World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v6.i2.278

World J Transplant 2016 June 24; 6(2): 278-290
ISSN 2220-3230 (online)

REVIEW

Liver transplantation and the management of progressive familial intrahepatic cholestasis in children

Ashley Mehl, Humberto Bohorquez, Maria-Stella Serrano, Gretchen Galliano, Trevor W Reichman

Ashley Mehl, University of Queensland-Ochsner Clinical School of Medicine, Jefferson, LA 70118, United States

Humberto Bohorquez, Trevor W Reichman, Multi-Organ Transplant Institute, Ochsner Medical Center, New Orleans, LA 70118, United States

Maria-Stella Serrano, Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Ochsner Medical Center, New Orleans, LA 70118, United States

Gretchen Galliano, Department of Pathology, Ochsner Medical Center, New Orleans, LA 70118, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: The authors have indicated they have no potential conflicts of interest to disclose.

Correspondence to: Trevor W Reichman, MD, PhD, FACS, Multi-Organ Transplant Institute, Ochsner Medical Center, 1514 Jefferson Hwy, New Orleans, LA 70118, United States. treichman@ochsner.org
Telephone: +1-504-8423925
Fax: +1-504-8425746

Received: December 14, 2015
Peer-review started: December 18, 2015
First decision: January 18, 2016
Revised: February 24, 2016
Accepted: March 9, 2016
Article in press: March 14 2016
Published online: June 24, 2016

Abstract

Progressive familial intrahepatic cholestasis (PFIC) is a constellation of inherited disorders that result in the impairment of bile flow through the liver that predominantly affects children. The accumulation of bile results in progressive liver damage, and if left untreated leads to end stage liver disease and death. Patients often present with worsening jaundice and pruritis within the first few years of life. Many of these patients will progress to end stage liver disease and require liver transplantation. The role and timing of liver transplantation still remains debated especially in the management of PFIC1. In those patients who are appropriately selected, liver transplantation offers an excellent survival benefit. Appropriate timing and selection of patients for liver transplantation will be discussed, and the short and long term management of patients post liver transplantation will also be described.

Key words: Pediatric liver transplant; Progressive familial intrahepatic cholestasis; Familial intrahepatic cholestasis protein 1; Cholestasis; Multidrug resistance protein 3; Pediatric jaundice; Bile salt excretion protein

Core tip: Progressive familial intrahepatic cholestasis is a rare disorder that predominantly affects young children. If left untreated, children develop debilitating cholestasis and eventually progress to liver failure. Liver transplantation is curative of symptoms related to liver disease but in some cases worsens the extrahepatic symptoms. A multidisciplinary approach is critical to obtaining good long-term outcomes.

Mehl A, Bohorquez H, Serrano MS, Galliano G, Reichman TW. Liver transplantation and the management of progressive

familial intrahepatic cholestasis in children. *World J Transplant* 2016; 6(2): 278-290 Available from: URL: http://www.wjgnet.com/2220-3230/full/v6/i2/278.htm DOI: http://dx.doi.org/10.5500/wjt.v6.i2.278

INTRODUCTION

Cholestasis in children is caused by many different entities. Progressive familial intrahepatic cholestasis (PFIC), which is also referred to as Byler's disease, Byler's syndrome, or Greenland-Eskimo familial cholestasis, is an autosomal recessive inherited disease that disrupts the genes encoding protein transporters responsible for bile formation[1]. These mutant proteins result in the impairment of bile flow through the liver leading to severe intrahepatic cholestasis and progressive chronic liver disease[2]. Recently, mutations in a gene important for the formation of tight junctions was also reported that leads to progressive intrahepatic cholestasis[3].

Familial conditions of cholestasis were first reported in the 1950s with Ahrens *et al*[4] reporting 4 patients with congenital absence of their intrahepatic bile ducts. These patients had persistent jaundice very early in life, severe growth retardation, malabsorption, pruritus and xanthomatosis with marked hypercholesterolemia. Liver biopsies of these patients revealed complete absence of interlobular bile ducts and bile stasis, despite a normal lobular architecture and extra hepatic biliary system. All four of these children died at an early age[4]. Similarly, in 1966, Gray *et al*[5] reported two sisters with jaundice, marked growth retardation, malabsorption, and pruritus. The course was progressive for both sisters and they died before the age 3[5]. Clayton *et al*[6], Juberg *et al*[7], and Sharp *et al*[8] also reported additional cases of children with progressive cholestasis and liver failure resulting in death. Similarities among these early reported cases were described in an early review on PFIC by Ballow *et al*[9] and included: A familial occurrence, a clinical history of fluctuating jaundice, pruritus, malabsorption, growth retardation early in life and hepatosplenomegaly. Similar biochemical findings included conjugated hyperbilirubinemic obstructive cholestasis with normal blood cholesterol levels[9].

SEARCH STRATEGY

A literature search of English language publications from 1990-2014 was used to identity published data on liver transplantation for PFIC using the Patients Intervention Comparator Outcomes outline (Table 1)[10]. Databases searched were PubMed, Ovid MEDLINE, and Cochrane Reviews. Terms used in the search were "liver transplantation" AND one of the following terms "progressive familial intrahepatic cholestasis", "PFIC", "PFIC1", "PFIC2", "PFIC3", "Byler's Syndrome" or "Byler's Disease".

EPIDEMIOLOGY

The incidence of any of the defective genes involved in the development of PFIC is 1:50000-100000 births and has not shown predominance in any specific geographical area[2,11]. However, there have been communities that have noted cohorts of patients including Faeroe Islands, Inuit (Eskimo) Indians (Greenland and Canada), and the Amish[6,12-15]. PFIC is responsible for 10%-15% of cases of neonatal cholestasis syndrome and is one of the leading indications for pediatric liver transplantation[16,17].

PATHOPHYSIOLOGY

Bile formation at the level of the hepatocytes involves active transport of bile salts, phospholipids, and cholesterol from the portal blood at the basolateral membrane. In PFIC, these transporters function abnormally (Figure 1). Bile then flows from the bile canaliculi lined by adjacent hepatocytes into the canals of Hering that are lined on one side by hepatocytes and one side by cholangiocytes. From there, bile drains into the larger bile ductules.

PFIC1

PFIC1 is an autosomal recessive condition. The mutant gene responsible for the disorder is the *ATP8B1* gene encoding the FIC1 protein[18,19]. The gene locus for ATP8B1 is located on chromosome 18 (18q21-22). FIC1 is a member of the type 4 subfamily of P type adenosine triphosphatase transporters and is involved in phospholipid translocation. The protein is located on the canalicular membrane of hepatocytes and facilitates movement of phosphatidylserine and phosphatidylethanolamine from the outer to inner leaflet of the plasma membrane of the hepatocyte. In addition, it helps to protect the membrane from high bile salt concentration in the canalicular lumen[20].

Mutation of this protein significantly impairs bile salt secretion. The exact mechanism for how deficiency of FIC1 leads to cholestasis is not fully understood[1]. Varying severities of PFIC1 are however noted[11].

PFIC2

PFIC2 is caused by mutation of the ATP binding cassette family B member 11 (*ABCB11*) gene encoding the bile salt excretion protein (BSEP) protein. The gene locus is on chromosome 2 (2q24) and is similarly inherited in an autosomal recessive fashion. BSEP, like FIC1, is a transporter protein that is expressed at the canalicular membrane of hepatocytes, and is the primary exporter of bile acids[21]. BSEP malfunction leads to failure of bile salt secretion from hepatocytes into bile canaliculi and accumulation of bile inside the hepatocytes. This results in severe impaired bile flow and hepatocellular damage[1]. On immunohistochemical staining, BSEP is usually not detectable in PFIC2, and if there is any protein present, it is usually non-functional[22-26].

Table 1 Patients Intervention Comparator Outcomes table for assessment of progressive familial intrahepatic cholestasis

P	I	C	O
Pediatric patients with PFIC	Liver transplantation	Biliary diversion and medical management	Patients survival, graft survival, post operative morbidity

PFIC: Progressive familial intrahepatic cholestasis; P: Patients; I: Intervention; C: Comparator; O: Outcomes.

