

## Polycystic Disease of the Liver

Gregory T. Everson,<sup>1</sup> Matthew R. G. Taylor,<sup>2</sup> and R. Brian Doctor<sup>1</sup>

**Autosomal dominant polycystic disease is genetically heterogeneous with mutations in two distinct genes predisposing to the combination of renal and liver cysts (AD-PKD1 and AD-PKD2) and mutations in a third gene yielding isolated liver cysts (the polycystic liver disease gene). Transcription and translation of the PKD1 gene produces polycystin-1, an integral membrane protein that may serve as an extracellular receptor. Mutations occur throughout the PKD1 gene, but more severe disease is associated with N-terminal mutations. The PKD2 gene product, polycystin-2, is an integral membrane protein with molecular characteristics of a calcium-permeant cation channel. Mutations occur throughout the PKD2 gene, and severity of disease may vary with site of mutation in PKD2 and the functional consequence on the resultant polycystin-2 protein. Polycystic liver disease is genetically linked to protein kinase C substrate 80K-H (PRKCSH). The PRKCSH gene encodes hepatocystin, a protein that moderates glycosylation and fibroblast growth factor receptor signaling. More prominent in women, hepatic cysts emerge after the onset of puberty and dramatically increase in number and size through the child-bearing years of early and middle adult life. Although liver failure or complications of advanced liver disease are rare, some patients develop massive hepatic cystic disease and become clinically symptomatic. There is no effective medical therapy. Interventional and surgical options include cyst aspiration and sclerosis, open or laparoscopic cyst fenestration, hepatic resection, and liver transplantation. (HEPATOLOGY 2004;40:774–782.)**

Only hemochromatosis ranks above autosomal dominant polycystic kidney disease (AD-PKD) in inherited disorders involving the liver.<sup>1,2</sup> Mutations in three distinct genes have been linked to human polycystic liver disease. Two of these genes, PKD1 and PKD2, are associated with AD-PKD where cystic liver disease is the most prevalent extrarenal manifestation. The third gene, protein kinase C substrate 80K-H (PRKCSH), accounts for a comparatively rare, isolated form of autosomal dominant polycystic liver disease (PCLD) that displays no renal involvement. Interestingly, liver cystic disease is phenotypically similar in AD-PKD and PCLD patients. In this review, the natural history, genetics and molecular biology, and clinical management of autosomal dominant forms of PCLD are described.

### Natural History of PCLDs

The most common form of autosomal dominant PCLD coexists with renal cystic disease (AD-PKD) and is linked to mutations in either *PKD1* or *PKD2*.<sup>3–6</sup> Patients with mutations in *PKD2* tend to have later onset of disease and approximately 16 years of increased life expectancy compared with patients who have mutations in *PKD1*.<sup>7</sup> *PKD1* mutations account for 85% to 90% of mutations in AD-PKD families; the remaining 10% to 15% are due to mutations in *PKD2*.<sup>8</sup> Two unrelated families have been described who, by genetic linkage analysis, lack mutations in either *PKD1* or *PKD2*.<sup>9,10</sup> These findings are controversial but suggest that mutations in at least a third gene may be responsible for AD-PKD.<sup>11</sup> In contrast to the concomitant renal and liver cystic disease characteristic of mutations in *PKD1* and *PKD2*, mutations in the *PRKCSH* gene give rise to isolated PCLD. Families with PCLD do not develop renal cystic disease, making them both genetically and phenotypically distinct from AD-PKD families.

Genetic and molecular events responsible for autosomal recessive polycystic kidney disease are also being studied, with responsible mutations isolated to *PKHD1*, the gene coding fibrocystin and located on chromosome 6p. Autosomal recessive polycystic kidney disease is far less common than AD-PKD, with an incidence of 1:20,000

Abbreviations: PRKCSH, protein kinase C substrate 80K-H; AD-PKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease; PC-1, polycystin-1; PC-2, polycystin-2.

From the <sup>1</sup>Division of Gastroenterology & Hepatology, <sup>2</sup>Adult Medical Genetics Program, University of Colorado School of Medicine, Denver, CO

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Address reprint requests to: Gregory T. Everson, Professor of Medicine, Director, Section of Hepatology, Division of Gastroenterology and Hepatology, 4200 East Ninth Avenue, B-154, Denver, CO 80262. E-mail: greg.everson@uchsc.edu; fax: 303-372-8868.

