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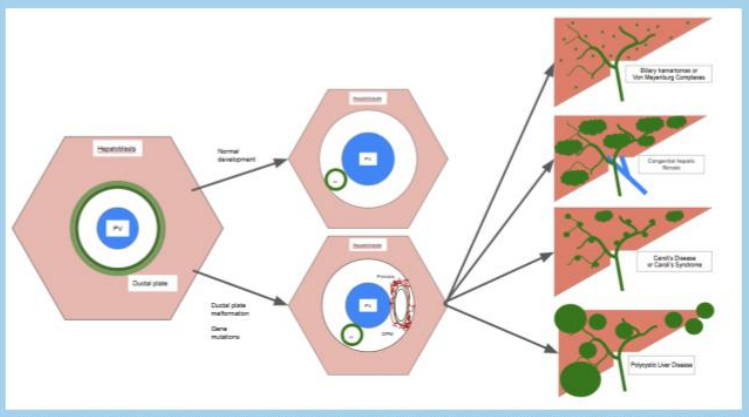

Simplified development of the bile duct and schematic morphology of fibrocystic liver diseases.

The differences between fibrocystic liver disease and standard hepatobiliary pathologies require multidisciplinary care.

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Ductal plate malformation revisited – Hepatobiliary manifestations of polycystic kidney and liver disease

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ABSTRACT

Polycystic kidney diseases are linked to a myriad of hepatobiliary diseases. Patients with such diseases have a higher risk of admission. Clinical manifestations and complementary testing differ from healthy controls leading to suboptimal care. This review focuses on the different hepatobiliary diseases linked to polycystic kidney diseases, their diagnosis, clinical manifestations and management.

Keywords: Polycystic kidney diseases. Caroli disease. Polycystic liver disease. Cholangitis. Congenital hepatic fibrosis. Liver transplantation.

INTRODUCTION

Renal polycystic diseases encompass a spectrum of systemic manifestations. Among those, hepatobiliary involvement is one of the most frequent(1). Other organs of the gastrointestinal tract may be affected such as the colon(2) and pancreas(3,4). Patients with autosomal dominant polycystic kidney disease (ADPKD) have a higher risk of biliary tract

diseases, with higher admission rates and greater severity (5). Moreover, patients with autosomal recessive polycystic kidney disease (ARPKD) may present a more complex phenotype, with multiple hepatic diseases linked to it (6). Such entities, ranging from congenital hepatic fibrosis (CHF) to ADPKD linked polycystic liver disease (ADPKD-PCLD) are englobed into the term of fibrocystic liver disease (FLD)(7). All FLDs share a common origin in the embryology and development of the biliary tract.

Although they share the same origin, their clinical profiles differ from each other and compared to the standard diseases of the normal population. As previously mentioned, they experience a higher risk of biliary tract infections that present atypical clinical features(8).

ADPKD is the first cause of genetic end-stage kidney disease (ESKD) and ranks fourth overall(1). More than half of ADPKD patients develop ESKD at the 6th decade of life. Its most frequent extrarenal manifestation is polycystic liver disease (PCLD), which affects 94% of patients by the age of 35(1). ARPKD, on the other hand, manifests in childhood. It has an estimated incidence of 1 out of 20.000 viable pregnancies. Up to 45% of these patients suffer from a hepatobiliary disease at birth, from CHF to Caroli's syndrome (CS) among others(9).

The underlying mechanism involves ductal plate malfunction (DPM), a structure that appears during embryogenesis that leads to the biliary tract(10). Such DPMs constitute a diverse, complex and atypical compendium of hepatobiliary diseases. While other reviews focus on the imaging(11) or exclusively on polycystic liver disease, we aim to provide a comprehensive clinical perspective on FLDs with updated clinical algorithms. We integrate the most recent guidelines from the European Association for the Study of the Liver (EASL)**(12)**, the Spanish ADPKD Consensus**(13)** and the Kidney Disease: Improving Global Outcomes (KDIGO)**(14)** in order to provide a current, clinically oriented review.