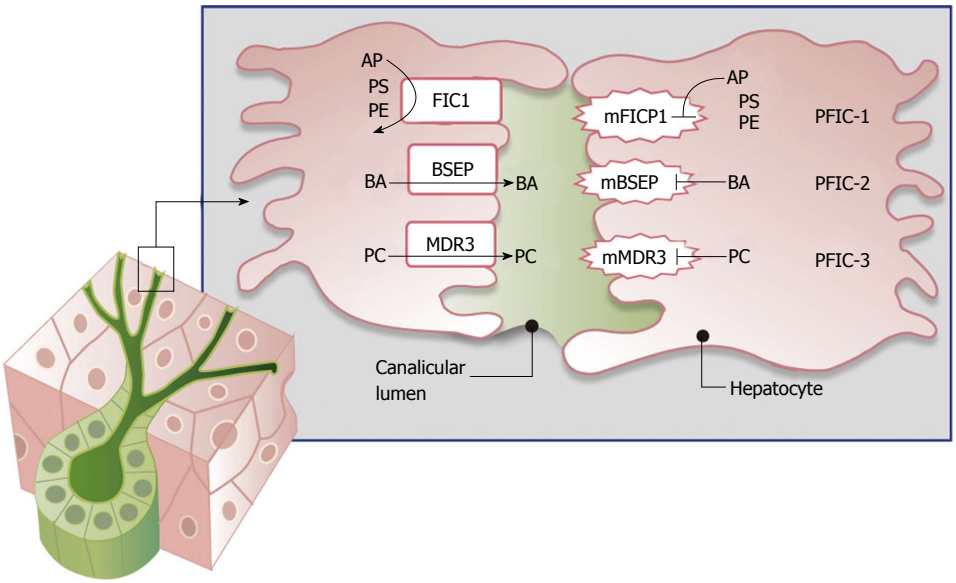

Figure 1 Disruption of bile flow and progressive familial intrahepatic cholestasis. AP: Aminophospholipids; PS: Phosphatidylserine; PE: Phosphatidylethinolamine; BA: Bile acids; PC: Phosphatidylcholine; FIC1: Familial intrahepatic cholestasis protein 1; BSEP: Bile salt exporter pump; MDR3: Multidrug resistance protein 3; mFIC1: Mutant familial intrahepatic cholestasis protein 1; mBSEP: Mutant bile salt exporter pump; mMDR3: Mutant multidrug resistance protein; PFIC: Progressive familial intrahepatic cholestasis.

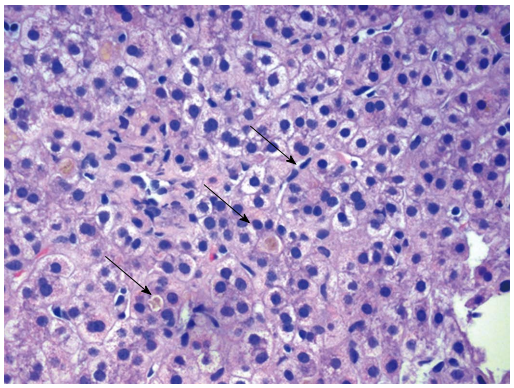

Figure 2 Progressive familial intrahepatic cholestasis type 1 with severe bland lobular cholestasis and lobular disarray. The image shows bile plugging with surrounding pseudorosette formation (arrows). In PFIC1, the canalicular bile is course on electronic microscopy and also referred to as "Byler bile". Thick bile is seen within the pseudorosette here on H and E stain. There is an absence of lobular inflammation and typically no features of neonatal giant cell hepatitis. PFIC: Progressive familial intrahepatic cholestasis.

PFIC3

A mutation in adenosine triphosphate-binding cassette subfamily B member 4 (*ABCB4*) gene encoding the MDR3 protein leads to the development of PFIC3[27,28]. The gene locus is on chromosome 7 (7q21). MDR3 protein is a p-glycoprotein that secretes phospholipids, primarily phosphatidylcholine within bile acid. Dysfunction leads to a decrease in phospholipid excretion[28]. MDR3 defects results in biliary epithelium injury and bile canaliculi injury as well as cholestasis. In addition, there is destabilization of micelles and promotion of cholesterol crystallization that results in increased biliary lithogenicity. This subtype of PFIC is usually present on both alleles and yields complete loss of the MDR3 protein either from a truncated MDR3 from a premature stop codon or missense mutations. All mutations result in severe defective transport of phospholipids and intracellular misprocessing[29].

PFIC4

PFIC4 is a recently described genetic mutation involving the *TJP2* gene that encodes for the tight junction protein 2[3]. TJP2 is a cytosolic protein that interacts with several cytoskeletal proteins and integral membrane proteins and plays an important role in localizing proteins such as Claudins (*e.g.*, CLDN1) to these structures[30]. Patients who presented with PFIC were found to have protein-truncating mutations that resulted in inappropriate localization and disruption of the tight junctions[31].

HISTOLOGIC ALTERATIONS IN PFIC

Even within the different subtypes of PFIC, there are common features and some distinct features. Specific

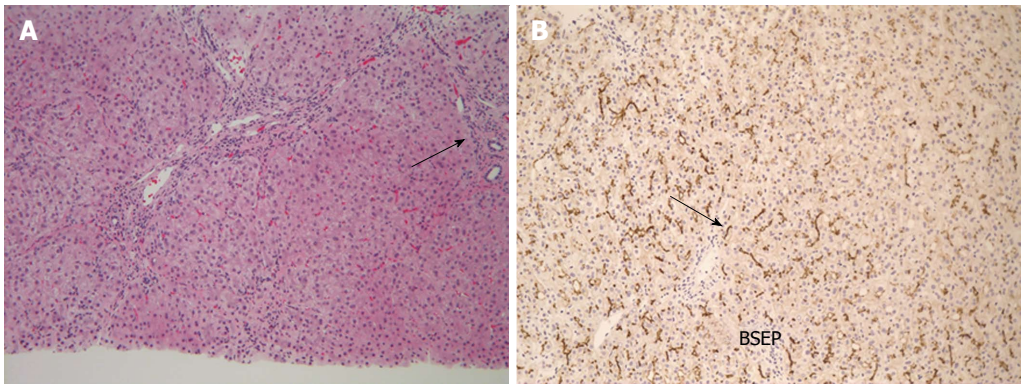

Figure 3 Progressive familial intrahepatic cholestasis type 2 is characterized by mutations in the *ABCB11* gene. A: Patients with progressive familial intrahepatic cholestasis type 2 (PFIC2) can initially present clinically similarly to PFIC1, but with more rapid progression of liver disease. Early on in the disease patients may present with neonatal giant cell hepatitis and lobular inflammation. However, there can be rapid progression with prominent duct reaction and progression to cirrhosis. This figure demonstrates prominent duct reaction in a patient with PFIC2 and advancing fibrosis (arrow). Duct reaction and cholestasis can also occur in patients with extrahepatic biliary obstruction so correlation with clinical findings is required; B: PFIC2 is also called BSEP disease and is characterized by mutations in the *ABCB11* gene. *ABCB11* encodes for the major canalicular bile salt exporter BSEP. Patients with normal BSEP expression show positive immunohistochemistry for BSEP with a canalicular pattern of staining (arrow). In some cases of PFIC2, there is complete lack of staining for BSEP. BSEP: Bile salt exporter pump.

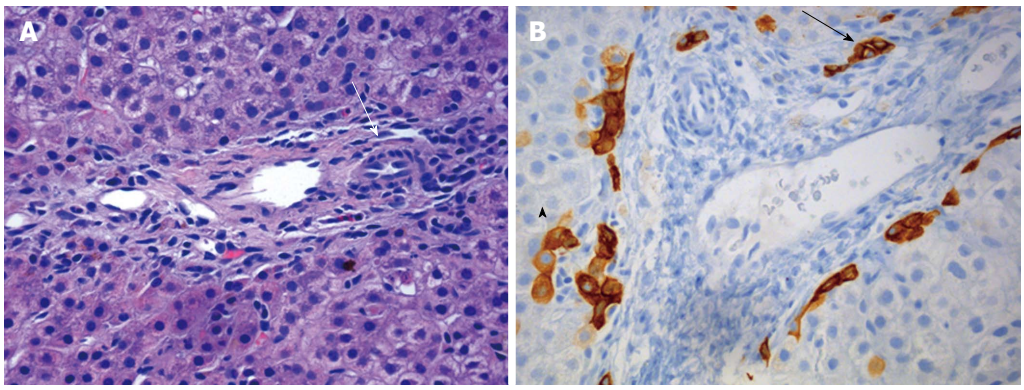

Figure 4 Progressive familial intrahepatic cholestasis type 1 and 2 can also present with duct paucity. A and B: The portal tracts show an absence of bile duct with periportal duct reaction; B: A higher power view of the portal tract with vein on the left artery on the right (arrow) and no appreciable bile duct. Keratin 7 is negative in this portal tract in B and positive in the bile duct reaction (arrow) with some bile duct progenitor cells (paler brown staining arrowhead).

signs on biopsy of PFIC1 (Figure 2) include bland cholestasis, mild lobular fibrosis, and centrilobular canalicular cholestasis with acinar or pseudo rosette formation[1,32]. Early in the disease, the initial biopsy typically demonstrates hypoplastic and threadlike interlobular bile ducts. With progression of the disease, centrilobular hepatocyte loss occurs with resulting pericanilicular and periportal fibrosis. Over time, there is progression to portal-portal and portal-central bridging fibrosis that leads ultimately to micronodular cirrhosis. Interestingly, fibrosis progresses in the absence of significant inflammation and ductular reaction[32].

Findings in the PFIC2 subtype (Figure 3) include cholestasis, giant cell hepatitis, hepatocellular necrosis, portal fibrosis and neonatal giant cell hepatitis with hepatocellular and canalicular cholestasis[32]. The fibrosis begins both in the portal tracts and in centrilobular regions and progresses through a biliary pattern type cirrhosis leading to micro nodular cirrhosis with slight ductular reaction[32]. Both PFIC1 and PFIC2 can show a paucity of bile ducts (Figure 4).

In PFIC3 (Figure 5), there is bile ductular proliferation, inflammatory infiltrate and biliary fibrosis with mild expansion of portal tracts due to a ductular reaction[32]. Canalicular cholestasis is present in centrilobular areas, and biliary/micro nodular cirrhosis supervenes with a biliary halo around cirrhotic nodules. There is also often the presence of ductular reaction and bile plugs[1].