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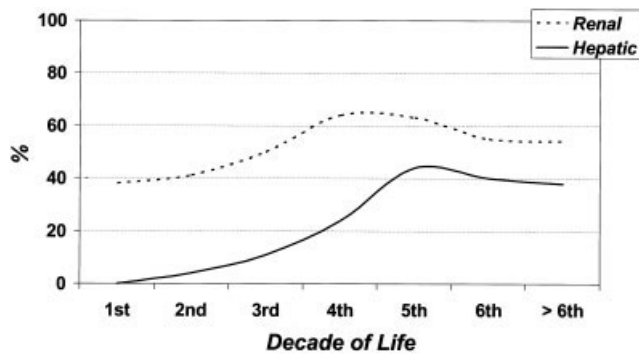


Fig. 1. Prevalence of hepatic and renal cysts in AD-PKD. The frequency of renal and hepatic cysts is displayed by age in at-risk members of kindreds known to be affected by AD-PKD. Cysts were detected using real-time ultrasonography. The population at risk included 239 patients with AD-PKD and 189 unaffected family members. Hepatic cysts are rarely detected before puberty, but by the 5th decade of life approximately 80% of patients with renal cysts have liver cysts (from Gabow et al.<sup>3</sup>).

to 1:40,000, but the high mortality rate makes it an important cause of pediatric disease.<sup>12,13</sup> The most common hepatic association of autosomal recessive polycystic kidney disease is congenital hepatic fibrosis.

The natural history of autosomal dominant forms of PCLD, regardless of etiologic mutation, is strikingly similar. Hepatic cysts are rarely observed prior to puberty, arise with the onset of puberty, are more prevalent and prominent in women, and increase dramatically in number and size through the child-bearing years (Fig. 1). Patients with small (<2 cm) or sparse hepatic cysts tend to be clinically asymptomatic. In contrast, patients who develop massive hepatic cystic disease become symptomatic with abdominal pain, early postprandial fullness, or shortness of breath. Rarely, patients may experience complications of advanced liver disease such as portal hypertension with variceal hemorrhage. As patients with AD-PKD live into late adult life, there is risk of renal failure, hemodialysis, or renal transplantation as a result of renal cystic disease. One center has reported a trend toward development of liver complications in younger patients and high rates of complications (21%) in patients on dialysis.<sup>14</sup> A contradictory report from another center failed to demonstrate higher morbidity or mortality.<sup>15</sup>

### Risk Factors for Cyst Development and Progression

The prevalence and number of hepatic cysts in patients with AD-PKD increase with increasing age, female sex, severity of renal cystic disease, and severity of renal dysfunction.<sup>3-6,16</sup> By age 60, nearly 80% of patients have hepatic cysts (see Fig. 1). Men and women have equal lifetime risk to develop hepatic cysts, but women experi-

ence greater numbers and larger sizes of hepatic cysts.<sup>3,5,6</sup> Severe hepatic cystic disease correlates with both pregnancy and use of exogenous female steroid hormones.<sup>3-6,17</sup> Female tendency to develop massive hepatic cystic disease is also characteristic of isolated PCLD. One longitudinal study of anovulatory women with AD-PKD treated with hormone replacement suggested that estrogens may selectively increase severity of hepatic cystic disease.<sup>18</sup> The severity of hepatic cystic disease in AD-PKD also correlates with both the severity of renal cystic disease and the degree of renal dysfunction.<sup>3,4</sup>

### Genetics and Molecular Biology

**PKD1 and Polycystin-1.** In 1957, Dalgaard demonstrated autosomal dominant inheritance in over 90% of cases of polycystic renal disease.<sup>19</sup> In 1985, linkage techniques localized the first gene for AD-PKD, *PKD1*, to the short arm of chromosome 16p13.3-p13.12.<sup>20</sup> The *PKD1* gene was subsequently cloned and sequenced, and the resultant protein was characterized.<sup>21</sup> *PKD1* encodes a 14.1-kb message that translates into a 4304-amino acid protein, polycystin-1.<sup>22,23</sup> *PKD1* genetics are complicated by the presence of at least three other copies of exons 1-34 adjacent to the active *PKD1* locus. The duplicated copies are probably nonfunctional and fail to express protein. However, their presence has posed a challenge to the development of molecular genetic testing.