EMBRYOLOGY AND PATHOGENESIS

The ductal plate is a structure that arises from hepatoblasts at the 8th week of gestation. It consists of two layers of periportal hepatoblasts that surround the portal radicles, migrate into the portal stroma and develop into bile ducts. However, if this process is disturbed, DPMs occur and develop in the margins of the portal triad, sometimes enclosed in a fibrous capsule(10).

In polycystic kidney disease, several genes that encode ciliary proteins are involved in the ductal plate's embryogenesis. ADPKD is caused by mutations in genes encoding polycystin-1 and polycystin-2 via PKD1 (which is mutated in 78% of patients with ADPKD) and PKD2 (15%) as well as others such as GANAB, ALG9 and DNAJB11**(1,15)**. These proteins are responsible for the correct function of the main cilia in both the ductal plate and renal epithelium**(16,17)**. In ARPKD, fibrocystin is encoded by PKHD1 and DZIP1L, among other genes(7). Although fibrocystin's role is not clarified, it is theorized to function at the ciliary basal body and has molecular interactions with polycystins(7). When these proteins lose their function, ciliary dysfunction leads to abnormal remodelling of the ductal plate resulting in DPMs and, ultimately, FLDs. Beyond PCLD, FLDs share common characteristics including low incidence, congenital origin and shared pathogenesis(7). Depending on the level at which DPMs form during the remodelling phase of the ductal plate, the clinical entity varies as summarized in Table 1 and Figure 1.

Table 1. Main summary of fibrocystic liver diseases due to ductal plate malformation, clinical manifestations, imaging findings and prognosis.

FLDs	Microscopic description	Symptoms	Ultrasound findings	MRI findings	Prognosis
Von Meyenburg	DPM < 20 µm	Mostly asymptomati	Small (<10mm)	In T2 sequences,	May be a cause of

Complexes	Clusters of **undevolved dilated cystic DPMs** Single cuboidal cell layers surrounded by stroma	c	hyperechoic lesions with **comet-tail echoes**. Larger may appear hypo or anechoic	hyperintense, scattered, tiny cyst conforming a **starry sky pattern**. No biliary communication	recurring infection Controversial risk of cholangiocarcinoma
Congenital hepatic fibrosis	DPM 20-50 µm Irregularly shaped bile ducts and **periportal fibrosis**	Pediatric age: Variceal GI bleeding Adult age: variceal GI bleeding or cholangitis	Dysmorphic liver with features of portal hypertension Atrophic right lobe Hypertrophic left lateral segment	T2 sequences: periportal high signal intensity	High risk of upper gastrointestinal bleeding ⅓ patients present with a cholestatic phenotype
Caroli's Disease	DPM > 20 µm Incomplete	Asymptomatic Acute	Intrahepatic saccular dilations of the bile duct.	T2 sequences: cystic **string of pearls** image due to	Risk of hepatolithiasis

	ductal plate remodelling	cholangitis		bile duct dilations T2 sequences: **Central dot sign**	Risk of cholangiocarcinoma
Polycystic liver disease	DPM < 20 µm Von Meyenburg complexes with viable cholangiocytes that lead to fluid buildup	Asymptomatic Compression symptoms Cyst-related complications	More than 10 anechoic cysts on the liver	T1 sequences: hypointense cysts T2 sequences: hyperintense cysts	Do not have risk of malignant transformation Symptoms due to cyst growth

FLDs: fibrocystic liver diseases

MRI: magnetic resonance imaging

DPM: ductal plate malformation

GI: gastrointestinal

Another affected structure is the common bile duct, though its relationship with cilia and DPM remains unclear. Some authors suggest that choledochal cysts arise from DPM(11). However, patients with ADPKD have been reported to present larger common bile ducts

than controls, without evidence of obstructive pathology**(18)**. The reasons may include obstruction of peribiliary cysts, ciliary dysfunction leading to biliary stasis**(16)** or an increase in extracellular matrix production(2). This anomaly may result in more diagnostic tests ordered, including invasive procedures such as endoscopic retrograde colangiopancreatography (ERCP), which may lead to a higher, long-term risk of biliary tract infections(5).

