Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment

Mithat Gunaydin1
Asudan Tugce Bozkurter Cil2
1Avicenna Hospital, Department of Pediatric Surgery, Istanbul, Turkey; 2Medicana International Samsun Hospital, Department of Pediatric Surgery, Samsun, Turkey

Abstract: Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive cholestatic liver diseases which are subgrouped according to the genetic defect, clinical presentation, laboratory findings and liver histology. Progressive liver fibrosis, cirrhosis, and end stage liver disease (ESLD) may eventually develop. PFIC was first described in Amish descendants of Jacob Byler, therefore it was originally called Byler disease. But it can be seen anywhere on the globe. This review summarizes the main features of the subtypes of the disease and discusses the current available diagnosis, conservative and surgical therapeutic options.

Keywords: intrahepatic cholestasis, jaundice, biliary diversion.

Introduction

Impaired production and excretion of bile results in cholestatic liver disease, where biliary substances cannot be eliminated from the liver and thus reenter the circulation. This results in the deposition of bilirubin pigments in the tissues as skin, sclerae, mucous membranes and so on, which overall is called jaundice.1

Pruritus is the most obvious and the most unbearable symptom in cholestasis. In the patients, pruritus is probably induced by the stimulation of nonmyelinated subepidermal free nerve ends because of increased serum bile acids.2

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of liver disorders of autosomal recessive inheritance, characterized by an early onset of cholestasis (usually during infancy) with pruritus and malabsorption, which rapidly progresses and ends up as liver failure.3,4 PFIC appears equally in both genders.

PFICs are responsible for about 10–15% of children with cholestatic liver diseases. PFIC-1 and 2 are rare diseases with an estimated incidence of 1:50–100,000. The total number of cases from the two subtypes reported in the literature is less than 200. PFIC-3 subtype is even rarer with a reported case number of less than 20.5,6

PFIC cases are more often observed in some cultures where consanguineous marriages are more popular. They were first described in Amish descendants of Jacob Byler, therefore it was originally called Byler disease. But they can be seen anywhere on the globe. So the name has been superseded by PFIC.7

General approaches to PFIC

PFICs are subgrouped according to the genetic defect, clinical presentation, laboratory findings, and liver histology. The disease has been classified into three subgroups. All the three types of PFIC are caused by defects in bile secretion from hepatocyte.
to canaliculi. In PFIC-1 and PFIC-2, bile acid secretion is depleted, while in PFIC-3, bile phospholipid secretion is impaired.3,9

All subtypes are shown in the Tables 1–4. The PFIC subgroups will be closely reviewed at the end of the article.

Diagnosis
Diagnosis is made through a detailed history, physical examination, laboratory tests, radiologic or histological evaluations if needed.

Biliary atresia, infections, hormones, drugs, parenteral nutrition, extrahepatic obstruction due to common bile duct stones or choledochal cysts, sclerosing cholangitis, hypothyroidism and panhypopituitarism, metabolic disorders as tyrosinemia type I, galactosemia, inborn errors of bile acid metabolism, alpha-1-antitrypsin deficiency, cystic fibrosis, benign recurrent intrahepatic cholestasis (BRIC), intrahepatic cholestasis of pregnancy (ICP), Alagille syndrome, and Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) may also cause neonatal cholestasis and should be included in differential diagnosis of PFICs.5,10–13

History
In a patient with abnormal liver function tests, obtaining a detailed history is critical. It should include age of onset of jaundice, age of onset of abnormal liver function tests, pattern of abnormal liver function tests either hepatocellular or cholestatic, any infections, medication, feeding, bowel movements, stool color, urine color and the family history as well. Cholestasis should be considered in a baby with irritability, pruritus, cutaneous mutilation, scratching, jaundice, watery diarrhea, steatorrhea and failure to thrive.1,3,9

Physical examination
Cholestatic liver diseases have a wide spectrum of presentation from isolated abnormalities in liver function tests to liver failure. Patients with PFIC can further present with jaundice, pruritus, splenomegaly, hepatomegaly, and altered anthropometrics (Figure 1).1,3,9

Pruritus is induced by the stimulation of nonmyelinated subepidermal free nerve ends related with the increased serum bile acids and is the most prominent and distressing symptom.10

PFIC-1 patients may also present with short height, growth retardation, deafness, diarrhea, pancreatitis, increased sweat electrolyte concentration, hepatic steatosis and epistaxis despite bleeding diathesis. Secondary vitamin K deficiency related with fat malabsorption and inadequate dietary intake, may predispose to hemorrhagic disease of the newborn (HDN) and late HDN (seen in infants aged 1 week to 6 months) may be associated with serious and life-threatening intracranial hemorrhage.14 PFIC-2 may directly refer with a malignancy. PFIC-3 patients are likely to present with cirrhosis in late childhood and young adulthood.