There are over 230 distinct mutations of the *PKD1* gene (<http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html>) that are evenly dispersed without evidence for clustering.<sup>24</sup> The majority are missense or nonsense mutations, but splicing mutations and gene rearrangements have also been reported. Approximately 60% of all mutations introduce premature stop codons that result in truncated proteins.<sup>24</sup> Some studies have suggested that type or position of mutation may predict the patient phenotype. Certain mutations are linked to intracranial aneurysms and more severe polycystic disease within individual AD-PKD families,<sup>25</sup> and the relative position of *PKD1* mutations may predict subsequent development of intracranial aneurysms.<sup>26</sup> Furthermore, a study of 80 families with AD-PKD due to mutations in *PKD1* indicated that location of a mutation in the 5' end of the gene predicted more rapid progression and greater severity of end-stage renal disease.<sup>27</sup> Effect of type or position of mutation on hepatic cystic disease has not been analyzed.

**PKD2 and Polycystin-2.** In 1993, a second genetic locus linked to AD-PKD was established on chromosome 4q21-q23,<sup>28</sup> and 3 years later the *PKD2* gene was identified, sequenced and cloned.<sup>29</sup> *PKD2* produces a 5.3 kb message that codes for a 968 amino acid protein. There

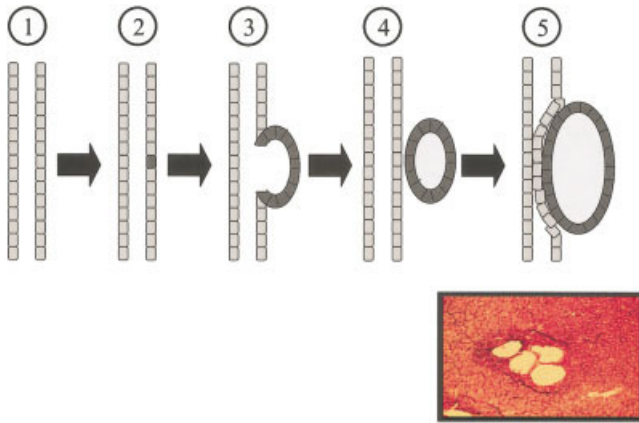


Fig. 2. "Two-hit" model of cyst initiation and progression in AD-PKD. A germline mutation (the "first hit"; light grey cells) is present in one copy of the *PKD1* or *PKD2* gene in all cells (Step 1). A somatic mutation (the "second hit"; dark grey cell) then occurs in an individual intrahepatic bile duct epithelial cell (Step 2), resulting in loss of function of PC-1 or PC-2 and clonal expansion of the mutated cell (Step 3). Expanding cysts detach from the intrahepatic bile duct (Step 4) and subsequently expand and compress the surrounding parenchyma. The liver section shown is of early cysts observed in *pkd2* WS25/− mouse livers developed by Stephan Somlo (Yale University, New Haven, CT).

are over 60 identified mutations of the *PKD2* and, like the mutations of *PKD1*, the mutations of *PKD2* are evenly dispersed throughout the gene without clustering at any particular position.<sup>30</sup> Relationships of the mutations of *PKD2* to phenotypic expression of polycystic disease are under study but no clear relationships have yet been reproducibly defined. A recent study failed to identify specific *PKD2* mutations linked to specific phenotypes, but phenotypic variability for individuals with the same *PKD2* mutation was less than phenotypic variability observed between individuals or families with different mutations.<sup>31</sup>

#### "Two-Hit" Model of Initiation of Cyst Formation.

Although AD-PKD is phenotypically autosomal dominant, at the cellular level it is likely to be a "molecular recessive" disease, requiring a second somatic mutation. This "two-hit" model requires an initial germline mutation in either *PKD1* or *PKD2* (first hit) (Fig. 2). A second, loss-of-function mutation in the functional gene copy (second hit) then initiates cell proliferation and cyst formation in the individual cell that received the second hit.<sup>32–34</sup> In humans with AD-PKD, cysts arise focally from the nephron or intrahepatic biliary tree and epithelial cells from these independent cysts are monoclonally derived.<sup>32,35</sup> In animal models, homozygous *PKD1* or *PKD2* null mice die before or shortly after birth. In contrast, heterozygous animals with a recombination-sensitive second allele, which allows development of spontaneous null mutations, results in age-related formation of focal renal and liver cysts, similar to human dis-

ease.<sup>33,34</sup> The two-hit model has not been investigated in isolated PCLD.

