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Liver transplantation in chronic cholestatic conditions

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1. ABSTRACT

Primary biliary cirrhosis and primary sclerosing cholangitis are two most frequently encountered cholestatic condition in adults. Liver transplantation is an excellent option in patients who progress to end-stage liver disease. In these patients typical indications for liver transplantation are no different than in other conditions requiring transplantation. Liver transplantation however might be also suggested for specific indications even in patients with otherwise well preserved liver function. 5-year survival after liver transplantation in primary biliary cirrhosis was reported to be between 78 and 87%. Survival rates after liver transplantation in primary sclerosing cholangitis are considered favorable when compared to many other indications for this procedure. Nevertheless, in both primary biliary cirrhosis and primary sclerosing cholangitis recurrence of the disease after liver transplantation can be observed. Cystic fibrosis, biliary atresia, Alagille syndrome and progressive familiar intrahepatic cholestasis are cholestatic conditions in children. Liver transplantation represents an effective treatment in majority of cases fulfilling the criteria for this procedure.

2. INTRODUCTION

In chronic cholestatic disease liver transplantation (LTx) may be indicated purely for features of cholestasis, including intractable pruritus and malabsorption-induced malnutrition. More commonly the indication is a feature of hepatocellular failure or portal hypertension arising as a consequence of advanced disease. In this review we summarize the current knowledge on LTx in the two cholestatic condition most frequently encountered in adults; primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). We also discuss briefly the indications and outcome of LTx in common cholestatic conditions in children.

3. PRIMARY BILIARY CIRRHOSIS

PBC is a chronic cholestatic liver condition characterized by the damage of interlobular and septal bile ducts (1). In an undefined proportion of patients PBC leads to progressive fibrosis and eventually cirrhosis (2). Its aetiology is considered to be autoimmune but remains to be fully elucidated. The disease largely affects middle aged

women and is often associated with various autoimmune conditions, of which the commonest are sicca syndrome and Hashimoto thyroiditis, usually diagnosed at the stage of hypothyroidism. Clinically the commonest complaints are of pruritus and chronic fatigue (3). Liver biochemistry classically shows elevated alkaline phosphatise and gamma glutamyl transpeptidase. The serological hallmark of PBC is the M2 antimitochondrial antibody (AMA) which is present in a vast majority of patients. The natural history of the disease differs widely from patient to patient, in some progressing to liver failure within ten years whereas in others minimal or no progression is observed over several decades. Available medication, namely ursodeoxycholic acid, in particular if introduced early in the course of the disease may slow progression of the condition in a majority of patients but curative medical treatment for PBC does not exist (4). LTx is an excellent option in that proportion of patients who progress to end-stage liver disease (5).

3.1. Indications for transplantation and its timing

In patients with end-stage PBC typical indications for LTx are no different than in other conditions requiring transplantation and include: refractory ascites, spontaneous bacterial peritonitis; hepatocellular carcinoma within the defined criteria of Milano/University of San Francisco (6, 7); recurrent episodes of variceal bleeding or overt encephalopathy; progressive muscle wasting. More specifically for PBC, intractable pruritus and chronic fatigue may also merit consideration for transplant assessment. In a small proportion of patients who do not respond to any available treatment aimed at amelioration of itching, LTx remains the last resort. In such cases LTx might be suggested even in patients with otherwise well preserved liver function. Chronic fatigue is frequently associated with PBC (8) and exerts a significant effect on the patient's quality of life, generating profound disability and distress, often out of proportion to the patient`s physical status (9). Although chronic fatigue has been a rare indication for LTx, the symptom may not be fully ameliorated but persist after the procedure (10).

More generally, LTx is considered when life expectancy following surgery clearly exceeds that without the operation. It has been shown that in patients with PBC the above aim is gained when serum bilirubin reaches 10mg/dl (170umol/l) (11). It is recommended that patients should be referred for their initial assessment when their bilirubin approaches 5.9mg/dl (100 μmol/l). The Mayo risk score, introduced in 1989, and based on the patient`s age, bilirubin, albumin, prothrombin time, presence of peripheral oedema, and the necessity of treatment with diuretics has been demonstrated to be superior to the Child-Pugh score in predicting the outcome of LTx in patients with PBC (12). A threshold Mayo risk score of 7.8 identifies subjects with a significantly increased risk of death after LTx (13) and the formula for its calculation is available on the internet: *http://www.mayoclinic.org/gi-rst/mayomodel2.html.* The Model of End Stage Liver Disease (MELD) score, available on the internet (*http://www.mayoclinic.org/meld/mayomodel6.html*), has also been found superior to Child-Pugh score in predicting mortality in patients with end-stage liver disease awaiting LTx (14). This mathematical formula takes into account serum bilirubin, INR, creatinine and necessity of dialysis.