Immunohistochemistry (IHC), electron microscopy (EM) and bile analysis can also provide important information regarding the different subtypes of PFIC. IHC for the different proteins associated with the different PFIC phenotypes is typically performed. However, normal IHC does not necessarily rule out a diagnosis of PFIC since some mutations are solely functional mutations and do not alter protein synthesis or expression[22]. Immunohistochemical stains can be particularly helpful in the identification of the BSEP protein at the canalicular membrane[22]. In PFIC3 patients, canalicular MDR3 immunoreactivity is typically detectable and the diagnosis of PFIC3 requires gene sequencing[24].

EM is also useful in differentiating the different PFIC subtypes. In PFIC1, the EM is coarse and granular in

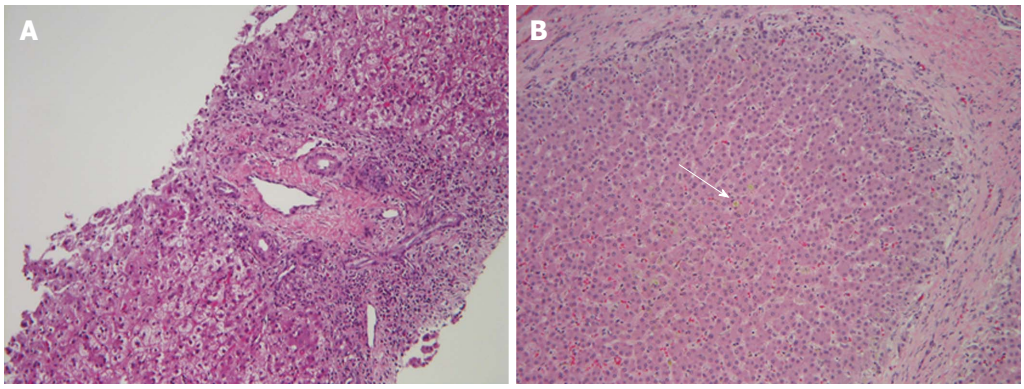

Figure 5 Clinical presentation of progressive familial intrahepatic cholestasis type 3. A: Progressive familial intrahepatic cholestasis type 3 (PFIC3) has a variable clinical presentation and may show nonspecific biliary pattern of injury that can mimic extrahepatic biliary atresia such as bile duct proliferation and cholestasis. In this patient with PFIC3 there is cholestasis, inflammation, and bile duct proliferation; B: Biliary type cirrhosis in a patient with PFIC3 with severe cholestasis (arrow) and micronodular cirrhosis.

appearance that is the characteristic "Byler's bile". In contrast, PFIC2 EM has an amorphous appearance[33,34]. EM findings in PFIC3 patients have not been reported. In PFIC4, EM of the liver tissue of these patients demonstrated elongated tight junctions that lacked the densest part of the zona occludens[3].

CLINICAL PRESENTATION

The hallmark sign and symptom of the disease is jaundice and pruritus. For children and their parents, pruritus is an extremely distressing manifestation of disease and its relief is often the goal of early therapy. Significant pruritus leads to cutaneous mutilation, loss of sleep, irritability, poor attention and impaired school performance. In addition to pruritus, other symptoms include icterus, hepatosplenomegaly, excoriations, hyperpigmentation of the skin, shiny nails, growth retardation, pale stools, and fat malabsorption[1,11]. Most cases of PFIC present in infancy or early childhood with jaundice, and progress rapidly to fibrosis and end-stage liver disease. If left untreated, end stage liver disease will result in death.

There are many similarities and few distinct differences between the different PFIC subtypes[35,36]. Signs specific to PFIC1 include presentation in early infancy as opposed to neonatal period or later in childhood. Foul-smelling, high volume stools and failure to thrive are also hallmarks for PFIC1[35]. Gastrointestinal involvement even after liver transplant with secretory diarrhea can be significant[35,37]. Hemorrhage is also a possible sequelae and is potentiated by vitamin K deficiency and similarly can be the first clinical manifestation[1]. Classic biochemical signs include low or normal gamma-glutamyl transpeptidase (GGT), high alkaline phosphatase and a lower serum albumin as compared to PFIC2. Additionally, there is typically more severe cholestasis and recurrent jaundice, extrahepatic disease and portal hypertension. These sequelae often lead to decompensation in early childhood.

In contrast to PFIC1, PFIC2 tends to present in the neonatal period rather than later in infancy or childhood and tends to progress more rapidly. Biochemically, patients generally have a low or normal GGT, higher serum aminotransferases, higher serum bile acids and higher α-fetoprotein[35]. Patients present with severe cholestasis and persistent jaundice typically within the first month of life. Consistent with the restricted expression of ABCB11 to the liver, there are no extrahepatic manifestations of PFIC2. Progression to end stage liver disease results in portal hypertension and other manifestations of end stage liver disease. PFIC2 tends to progress to end-stage liver disease more rapidly, with cirrhosis, liver failure and death in the first decade of life, most commonly in the first year of life, if a liver transplant is not performed[35].

PFIC3 usually presents in adulthood or late adolescence[38,39]. It is characterized by cholestasis and gastrointestinal bleeds secondary to cirrhosis and portal hypertension. Gastrointestinal bleeding may be the first presenting symptoms in older children or young adults. Biochemically, PFIC3 patients tend to have an elevated GGT. There is also an increased risk of cholesterol and drug induced cholestasis in patients with MDR3 mutations and PFIC3[40,41].

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Initial investigations of the jaundiced child include a combination of clinical, radiological, and laboratory testing with the goal of ruling out biliary obstruction and extra hepatic causes of jaundice. In addition, infectious or metabolic etiologies should also be ruled out. Important screening and confirmatory laboratory tests include a complete blood count, chemistries including electrolytes, serum glucose, liver enzymes, total and direct bilirubin, GGT, thyroid function studies, C-reactive protein, ferritin, and coagulation studies. In addition to the above labs, serum bile acids, urinary bile acids, lactic acid, alpha-1-antitrypsin phenotype,

Table 2 Review of documented liver transplantation outcomes for progressive familial intrahepatic cholestasis patients (≥ 3 patients)

Ref.	PFIC type	Age at transplant (years old)	Previous management	Graft survival	Patient survival	Notes
Soubrane *et al*[45]	14 "byler disease" PFIC type unspecified	6.5 (0.4-13)	NR	93.3%	92.8%	Consanguineous to the 2nd degree in 8 cases
Emond *et al*[91]	11 PFIC unspecified type	4.6 ± 3.4	2 had previous partial biliary diversion procedures	76.9%	73%	LT performed on those with advanced cirrhosis (6 received diversion procedures only)
Ismail *et al*[80]	8 PFIC of unspecified type	Unknown	1 patient PEBD, all received cholestyramine, phenobarbital, rifampicin, UDCA	100%	85.7%	6 cadaver livers, 2 living donors
Kondo *et al*[63]	4 PFIC of unspecified type	2-7	NR	75%	75%	
Bassas *et al*[56]	5 PFIC3 8 "low GGT PFIC" PFIC1/2	10-40 mo	NR	84.6%	84.6%	Parents of 12 out of 13 were 1st cousins
Cutillo *et al*[57]	6 PFIC1/2 1 PFIC3	4-53 mo	NR	100%	75%	
Englert *et al*[44]	33 patients PFIC2 and 3	Unknown	UDCA 10 of 33 received biliary diversion then LT	100% with prior diversion 89% without prior diversion	100%	
Aydogdu *et al*[52]	10 PFIC1/2 2 PFIC3	43.2 ± 27 mo	UDCA	69.2%	75%	Surviving patients show good quality of life, exacerbation of diarrhea as the exception, mix of LDLT and cadaveric
Hori *et al*[50,51] Miyagawa-Hayashino *et al*[54], Egawa *et al*[53]	11 PFIC1 3 PFIC2	0.6-18.2 years old	Total external biliary diversion performed at time of re-transplantation in one PFIC1 patient	82.4% total graft survival (14/17)	PFIC1 - 90.9% at 5 yr, 72.7% at 10 yr, 54.5% at 15 yr; PFIC2 - 100% at 5 yr	Digestive symptoms in 10 out of 11 PFIC1; 8 out of 11 PFIC1 recipients exhibited steatosis; 9 out of 11 PFIC1 recipients exhibited fibrosis
Kaur *et al*[58]	2 PFIC3 2 PFIC1/2	2, 2.5, 6 and 9 years old males	UDCA, phenobarbital and ondansetron	100%	75%	

LT: Liver transplantation; PEBD: Partial external biliary diversion; UDCA: Ursodeoxycholic acid; PFIC: Progressive familial intrahepatic cholestasis; GGT: Gamma-glutamyl transpeptidase; LDLT: Living donor liver transplantation; NR: Not reported.

alpha-fetoprotein, ammonia, cortisol, viral serologies, carnitine and acyl carnitine profile, and plasma amino acids levels should also be considered[14]. GGT levels not only assist in the differentiation of the type of PFIC, but may also be a helpful prognostic indicator[42]. A serum albumin, which if low, may indicate advanced disease or malnutrition[10]. The presence of coagulopathy may also increase the suspicion of advanced disease[10]. Genetic studies for JAG1 mutations as well as for the described PFIC mutations should also be performed to clarify the etiology of cholestasis. Once a diagnosis of PFIC is made, differentiating between the subtypes, such as PFIC1 and 2 in newborns and young infants, is important since options for optimal treatment may differ between subtypes. Genetic testing is the gold standard for diagnosis using a "gene chip". One chip allows for the analysis of 27 coding regions and their splice junctions from 5 different genes known to be involved in inherited syndromes of intrahepatic cholestasis[43].