***PRKCSH and Hepatocystin.*** The molecular underpinnings of isolated PCLD have begun to emerge. The first demonstration that PCLD was genetically distinct from *PKD1* and *PKD2* was from phenotypic and genetic studies of a family affected by PCLD in three generations.<sup>36</sup> This kindred lacked evidence of polycystic kidney disease and were genetically distinct from *PKD1* and *PKD2*, findings that triggered an earnest search for the PCLD gene. PCLD is caused by mutations in *PRKCSH* on chromosome 19p13.<sup>37–39</sup> *PRKCSH* encodes for hepatocystin. Mutations that affect messenger RNA splicing or truncate hepatocystin have been reported in PCLD families. However, the distribution of mutations within the gene as well as genotype–phenotype relationships remain speculative.

## Cellular Biology of Liver Cyst Formation and Expansion

***Liver Cyst Epithelium Retains Characteristics of Biliary Epithelium.*** Liver cysts arise from intrahepatic bile duct epithelial cells. The bile duct epithelium normally comprises 2% to 4% of the liver cell mass and serves to dilute and alkalinize bile in hormone-dependent fashion. Secretin stimulates cAMP-dependent  $\text{Cl}^-$  and  $\text{HCO}_3^-$  secretion by biliary epithelia. Liver cyst epithelial cells retain differentiated secretory function as AD-PKD liver cysts secrete fluid and generate a positive luminal pressure after intravenous secretin administration.<sup>40</sup> Despite these differentiated characteristics, cystic epithelia proliferate and form cysts rather than biliary epithelium. Although mechanistic pathways underlying cyst formation and expansion are unresolved, cellular functions of polycystin-1, polycystin-2, and hepatocystin have been partially elucidated.

#### ***Characteristics of Polycystin-1 and Polycystin-2.***

Polycystin-1 (PC-1) is a large ( $\approx 460$  kd) integral membrane protein with a prominent extracellular NH<sub>2</sub>-terminal domain, 11 putative transmembrane domains, and a small intracellular COOH-terminal domain. The extracellular NH<sub>2</sub>-terminus constitutes two thirds of the total protein with a region of leucine-rich repeats, an array with C-type lectin characteristics, another with low density lipoprotein-like features, and 16 immunoglobulin G-like PKD repeats.<sup>41</sup> These domains are capable of participating in protein–protein or protein–carbohydrate interactions, including self-association through interactions of the PKD repeats.<sup>42,43</sup> The discovery of an REJ domain, which is known to regulate ion transport, supports the hypothesis that PC-1 also serves to regulate  $\text{Ca}^{2+}$  signal-

ing. The intracellular COOH-terminal domain interacts with components of G-protein signaling pathways, and a coiled-coil domain in the far COOH-terminus interacts with the paired coiled-coil domain at the COOH terminus of polycystin-2.<sup>32,44</sup> The latter interaction suggests that the two AD-PKD proteins are directly linked to common cellular functions and may account for the similar phenotypic expression of AD-PKD that stems from mutations in either *PKD1* or *PKD2*.

Polycystin-2 (PC-2) is a 110-kd integral membrane protein with intracellular NH<sub>2</sub> and COOH tails. The transmembrane domains share marked homology with voltage-gated cation channels, and the COOH terminus has an EF-hand domain, a motif often expressed in voltage-gated calcium channels. Biophysical studies have confirmed that PC-2 functions as a cation channel.<sup>45–48</sup> Together, the PC-1 and PC-2 complex is predicted to form a signal transduction unit that translates extracellular cues into intracellular information. This would arise both from modifying G-protein signaling and moderating intracellular Ca<sup>2+</sup> levels. The PC-2-dependent Ca<sup>2+</sup> transients may be further amplified by the interaction of PC-2 with the transient receptor potential channel, a calcium-activated calcium channel.<sup>49</sup>

***Polycystin-1 and Polycystin-2 Form a Mechano-transduction Complex in Cilia.*** The increase in basic knowledge of function of PC-1 and PC-2 stimulated studies to link these functions to changes in proliferation, differentiation, apoptosis, and secretion that occur within the cystic epithelium. Early reports indicated that PC-1 localized to lateral and basal membranes as well as junctional complexes, consistent with function in cell–cell and cell–matrix interactions. Distinct from PC-1, PC-2 localized along the basolateral membrane and within the endoplasmic reticulum.<sup>50–57</sup> Recent studies colocalized PC-1 and PC-2 to the primary cilium of epithelial cells,<sup>58,59</sup> a site where a dysfunctional PC-1/PC-2 complex could transduce faulty signals of extracellular conditions to the cell interior. Interestingly, two other proteins that give rise to epithelial cysts—polaris and cystin—also localize to the primary cilium of epithelial cells.<sup>59</sup> Furthermore, fibrocystin, the protein linked to autosomal recessive polycystic kidney disease, is localized to the primary cilium of biliary epithelia, and reduction of fibrocystin expression leads to loss of ciliary structure.<sup>60</sup>