3.2. Transplantation trends

A recent study from North America, analysing the period between 1995 and 2006 demonstrated a clear trend towards a reduction in the rate of LTx for PBC (15). During that period the overall number of transplants showed an average increase of 249 transplants per year whereas the number of transplants done for PBC decreased gradually by an average of 5.4 cases per year. The median age at LTx remained unchanged. These findings are of interest in view of the fact that both the incidence and prevalence of PBC show a steady increase (16) and suggest that ursodeoxycholic acid, which is now almost universally prescribed in patients with PBC, has influenced the natural history of this condition so as to decrease the need for LTx.

A similar trend has also been observed in Europe. Of the 42,957 transplants done between January 1988 and June 2009 and recorded by European Liver Transplant Registry (ELTR, available on the internet: *http://www.eltr.org/publi/index_rv.php3*), 4377 (10%) were performed in patients with PBC. This proportion had declined significantly when compared to early days of LTx (32). The same tendency was seen within large liver transplant centres, the Liver Unit, Birmingham, United Kingdom (UK), being a good example. Liermann-Garcia *et al*, in their retrospective study on 400 consecutive patients transplanted for PBC showed that the proportion of patients transplanted for PBC had dropped from 35% in 1990 to 21% in 1999 (17).

3.3. Survival after transplantation

The ELTR records 1, 5 and 10-years survival rates in PBC of 86, 79 and 71% respectively. Five year survival in patients with PBC who underwent LTx in 1997 in North America was 86.2% (10). These data are comparable to those reported from large European centres where 5-year survival was reported to be between 78 and 87% (17-19). As observed with other indications for LTx, significant improvement of post-transplant survival is seen when patients transplanted in the 1980's and 1990's are compared. For example, data from Birmingham, UK showed that patients transplanted in the 1980's had 3 and 5-years survival of 70 and 66% compared to 83 and 80% in these transplanted in the subsequent decade (17). Similarly, Mayo and Dallas data showed an improvement of 3-years survival from 72% in 1980's to 88% in 1990's (13, 20). The 1 and 5-year graft survivals after living donor liver transplantation for PBC are 86 and 82%, respectively. Patient survivals are 92% and 87%, respectively (21)

3.4. Recurrence of the disease

Recurrent PBC after LTx was first reported in 1982 (22) and since then numerous studies have confirmed that the disease may recur after transplantation. Fatigue and pruritus remain the most common clinical symptoms though pruritus, in particular, is rarer than in pre-LTx PBC. Unlike patients with PBC in their native livers, the majority of patients with recurrent PBC have liver

Table 1. Recurrence of primary biliary cirrhosis and primary sclerosing cholangitis after liver transplantation

A. Recurrence of primary biliary cirrhosis after liver transplantation						
Centre	Year of publication	Number of patients	Median follow up after LTx	Recurrence	Median time to recurrence	Risk factors for the recurrence
Birmingham (UK)	2001	400	56 months	17%	36 months	Tacrolimus based immunosupression
Baylor, Dallas	2003	156	72 months	11%	50 months	-
Mayo Clinic	2003	100	44 months	17%	56 months	-
Birmingham (UK)	2004	485	79 months	23%	-	Tacrolimus based immunosupression
Berlin	2006	100	118 months	14%	61 months	Tacrolimus based immunosupression Recipient age
Mayo Clinic	2007	154	-	34%	-	Tacrolimus based immunosupression Male recipient
[1] Kyoto	2007	70	36 months	18%	19 months	Lower number of HLA-A, HLA-B, and HLA-DR mismatches between donor and recipient
B. Recurrence of primary sclerosing cholangitis after liver transplantation						
Centre	Year of publication	No of patients	Median follow up after LTx	Recurrence	Median time to recurrence	Risk factors for the recurrence
Birmingham (UK)	2002	152	53 months	37%	36 months	Intact colon before LTx Male recipient
Denver	2003	71	-	21%	53 months	Orthoclone (OKT3) therapy
Burlington	2003	51	-	12%	-	Recipient-donor gender mismatch
Oslo	2005	49	77 months	18%	-	Steroids resistant rejection
Royal Free, London	2008	69	110 months	14%	60 months	Steroids for UC more than 3 months after LTx
Seattle	2008	69	50 months	10%	68 months	Acute rejection Donor or recipient HLA DRB1*08
Denver	2008	130	66 months	17%	-	CCA before transplantation