In addition to laboratory testing, radiologic investigations are also critical and almost always include an initial abdominal ultrasound. In addition, magnetic resonance cholangiopancreatography can provide additional information especially in older children and help exclude other diagnoses such as primary sclerosing cholangitis that may be high on the differential list particularly in patients with high levels of GGT and cholestasis.

ROLE OF LIVER TRANSPLANTATION

Liver transplantation is currently the only definitive treatment available for PFIC. It corrects the genetic defect and reverses many if not all of the effects of chronic liver disease. Several series have been published examining the outcomes of liver transplantation for PFIC (Table 2). Of the cumulative 131 patients of all subtypes documented, graft survival and patient survival was 76.6% and 85.2% respectively with the

longest reported follow up interval being 19 years post-transplantation.

In the largest series by Englert *et al*[44], 23 patients (PFIC2 or 3) underwent orthotopic liver transplantation as their first line of treatment and 10 received liver transplantation after an initial biliary diversion procedure. The graft survival rate of those who received a liver transplant initially was 89%, whereas graft survival rates of those who first received biliary diversion and subsequent transplantation were 100%. Patient survival between the two groups was 100%[44]. Soubrane *et al*[45] reported similar excellent outcomes. Of the 14 patients transplanted, 13 patients were alive at was an average follow up of 17 mo with normal family life and all children returning to school[45].

Earlier transplantation for PFIC2 appears to be warranted as this subtype appears to progress to cirrhosis faster and also carries an increased risk for the development of primary liver cancers. Hepatoblastoma, hepatocellular carcinoma, and cholangiocarcinoma have all been reported in PFIC2[46-48]. Transplantation in these patients is well tolerated with high graft and patient survival rates as well as great improvements in quality of life. Shimizu *et al*[49] reports two PFIC2 patients that were transplanted prior to the development of end-stage liver disease. Both siblings presented with jaundice and pruritus before 1 year of age. The elder sibling also demonstrated symptoms including acholic stools and failure to thrive. Histopathology revealed the classic findings of PFIC2 but no cirrhotic or malignant changes were identified. Neither sibling experienced major post-surgical complications.

Unlike in PFIC2, early transplantation in PFIC1 is controversial. Although liver transplantation corrects the *FIC1* gene in the liver and theoretically reverses the symptoms related to liver disease, the outcomes post-transplant are mixed. Hori *et al*[50,51] reported one of the largest series for patients that underwent liver transplantation for PFIC1. Eleven PFIC1 patients who received living-donor liver transplants were reported. Post-transplant steatosis was significant (moderate-severe) in 8 of the PFIC1 recipients (72.7%). Four of the 11 recipients eventually showed signs of cirrhosis post-transplant such as esophageal varices and splenomegaly[50]. Two of the 11 PFIC1 patients suffered graft losses, and 10 of 11 patients (90.9%) reported digestive symptoms post liver transplantation. The survival rates of the PFIC1 patients at 5, 10 and 15 years liver transplantation were 90.9%, 72.7% and 54.5% respectively. Additional studies have also highlighted the presence or aggravation of severe digestive symptoms in addition to higher mortality rates following transplantation for PFIC1[52-55]. Therefore, an attempt at medical management of symptoms and/or biliary diversion in PFIC1 patients should be considered prior to transplant. In additions, medical and/or surgical procedures to post liver transplantation should also be considered[52-55].

In addition to considering delaying liver transplantation in PFIC1 patients, the exact mutation specific to the PFIC1 patient may play a role in the development of steatohepatitis in the transplanted liver graft. Three of the 11 patients in this study had distinct mutations in the *FIC1* gene that did not result in persistent post-transplant diarrhea or steatosis[54]. Lykavieris *et al*[37] reported two PFIC1 patients with specific mutations that both resulted in diarrhea exacerbation, appearance of liver steatosis and no catch-up of stature growth at 11 and 7.5 years post-transplant. Nicastro *et al*[55] similarly reported a PFIC1 patient upon whom gene analysis was done and was found to have double heterozygosity for two missense mutations. This mutation was associated with unremitting diarrhea, steatohepatitis and progressive fibrosis.

There is less data reporting on the outcomes of transplantation for patients with PFIC3. In patients that require transplantation, small series have reported excellent graft and patient survival[44,52,56-58]. Like with PFIC2, liver transplantation is curative with resolution of pruritus and other manifestations of chronic liver disease. There are no reported cases of worsening of extrahepatic symptoms. The only post transplantation complications noted specifically for a PFIC3 patient was documented by Kaur *et al*[58] who noted grade 1 acute rejection in 1 post-operative patient. Greater than 80% patient survival rates in the groups that included known PFIC3 transplant recipients have been reported however post-operative quality of life for these patients needs to be further investigated.

In conclusion, liver transplantation is typically viewed as an option when patients have failed medical treatment and/or biliary diversion and have a poor quality of life due to refractory pruritus. Liver transplantation is also considered when patients have end stage liver disease or carcinoma. In regions where wait times potentially are shorter and/or living donation is available, liver transplantation can be considered earlier with excellent long-term survival and quality of life without the need to perform a biliary diversion. However, in cases of PFIC1, liver transplantation can be associated with an increase in extra hepatic manifestations, in particular chronic watery diarrhea and continued growth failure. Transplantation in this setting should be weighed against other options.

LIVING DONOR LIVER TRANSPLANTATION

Living donor liver transplantation (LDLT) has been shown to have outcomes equivalent to deceased donor liver transplantation[59-61]. There is a significant survival advantage to patients transplanted with living donors as compared to those patients on the deceased donor waiting list by preventing death on the waiting list. This can be as high as 20% at some United States centers[62]. In other parts of the world where deceased donation is non-existent, LDLT is the only option for patients with

ESLD. However, given that PFIC is an inherited disease, there was some concern that outcomes post transplant might be compromised when compared with deceased donor grafts from non-related donors. There have been several reports examining outcomes from LDLT that have refuted this notion.

All 13 PFIC patients who received a liver transplantation reported by Bassas *et al*[56] received a living related donor transplant. Eleven of the 13 patients survived and were without complications. The authors commented on the success of the grafts being due to adequate matching and graft size rather than the presence or lack of heterozygosity of gene variants in the donor. Similarly, of the 12 patients reported by Aydogdu *et al*[52], 6 received left lateral segment from living donors. All donors were biological parents. Four of the 6 patients were alive (66.7%) at 1 year follow-up. One patient death was due to hepatic artery thrombosis requiring re-transplantation and subsequent early post-operative death and the other patient developed post-transplant lympho-proliferative disease at 6 mo.

Several other smaller series and case reports have also corroborated these findings[49,57,58,63]. Cutillo *et al*[57] reported 7 PFIC patients who received living related donor transplantation from parental donors. A previous family history of PFIC was found in three families and parental consanguinity in one family. Parental donors had normal liver functions tests and no personal past history of liver disease, gallstones, jaundice or cholestasis of pregnancy. They were alive and well at the time of follow up.

There is a natural concern for living related donor liver transplantation in patients with an inheritable intrahepatic cholestatic disease. However, grafts from related donors do not appear to be at higher risk for failure from PFIC-related causes. Living donation provides an excellent alternative to deceased donation and can provide timely liver transplant to patients.

ADVERSE OUTCOMES FOLLOWING LIVER TRANSPLANTATION

Like liver transplantation for other pediatric disorders, several well known complications have also been recorded such infection and rejection after transplantation for PFIC. These do not appear to occur at increased frequency post-transplant[64]. In addition to the general complications associated with transplantation, there are some that are specifically associated with PFIC.

In patients with PFIC1, an undesired effect of liver transplant is the potential worsening of the extra hepatic manifestations like diarrhea and short stature[52-55]. However, the manifestation and severity of these symptoms is unpredictable[54]. The diarrhea is almost always associated with steatosis on liver histology as well[50]. When these patients are treated with liver transplantation, the impairment of bile salt secretion is corrected, and subsequently, there is a large increase in bile acid secretion relative to what the patient's body is accustomed to. The intestinal manifestations after transplant may reflect an important role for FIC1 in the intestine, where it is highly expressed. This increase in bile acids in the stool causes high volume osmotic diarrhea that has a significant impact on quality of life.

Bile acid resins and partial biliary diversion procedures have been shown to improve these symptoms. Cholestyramine has been reported to be very effective in these patients for managing post-operative diarrhea as well as aiding in overall growth progression[37,50,53,54]. External biliary diversion post-transplantation in patients with PFIC1 who are experiencing an exacerbation of watery diarrhea has also been shown to improve symptoms as well as improve the steatosis on liver histology[55,65].