The primary cilium is a lone, nonmotile, microtubule-based structure found on the luminal surface of many different epithelial cells, including intrahepatic bile duct epithelial cells. In epithelial cells, the primary cilium functions as a flow sensor with ciliary bending resulting in increased Ca<sup>2+</sup> influx.<sup>61</sup> Importantly, mutations in *PKD1* result in failure of cilia to raise intracellular calcium levels

in response to increased fluid flow over the apical membrane surface.<sup>62</sup> This indicates that PC-1 and PC-2 form the core of a mechanotransduction signaling complex within ciliated epithelial cells. How dysfunctional calcium signaling from cilia results in errant cell growth and differentiation remains to be delineated.

***Hepatocystin Gives Rise to PCLD Liver Cysts.*** Hepatocystin is a 59-kd protein that is expressed in many different tissues.<sup>38</sup> Prior to its genetic and physical linkage to PCLD, hepatocystin was implicated in the moderation of protein glycosylation within the endoplasmic reticulum and fibroblast growth factor receptor signaling at the plasma membrane.<sup>39,63</sup> To date, hepatocystin has not been described within the primary cilium. Hepatocystin does have two EF-hand domains, spurring speculation that misregulation of Ca<sub>i</sub><sup>2+</sup> may provide a common link between the polycystins, hepatocystin, and liver cyst formation. It is hoped that the delineation of the molecular interactions and cellular functions of hepatocystin may be compared and contrasted with those of other cystogenic proteins—including PC-1 and PC-2—to define common, causal pathways underlying hepatic cyst formation.

***Contributory Events in Cyst Expansion.*** Proliferating epithelial cells form nascent cysts that detach from the original duct to form autonomous structures that no longer communicate directly with the duct (see Fig. 2). Expansion of these autonomous cysts can be promoted by luminal fluid secretion, remodeling of the underlying matrix, and neovascularization. Normal intrahepatic bile duct cells function as both absorptive and secretory epithelium in which net absorption is favored under basal conditions. Secretion is triggered by hormonal signaling, primarily via secretin. Retaining characteristics of intrahepatic bile duct epithelial cells, human hepatic cysts generate a positive intraluminal pressure under basal conditions and have increased rates of fluid secretion following intravenous administration of secretin.<sup>40,64</sup> Increasing intraluminal pressure in cell culture models of epithelial cysts increases rates of epithelial cell proliferation.<sup>65,66</sup> Thus, despite their transformation into a proliferative epithelium, the liver cyst epithelial cells retain their regulated secretory capability, and the resultant positive intraluminal pressure within the closed cyst may directly signal the lining epithelial cells to proliferate.

For a proliferating epithelium to invade the surrounding tissues, the extracellular matrix must be remodeled. Matrix remodeling occurs through the secretion of metalloproteases into the surrounding matrix. Accordingly, metalloprotease activity and secretion has been measured in a mouse model of AD-PKD renal cysts and in isolated human liver cyst epithelia, respectively.<sup>67–69</sup> Likewise, the proliferating autonomous cyst requires vascularization for

metabolic support. The density of vascular beds within liver cysts has not been reported, but AD-PKD renal cysts are densely vascularized.<sup>70</sup> This vascularization is likely a response to the production and secretion of vascular endothelial growth factor by the cystic epithelium. Indeed, the cystic renal epithelial cells generate and secrete a rich cocktail of cytokines and growth factors that can contribute in an autocrine, paracrine, or exocrine fashion to promote epithelial secretion, cell proliferation, matrix remodeling, and neovascularization.<sup>71-73</sup> In preliminary studies, human liver cyst epithelial cells also secrete a rich but distinct profile of cytokines and growth factors.<sup>74</sup>