Clinical presentation, liver biochemistry, radiological and histological evaluations all help to diagnose PFIC and help to distinguish the subtype.

Laboratory evaluation
Liver function tests, serum bile acids and imaging studies help to rule out the cause of liver disease. Since PFIC is a rare disease, all other more common liver diseases and biliary diseases such as biliary atresia, Alagille syndrome, alpha-1 antitrypsin deficiency, cystic fibrosis, sclerosing cholangitis, and biliary obstruction shall be excluded first.

Table 1 Genetic features of PFIC subtypes

| Disease | Byler disease (PFIC 1) | SPGP/BSEP deficiency (PFIC 2) | MDR3 deficiency (PFIC 3) |
|---------|------------------------|-----------------------------|-------------------------|
| Chromosome | 18q21-q22 | 2q24 | 7q21 |
| Gene | FIC 1 (ATP8B1) | BSEP (ABCB11) | PGP3 (ABCB4, MDR 3) |
| Gene function | FIC1 translocates phospholipids from outer to inner canalicular membrane |

Abbreviations: ABCB11, ATP Binding Cassette Subfamily B Member 1; ABCB4 (PGP3), ATP binding cassette subfamily B member 4; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis; MDR3, multidrug resistance Class III; PFIC, progressive familial intrahepatic cholestasis.

Table 2 Laboratory findings in PFIC subtypes. (N= normal, H= high/elevated, L= low/depleted)

| PFIC type | PFIC type 2 | PFIC type 3 |
|-----------|-------------|-------------|
| Serum GGT | N | N | H |
| Serum direct bilirubin | H | H | H |
| Serum bile acids | H(+++) | H(+++) | H(+) |
| Serum ALP | H | H | H |
| Serum ALT | H | H | H |
| Biliary phospholipids | N | N | L |
| Serum5′-nucleotidase | H | H | H |
| Serum AFP | N | H | N |

Abbreviations: PFIC, progressive familial intrahepatic cholestasis; AFP, alphafetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase.
While evaluating a jaundiced infant, the initial step is measuring the serum total (TB) and direct bilirubin. In PFICs, laboratory abnormalities include increased serum alkaline phosphatase (ALP), variable elevation of bilirubin, decreased/increased gamma-glutamyltransferase (GGT) and increased bile acids, serum copper, ceruloplasmin, cholesterol and lipoprotein X. Accompanying tests shall include alanine aminotransferase (ALT), aspartate aminotransferase
(AST), prothrombin time (PT), international normalized ratio (INR), serum 5′-Nucleotidase, glucose and albumin. When TB is elevated, a direct/conjugated ratio greater than 1.0 mg/dL (17 mmol/L) is considered abnormal.1,9

Patients with PFIC-1 and PFIC-2 have normal GGT levels, while patients with PFIC-3 have increased GGT levels. All 3 subtypes of PFIC have increased serum bile acid levels.

Radiologic studies
In cholestasis patients, ultrasound (US) comes first in radiologic studies. Magnetic Resonance Cholangiopancreatography (MRCP) contributes in excluding extrahepatic biliary obstruction and sclerosing cholangitis. The use of hepatic scintigraphy is under evaluation.9,15

Liver biopsy
A liver biopsy may help in the diagnosis of PFIC. But, assessment of liver biopsy specimens is not adequate in the differential diagnosis. Typical pattern of laboratory findings in serum contribute for diagnosis, especially low to normal level of gamma glutamyl transferase (GGT), absent lipoprotein X, low cholesterol level, and high levels of bile acids.