PFIC2 patients with subtypes that have no immunodetectable BSEP in their native liver also appear to be at risk for the development of recurrent disease[66,67]. Certain patients have developed antibodies against the BSEP protein in the donor liver[66,68,69]. These antibodies cause similar symptoms of cholestasis, steatosis and fibrosis that were present in the original disease process. In some cases, these antibodies have resulted in recurrent graft failure[70]. When allo-antibodies are detected, changes in immunosuppression and implementing plasmapheresis/molecular adsorbent recirculating system therapies have been shown to improve cholestatic episodes post-transplant in some of these PFIC2 patients[70]. The use of rituximab has also been reported and shown to improve symptoms[71].

ALTERNATIVES TO LIVER TRANSPLANTATION: MEDICAL AND SURGICAL THERAPIES

Both medical and surgical therapies play important roles in the management of patients with PFIC both as definitive therapy and as a bridge to transplant. In some cases, they have also been used to manage post-transplant complications.

Medical treatment for portal hypertension includes β-blockers and endoscopic management of esophageal and gastric varices when amenable. Fat-soluble vitamin supplementation and aggressive nutritional support with medium chain triglyceride - rich and high calorie concentrated formulas in infants is also important for the treatment of these patients as well.

Urso-deoxycholic acid (UDCA) increases hepatocyte excretion of bile acids and limits return to the liver by inhibiting their intestinal reabsorption. UDCA has been shown to improve symptoms and liver function tests in some patients with PFIC and is typically viewed as frontline therapy[72-74]. Patients who experience the greatest benefit typically have milder forms of the disease, whereas patients with a total defect in MDR3

tend to be the non-responders to UDCA treatment. Recently, the degree of floppase activity in MDR3 was linked to response to UDCA treatment[39]. In some cases, reversal of fibrosis with long term UDCA therapy has been noted[75]. Combining 4-phenylbutyrate (4-PB) and UDCA treatment together has also been shown to be a promising pre transplant therapy for patients with PFIC2 in an effort to increase BSEP presence at the canalicular membrane[76].

Cholestyramine and rifampicin are also used to provide symptomatic relief. Cholestyramine is a resin that binds bile salts in the intestinal lumen and thus reduces absorption and increases fecal bile salt excretion. Cholestyramine is the first line oral management for pruritus and is effective in up to 80%. Rifampicin aids in the excretion of bile salts and bilirubin in the urine, and aids in the treatment of pruritis.

Recently, Engelmann *et al*[77] documented the use of steroids in PFIC2. These two patients were reported who were incidentally started on steroids for other medical reasons and who subsequently had complete resolution of symptoms and resolution of elevated bile salts.

Biliary diversion procedures

Biliary diversion procedures decrease the enterohepatic circulation of bile reducing its toxic effects. When offered early, biliary diversion is successful in reducing symptoms from pruritus and also slowing the progression of fibrosis[11]. There are both partial external and internal biliary diversions that have been described. Nasobiliary drainage procedures when performed preoperatively can be helpful in the selection of patients that will have the highest success rate from the surgical diversion procedure[17].

Partial external biliary diversion which was first described by Whitington uses a 10-15 cm jejunal conduit between the gallbladder and the abdominal wall creating a permanent biliary stoma[78]. This procedure has been shown to improve growth, normalize liver function, reduce serum bile acids and improve liver histology[79]. In many cases, this procedure is the first line surgical option and should be offered prior to the development of cirrhosis. However, once cirrhosis has been documented, these patients have poorer outcomes and should undergo liver transplantation[80]. Success as documented by not progressing to liver transplantation is reported to be 23%-75%[44,79-83]. This technique is also associated with significant complications including prolapse of the anastomosis, infection, and high volume bile excretion[84]. Additionally, 1/3 of patients experience moderate to severe dehydration and hyponatremia[84]. Modifications of this technique have included the use of a button cholecystostomy and also the use of the appendix in place of the jejunum as a conduit[85,86].

Partial internal biliary diversion has the advantage in that it avoids an external stoma and the complications associated with it. The most common partial internal biliary drainage links the gallbladder drainage to the colon[87-89]. A modification of this procedure involving a laparoscopic cholecystocolostomy has also been described[90]. Initial results from these techniques have been promising, but longer follow-up is needed. Internal diversion to bypass the distal 15% of the small intestine by creating an ileal colonic bypass has also been attempted but outcomes were poor[82].

CONCLUSION

Until more research regarding targeted gene therapies and an increase in the development of the medical management for PFIC, liver transplant remains the most definitive treatment for those with PFIC. However, it is also important to consider current medical therapies and additional surgical interventions like biliary diversion that can potentially create a synergistic outcome. In particular, in patients with PFIC1, often the best clinical outcome and quality of life is an appropriate combination of all three of these therapies. Identification and better understanding of certain mutations in *FIC1* gene might lead to better patient selection. Similarly, in patients with PFIC2, the need for additional medical management can best be determined by pre-operative immunohistochemical studies which can help provide better clinical outcomes. Although the data for liver transplantation for PFIC3 is still lacking, it appears to be the preferred method of treatment with excellent long-term outcomes. There is currently no available clinical data regarding transplantation in the setting of mutations in *TJP2* gene (PFIC4).

REFERENCES

1 **Nakanishi Y**, Saxena R. Pathophysiology and Diseases of the Proximal Pathways of the Biliary System. *Arch Pathol Lab Med* 2015; **139**: 858-866 [PMID: 26125426 DOI: 10.5858/arpa.2014-0229-RA]

2 **Nguyen KD**, Sundaram V, Ayoub WS. Atypical causes of cholestasis. *World J Gastroenterol* 2014; **20**: 9418-9426 [PMID: 25071336 DOI: 10.3748/wjg.v20.i28.9418]

3 **Sambrotta M**, Strautnieks S, Papouli E, Rushton P, Clark BE, Parry DA, Logan CV, Newbury LJ, Kamath BM, Ling S, Grammatikopoulos T, Wagner BE, Magee JC, Sokol RJ, Mieli-Vergani G, Smith JD, Johnson CA, McClean P, Simpson MA, Knisely AS, Bull LN, Thompson RJ. Mutations in TJP2 cause progressive cholestatic liver disease. *Nat Genet* 2014; **46**: 326-328 [PMID: 24614073 DOI: 10.1038/ng.2918]

4 **Ahrens EH**, Harris RC, Macmahon HE. Atresia of the intrahepatic dile ducts. *Pediatrics* 1951; **8**: 628-647 [PMID: 14891320]

5 **Gray OP**, Saunders RA. Familial intrahepatic cholestatic jaundice in infancy. *Arch Dis Child* 1966; **41**: 320-328 [PMID: 5940621]

6 **Clayton RJ**, Iber FL, Ruebner BH, McKusick VA. Byler disease. Fatal familial intrahepatic cholestasis in an Amish kindred. *Am J Dis Child* 1969; **117**: 112-124 [PMID: 5762004]

7 **Juberg RC**, Holland-Moritz RM, Henley KS, Gonzalez CF. Familial intrahepatic cholestasis with mental and growth retardation. *Pediatrics* 1966; **38**: 819-836 [PMID: 5954222]

8 **Sharp HL**, Carey JB, White JG, Krivit W. Cholestyramine therapy in patients with a paucity of intrahepatic bile ducts. *J Pediatr* 1967; **71**: 723-736 [PMID: 6054760]

9 **Ballow M**, Margolis CZ, Schachtel B, Hsia YE. Progressive familial intrahepatic cholestasis. *Pediatrics* 1973; **51**: 998-1007 [PMID: 4710460]

10 **Haroon M**, Phillips R. "There is nothing like looking, if you want to find something" - asking questions and searching for answers - the evidence based approach. *Arch Dis Child Educ Pract Ed* 2010; **95**: 34-39 [PMID: 20351149 DOI: 10.1136/adc.2009.161570]

11 **Srivastava A**. Progressive familial intrahepatic cholestasis. *J Clin Exp Hepatol* 2014; **4**: 25-36 [PMID: 25755532 DOI: 10.1016/j.jceh.2013.10.005]

12 **Klomp LW**, Vargas JC, van Mil SW, Pawlikowska L, Strautnieks SS, van Eijk MJ, Juijn JA, Pabón-Peña C, Smith LB, DeYoung JA, Byrne JA, Gombert J, van der Brugge G, Berger R, Jankowska I, Pawlowska J, Villa E, Knisely AS, Thompson RJ, Freimer NB, Houwen RH, Bull LN. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. *Hepatology* 2004; **40**: 27-38 [PMID: 15239083 DOI: 10.1002/hep.20285]

13 **Nielsen IM**, Ornvold K, Jacobsen BB, Ranek L. Fatal familial cholestatic syndrome in Greenland Eskimo children. *Acta Paediatr Scand* 1986; **75**: 1010-1016 [PMID: 3564958]

14 **Ornvold K**, Nielsen IM, Poulsen H. Fatal familial cholestatic syndrome in Greenland Eskimo children. A histomorphological analysis of 16 cases. *Virchows Arch A Pathol Anat Histopathol* 1989; **415**: 275-281 [PMID: 2503928]