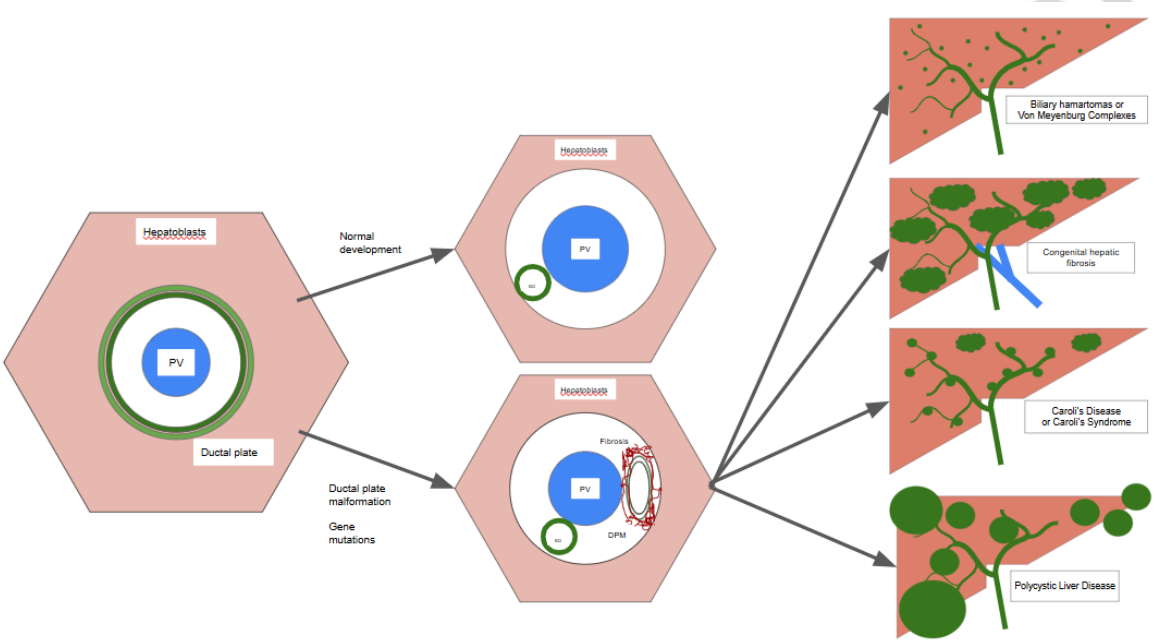

Figure 1. Simplified development of the bile duct and schematic morphology of Ductal Plate Malformations. Starting from the 8th week of gestation, the ductal plate develops around radical portal veins (PV). Stroma surrounds the inner layer that leads to cholangiocytes and the bile duct (BD). When this mechanism is disrupted, remnants of the ductal plate are engulfed by stroma (red) and lead to ductal plate malformations (DPM).

CLINICAL MANIFESTATIONS

VON MEYENBURG COMPLEXES (VMCs) OR BILIARY HAMARTOMATOSIS

VMCs appear in up to 5% of the population in some autopsy series**(19)**. They consist of multiple uniform lesions smaller than 10mm that do not communicate with the biliary tree.

They are composed of a single-layered, non-functional cuboidal epithelium.(11)

Clinical features

VMCs are usually benign and asymptomatic, requiring neither follow-up or treatment**(12,20)**. There is controversy surrounding the risk of degeneration into cholangiocarcinoma**(19,21)**. Another possibility is the risk of infection, as case reports have described patients with recurrent sepsis due to enterobacter without evidence of bile flow obstruction to the bile flow in which the origin may result from VMCs**(22)**. Immunosuppressant therapy, i.e. in case of renal transplantation, is a risk factor for these recurrent episodes.(5)

Imaging

Conventional studies by computed tomography (CT) scan or ERCP may appear normal in these patients. On MRI, VMCs are described as multiple hypointense lesions on T1 sequences and hyperintense on T2 sequences that do not show diffusion restriction. They may be confused with other entities such as biliary cystoadenocarcinoma**(23)**. Nuclear medicine techniques including positron emission tomography (PET-CT) or marked white blood cells can reveal pathological liver findings in case of infection.**(24)**

Management

In case of recurrent infections despite antibiotic therapy, liver transplantation has been described as an exceptional measure, with good mid-term outcome**(25)**.