At a liver biopsy, canalicular cholestasis can be seen in PFIC-1 and PFIC-2 with more fibrosis and a giant cell hepatitis in PFIC-2 subtype. PFIC-3 specimens usually show proliferation of the bile ducts and fibrosis. The defective bile salt export pump protein (BSEP) in PFIC-2 and the multidrug resistance three protein (MDR3) in PFIC-3 can be stained and the subtype can be named.7,9

Immunohistochemistry studies of liver biopsy specimen may be useful in the diagnosis. BSEP antibodies for PFIC2 and MDR3 antibodies for PFIC3 are available. But, there is no standardized antibodies for PFIC-1. Absent or decreased hepatic canalicular expression of these antibodies may be diagnostic for PFIC2 and PFIC3.16

Electronmicroscopy (EM)
Evaluation of the composition of bile may also support diagnosis of PFIC. Bile salt concentration is low in PFIC-1 and PFIC-2 and phospholipid level is low in the bile in PFIC-3.

On light microscopy and transmission electron microscopy of liver tissues of PFIC-1 patients have coarsely granular bile. While canalicular dilatation, microvilli loss, abnormal mitochondrial internal structure, and varying intracanalicular accumulation of finely granular, rather amorphous or finely filamentous bile is seen in PFIC-2 patients.

Genetic testing
Genetic testing can further confirm the diagnosis of PFIC in the vast of patients. Deletion/duplication analysis, sequence analysis of the coding region, targeted variant analysis can be performed. Targeted next-generation sequencing (NGS) has successfully been used for molecular genetic diagnosis in subjects with neonatal/infantile intrahepatic cholestasis.17

Treatment
Treatment includes medical and surgical approaches. Diets, medications, and vitamins are used for medical treatment and external or internal biliary diversions are applied for surgical treatment.17,18 Surgical approaches have an important role in the relief of symptoms such as pruritus and prevention of development of cirrhosis of the liver. Details of the treatment approaches are discussed below.

Diet
Dietary fat is mainly provided as medium chain triglycerides. The fat-soluble vitamin supplements (A, D, E and K) are administered to ensure proper absorption. Calcium intake and adequate exposure to sunlight are also essential.

The patients can also benefit from cold tubs, local steroids and moisturizers, antihistaminics and sedatives as for pruritus. Phototherapy and plasmapheresis are other conservative options.18,19

Drug treatment
Drug therapy is the first line of treatment in all PFIC patients. The purpose of medical treatment in cholestasis and its complications can be summarized as follows; enhancing the bile flow and inhibiting the accumulation of metabolites in the liver (choleresis), treatment of toxic effects of bile reentering the systemic circulation, avoiding the malabsorption of fat and fat soluble vitamins, preventing acute and chronic malnutrition and ensuring continuity of growth.

In the treatment of PFIC, general treatment principles of cholestasis are followed and infant formulas enriched with medium-chain triglycerides, fat-soluble vitamins, antihistamines, etc, are used.

Drug treatment aims to relieve pruritus which is the most distressing symptom in PFIC, to slow the disease progression, to improve the nutritional status, to correct vitamin deficiencies and to treat the complications of advanced liver disease like ascites and variceal bleeding. However, medical treatment often fails and surgical alternatives and liver transplantation might be necessary.20
Ursodeoxycholic acid (UDCA)
UDCA is the initial treatment for all PFIC subtypes. Some reports suppose, at a dose of 10–30 mg/kg per day, it dissolves cholestasis and is successful in the treatment. It is a nontoxic hydrophilic bile acid and thought to reverse the potential hepatotoxicity of the accumulating endogenous bile acids. It regulates bile acid distribution, reduces the amount of cholesterol in the bile, and provides mitochondrial integrity. It has choleretic, immunomodulatory, antioxidant, antiapoptotic and cytoprotective effects.

UDCA is effective in two thirds of patients with PFIC-3 with ABCB4 alterations. In one third, where mutations resulted in no expression of the MDR3 protein, patients are usually non-responders to UDCA therapy. Progression of disease and insufficient symptom relief may necessitate further intervention.

Cholestyramine
Cholestyramine is an oral bile acid binding resin used to resolve pruritus. It forms nonabsorbable micelles with the bile acids in the intestines and prevents bile acids from entering the enterohepatic cycle. Cholestramine should be taken at least 1 hour before or 4–6 hours after meals, 1–4 gr/day. This drug induces liver enzyme activity and increases bilirubin excretion. In patients with reduced serum bilirubin levels, pruritus also regresses.

