inflammatory cells [16]. Importantly, ¹⁸FDG is not nephro- or hepatotoxic and has been successfully used in patients with renal function ranging from mildly reduced GFR to ESRD [2, 17]. First, ¹⁸FDG-PET alone proved helpful in identifying or excluding renal and hepatic cyst infection in case reports and two retrospective series [2, 11, 18]. To further improve the localization of infectious sites, PET was combined with CT to integrate metabolic data from PET with anatomical information from CT [16]. In our series, ¹⁸FDG-PET/CT yielded positive results in 87% of cyst infection cases [5]. PET/CT was considered as positive for cyst infection when the uptake of ¹⁸FDG was focally increased around at least one cyst in comparison to the physiological accumulation in the parenchyma, and was located at distance from the pelvicalyceal excretion (Figure 2). PET/CT yielded two false-negative results in a diabetic RTR during the immediate post-transplantation period and in a 62-year-old non-diabetic woman with Stage IV CKD. By contrast, three liver pyocysts could be percutaneously drained only after

localization by PET/CT. The median delay between the onset of symptoms and PET/CT imaging was 9 days, and the mean maximal standardized uptake value (SUVmax) reached 5.1 ± 1.7 g/mL. The measurement of SUVmax allows standardized quantification of the inflammatory process in addition to the visual evaluation [17]. Repeated measurements of SUVmax may help follow-up the inflammatory process over time. Piccoli *et al.* [10] reported on the clinical management of 10 patients with suspected cystic infection, which was tailored upon ¹⁸FDG-PET/CT results. PET/CT identified five kidney and one liver cyst infections. The mean SUVmax reached 8.4 ± 5.4 g/mL on initial PET/CT images. The follow-up of four patients included a comparative PET/CT performed 3–6 weeks later, which showed a visual reduction of pathological ¹⁸FDG uptake but no significant change of SUVmax. Three patients underwent a third PET/CT 7–9 weeks after the initial imaging, which disclosed no residual ¹⁸FDG uptake. Of note, the normalization of serum CRP levels preceded PET/CT normalization. The clinical relevance of persistent altered PET/CT images to treated infectious diseases remains unclear. The literature in oncology supports that the follow-up by ¹⁸FDG-PET/CT of therapeutic responses to chemo- or radiotherapy varies from 3 to 12 weeks depending upon the type of cancer and the administered therapy. However, the pathophysiology of infection is intrinsically different from

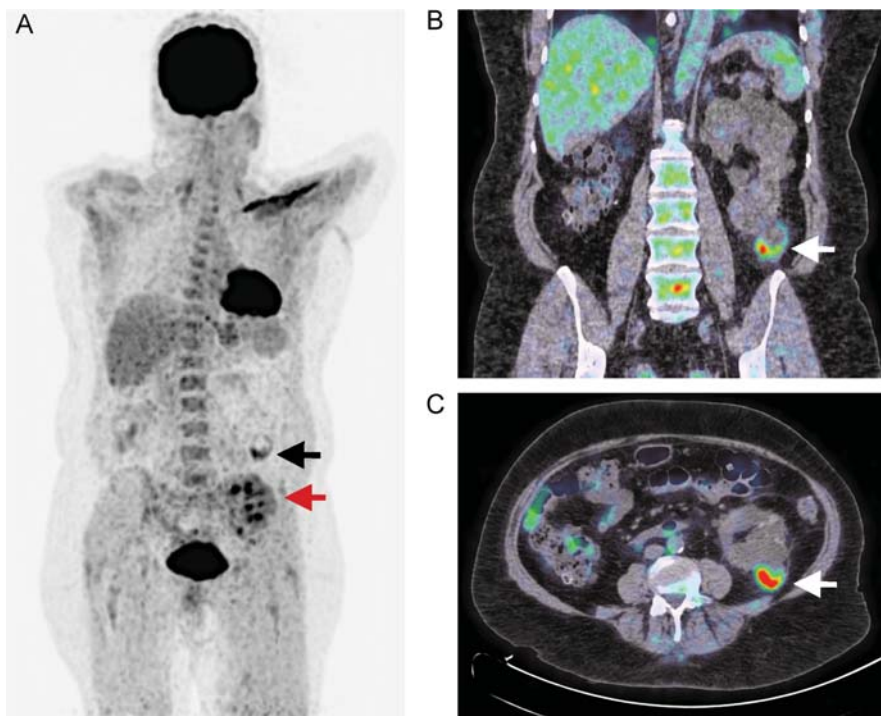


Fig. 2. Representative PET after intravenous injection of ¹⁸FDG, coupled with CT, of cyst infection in patients with ADPKD. ¹⁸FDG-PET imaging in maximal intensity projection mode (A) and fused ¹⁸FDG-PET/CT slices in coronal (B) and transverse planes (C) disclose a pathological accumulation of ¹⁸FDG surrounding a cyst located at the lower pole of the native left kidney (white and black arrows) in a female RTR with ADPKD presenting with fever, abdominal pain and increased plasma CRP levels. The SUVmax reaches 3.51 g/mL. SUVmax is calculated by drawing a region of interest around the hottest spot on PET images and using the formula: $[\text{Pixel value (Bq/mL)} \times \text{patient weight (kg)}] / [\text{injected dose (Bq)} \times 1000 \text{ (g/kg)}]$. Blood culture grew *Escherichia coli*. Right nephrectomy had been performed before renal transplantation for recurrent cyst infections. Note that physiological excretion of ¹⁸FDG is observed in the kidney graft (red arrow).

neoplasia, and cyst infection is associated with the additional challenge of antibiotic diffusion into a chronically damaged organ and a cystic cavity. Consequently, ^{18}F -FDG-PET/CT probably represents an optimal tool for the detection and localization of pyocysts in ADPKD patients, but its role in the follow-up after antibiotic therapy remains uncertain.