Abbreviations: LTx: liver transplantation; UK: United Kingdom; UC: ulcerative colitis; HLA: human leukocyte antigen; CCA: cholangiocarcinoma, [1] Living related donor transplants

cholestatic enzymes which are either normal or only mildly abnormal at the time of diagnosis (23-25). AMA usually disappears shortly after LTx but returns later in various titres which do not correlate with the development of recurrent disease (25). As neither biochemical nor serological data are reliable in the diagnosis of the recurrent PBC, histology remains crucial for the diagnosis. It usually shows granulomatous cholangitis or the florid duct lesion (Figure 1). While recurrence of PBC does not exert any significant effect on short- and medium-term outcomes, it has been speculated that continued follow-up may find reduced long-term graft and patient survival due to disease recurrence. Indeed, some studies have already documented graft loss or death attributed to recurrent disease in a very small proportion of patients (17). Selected papers (17, 18, 23-27) on disease recurrence are summarized in Table 1A. According to some experts attention should be focused on defining the risk factors for recurrent PBC in order that strategies for its prevention and treatment could be developed.

4. PRIMARY SCLEROSING CHOLANGITIS

PSC is a chronic, inflammatory and cholestatic liver condition affecting both intra and extrahepatic bile ducts and leading to the formation of multiple biliary strictures (28). It may lead to a secondary biliary cirrhosis with development of portal hypertension and its complications. The aetiology of PSC appears to be multifactorial with genetic, autoimmune, inflammatory and possibly infective factors all playing their role. Unlike PBC, most patients are male and a significant proportion is asymptomatic at the time of diagnosis. The most common complaints are of abdominal pain, icterus, skin itching, and recurrent episodes of fever. Inflammatory bowel disease (IBD), mostly ulcerative colitis (UC) occurs in up to 75% of PSC patients. Endoscopic retrograde cholangiopancreatography (ERCP) remains a gold standard in the diagnosis of PSC but can be associated with complications (pancreatitis, cholangitis). Magnetic resonance cholangiopancreatography (MRCP) is now recommended, particularly in the absence of clinical symptoms or imaging studies which demonstrate an indication for therapeutic endoscopy. A proportion of patients may have normal ERCP/MRCP but suffer from IBD and have histology compatible with PSC; this variant is called small duct PSC and carries significantly better prognosis in terms of disease progression and risk of cholangiocarcinoma (CCA) (29). Life time risk of CCA in patients with PSC is estimated to be 10-12%. In addition, the risk of colorectal cancer in those with PSC and UC is estimated to be five-fold higher than for those with UC alone, typically involving the right colon.

4.1. Indications for transplantation and its timing

In patients with end stage liver disease who manifest symptoms of advanced liver failure and features of portal hypertension the decision to proceed to assessment for liver transplant is straightforward. Patients who develop recurrent episodes of cholangitis and who have dominant strictures for which endoscopic management is not effective are also good candidates due to the risks from sepsis. Occasionally, intractable pruritus can be in itself an indication for surgery. However such patients comprise only a minority of these with PSC. Thus the timing of the operation poses a significant challenge in this group not least because CCA, once it has developed is considered by most centres to be a contraindication to LTx. Patients with PSC comprise a population of relatively young and frequently clinically stable subjects in whom

prophylactic LTx, merely on the grounds that 10-15% of them may at one point develop CCA, cannot be justified; such apparent benefit is counterbalanced by the short-term mortality which follows LTx. Effective surveillance for CCA does not exist and its detection leaves the caring hepatologist with an extremely difficult clinical impasse. To circumvent this, authors from Mayo Clinic proposed a protocol embracing scrupulous staging and neoadjuvant chemoradiation which permitted LTx in carefully selected patients with PSC and CCA and were able to obtain 5 year survival in 82% of patients as compared to only 21% in these who underwent surgical resection (30).