15 **Tygstrup N**, Steig BA, Juijn JA, Bull LN, Houwen RH. Recurrent familial intrahepatic cholestasis in the Faeroe Islands. Phenotypic heterogeneity but genetic homogeneity. *Hepatology* 1999; **29**: 506-508 [PMID: 9918928 DOI: 10.1002/hep.510290214]

16 **Hori T**, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 570-578 [PMID: 21134824]

17 **Jacquemin E**. Progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol* 2012; **36** Suppl 1: S26-S35 [PMID: 23141890 DOI: 10.1016/S2210-7401(12)70018-9]

18 **Bull LN**, van Eijk MJ, Pawlikowska L, DeYoung JA, Juijn JA, Liao M, Klomp LW, Lomri N, Berger R, Scharschmidt BF, Knisely AS, Houwen RH, Freimer NB. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. *Nat Genet* 1998; **18**: 219-224 [PMID: 9500542 DOI: 10.1038/ng0398-219]

19 **van Mil SW**, Klomp LW, Bull LN, Houwen RH. FIC1 disease: a spectrum of intrahepatic cholestatic disorders. *Semin Liver Dis* 2001; **21**: 535-544 [PMID: 11745041 DOI: 10.1055/s-2001-19034]

20 **Paulusma CC**, Folmer DE, Ho-Mok KS, de Waart DR, Hilarius PM, Verhoeven AJ, Oude Elferink RP. ATP8B1 requires an accessory protein for endoplasmic reticulum exit and plasma membrane lipid flippase activity. *Hepatology* 2008; **47**: 268-278 [PMID: 17948906 DOI: 10.1002/hep.21950]

21 **Strautnieks SS**, Kagalwalla AF, Tanner MS, Knisely AS, Bull L, Freimer N, Kocoshis SA, Gardiner RM, Thompson RJ. Identification of a locus for progressive familial intrahepatic cholestasis PFIC2 on chromosome 2q24. *Am J Hum Genet* 1997; **61**: 630-633 [PMID: 9326328 DOI: 10.1086/515501]

22 **Evason K**, Bove KE, Finegold MJ, Knisely AS, Rhee S, Rosenthal P, Miethke AG, Karpen SJ, Ferrell LD, Kim GE. Morphologic findings in progressive familial intrahepatic cholestasis 2 (PFIC2): correlation with genetic and immunohistochemical studies. *Am J Surg Pathol* 2011; **35**: 687-696 [PMID: 21490445 DOI: 10.1097/PAS.0b013e318212ec87]

23 **Jansen PL**, Strautnieks SS, Jacquemin E, Hadchouel M, Sokal EM, Hooiveld GJ, Koning JH, De Jager-Krikken A, Kuipers F, Stellaard F, Bijleveld CM, Gouw A, Van Goor H, Thompson RJ, Müller M. Hepatocanalicular bile salt export pump deficiency in patients with progressive familial intrahepatic cholestasis. *Gastroenterology* 1999; **117**: 1370-1379 [PMID: 10579978]

24 **Keitel V**, Burdelski M, Warskulat U, Kühlkamp T, Keppler D, Häussinger D, Kubitz R. Expression and localization of hepatobiliary transport proteins in progressive familial intrahepatic cholestasis. *Hepatology* 2005; **41**: 1160-1172 [PMID: 15841457 DOI: 10.1002/hep.20682]

25 **Strautnieks SS**, Byrne JA, Pawlikowska L, Cebecauerová D, Rayner A, Dutton L, Meier Y, Antoniou A, Stieger B, Arnell H, Ozçay F, Al-Hussaini HF, Bassas AF, Verkade HJ, Fischler B, Németh A, Kotalová R, Shneider BL, Cielecka-Kuszyk J, McClean P, Whitington PF, Sokal E, Jirsa M, Wali SH, Jankowska I, Pawłowska J, Mieli-Vergani G, Knisely AS, Bull LN, Thompson RJ. Severe bile salt export pump deficiency: 82 different ABCB11 mutations in 109 families. *Gastroenterology* 2008; **134**: 1203-1214 [PMID: 18395098 DOI: 10.1053/j.gastro.2008.01.038]

26 **Wang L**, Soroka CJ, Boyer JL. The role of bile salt export pump mutations in progressive familial intrahepatic cholestasis type II. *J Clin Invest* 2002; **110**: 965-972 [PMID: 12370274 DOI: 10.1172/JCI15968]

27 **de Vree JM**, Jacquemin E, Sturm E, Cresteil D, Bosma PJ, Aten J, Deleuze JF, Desrochers M, Burdelski M, Bernard O, Oude Elferink RP, Hadchouel M. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. *Proc Natl Acad Sci USA* 1998; **95**: 282-287 [PMID: 9419367]

28 **Deleuze JF**, Jacquemin E, Dubuisson C, Cresteil D, Dumont M, Erlinger S, Bernard O, Hadchouel M. Defect of multidrug-resistance 3 gene expression in a subtype of progressive familial intrahepatic cholestasis. *Hepatology* 1996; **23**: 904-908 [PMID: 8666348 DOI: 10.1002/hep.510230435]

29 **Jacquemin E**. Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. *Semin Liver Dis* 2001; **21**: 551-562 [PMID: 11745043 DOI: 10.1055/s-2001-19033]

30 **Fanning AS**, Van Itallie CM, Anderson JM. Zonula occludens-1 and -2 regulate apical cell structure and the zonula adherens cytoskeleton in polarized epithelia. *Mol Biol Cell* 2012; **23**: 577-590 [PMID: 22190737 DOI: 10.1091/mbc.E11-09-0791]

31 **Sambrotta M**, Thompson RJ. Mutations in TJP2, encoding zona occludens 2, and liver disease. *Tissue Barriers* 2015; **3**: e1026537 [PMID: 26451340 DOI: 10.1080/21688370.2015.1026537]

32 **Morotti RA**, Suchy FJ, Magid MS. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis* 2011; **31**: 3-10 [PMID: 21344347 DOI: 10.1055/s-0031-1272831]

33 **Bull LN**, Carlton VE, Stricker NL, Baharloo S, DeYoung JA, Freimer NB, Magid MS, Kahn E, Markowitz J, DiCarlo FJ, McLoughlin L, Boyle JT, Dahms BB, Faught PR, Fitzgerald JF, Piccoli DA, Witzleben CL, O'Connell NC, Setchell KD, Agostini RM, Kocoshis SA, Reyes J, Knisely AS. Genetic and morphological findings in progressive familial intrahepatic cholestasis (Byler disease [PFIC-1] and Byler syndrome): evidence for heterogeneity. *Hepatology* 1997; **26**: 155-164 [PMID: 9214465 DOI: 10.1002/hep.510260121]

34 **Kurbegov AC**, Setchell KD, Haas JE, Mierau GW, Narkewicz M, Bancroft JD, Karrer F, Sokol RJ. Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile. *Gastroenterology* 2003; **125**: 1227-1234 [PMID: 14517804]

35 **Davit-Spraul A**, Fabre M, Branchereau S, Baussan C, Gonzales E, Stieger B, Bernard O, Jacquemin E. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. *Hepatology* 2010; **51**: 1645-1655 [PMID: 20232290 DOI: 10.1002/hep.23539]

36 **Pawlikowska L**, Strautnieks S, Jankowska I, Czubkowski P, Emerick K, Antoniou A, Wanty C, Fischler B, Jacquemin E, Wali S, Blanchard S, Nielsen IM, Bourke B, McQuaid S, Lacaille F, Byrne JA, van Eerde AM, Kolho KL, Klomp L, Houwen R, Bacchetti P, Lobritto S, Hupertz V, McClean P, Mieli-Vergani G, Shneider B, Nemeth A, Sokal E, Freimer NB, Knisely AS, Rosenthal P, Whitington PF, Pawlowska J, Thompson RJ, Bull LN. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. *J Hepatol* 2010; **53**: 170-178 [PMID: 20447715 DOI: 10.1016/j.jhep.2010.01.034]

37 **Lykavieris P**, van Mil S, Cresteil D, Fabre M, Hadchouel

M, Klomp L, Bernard O, Jacquemin E. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. *J Hepatol* 2003; **39**: 447-452 [PMID: 12927934]

38 **Davit-Spraul A**, Gonzales E, Baussan C, Jacquemin E. The spectrum of liver diseases related to ABCB4 gene mutations: pathophysiology and clinical aspects. *Semin Liver Dis* 2010; **30**: 134-146 [PMID: 20422496 DOI: 10.1055/s-0030-1253223]

39 **Gordo-Gilart R**, Andueza S, Hierro L, Martínez-Fernández P, D'Agostino D, Jara P, Alvarez L. Functional analysis of ABCB4 mutations relates clinical outcomes of progressive familial intrahepatic cholestasis type 3 to the degree of MDR3 floppase activity. *Gut* 2015; **64**: 147-155 [PMID: 24594635 DOI: 10.1136/gutjnl-2014-306896]

40 **Ganne-Carrié N**, Baussan C, Grando V, Gaudelus J, Cresteil D, Jacquemin E. Progressive familial intrahepatic cholestasis type 3 revealed by oral contraceptive pills. *J Hepatol* 2003; **38**: 693-694 [PMID: 12713886]