Key recommendations

- VMCs may be a cause of recurrent fever, nuclear techniques such as PET-CT or marked white blood cells scans can be used to identify them as the infectious source.
- In case of recurrent fever, liver transplantation may be considered.

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CONGENITAL HEPATIC FIBROSIS (CHF)

In CHF, DPM occurs at the level of interlobular bile ducts. There is a strong fibrous reaction which leads to progressive peribiliary and periportal fibrosis, causing the disease.

Clinical features

CHF is usually diagnosed at childhood, though some patients remain asymptomatic until late stages of life**(26,27)**. Clinical presentation varies between pediatric and adult ages. In children, it usually manifests with a portal hypertension phenotype, with upper gastrointestinal bleeding (UGIB) being more common than ascites. In adults, however, the clinical manifestations are varied. Some patients are asymptomatic except for high levels of gamma-glutanyl transferase (GGT)**(28)**. Between 35 and 65% of patients present clinically significant portal hypertension, while 45% present with a cholestatic phenotype characterised with recurrent acute cholangitis and/or hepatolithiasis(6).

Imaging

On ultrasound, CHF presents as a dysmorphic liver with heterogenous parenchyma and hyperechoic portal triads. It differs from cirrhosis in showing right liver lobe atrophy with medial left liver enlargement and/or hypertrophy of lateral left liver segments. Finally, on MRI, a hyperintense T2 signal due to periportal fibrosis is characteristic(11).

Management

Management depends on the clinical phenotype. In children with portal hypertension, primary prophylaxis with non-selective beta blockers (NSBBs) is not recommended, despite mortality from bleeding being higher in pediatric compared with adult populations. After a first episode of UGIB, NSBBs or endoscopic band ligation are indicated, and once the patient reaches adulthood, portal hypertension management follows standard EASL guidelines. Both splenomegaly and thrombocytopenia serve as indirect markers of portal hypertension**(28)**.

Patients with CHF who consult in the emergency department with fever should be treated for acute cholangitis, even if laboratory tests are inconclusive, (9). In patients with the cholestatic phenotype, biliary stasis and DPM lead to higher risk and mortality. In such cases, however, blood cultures have lower diagnostic yield, often below 50%**(29)**.

Key recommendations

- Consider CHF in patients with dysmorphic livers that resemble cirrhosis.
- Although CHF typically presents in children with portal hypertension and UGIB, clinical manifestations in adults vary, with some resembling cholestatic disease.

CAROLI'S DISEASE AND SYNDROME

When DPM expands to intrahepatic bile ducts, cystic formations develop in contact with the bile duct, resulting in ectasia. Cystic dilation of the bile duct is known as Caroli's Disease (CD) and, if it presents along CHF in the same liver, as Caroli's Syndrome (CS)**(12)**.

Clinical features

CD can present as diffuse, lobar or segmentary hepatic involvement, depending on the extent of affected segments.

These patients face a higher risk of intrahepatic cholangiocarcinoma, with a prevalence up to 7%. Therefore, annual screening with MRI is recommended. However, ERCP screening is not recommended due to higher risk of biliary tract infections. Screening with CEA and Ca 19-9 is also not recommended**(12)**.

Biliary stasis due to CD increases the risk of both hepatolithiasis and recurring acute cholangitis. Although cholangitis in these patients can manifest with Charcot's Triad (right upper quadrant pain, jaundice and fever), there are instances of non-specific cases where MRI and PET-CT detect inflammatory activity at the liver, even in patients without visible

DPMs**(30,31)**. These recurring episodes lead to chronic liver inflammation that progresses to secondary biliary cirrhosis.

Imaging

An extrahepatic bile duct dilation may be seen without evidence of bile flow obstruction and it might be due to previous cholangitis or choledocolithiasis.

Concerning its diagnosis, ultrasound reveals an intrahepatic bile duct cystic dilation. If cholangitis is suspected, periportal thickening can be found**(29)**. However, ultrasound alone does not confirm the diagnosis of CD, as we must demonstrate communication between the cystic dilations and the bile duct. MRI with specific liver contrast allows for this connection to be established. A characteristic finding is a **central dot** due to the grouping of biliary cysts around a radical portal vein. Another common finding is the formation of hepatolithiasis due to biliary stasis**(11)**.