Rifampicin
Rifampicin acts by upregulating detoxification enzymes and export pumps through farnesoid X receptor (FXR) dependent mechanisms. Rifampicin indirectly induces hydroxylation of bile salts which are further glucuronidated and excreted in urine. It also induces conjugation and excretion of bilirubin through uridine diphosphate (UDP)-glucuronosyl transferase. It is used 5–10 mg/kg/day.

Phenobarbital
Phenobarbital, is used to induce CYP/CYP450 system in the treatment of newborn hyperbilirubinemia and chronic cholestasis with low bilirubin levels at a dose of 3–10 mg/kg/day.

4-phenylbutyrate
Hasegawa et al evaluated the therapeutic potency of 4-phenylbutyrate in three patients with PFIC1 and observed that at a dosage of 350 or 500 mg/kg/day per orally significantly relieved the intractable itch. Naoi et al evaluated the effect of 4-phenylbutyrate in one patient with PFIC-2 and concluded that in patients with decreased cell-surface expression of BSEP among PFIC-2s, 4-phenylbutyrate (4PB) therapy has partially restored BSEP expression at the canalicular membrane, significantly improved liver tests and pruritus at a dosage of 500 mg/kg/day.

Other drugs
Antihistaminic agents, opiate antagonists, ondansetron, steroids, propofol, and carbamazepine are part of the other medical therapy options.

Nasobiliary drainage
Nasobiliary drainage is the non-surgical, temporary diversion of bile through an endoscopically introduced nasobiliary drain. The risk of pancreatitis should not be ignored.

Surgical management
Intractable pruritus despite medical treatment, growth failure and nutritional deficiencies necessitate surgery. Pruritus is assessed according to the Whitington scale. The severity of pruritus is important in the decision to proceed with surgery. There is epidermal bleeding at grade four according to this scale.

Biliary diversion procedures aim to interrupt the enterohepatic recirculation of bile salts via an anastomosis of the biliary tract to the intestines (internal drainages) or to the skin (external diversions). Thus, accumulating excess serum bile salts decrease, biliary acid composition changes, pruritus regresses, progression to cirrhosis delays. Partial biliary diversions have been used successfully in many patients with PFIC-1 and 2, who do not respond to medical therapy and are as yet not candidates for liver transplant.23 Diversions help to improve liver functions, growth, liver histology, reduce progression of fibrosis and extend the time interval before liver transplantation in the majority of patients with PFIC-1 and 2.

If the patients have not developed cirrhosis at the time of surgery, the results are even more satisfying, therefore biliary diversions should be offered early before development of cirrhosis.

Partial external biliary diversions (PEBD)
The PEBD procedure, once described by Whitington et al, involves use of a 10–15 cm jejunal conduit between the fundus of the gallbladder and abdominal skin where a permanent stoma is created. Diversion of bile interrupts the enterohepatic circulation of bile salts, diminishes subsequent reuptake and decreases the pool of bile salts.24–29 PEBD has gained popularity over the last few years. So far other modifications of the conduit between gall bladder and skin have been defined as the use of a button of gall
bile acid transporter (ASBT) inhibitors, FXR agonists and FGF19 hormone reduces endogenous bile acid synthesis, protects hepatocytes from bile acid toxicity and promotes secretion of bile acids, together with apical sodium-dependent bile acid transporters does have benefits. In a human phase I trial, ASBT inhibitors reduced the total serum bile acids with increased fecal bile acid excretion. Since FXR activation and increased production of the FGF19 hormone reduces endogenous bile acid synthesis, protects hepatocytes from bile acid toxicity and promotes secretion of bile acids, together with apical sodium-dependent bile acid transporter (ASBT) inhibitors, FXR agonists and
FGF19 mimetics represent the most promising anticholestatic strategies and are being tested in several clinical trials.\textsuperscript{44}

FXR agonists have been successfully tested in animal models of cholestasis but dyslipidemia frequency rose among cholestatic patients.

Overexpression of FGF19 in mice has also been associated with HCC development. So a non-tumorigenic FGF19-like peptide has recently been designed to eliminate this negation.\textsuperscript{47} But further studies are still required for effective treatment in the management of PFIC.