4.2. Transplantation trends

The United Network for Organ Sharing database showed that in spite of a steady raise of the overall number of liver transplants in the United States between 1995 and 2006, the number of transplants for PSC showed no change over the same period (15). Interestingly, there was a tendency towards a decline in placing patients with PSC on the waiting list. Interpretation of this observation is difficult as in terms of the number of transplants it may be related to the relatively low MELD scores held by the patients and better pre-transplant treatment (ursodeoxycholic acid, endoscopic methods).

4.3. Survival after transplantation

Survival rates after LTx in PSC are considered favourable when compared to many other indications for this procedure. Because the disease frequently affects the common bile duct and may recur after LTx, the preferred biliary anastomosis in patients with PSC is a Roux-en-Y choledochojejunostomy. A single centre study from the Mayo Clinic comprising 150 consecutive subjects transplanted for this indication showed actuarial patient survival at 1, 2, 5, and 10 years of 94%, 92%, 86%, and 70%, respectively, and corresponding rates for graft survival of 83%, 83%, 79%, and 61%. (31). The most recent and the largest study in this field from Birmingham, UK which included 230 consecutive PSC patients showed overall 1, 5 and 10 years patients survival of 80%, 68% and 57% and graft survival of 75%, 60% and 50% respectively (32). As overall survival may be influenced by the risk of colorectal cancer in patients with concomitant UC it is recommended that these patients should undergo annual surveillance colonoscopy. Unlike UC which occurs in the absence of PSC, colitis is typically right sided, may spare the rectum (33) and enhance the risk of right sided colonic cancer (34). The 1 and 5-year graft survivals after living donor liver transplantation for PSC are 90 and 80%, respectively. Patient survivals are 97% and 87%, respectively (21).

4.4. Recurrence of the disease

PSC may recur after surgery in up to 37% of patients (35). It is essential that other risk factors for non-anastomotic biliary strictures have been excluded before the diagnosis of recurrent PSC is made. It has been reported that an active IBD requiring steroids, male gender and the history of acute rejection all increase the risk of recurrent PSC. It has also been suggested that the presence of an intact colon significantly increases the risk of recurrence. In their initial report Vera *et al* have shown that cumulative, 10 years risk of PSC recurrence after grafting in patients in whom their colons were removed before or during LTx was 0.1 as compared to 0.7 in these who had their colons intact (35). They also showed that recurrence may lead to graft loss and necessity of re-grafting. These observations have been recently confirmed by the same group in a larger cohort of patients. A diagnosis of recurrent PSC was made in 61 (23%) out of 263 transplanted grafts. They found that colectomy before LTx confers a protective effect against recurrence of PSC and this should therefore be a significant factor in deciding for or against colectomy at the time of LTx. Of importance, 23 grafts were lost due to recurrence and required retransplantation (32). The most recent American Association for the Study of Liver Diseases Practice Guidelines for the Diagnosis and Management of PSC do not suggest any particular treatment of recurrent PSC. Selected studies (35-41) on recurrence of PSC after LTx are shown in Table 1B.

5. CHOLESTATIC CONDITIONS WHICH MANIFEST IN CHILDHOOD

5.1. Cystic fibrosis

Cystic fibrosis (CF), one of the most common autosomal recessive diseases, is caused by a mutation in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) (42). CFTR is a chloride channel involved in production of sweat, digestive juices and mucus (43). CFTR dysfunction causes exocrine secretions to be thick and viscous, resulting in a multiorgan disorder with manifestations involving the respiratory and gastrointestinal tracts, sweat glands, and other exocrine tissues. While life expectancy has increased significantly in recent decades due to improvements in pulmonary management and anti-infectious therapy, (44, 45) liver disease has become more prevalent and is now considered to be the second most common cause of death associated with CF (46). About 17% of patients with CF develop clinically significant liver disease (47). In these patients hepatosplenomegaly and ascites diminish diaphragmatic movement, thus further impairing the already compromised lung function. Once portal hypertension is established, the prognosis is poor (48). LTx offers the only potentially curative treatment (49), however coexisting restrictive lung disease makes the transplant surgery challenging. Combined, triple heart-lung-liver transplantation has been performed in patients with both end-stage liver and lung disease, but the outcomes were unsatisfactory, (50) although at least one patient in the Birmingham series survived more than 20 years following such a triple transplant for CF (personal communication)**.** It is surmised that unusually long term functioning of transplanted lungs in multi-organ transplantees is in part due to the graft tolerance which ensues from implanting a greater mass/load of donor antigens (51). Nevertheless, shortage of donors for lung transplantation has diminished enthusiasm for combined liver and lung or heart-lung-liver transplantation in CF. Success from isolated LTx in CF patients was initially considered highly unlikely because of the risk of infection associated with posttransplant immunosupression, exacerbating pulmonary disease (52).