### Molecular Diagnostics

The molecular diagnostic approaches to AD-PKD have advanced considerably with the availability of direct gene sequencing. Previously, the use of genetic testing in AD-PKD families was restricted to linkage analysis. Although linkage analysis is a powerful tool for identifying patients with likely PKD mutations, it is limited by its requirement of a suitable number of DNA samples from a family. In small families, or in families in which key relatives are deceased, unavailable, or unwilling to provide a genetic sample, the predictive power of linkage analysis is limited. Additionally, from a clinical perspective, approaches that require multiple family members to be evaluated and sampled (*i.e.*, for DNA) is a complicated process that requires coordination of genetic counseling and often the approval of multiple third-party payers to defray the cost of testing. As noted, the large size of both *PKD1* and *PKD2*, coupled with the partial duplications of a sizable portion of *PKD1*, were significant obstacles to the development of molecular testing. Technological advances have overcome these hurdles, and both direct sequencing and denaturation high performance liquid chromatography approaches have been reported.<sup>24,26,75</sup> Direct sequencing was able to detect pathological mutations in 76% of families, whereas the denaturation high performance liquid chromatography detection rate was 44%. Importantly, the study using denaturation high performance liquid chromatography reported results only for *PKD1*; consequently, the sensitivity for other genes cannot be inferred from this study, although the authors estimated it to be greater than 50%. The reported rate of detecting mutations in *PKD2*, which is not complicated by gene duplications, is in the range of 75%.

Although molecular genetic testing is relatively new and consensus guidelines are lacking, there are clinical circumstances for which its use may be considered. In young (age <30 years), presymptomatic individuals at risk for AD-PKD, molecular genetic testing may offer a number of advantages, because in this group ultrasonog-

raphy may lack sensitivity, and linkage analysis is impractical. The identification of a *PKD1* or *PKD2* mutation could affect family planning and choice of future diagnostic studies. Discovery of AD-PKD mutations may also encourage regular blood pressure monitoring and screening for associated conditions such as cerebral aneurysm or mitral valve prolapse. Genetic testing may have a role in the evaluation of living related donors for renal transplantation who lack overt evidence of AD-PKD. Clarifying the mutation status as negative in such potential donors would reduce future risks to both the donor and the recipient.

Clinical genetic testing for PCLD is also available in Europe and includes genetic sequencing of the coding portion of *PRKCSH*. Because there is no clinically available linkage test for *PRKCSH*, the molecular approach is the sole DNA-based option. Because sensitivity of ultrasound in PCLD is undefined, use of *PRKCSH* testing to identify presymptomatic patients at risk for the disease may have even more relevance than in AD-PKD.

### Clinical Features

Most patients with polycystic liver are asymptomatic or may note only a protuberant abdomen. Patients with PCLD can be arbitrarily divided into two groups, massive or minimal, based on a definition for mass of total liver cyst/parenchymal volume ratio > 1.<sup>76</sup> Using this definition, most symptomatic cases are restricted to patients with massive hepatic cystic disease with abdominal pain and discomfort and shortness of breath correlating with severity of hepatic cystic disease.<sup>18</sup> Typically, liver parenchymal volume is preserved despite extensive hepatic cystic disease and extraordinary distortion of hepatic architecture (Fig. 3). The only blood test abnormality is modest elevation of  $\gamma$ -glutamyltransferase, which correlates with hepatic cyst burden.<sup>76</sup> Rarely, a patient with PCLD will experience hepatic decompensation and variceal hemorrhage, ascites, or encephalopathy. Quantitative tests of hepatic function indicate that most polycystic patients have preserved hepatic function. There is a slight but significant decrease in clearance of antipyrine and first-pass elimination of cholate in those with massive hepatic cystic disease.<sup>5</sup>

The most common, clinically relevant complications arising in hepatic cysts are intracystic hemorrhage, infection,<sup>77</sup> or posttraumatic rupture. Cyst adenocarcinoma, biliary obstruction, Budd-Chiari syndrome,<sup>78,79</sup> or hepatic failure are rarely reported. Table 1 lists the complications, the preferred method of diagnosis, and options for medical or surgical management. Associated conditions include mitral valve prolapse, diverticulosis, inguinal hernia, and cerebral aneurysm.<sup>80</sup>

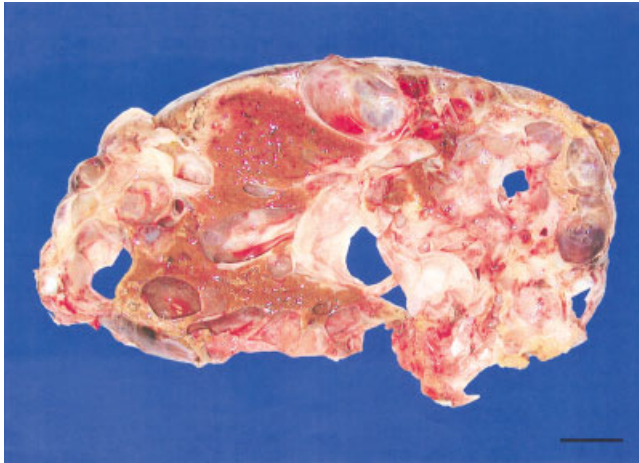


Fig. 3. Cross section of an explanted polycystic liver from a female transplant recipient. This liver has massive hepatic cystic disease, islands of preserved hepatocytes (rusty brown areas), and marked architectural distortion.