41 **Pasmant E**, Goussard P, Baranes L, Laurendeau I, Quentin S, Ponsot P, Consigny Y, Farges O, Condat B, Vidaud D, Vidaud M, Chen JM, Parfait B. First description of ABCB4 gene deletions in familial low phospholipid-associated cholelithiasis and oral contraceptives-induced cholestasis. *Eur J Hum Genet* 2012; **20**: 277-282 [PMID: 21989363 DOI: 10.1038/ejhg.2011.186]

42 **Lu FT**, Wu JF, Hsu HY, Ni YH, Chang MH, Chao CI, Chen HL. γ-Glutamyl transpeptidase level as a screening marker among diverse etiologies of infantile intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr* 2014; **59**: 695-701 [PMID: 25141230 DOI: 10.1097/MPG.0000000000000538]

43 **Liu C**, Aronow BJ, Jegga AG, Wang N, Miethke A, Mourya R, Bezerra JA. Novel resequencing chip customized to diagnose mutations in patients with inherited syndromes of intrahepatic cholestasis. *Gastroenterology* 2007; **132**: 119-126 [PMID: 17241866 DOI: 10.1053/j.gastro.2006.10.034]

44 **Englert C**, Grabhorn E, Richter A, Rogiers X, Burdelski M, Ganschow R. Liver transplantation in children with progressive familial intrahepatic cholestasis. *Transplantation* 2007; **84**: 1361-1363 [PMID: 18049123 DOI: 10.1097/01.tp.00002828-69.94152.4f]

45 **Soubrane O**, Gauthier F, DeVictor D, Bernard O, Valayer J, Houssin D, Chapuis Y. Orthotopic liver transplantation for Byler disease. *Transplantation* 1990; **50**: 804-806 [PMID: 2238055]

46 **Knisely AS**, Strautnieks SS, Meier Y, Stieger B, Byrne JA, Portmann BC, Bull LN, Pawlikowska L, Bilezikçi B, Ozçay F, László A, Tiszlavicz L, Moore L, Raftos J, Arnell H, Fischler B, Németh A, Papadogiannakis N, Cielecka-Kuszyk J, Jankowska I, Pawłowska J, Melín-Aldana H, Emerick KM, Whitington PF, Mieli-Vergani G, Thompson RJ. Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. *Hepatology* 2006; **44**: 478-486 [PMID: 16871584 DOI: 10.1002/hep.21287]

47 **Richter A**, Grabhorn E, Schulz A, Schaefer HJ, Burdelski M, Ganschow R. Hepatoblastoma in a child with progressive familial intrahepatic cholestasis. *Pediatr Transplant* 2005; **9**: 805-808 [PMID: 16269056 DOI: 10.1111/j.1399-3046.2005.00380.x]

48 **Scheimann AO**, Strautnieks SS, Knisely AS, Byrne JA, Thompson RJ, Finegold MJ. Mutations in bile salt export pump (ABCB11) in two children with progressive familial intrahepatic cholestasis and cholangiocarcinoma. *J Pediatr* 2007; **150**: 556-559 [PMID: 17452236 DOI: 10.1016/j.jpeds.2007.02.030]

49 **Shimizu H**, Migita O, Kosaki R, Kasahara M, Fukuda A, Sakamoto S, Shigeta T, Uemoto S, Nakazawa A, Kakiuchi T, Arai K. Living-related liver transplantation for siblings with progressive familial intrahepatic cholestasis 2, with novel genetic findings. *Am J Transplant* 2011; **11**: 394-398 [PMID: 21219577 DOI: 10.1111/j.1600-6143.2010.03397.x]

50 **Hori T**, Egawa H, Miyagawa-Hayashino A, Yorifuji T, Yonekawa Y, Nguyen JH, Uemoto S. Living-donor liver transplantation for progressive familial intrahepatic cholestasis. *World J Surg* 2011; **35**: 393-402 [PMID: 21125272 DOI: 10.1007/s00268-010-0869-6]

51 **Hori T**, Egawa H, Takada Y, Ueda M, Oike F, Ogura Y, Sakamoto S, Kasahara M, Ogawa K, Miyagawa-Hayashino A, Yonekawa Y, Yorifuji T, Watanabe K, Doi H, Nguyen JH, Chen F, Baine AM, Gardner LB, Uemoto S. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. *Clin Transplant* 2011; **25**: 776-785 [PMID: 21158920 DOI: 10.1111/j.1399-0012.2010.01368.x]

52 **Aydogdu S**, Cakir M, Arikan C, Tumgor G, Yuksekkaya HA, Yilmaz F, Kilic M. Liver transplantation for progressive familial intrahepatic cholestasis: clinical and histopathological findings, outcome and impact on growth. *Pediatr Transplant* 2007; **11**: 634-640 [PMID: 17663686 DOI: 10.1111/j.1399-3046.2007.00722.x]

53 **Egawa H**, Yorifuji T, Sumazaki R, Kimura A, Hasegawa M, Tanaka K. Intractable diarrhea after liver transplantation for Byler's disease: successful treatment with bile adsorptive resin. *Liver Transpl* 2002; **8**: 714-716 [PMID: 12149765 DOI: 10.1053/jlts.2002.34384]

54 **Miyagawa-Hayashino A**, Egawa H, Yorifuji T, Hasegawa M, Haga H, Tsuruyama T, Wen MC, Sumazaki R, Manabe T, Uemoto S. Allograft steatohepatitis in progressive familial intrahepatic cholestasis type 1 after living donor liver transplantation. *Liver Transpl* 2009; **15**: 610-618 [PMID: 19479804 DOI: 10.1002/lt.21686]

55 **Nicastro E**, Stephenne X, Smets F, Fusaro F, de Magnée C, Reding R, Sokal EM. Recovery of graft steatosis and protein-losing enteropathy after biliary diversion in a PFIC 1 liver transplanted child. *Pediatr Transplant* 2012; **16**: E177-E182 [PMID: 21672103 DOI: 10.1111/j.1399-3046.2011.01514.x]

56 **Bassas A**, Chehab M, Hebby H, Al Shahed M, Al Husseini H, Al Zahrani A, Wali S. Living related liver transplantation in 13 cases of progressive familial intrahepatic cholestasis. *Transplant Proc* 2003; **35**: 3003-3005 [PMID: 14697961]

57 **Cutillo L**, Najimi M, Smets F, Janssen M, Reding R, de Ville de Goyet J, Sokal EM. Safety of living-related liver transplantation for progressive familial intrahepatic cholestasis. *Pediatr Transplant* 2006; **10**: 570-574 [PMID: 16856993 DOI: 10.1111/j.1399-3046.2006.00524.x]

58 **Kaur S**, Sharma D, Wadhwa N, Gupta S, Chowdhary SK, Sibal A. Therapeutic interventions in progressive familial intrahepatic cholestasis: experience from a tertiary care centre in north India. *Indian J Pediatr* 2012; **79**: 270-273 [PMID: 21769524 DOI: 10.1007/s12098-011-0516-8]

59 **Freise CE**, Gillespie BW, Koffron AJ, Lok AS, Pruett TL, Emond JC, Fair JH, Fisher RA, Olthoff KM, Trotter JF, Ghobrial RM, Everhart JE. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL Retrospective Cohort Study. *Am J Transplant* 2008; **8**: 2569-2579 [PMID: 18976306 DOI: 10.1111/j.1600-6143.2008.02440.x]

60 **Hoehn RS**, Wilson GC, Wima K, Hohmann SF, Midura EF, Woodle ES, Abbott DE, Singhal A, Shah SA. Comparing living donor and deceased donor liver transplantation: A matched national analysis from 2007 to 2012. *Liver Transpl* 2014; **20**: 1347-1355 [PMID: 25044564 DOI: 10.1002/lt.23956]

61 **Reichman TW**, Katchman H, Tanaka T, Greig PD, McGilvray ID, Cattral MS, Renner EL, Selzner M, Ghanekar A, Levy G, Grant DR. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. *Transpl Int* 2013; **26**: 780-787 [PMID: 23746118 DOI: 10.1111/tri.12127]

62 **Shah SA**, Levy GA, Greig PD, Smith R, McGilvray ID, Lilly LB, Girgrah N, Cattral MS, Grant DR. Reduced mortality with right-lobe living donor compared to deceased-donor liver transplantation when analyzed from the time of listing. *Am J Transplant* 2007; **7**: 998-1002 [PMID: 17391140 DOI: 10.1111/j.1600-6143.2006.01692.x]

63 **Kondo S**, Hashimoto T, Suzuki T, Nakamura T, Shimizu Y, Nakamura Y, Hayashi S, Itoh K, Manabe T. Living related liver transplantation in two Byler disease families. *Transplant Proc* 2000; **32**: 2185-2186 [PMID: 11120125]

64 **Berumen J**, Feinberg E, Todo T, Bonham CA, Concepcion W, Esquivel C. Complications following liver transplantation for progressive familial intrahepatic cholestasis. *Dig Dis Sci* 2014; **59**: 2649-2652 [PMID: 24879297 DOI: 10.1007/s10620-014-3220-5]

65 **Usui M**, Isaji S, Das BC, Kobayashi M, Osawa I, Iida T, Sakurai H, Tabata M, Yorifuji T, Egawa H, Uemoto S. Liver retransplantation with external biliary diversion for progressive familial intrahepatic cholestasis type 1: a case report. *Pediatr Transplant* 2009; **13**: 611-614 [PMID: 18785905 DOI: 10.1111/j.1399-3046.2008.00878.x]