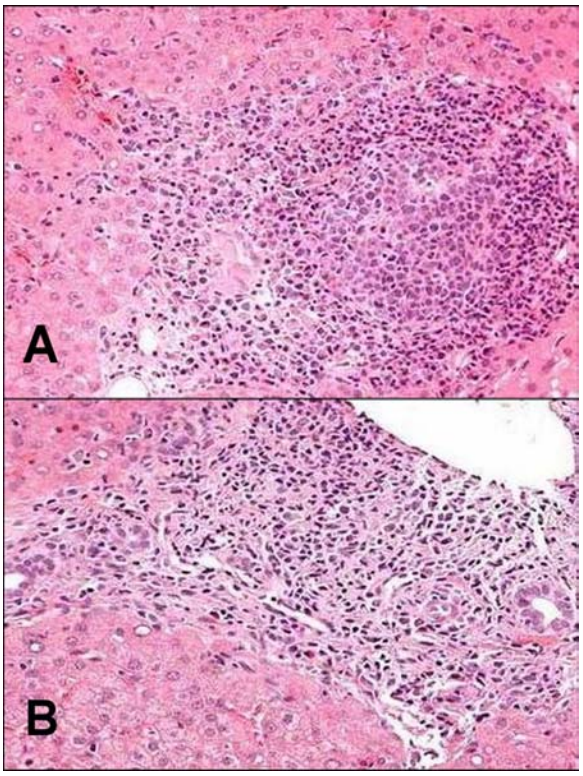

Figure 1. Recurrent PBC. A. Dense lymphoplasmatic infiltrates of portal tract area. B. Proliferation and damage of bile ducts. (Courtesy of prof. E. Urasinska, Dept of Pathology, Pomeranian Medical University)

Nonetheless several studies have now shown that single organ LTx is beneficial for patients with CF. Correct selection of patients and optimal timing for transplantation are crucial to such success. Studies have shown that awaiting progress to end-stage lung disease is associated with a significantly worse outcome of LTx (50). Therefore LTx should be considered in younger patients with well-preserved lung function. In these patients stabilization or even improvement in respiratory function after LTx have been reported (50, 53-55). To help in assessment of these patients for LTx we proposed a simple scoring system (49) which modifies the previous score designed by Noble-Jamieson *et al* (53) and in our cohort, showed significantly improved discriminative value. In patients receiving LTx for cystic fibrosis postoperative prophylactic antimicrobial management is mandatory to prevent exacerbation of respiratory infections due to high dose induction of immunosupression (49). On the positive side, LTx may provide relief of intraabdominal pressure, diaphragmatic splinting, intrapulmonary shunting and remove the contribution of hypoalbuminemia to pulmonary edema (56). Furthermore, it is postulated, that steroidal and non-steroidal anti-inflammatory drugs, along with immunosuppression block cytokine production, resulting in decreased airway inflammation (49, 57, 58)**.** In addition to pulmonary issues, the posttransplant period in patients with CF is associated with increased risk of biliary problems and severe ascites, when compared with patients undergoing LTx for other indications. Postoperative biliary anastamotic strictures occur mainly when the recipient's common bile duct is used for biliary reconstruction and several studies have shown that it can be avoided by using a Roux-en-Y choledochojejunostomy (54, 55, 59). Severe ascites is more frequent in malnourished patients and significantly worsens postoperative outcome (60). This emphasizes the significance of intensive nutritional support during the pretransplant period and listing the patient for LTx before advanced malnutrition develops (49). Thus single LTx is now considered to be acceptable therapy in selected, young patients with well preserved pulmonary function, with the expectation that it will lead to improvements in respiratory function and relief of portal hypertension. Posttransplant 1- and 10-year survival ranges from 75% to 91,6% (53, 54, 61) and from 56% to 67%, respectively (54, 60) and is comparable to that achieved when LTx has been performed for other indications.