PET/CT in ADPKD patients with suspected cyst infection offers the additional advantage of entirely scanning the abdominal cavity, thereby occasionally identifying non-cystic inflammatory disorders and adjusting the therapy. In our series, ^{18}F -FDG-PET/CT identified distinct non-cystic infectious conditions, such as angiocholitis, small intestine diverticulitis associated with psoas abscess, right colon diverticulitis, prostatitis, kidney graft pyelonephritis and infection of abdominal aorta aneurysm. PET/CT results significantly changed the management of 26% of cases [5]. Moreover, PET/CT confirmed two kidney cyst infections although both patients did not meet all four of the standardized criteria [6]. In series of Piccoli *et al.* [10], PET/CT imaging excluded cyst infection in 4 of the 10 cases, but collaterally detected abnormal ^{18}F -FDG uptake in a peripancreatic lymph node caused by mesenchymal neoplasia.

The advantages of ^{18}F -FDG-PET/CT are rapid imaging, minimal labour intensity, high target-to-background ratio, high inter-observer agreement and a simultaneous co-registration with low-dose CT without administration of contrast medium [17]. Limitations of PET/CT include its cost, restricted availability and relative inability to reliably distinguish infectious from non-infectious inflammation or malignancy. The differentiation of ^{18}F -FDG accumulation in residual functional renal parenchyma from that in inflammatory cells lining pyocysts remains debatable [16]. The distinction between cyst infection and pyelonephritis may not be easy. The PET/CT pattern of pyelonephritis usually includes a diffuse ^{18}F -FDG uptake in an oedematous cortex and loco-regional hypermetabolic adenopathies, which contrasts with the focally increased uptake of ^{18}F -FDG lining the pyocyst. Besides infectious processes, ^{18}F -FDG uptake can be increased in other conditions, such as cancer. The actual risk of malignancy in ADPKD patients does not seem to be increased [19]. Liver cystadenocarcinoma is very uncommon, and most kidney tumours show low-grade malignancy leading to low ^{18}F -FDG uptake. However, 'false-positive' rate of ^{18}F -FDG-PET/CT in cyst infection diagnosis remains to be prospectively investigated. The relevance of alternative tracers, such as ^{18}F -L-thymidine and ^{124}I -cG250, should be addressed in patients with kidney cyst infection. Finally, PET/CT has not been evaluated in intracystic bleeding, the main differential diagnosis of cyst infection in ADPKD patients. Accumulation of ^{18}F -FDG has been reported in the setting of extra-renal haematoma [20]. Thus, the specificity of ^{18}F -FDG-PET/CT for cyst infections remains to be assessed. Conversely, ^{18}F -FDG uptake may vary upon its diffusion into the lesion, the size of the lesion and the degree of respiratory mobility of the organ under investigation [17]. Each of these conditions may be responsible for 'false-negative' PET/CT. Therefore, the collaboration of clinicians with radiologists and

physicians in nuclear medicine is essential for the optimization of the interpretation of PET/CT images in the clinical context of suspected cyst infection.

Perspectives in the diagnostic approach for suspected kidney and liver cyst infection

The main diagnostic objectives in ADPKD patients presenting with suspected cyst infection are to (i) rule out non-cystic infections, (ii) determine the location of pyocysts, (iii) identify the causative germ and (iv) exclude concomitant conditions, such as urinary tract obstruction. Practically, the diagnosis of cyst infection relies on the concurrent manifestation of common clinical, biological and radiological parameters summarized by Sallée *et al.* [2]. The identification of the infectious agent by blood and/or urine cultures is essential for tailoring the antibiotic therapy, but does not reliably distinguish cystic from non-cystic infections. Elevated serum CA19-9 levels have been associated with liver cyst infection, although a diagnostic cut-off level is still lacking [7]. The large inter-individual variations suggest that a comparative assessment to baseline CA19-9 levels in each ADPKD patient might be more useful. Finally, current literature highlights the limitations of conventional imaging techniques, such as CT and MRI, and emphasizes the promising role of ^{18}F -FDG-PET/CT in the identification and localization of kidney and liver cyst infection in ADPKD patients. However, several questions regarding the sensibility and specificity of each clinical, biological and radiological sign of cyst infection need to be addressed, individually and in combination with one another. Clinical trials should focus on determining the most appropriate timing of biological and imaging investigations after the onset of symptoms. The cost-benefit ratio and eventual pattern of repeated tests after therapy initiation, such as sequential measurements of serum CA19-9 levels or follow-up imaging by PET/CT, remain to be established. Particularly, the limited availability of PET imaging, as well as the ongoing budget restrictions in health care systems, may hamper the systematic use of ^{18}F -FDG-PET/CT in the diagnosis of cyst infection. In addition, the specificity of each diagnostic modality should be addressed in comparison with non-infectious cyst complications, such as haemorrhage. Finally, innovative imaging techniques, such as PET/MRI, are currently under clinical evaluation and may further improve our diagnostic strategy in ADPKD patients presenting with fever and abdominal pain.

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