Management

Fever may be the only sign of active infection in CD. Therefore, we should consider it in patients presenting with recurring fevers and negative GRAM-stain bacteria in blood cultures or negative blood cultures altogether**(9,32)**.

Ursodeoxycholic acid (UDCA) has shown limited benefits in reducing the risk of both hepatolithiasis and recurring acute cholangitis**(33)**.

When CD is complicated by recurring cholangitis, LT should be considered. It should be preferred over surgical resection in cases of bilobar involvement or when it has been excluded because of hepatic comorbidities (portal hypertension, for instance)**(12)**.

Key recommendations

- MRI diagnoses CD by demonstrating connection between the cystic dilations and the bile duct.

- UDCA may be useful in cases of hepatolithiasis and recurring acute cholangitis.

- Bilobar, diffuse CD may benefit from LT in case of recurring cholangitis or secondary biliary cirrhosis.

POLYCYSTIC LIVER DISEASE (PCLD)

Up to 94% of patients with ADPKD will develop PCLD at 35 years old. It is defined as the presence of more than 10 cysts in the liver at any time point(1).

Clinical features

Although many patients remain asymptomatic, clinical manifestations can arise due to mass effect or cyst complications (Figure 2). Symptomatic PCLD is more frequent in young women due to the effect of estrogens on cyst growth**(2,12)**.

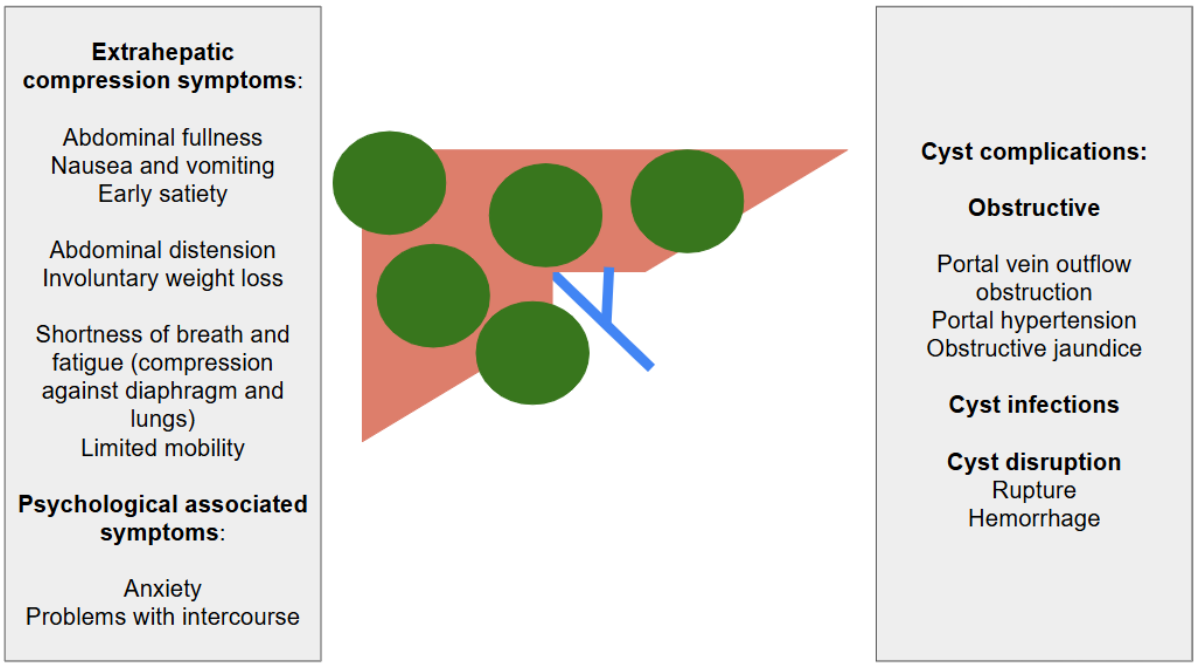

Figure 2. Summary of PCLD complications regarding liver volume (left) and cyst complications (right). Patients may present cyst complications regardless of total liver volume and growth rate.