5.2. Biliary atresia

Biliary atresia (BA), one of the most common causes of neonatal cholestasis, is the indication for LTx in over 50% of pediatric cases. The disease is characterized by complete fibroinflammatory obliteration of the extrahepatic biliary system with variable involvement of the intrahepatic ducts, resulting in severe cholestasis, liver cirrhosis and if untreated, death in early childhood (62). The cause of BA is most likely multifactorial and remains to be elucidated (63). Ten to thirty five percent of patients exhibit associated anomalies, mainly congenital heart disease. No medical treatment is effective and surgical intervention is the only option for the management of BA. There is no consensus as to whether Kasai portoenterostomy or LTx is the best initial therapy (64-66). Kasai portoenterostomy has excellent medium term results, provided the procedure is performed by an experienced surgeon within the few first months of a patient's life, before liver cirrhosis is developed (67, 68). Nevertheless, more than 60% of infants undergoing the Kasai portoenterostomy ultimately require LTx because of progressive liver damage and portal hypertension (69, 70). Small children can be successfully transplanted by use of a reduced-size deceased liver graft or a portion of the liver from a living-related donor (71, 71, 72). Overall, 1- and 5-year survival rates in Patients who underwent LTx for BA are estimated to be 93% and 85%, respectively, which is considered the best outcome following pediatric transplantation of any group of patients (72-74).

5.3. Alagille syndrome

Alagille syndrome (AS) is an autosomal dominant disorder caused by mutations in the *JAG1* gene encoding a critical ligand in the Notch signalling pathway, that is involved in ultimate cell fate determination (75-77). Defects in the pathway are associated with multisystemic developmental anomalies including interlobular bile duct paucity, congenital heart disease, ocular abnormalities, sagittal cleft ("butterfly-like") vertebrae, mental retardation and characteristic facial features (78-80). Clinical manifestations in AS vary greatly, from a mild phenotype to severe cardiovascular and renal disease (81). Congenital heart disease is the main cause of poor outcome in early childhood (80). In many children with longer survival

persistent cholestasis may lead to severe drug-resistant pruritus and in approximately 20% of patients to biliary cirrhosis. Many patients with AS require LTx for end-stage liver disease, however some subjects may benefit from LTx even without coexisting cirrhosis. This applies to patients with severe hypercholesterolemia and profound growth retardation unresponsive to enteral nutritional support (82). Intractable pruritus is nowadays a less common reason for LTx because of its responsiveness to partial biliary diversion (80, 83). The decision to list for LTx in patients with AS can be difficult because of the variety of extrahepatic manifestations and must take into consideration associated cardiovascular and renal morbidities. Therefore a careful preoperative assessment has to be performed, which in selected cases includes angiographic evaluations and dynamic stress tests, imitating hemodynamic conditions during surgery (84). A full clinical evaluation is also required in cases of living-related LTx as donors are likely to share disease-causing mutations (85). Twenty five percent of children with AS require LTx during their childhood (80), with a median age at the time of operation ranging from 3,5 to 7,8 years; they account for approximately 5% of all indications for pediatric LTx (84). The outcome of LTx is generally comparable to the results seen in other chronic cholestatic conditions in children (85), the risk of hemorrhagic complications being the most important factor limiting overall survival rates (80, 82, 84). This posttransplant bleeding has been linked to arterial hypertension secondary to high-dose steroid therapy and coexisting arterial malformations. Therefore, it is very important to properly control post-transplant arterial blood pressure (82).

5.4. Progressive familiar intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) refers to a wide spectrum of different autosomal recessive defects involving bile formation and its canalicular excretion. PFIC typically manifests itself in the first year of life with intense and persistent pruritus, recurrent episodes of jaundice, and features related to fat-soluble vitamin malabsorption. Liver damage is progressive and, if untreated, typically leads to cirrhosis within the first decade of life (86). However, depending of the type of genetic defect, PFIC may present as both more severe and milder phenotypes.