Being less invasive and repeatable, hepatocyte transdifferentiation or induced pluripotent stem cells (iPSCs) sources are being investigated as hepatocytes generated by transdifferentiation or induced pluripotent stem cells (iPSCs) derived hepatocyte-like cells.\textsuperscript{48,49}

**PFIcs subtypes**

The disease has been classified into three subtypes. All the three types of PFIC are caused by defects in bile secretion from hepatocyte to canaliculi. PFIC types 1 and 2 have been reported in all races. PFIC3 has been seen in Western European, White, and North African Arabic populations.

PFIC-1 patients may present with short height, growth retardation, deafness, diarrhea, pancreatitis, increased sweat electrolyte concentration, hepatic steatosis and epistaxis despite bleeding diathesis while PFIC-2 may directly refer with a malignancy. PFIC-3 patients are likely to present with cirrhosis in late childhood and young adulthood.

Clinical presentation, liver biochemistry, radiological and histological evaluations all help to diagnose PFIC and help to distinguish the subtype.

**PFIC type 1 (Byler Disease)**

PFIC-1 occurs due to a mutation of the assumed aminophospholipid transporter \textit{FIC1/ATP8B1} gene on chromosome 18 resulting in impaired hepatocellular bile salt secretion.\textsuperscript{50,51} It starts during infantile period with episodes of cholestasis (average onset of 3 months of age) and leads to liver cirrhosis and rapidly progresses to ESLD requiring liver transplantation. It was defined as Byler’s disease by Clayton et al\textsuperscript{7} in 1969.

Patients usually present with elevated alkaline phosphatase and serum primary bile acids (in particular chenodeoxycholic acid) while serum gamma-glutamyltransferase (GGT) activity is not elevated. Serum cholesterol levels are usually normal.

The mutated gene encoding for the protein FIC1, not only affects the protein expression in the liver but also in the pancreas, small intestine, urinary bladder, stomach, and prostate. That is why patients have extrhepatic manifestations, such as diarrhea, malabsorption, pancreatitis, short height, an increased sweat electrolyte concentration, and hepatic steatosis.

Benign recurrent intrahepatic cholestasis (BRIC-1, also known as \textit{Summerskill syndrome}) is a milder form of PFIC-1 which is also related with \textit{FIC1} gene mutation, where recurrent episodes of cholestasis occur but not necessarily leading to liver cirrhosis. However there are rare reported BRIC-1 cases progressing into PFIC-1. Since \textit{FIC1} gene is widely expressed in extrahepatic tissues, both diseases have manifestations such as diarrhea, pancreatitis, bile acid malabsorption and nephrolithiasis.

**PFIC type 2 (Byler Syndrome)**

PFIC-2 occurs due to a mutation of the major canalicular \textit{BSEP} gene on chromosome 2 (\textit{ABCB11}).\textsuperscript{52} Expression of this gene is limited to liver. Therefore although the clinical course of PFIC-2 is similar to that for PFIC-1, extrahepatic manifestations are absent.

PFIC2 frequently presents as nonspecific giant cell hepatitis at a few months of age with recurrent or chronic jaundice which is undistinguishable from idiopathic neonatal giant cell hepatitis. But it usually progresses even more quickly to ESLD than PFIC-1. Patients require liver transplantation during the first decade of life.

Hepatocellular carcinoma or cholangiocarcinoma may develop in the first year of life. Therefore right after diagnosis, prompt screening for malignancies is very important. This patients must follow with alpha-fetoprotein levels and hepatic ultrasound.

As in PFIC-1, serum bile acids, bilirubin and transaminases with a marked increase in ALT level to more than five times normal but GGT levels are low. PFIC-2 also has a lighter variant called Benign intrahepatic recurrent cholestasis-2 (BRIC-2) where the course of the disease is more moderate. Also, other missense mutations of the \textit{ABCB11} gene, as can be proved by genetic testing, may follow a milder course not necessitating typical treatment for PFIC2.

**PFIC type 3**

PFIC-3 occurs due to a mutation of adenosine triphosphate-binding cassette, subfamily B, member 4 (\textit{ABCB4}) gene encoding for the multidrug resistance class III (MDR3) protein related with the bile phospholipid export pump.\textsuperscript{53} Bile phospholipids are required for the formation of mixed micelles with bile acids and cholesterol. They protect
the bile duct epithelium from the detergent properties of bile acids. The bile flow is not impaired itself but impaired bile phospholipid excretion results in bile duct damage. The unmiscelie form bile acid monomers are toxic to cholan-
giocytes and hepatocytes. These patients may present with progressive cholestasis and cirrhosis later in childhood or young adulthood. Pruritus and short stature may be less apparent but variceal bleeding and portal hypertension are common in PFIC-3 patients.