Several clinical classifications have been proposed to categorize these patients. One recent system includes sex, genotype and annual liver growth rate. Patients with an annual adjusted growth rate higher than 6.6% have a higher risk of hospitalization compared to other ADPKD-PCLD patients**(34)**. Quality of life is also evaluated using the PLD-Q questionnaire, which assesses common symptoms such as abdominal distension or pain, as well as impairment in quality of life.**(35)**

Cyst complications.

Cyst complications include rupture, hemorrhage and infection. Cyst rupture should be suspected when patients present with acute abdominal pain, localized to the upper right quadrant or diffuse, accompanied by ascites or signs of peritonitis.**(36)**

Cyst infections require a different approach than standard biliary tract infections. Although the gold standard includes demonstrating neutrophils or bacteria on cyst aspiration, such technique is not always performed. In patients with ADPKD-PCLD who present with fever, with or without abdominal pain, cyst infection must be considered and antibiotic treatment must be started as soon as possible.

Imaging

The diagnosis is firstly established by ultrasound, but follow-up or characterization by MRI might be needed in cases of hepatomegaly to determine disease severity or liver volume**(14)**.

PET-CT is the optimal imaging technique for diagnosing cyst infection, as it compares metabolic activity between the cyst and liver parenchyma.**(31,37)** A qualitative classification comparing activity between cyst and parenchyma has been established to diagnose cyst infection.**(38)**

Management

Due to the various clinical phenotypes and complex management, KDIGO, the Spanish Group for ADPKD and EASL all recommend that **patients with ADPKD-PCLD should be**

followed by a multidisciplinary referral team(12–14). For instance, the most recent KDIGO guidelines recommend that patients who will receive hormonal therapy should be evaluated previously by a hepatologist**(14,39)**.

Patients with PLD-Q above 32 points benefit from either systemic, interventionist or surgical treatment**(35)**. Sarcopenia must also be tested, as systemic treatment does not improve weight loss and severe malnutrition is classified as a complication from PCLD**(40)**.

Medical treatment.

Regarding symptoms due to liver growth, the first line of treatment are somatostatin analogs (SST-An), which reduce liver growth up to 6% in 2 years.**(41,42)**. A 2021 metaanalysis including 7 randomized clinical trials concluded that SST-An slowed total liver and kidney growth rates but did not show effects on glomerular filtration rate**(43)**. If improvement is achieved, treatment should be maintained. SST-An reduces cyclic adenosine-monophosphate (AMPc) levels inside cystic cholangiocytes, reducing their proliferation and its secretion, thus leading to cystic reduction. Theoretically, premenopausal females benefit the most from these treatments, though more evidence is needed to affirm this hypothesis**(44)**. **Subcutaneous lanreotide at a 120mg dose each 4 weeks has the higher efficacy but higher risk of adverse effects compared to 90mg lanreotide**, which can also be used.

UDCA has also been proposed as a treatment, as it inhibits cystogenesis in experimental models**(45,46)**. A first clinical trial performed in 2016 did not show a reduction in total liver growth, though cyst volume remained unchanged in 24 weeks. As of 2025, **UDCA is not recommended as a treatment for reducing liver volume**, but it can be used to prevent biliary stones in patients treated with SST-An.**(39)**

Follow-up after systemic treatment should be considered after 6-12 months with imaging studies.(35)

Interventionist and surgical treatment.

In symptomatic, superficial cysts, percutaneous interventionist therapy can be applied, such as aspiration-sclerotherapy. Sclerotherapy and cyst aspiration may be considered on dominant cysts causing compression symptoms, with clinical improvement up to 70% but with a recurrence rate of 21% and a few adverse effects, being abdominal pain the most common**(13)**. In other cases, transarterial cyst embolization could be used for diffuse cystic disease with an improvement of symptoms higher than 70% but with risk of relapse.