## Therapy

**Medical Treatments.** There are no effective medical therapies for PCLD. Use of somatostatin analogue to block secretin-induced secretion by hepatic cysts failed to demonstrate any significant effect on hepatic cyst growth or size.<sup>81</sup> One of the more intriguing observations is the finding that hepatic cystic disease, but not renal cystic disease, may worsen under the influence of female gender, pregnancy, or use of exogenous female steroid hormones<sup>18</sup> (Fig. 4). These observations suggest that women with polycystic liver should avoid estrogen replacement

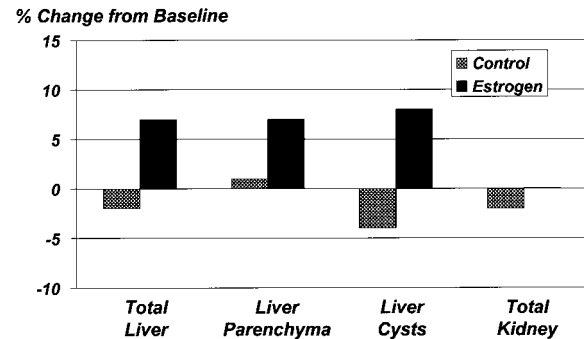


Fig. 4. Postmenopausal estrogen selectively increases liver volume. Percentage of volume change in liver and kidney following 1 year of postmenopausal estrogen treatment is shown. Estrogen treatment increases hepatic volume and hepatic cystic disease but does not influence renal cystic disease (Shrestha et al.<sup>18</sup>).

therapy. However, proof that avoidance of estrogen is efficacious is lacking, and anecdotal reports fail to indicate a beneficial effect of estrogen receptor blockade. The clinician must individualize hormonal replacement therapy in polycystic patients by weighing the potentially deleterious effect on hepatic cystic disease against other potential benefits and risks.

**Radiologic Cyst Aspiration and Sclerosis.** Symptomatic patients with one or few dominant cysts may be considered for cyst aspiration and sclerosis. Most patients with polycystic disease either have too many cysts or their cysts are of insufficient size to warrant this approach. Cyst sclerotherapy requires ultrasonographic or CT-guided percutaneous puncture of the targeted cyst and placement of an intracystic drainage catheter. For large cysts (>100 mL or diameter of  $\geq 6$  cm), the catheter may be left in place for 24 hours, and a second treatment may be performed the following day. Success in obliterating individual cysts in polycystic patients is approximately 70% to 90%.<sup>82,83</sup>

**Cyst Fenestration.** Cyst fenestration is a common surgical treatment in the management of symptomatic massive hepatic cystic disease. Two approaches have been used: open laparotomy and, more recently, laparoscopy. Several series of open laparotomy, encompassing large numbers of patients, indicate that this approach results in satisfactory resolution of symptoms.<sup>84</sup> However, open laparotomy is associated with prolonged hospitalization and the morbidity of major abdominal surgery. Operative mortality is low (<1%) and reported rates of postoperative complications (bleeding, infection, bile leak, ascites) range from 0% to 50%. Because of its less invasive nature, laparoscopic cyst fenestration is gaining increasing acceptance as an alternative surgical technique.<sup>85,86</sup> Advantages of laparoscopic surgery include: less morbidity, reduced hospital stay, and the potential for outpatient surgical management. One recent review of 40 cases indicated that

**Table 1. Clinical Complications of Polycystic Liver Disease**

Complication	Diagnostic Tests	Treatment Options
Cyst infection	CT, MRI, In-WBC scan	Antibiotics (fluoroquinolones), drainage if no response
Cyst hemorrhage	CT, MRI	Medical management, pain control
Cyst adenocarcinoma	CT, MRI, aspiration cytology	Surgical resection
Portal hypertension		
Variceal Bleed	Endoscopy	EST/EVL, portosystemic shunt, OLTx
Budd-Chiari	Hepatic venography	Cyst decompression, if unsuccessful, then resection or OLTx
Rupture of cyst	Clinical suspicion	Medical management, pain control
Biliary obstruction	ERCP	Stent placement, cyst decompression

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; In-WBC scan, indium-labeled white blood cell scan; EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; OLTx, orthotopic liver transplantation; ERCP, endoscopic retrograde cholangiopancreatography.