New subtypes
Tight junction protein two gene (chromosome 9) has recently been associated with PFIC as a new subtype, PFIC-4. TJ2 codes for a protein involved in the organization of epithelial and endothelial intercellular junctions that separate bile from plasma in the liver.

Furthermore, a fifth subtype of PFIC with farnesoid X receptor (FXR) mutations is distinguished.

During fasting, bile acids are stored in the gallbladder and they are secreted into the small intestine postprandially to participate in digestion. Then they are reabsorbed through the portal circulation into the liver to be recycled and just 5% of them are newly synthesized in the liver daily to sustain a proper bile acid pool in the organism. The farnesoid X receptor (FXR), which is a nuclear receptor and a product of \textit{NR1H4} gene, balances the production and circulation of bile acids. It is presented as the master regulator of bile acid homeostasis. FXR also provides protection against hepatocarcinogenesis.

Genetic studies have revealed that defects in FXR pathway account for different clinical types of cholestatic liver diseases, such as intrahepatic cholestasis of pregnancy (ICP), drug-induced cholestasis (DIC) or PFIC.

Gomez-Ospina et al.\textsuperscript{54} presented evidence for \textit{NR1H4} mutations resulting in complete absence of BSEP expression in the bile canaliculi and leading to cholestasis. It is also an autosomal recessive disorder characterized with an onset of intralobular cholestasis and severe vitamin K-independent coagulopathy in the neonatal period. It is rapidly progressive, leading to liver failure and death unless liver transplantation is performed. Here, serum GGT levels is low-to-normal and serum alpha-fetoprotein is elevated.

\textbf{Discussion}
PFIC is one of the most distressing cholestatic liver diseases of childhood resulting in cirrhosis and end stage liver disease. Pruritus associated with the accumulation of excessive bile acids, is the most disturbing symptom. There is a variety of medical therapeutics having limited benefits. And there are some surgical options defined having positive effects on symptoms and liver histology. The surgical technique preference depends on the gastrointestinal anatomy of the patient and the surgeon’s preference and experience.

Since relief from symptoms is not sustained in an acute manner, the disposable percutaneous transhepatic biliary drainage catheters are not suitable for this disease group.

External diversion techniques include a stoma, thus have stoma-related complications.

Internal drainage techniques avoid a stoma. They have lower complication rates and provide a better quality of life. But since they are rather new, they have limited long-term outcome reports.

In a study comparing the inferior long-term outcome of ileal bypass to PEBD reported recurrence of symptoms in 50% of the patients which was probably related to the re-absorption of bile acids over time. The large amounts of bile salts entering the colon induce choleretic diarrhea and rectal bleeding – a potential complication of PIBD – which can be treated with oral cholestyramine.

Diversions are shown to be more successful if performed at the early stages of the disease. Uncontrolled pruritus despite diversions or advanced liver disease may finally indicate liver transplantation. So if a prior alternative surgery will be performed, the least challenging procedure should be chosen.

Living-donor transplantation is reported to be safe and effective.\textsuperscript{55} Nevertheless, since liver transplantation still has significant morbidity and mortality rates, protocols to identify those patients early and to follow up properly are mandatory.

The knowledge on the biological role of bile acids in metabolic pathways is still evolving. Thus, novel pharmaceuticals affecting bile acid circulation/metabolism are also promising for PFIC patients.

Finally, the diagnosis and treatment of patients with PFIC are difficult. They may result in ESLD if not diagnosed before the development of cirrhosis and hepatic fibrosis. Therefore, cholestasis should be considered as a whole and the differential diagnosis should promptly be made. The treatment strategy must be planned before hepatic fibrosis and cirrhosis develop. External or internal biliary diversion and liver transplantation approaches should be performed in selected cases. Early diagnosis and biliary diversions may prevent significant morbidity and mortality from ESLD.

\textbf{Disclosure}
The authors report no conflicts of interest in this work.
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