5.4.1. PFIC1, Byler disease

PFIC1 is a result of genetic defects in the *ATP8B1* gene encoding the membrane protein ATPase class I type 8B (ATP8B1). ATP8B1 is involved in aminophospholipid translocation from the outer to the inner leaflet of the plasma membrane (87-89). ATP8B1 is expressed not only in liver tissue but also in various other organs, thus accounting for extrahepatic manifestations including secretory diarrhoea, sensorineural hearing loss, recurrent pancreatitis and chronic respiratory problems (90). So far, there is no clear explanation why loss of ATP8B1 activity causes liver disease, however alteration in bile acid homeostasis has been proposed as a possible cause of PFIC1 related liver damage (88). This idea is supported by the fact that surgical interruption of the enterohepatic bile acid circulation by partial external biliary diversion or ileal exclusion stabilizes or even improves liver histology and reduces pruritus in these patients (91-93). Because PFIC1 is potentially a systemic disorder, it is not completely corrected by LTx. Post-transplant, intractable chronic refractory diarrhea, pancreatitis, and persistent growth retardation has been reported in patients with PFIC1. Moreover after LTx some patients develop progressive fatty liver disease leading to cirrhosis (90). The cause of this phenomenon is unknown and intriguing. Development of graft damage and the increasing effectiveness of non-transplant surgical treatment nowadays combine to make PFIC1 a disputable indication for LTx.

5.4.2. PFIC2: Bile salt export pump disease

PFIC2 is caused by genetic defects in the *ABCB11* gene that encodes the bile salt export pump (BSEP) which is expressed exclusively at the hepatocyte canalicular membrane (94, 95). BSEP is the major canalicular bile acid pump, and *ABCB11* mutations are responsible for severe cholestasis and hepatocellular damage progressing to end-stage liver disease. Moreover, PFIC2 is associated with a high risk of hepatocellular carcinoma and CCA even in early childhood (96, 97). Early-onset liver damage and high risk of malignancy are the reasons why LTx is usually necessary before adolescence (98, 99). As PFIC2 is a liver-specific condition, LTx corrects all of the problems associated with BSEP deficiency. However, rarely, patients who have undergone LTx for PFIC2 develop a recurrence of their cholestasis, mimicking BSEP deficiency. This phenomenon is considered as an alloimmune response against the donor BSEP proteins in patients immunologically ‘‘naive” for BSEP (99-101).

5.4.3. PFIC3: MDR3 disease

PFIC3 is caused by mutations in the *MDR3* gene (also designated *ABCB4*). Class III Multidrug Resistance (MDR3) P-glycoprotein is a phospholipid translocator in the canalicular cell membrane involved in biliary phosphatidylcholine excretion (102). Patients with MDR3 dysfunction produce phospholipid-deficient, abnormally caustic bile that damages the hepatocytes and intrahepatic bile ducts. The absence of phospholipids also promotes lithogenicity of the bile leading to biliary obstruction (103). In PFIC3, patients have clinical symptoms similar to those in other types of PFIC, but liver damage progresses slowly. Ursodeoxycholic acid therapy has proven effective in patients with a partial MDR3 defect (104), but in the majority of cases LTx represents the only effective therapy. PFIC3 is liver-specific, so LTx is not complicated by extrahepatic disease and these patients have a good prognosis after successful LTx. The use of living related donors, who are likely to be heterozygous for the disease-causing gene, does not appear to compromise the outcome of LTx (105).

6. REFERENCES

1. J Neuberger: Primary biliary cirrhosis. *Lancet* 350, 875-879 (1997)

2. RE Poupon, KD Lindor, A Pares, O Chazouilleres, R Poupon, EJ Heathcote: Combined analysis of the effect of

treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. *J Hepatol* 39, 12-16 (2003)

3. U Leuschner: Primary biliary cirrhosis--presentation and diagnosis. *Clin Liver Dis* 7, 741-758 (2003)

4. C Corpechot, F Carrat, A Bahr, Y Chretien, RE Poupon, R Poupon: The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. *Gastroenterology* 128, 297-303 (2005)

5. P Milkiewicz: Liver transplantation in primary biliary cirrhosis. *Clin Liver Dis* 12, 461-472 (2008)

6. V Mazzaferro, E Regalia, R Doci, S Andreola, A Pulvirenti, F Bozzetti, F Montalto, M Ammatuna, A Morabito, L Gennari: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334, 693-699 (1996)