66 **Jara P**, Hierro L, Martínez-Fernández P, Alvarez-Doforno R, Yánez F, Diaz MC, Camarena C, De la Vega A, Frauca E, Muñoz-Bartolo G, López-Santamaría M, Larrauri J, Alvarez L. Recurrence of bile salt export pump deficiency after liver transplantation. *N Engl J Med* 2009; **361**: 1359-1367 [PMID: 19797282 DOI: 10.1056/NEJMoa0901075]

67 **Maggiore G**, Gonzales E, Sciveres M, Redon MJ, Grosse B, Stieger B, Davit-Spraul A, Fabre M, Jacquemin E. Relapsing features of bile salt export pump deficiency after liver transplantation in two patients with progressive familial intrahepatic cholestasis type 2. *J Hepatol* 2010; **53**: 981-986 [PMID: 20800306 DOI: 10.1016/j.jhep.2010.05.025]

68 **Kubitz R**, Dröge C, Kluge S, Stross C, Walter N, Keitel V, Häussinger D, Stindt J. Autoimmune BSEP disease: disease recurrence after liver transplantation for progressive familial intrahepatic cholestasis. *Clin Rev Allergy Immunol* 2015; **48**: 273-284 [PMID: 25342496 DOI: 10.1007/s12016-014-8457-4]

69 **Stindt J**, Kluge S, Dröge C, Keitel V, Stross C, Baumann U, Brinkert F, Dhawan A, Engelmann G, Ganschow R, Gerner P, Grabhorn E, Knisely AS, Noli KA, Pukite I, Shepherd RW, Ueno T, Schmitt L, Wiek C, Hanenberg H, Häussinger D, Kubitz R. Bile salt export pump-reactive antibodies form a polyclonal, multi-inhibitory response in antibody-induced bile salt export pump deficiency. *Hepatology* 2016; **63**: 524-537 [PMID: 26516723 DOI: 10.1002/hep.28311]

70 **Keitel V**, Burdelski M, Vojnisek Z, Schmitt L, Häussinger D, Kubitz R. De novo bile salt transporter antibodies as a possible cause of recurrent graft failure after liver transplantation: a novel mechanism of cholestasis. *Hepatology* 2009; **50**: 510-517 [PMID: 19642168 DOI: 10.1002/hep.23083]

71 **Lin HC**, Alvarez L, Laroche G, Melin-Aldana H, Pfeifer K, Schwarz K, Whitington PF, Alonso EM, Ekong UD. Rituximab as therapy for the recurrence of bile salt export pump deficiency after liver transplantation. *Liver Transpl* 2013; **19**: 1403-1410 [PMID: 24115678 DOI: 10.1002/lt.23754]

72 **Dinler G**, Koçak N, Ozen H, Yüce A, Gürakan F. Ursodeoxycholic acid treatment in children with Byler disease. *Pediatr Int* 1999; **41**: 662-665 [PMID: 10618887]

73 **Jacquemin E**, Hermans D, Myara A, Habes D, Debray D, Hadchouel M, Sokal EM, Bernard O. Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. *Hepatology* 1997; **25**: 519-523 [PMID: 9049190 DOI: 10.1002/hep.510250303]

74 **Wanty C**, Joomye R, Van Hoorebeek N, Paul K, Otte JB, Reding R, Sokal EM. Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy. *Acta Gastroenterol Belg* 2004; **67**: 313-319 [PMID: 15727074]

75 **Frider B**, Castillo A, Gordo-Gilart R, Bruno A, Amante M, Alvarez L, Mathet V. Reversal of advanced fibrosis after long-term ursodeoxycholic acid therapy in a patient with residual expression of MDR3. *Ann Hepatol* 2015; **14**: 745-751 [PMID: 26256905]

76 **Gonzales E**, Grosse B, Schuller B, Davit-Spraul A, Conti F, Guettier C, Cassio D, Jacquemin E. Targeted pharmacotherapy in progressive familial intrahepatic cholestasis type 2: Evidence for improvement of cholestasis with 4-phenylbutyrate. *Hepatology* 2015; **62**: 558-566 [PMID: 25716872 DOI: 10.1002/hep.27767]

77 **Engelmann G**, Wenning D, Herebian D, Sander O, Dröge C, Kluge S, Kubitz R. Two Case Reports of Successful Treatment of Cholestasis With Steroids in Patients With PFIC-2. *Pediatrics* 2015; **135**: e1326-e1332 [PMID: 25847799 DOI: 10.1542/peds.2014-2376]

78 **Whitington PF**, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. *Gastroenterology* 1988; **95**: 130-136 [PMID: 3371608]

79 **Schukfeh N**, Metzelder ML, Petersen C, Reismann M, Pfister ED, Ure BM, Kuebler JF. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. *J Pediatr Surg* 2012; **47**: 501-505 [PMID: 22424345 DOI: 10.1016/j.jpedsurg.2011.08.010]

80 **Ismail H**, Kaliciński P, Markiewicz M, Jankowska I, Pawłowska J, Kluge P, Eliadou E, Kamiński A, Szymczak M, Drewniak T, Revillon Y. Treatment of progressive familial intrahepatic cholestasis: liver transplantation or partial external biliary diversion. *Pediatr Transplant* 1999; **3**: 219-224 [PMID: 10487283]

81 **Arnell H**, Bergdahl S, Papadogiannakis N, Nemeth A, Fischler B. Preoperative observations and short-term outcome after partial external biliary diversion in 13 patients with progressive familial intrahepatic cholestasis. *J Pediatr Surg* 2008; **43**: 1312-1320 [PMID: 18639688 DOI: 10.1016/j.jpedsurg.2007.10.055]

82 **Kaliciński PJ**, Ismail H, Jankowska I, Kamiński A, Pawłowska J, Drewniak T, Markiewicz M, Szymczak M. Surgical treatment of progressive familial intrahepatic cholestasis: comparison of partial external biliary diversion and ileal bypass. *Eur J Pediatr Surg* 2003; **13**: 307-311 [PMID: 14618520 DOI: 10.1055/s-2003-43570]

83 **Yang H**, Porte RJ, Verkade HJ, De Langen ZJ, Hulscher JB. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. *J Pediatr Gastroenterol Nutr* 2009; **49**: 216-221 [PMID: 19561545 DOI: 10.1097/MPG.0b013e31819a4e3d]

84 **Mousavi SA**, Karami H. Partial internal biliary diversion in progressive familial intrahepatic cholestasis: introduction of a new approach. *Hepat Mon* 2014; **14**: e13549 [PMID: 24693315 DOI: 10.5812/hepatmon.13549]

85 **Rebhandl W**, Felberbauer FX, Turnbull J, Paya K, Barcik U, Huber WD, Whitington PF, Horcher E. Biliary diversion by use of the appendix (cholecystoappendicostomy) in progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr* 1999; **28**: 217-219 [PMID: 9932861]

86 **Schukfeh N**, Gerner P, Paul A, Kathemann S, Metzelder M. Laparoscopic button cholecystostomy for progressive familial intrahepatic cholestasis in two children. *Eur J Pediatr Surg* 2014; **24**: 433-436 [PMID: 24327224 DOI: 10.1055/s-0033-1360457]

87 **Bustorff-Silva J**, Sbraggia Neto L, Olímpio H, de Alcantara RV, Matsushima E, De Tommaso AM, Brandão MA, Hessel G. Partial internal biliary diversion through a cholecystojejunocolonic anastomosis--a novel surgical approach for patients with progressive familial intrahepatic cholestasis: a preliminary report. *J Pediatr Surg* 2007; **42**: 1337-1340 [PMID: 17706492 DOI: 10.1016/j.jpedsurg.2007.03.029]

88 **Gün F**, Erginel B, Durmaz O, Sökücü S, Salman T, Celik A. An outstanding non-transplant surgical intervention in progressive familial intrahepatic cholestasis: partial internal biliary diversion. *Pediatr Surg Int* 2010; **26**: 831-834 [PMID: 20563871 DOI: 10.1007/s00383-010-2638-x]

89 **Ramachandran P**, Shanmugam NP, Sinani SA, Shanmugam V, Srinivas S, Sathiyasekaran M, Tamilvanan V, Rela M. Outcome of partial internal biliary diversion for intractable pruritus in children with cholestatic liver disease. *Pediatr Surg Int* 2014; **30**: 1045-1049 [PMID: 25064227 DOI: 10.1007/s00383-014-3559-x]

90 **Diao M**, Li L, Zhang JS, Ye M, Cheng W. Laparoscopic cholecystocolostomy: a novel surgical approach for the treatment of progressive familial intrahepatic cholestasis. *Ann Surg* 2013; **258**: 1028-1033 [PMID: 23187749 DOI: 10.1097/SLA.0b013e318

27905eb]
91 **Emond JC**, Whitington PF. Selective surgical management of progressive familial intrahepatic cholestasis (Byler's disease). *J Pediatr Surg* 1995; **30**: 1635-1641 [PMID: 8749912]

P- Reviewer: Al Mehaidib A, Dehghani SM, Qin JM
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com