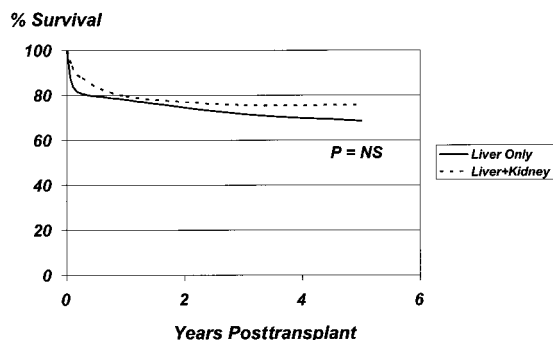


Fig. 5. Patient survival after liver transplantation for PCLD is shown for patients with either isolated hepatic transplantation (n = 128, solid line) or combined liver-kidney transplantation (n = 78, dotted line) (US Scientific Registry of Transplant Recipients, February 2004).

symptoms recurred in approximately half of those cases, all of whom required repeat laparoscopic cyst fenestration.<sup>87</sup> Although there were no deaths, surgical conversion to open cyst fenestration occurred in 10% of cases, and 35% of patients suffered complications.

**Liver Resection.** One center reported their experience with partial liver resection in the management of 31 patients with highly symptomatic, massive hepatic polycystic disease.<sup>88</sup> Their ages ranged from 34 to 69, the sex ratio (M/F) was 3:28, and renal function varied from normal to dialysis dependency. Nearly all patients experienced significant relief from symptoms, and long-term sustained reduction in symptoms was common (>95%). However, over 50% experienced significant perioperative morbidity and there was 1 perioperative death (due to rupture of intracranial aneurysm). Although resection may be promising for some patients, the morbidity associated with this procedure precludes widespread use, and most surgeons reserve hepatic resection for those cases that are refractory to cyst decompression.

**Liver Transplantation.** Polycystic liver patients with symptoms refractory to other treatments or symptomatic hepatic cystic disease with end-stage renal cystic disease may be considered for liver or combined liver-kidney transplantation. Rarer indications for hepatic transplantation include variceal hemorrhage, ascites, obstruction of hepatic venous outflow (Budd-Chiari equivalent), or biliary tract obstruction by extensive cystic disease not amenable to other interventions. Existing reports of small numbers of patients indicate posttransplant 1-year patient survivals of 70% to 90%.<sup>15,89-94</sup> In one review of the literature, over 80% of patients were women ranging from 23 to 63 years of age.<sup>14</sup> Approximately 25% had had prior surgical procedures, and 44% underwent combined liver-kidney transplantation. The overall outcome after liver transplantation for polycystic disease in the United States between the years 1987 and 2003 is shown in Fig. 5 ([\[transplant.org\]\(http://www.us-transplant.org\); from US Scientific Registry of Transplant Recipients with aid of Dawn Zinsser, Director of Analytic Support, February 2004\). Survival rates for 1, 3, and 5 years in patients undergoing isolated hepatic transplantation \(n = 128\) were 78.1%, 71.7%, and 68.7%, respectively. Survival rates for 1, 3, and 5 years in patients undergoing combined liver-kidney transplantation \(n = 78\) were 79.5%, 75.5%, and 75.5%, respectively.](http://www.us-</a></p>
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## Summary

This review highlights several unique features of the natural history, pathogenesis, genetics, molecular biology, and clinical management of PCLD. There are currently three well-defined genes linked to autosomal dominant PCLD. Mutations in *PKD1* (PC-1) and *PKD2* (PC-2) account for nearly all cases of concomitant hepatic and renal polycystic disease, and mutations in *PRKCSH* (hepatocystin) are responsible for isolated polycystic liver. The clinical manifestations and natural history of hepatic cystic disease is similar despite the molecular and genetic heterogeneity. Massive hepatic cystic disease is associated with female sex, pregnancy, and exposure to exogenous use of female steroid hormones. Polycystic liver is rarely associated with hepatic failure, complications of portal hypertension, or clinical decompensation of hepatic function. There are currently no medical treatments for polycystic liver. Interventional and surgical options for those with refractory symptoms include percutaneous puncture and sclerosis of cysts, cyst fenestration by open or laparoscopic technique, hepatic resection, and isolated hepatic or combined liver-kidney transplantation.

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