Surgical options are also available, including liver transplantation and liver resection. The latter is considered for symptomatic patients with a dominant cyst or cluster of cysts in a lobar or segmental distribution. Such cases have a high risk of complications, up to 50% and a mortality rate of 3%.**(12,13)**

Management of cyst complications.

In case of cyst rupture, surgery is recommended as the first line treatment.

Intracystic hemorrhage usually appears on cysts larger than 8cm and may develop spontaneously. It manifests as a dull upper right quadrant pain and can lead to hemodynamic instability in severe cases. If the patient is stable, a conservative approach with discontinuation of blood thinners is preferred. Such drugs can be restarted after 7 to 15 days.**(12)**

For cyst infection, treatment consists of intravenous third-generation cephalosporin combined with a quinolone, with a duration of 4 to 6 weeks. In case of non-responsiveness after 48 to 72 hours or high risk criteria exist (immunosuppressants, cysts larger than 8cm, hemodynamic instability), percutaneous drainage or surgical intervention must be considered**(35,39)**.

A summary of recommendations for PCLD is shown in Figure 3.

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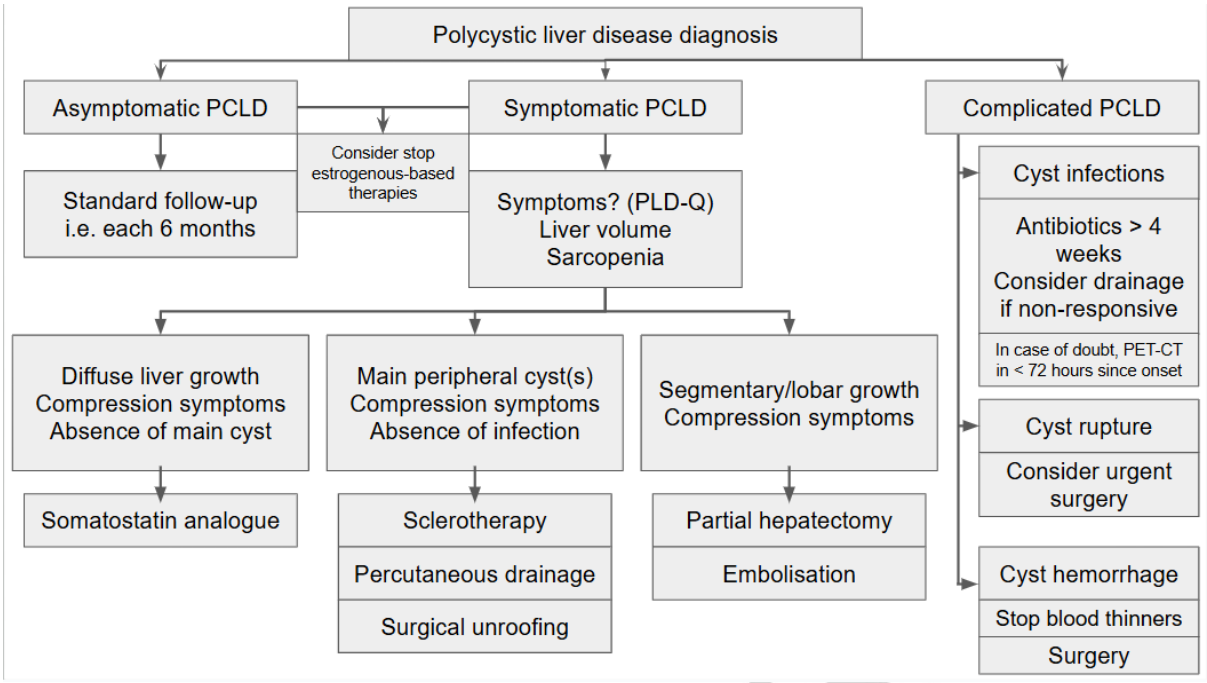

*Figure 3. Flowchart and treatment recommendation in patients with PCLD. Adapted from EASL**(12)**, KDIGO**(14)** guidelines and Müller et al**(35)**.*

Key recommendations

- Patients with ADPKD-PCLD should be followed up by a multidisciplinary team including hepatologists and nephrologists.
- MRI is a superior technique in order to establish PCLD severity. PET-CT enables diagnosis of cyst infection in case of doubt.
- In case of symptomatic PCLD due to liver growth, somatostatin analogues are the recommended therapy, with lanreotide at 90-120mg per week being the preferred option.

- For cyst infection, antibiotic therapy should be administered for at least 4 weeks.
- Surgical options are reserved for unstable patients or those unresponsive to medical treatment.

LIVER TRANSPLANTATION IN PATIENTS WITH FLDs.

Liver transplantation (LT) is the only curative treatment for FLDs but it should be reserved for severe cases**(12)**. The criteria for each entity may differ, but recurring biliary tract infections, complications from portal hypertension and the development of cirrhosis are the main indications. Patients with recurring infections in the context of VMC or PCLD benefit from exception points from MELD criteria, as their hepatic synthetic function is preserved**(25)**. The prognosis of LT is favorable, having lower risk of adverse events compared to patients with cirrhosis or other indications. However, the prognosis comparing sequential liver-kidney transplantation (SLKT) with LT or kidney transplant (KT) alone is subject to controversy in patients with FLDs.

While a study from the United States showed that patients undergoing SLKT have a 6.7-fold higher mortality risk compared to single-organ transplantation**(47)**, an European study found no mortality difference between SLKT and LT or KT, though LT had a higher 5-year-mortality than KT+**(48)**. Between 5-7% of patients undergoing either LT or KT may need a second transplant for the second organ in case of FLDs**(47,48)**.

In conclusion, **there is no consensus on whether these patients benefit from SLKT.** That reaffirms **the need for multidisciplinary care and a case-by-case approach** when liver transplantation is considered.

CONCLUSIONS

Fibrocystic liver diseases are a complex spectrum of hepatobiliary pathologies related to polycystic kidney disease. Their distinctive characteristics compared with standard pathologies emphasize the need for multidisciplinary care to achieve optimal quality

management and follow-up. A summary of these pathologies can be found in Table 2.

Table 2. Summary of differential diagnosis and recommendations with FLDs and their management.

FLDs	Main clinical phenotype	Preferred diagnostic modality	Infectious complications	Management	Indications for liver transplantation
Von Meyenburg Complexes	Usually asymptomatic Rarely: recurrent hepatobiliary infections	MRI If infection is suspected, PET-CT	Recurrent sepsis	Conservative with antibiotics in case of infection Do not require follow-up	Exceptional, cases with recurrent infections
Congenital hepatic fibrosis	Portal hypertension	Ultrasound: dysmorphic liver MRI: periportal fibrosis	May present with acute cholangitis, often with low blood culture yield	Portal hypertension management Early antibiotics in case of fever	Complications of portal hypertension
Caroli's Disease and Syndrome	Hepatolithiasis and choledocolithiasis Recurrent cholangitis	MRI: cysts communicate with the bile duct. Central dot sign.	Recurring cholangitis	UDCA for hepatolithiasis Annual MRI screening for cholangiocarcinoma.	Diffuse or bilobar disease with recurring cholangitis or secondary biliary cirrhosis
Polycystic liver disease	Mass effect symptoms Cyst complications	MRI: liver volume and cyst complications PET-CT: cyst infection	Cyst infection, often without classic cholangitis signs	Somatostatin analogues Interventionist / Surgery Antibiotic for 4-6 weeks in case of infection	Severe complications Refractory symptoms Recurrent cyst infections

FLDs: fibrocystic liver diseases
MRI: magnetic resonance imaging
PET-CT: positron emission tomography - computed tomography
UDCA: ursodeoxycholic acid.

In cases of fever, nuclear imaging techniques help clarify the infectious source when standard tests such as blood cultures or other imaging studies have failed. Common bile duct dilation may be present in these pathologies and may not need further study once an obstructive cause has been ruled out.

As highlighted by EASL and KDIGO guidelines, in polycystic liver disease, the use of somatostatine analogs can diminish the disease burden and liver volume, though liver transplantation remains the only curative treatment. In such cases, MELD exception points apply as these patients have a preserved liver function. However, there is no consensus on whether all patients benefit from sequential liver-kidney transplantation.

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