7. FY Yao, L Ferrell, NM Bass, JJ Watson, P Bacchetti, A Venook, NL Ascher, JP Roberts: Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 33, 1394-1403 (2001)

8. N Al-Harthy, T. Kumagi, C Coltescu, GM Hirschfield: The specificity of fatigue in primary biliary cirrhosis: evaluation of a large clinic practice. *Hepatology* 52, 562-570 (2010)

9. CR Gross, M Malinchoc, WR Kim, RW Evans, RH Wiesner, JL Petz, JS Crippin, GB Klintmalm, MF Levy, P Ricci, TM Therneau, ER Dickson: Quality of life before and after liver transplantation for cholestatic liver disease. *Hepatology* 29, 356-364 (1999)

10. GC MacQuillan, J Neuberger: Liver transplantation for primary biliary cirrhosis. *Clin Liver Dis* 7, 941-956 (2003)

11. E Christensen, B Gunson, J Neuberger: Optimal timing of liver transplantation for patients with primary biliary cirrhosis: use of prognostic modelling. *J Hepatol* 30, 285-292 (1999)

12. ER Dickson, PM Grambsch, TR Fleming, LD Fisher, A Langworthy: Prognosis in primary biliary cirrhosis: model for decision making. *Hepatology* 10, 1-7 (1989)

13. WR Kim, RH Wiesner, TM Therneau, JJ Poterucha, MK Porayko, RW Evans, GB Klintmalm, JS Crippin, RA Krom, ER Dickson: Optimal timing of liver transplantation for primary biliary cirrhosis. *Hepatology* 28, 33-38 (1998)

14. PS Kamath, RH Wiesner, M Malinchoc, W Kremers, TM Therneau, CL Kosberg, G D'Amico, ER Dickson, WR Kim: A model to predict survival in patients with end-stage liver disease. *Hepatology* 33, 464-470 (2001)

15. J Lee, A Belanger, JT Doucette, C Stanca, S Friedman, N Bach: Transplantation trends in primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 5, 1313-1315 (2007)

16. MI Prince, OF James: The epidemiology of primary biliary cirrhosis. *Clin Liver Dis* 7, 795-819 (2003)

17. RF Liermann Garcia, GC Evangelista, P McMaster, J. Neuberger: Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. *Hepatology* 33, 22-27 (2001)

18. J Neuberger, B Gunson, S Hubscher, P Nightingale: Immunosuppression affects the rate of recurrent primary biliary cirrhosis after liver transplantation. *Liver Transpl* 10, 488-491 (2004)

19. U Khettry, N Anand, PN Faul, WD Lewis, EA Pomfret, J Pomposelli, RL Jenkins, FD Gordon: Liver transplantation for primary biliary cirrhosis: a long-term pathologic study. *Liver Transpl* 9, 87-96 (2003)

20. BH Markus, ER Dickson, PM Grambsch, TR Fleming, V Mazzaferro, GB Klintmalm, RH Wiesner, DH Van Thiel, TE Starzl: Efficiency of liver transplantation in patients with primary biliary cirrhosis. *N Engl J Med* 320, 1709-1713 (1989)

21. R Kashyap, S Safadjou, R Chen, P Mantry, R Sharma, V Patil, P Maloo, C Ryan, C Marrocuin, C Barry, G Ramaraju, B Maliakkal, M Orloff. Living donor and deceased donor liver transplantation for autoimmune and cholestatic liver diseases--an analysis of the UNOS database. J Gastrointest Surg 14:1362-1369 (2010).

22. J Neuberger, B Portmann, BR Macdougall, RY Calne, R Williams: Recurrence of primary biliary cirrhosis after liver transplantation. *N Engl J Med* 306, 1-4 (1982)

23. P Charatcharoenwitthaya, S Pimentel, JA Talwalkar, FT Enders, KD Lindor, R. A. Krom, R. H. Wiesner: Long-term survival and impact of ursodeoxycholic acid treatment for recurrent primary biliary cirrhosis after liver transplantation. *Liver Transpl* 13, 1236-1245 (2007)

24. EQ Sanchez, MF Levy, RM Goldstein, CG Fasola, GW Tillery, GJ Netto, DL Watkins, JS Weinstein, NG Murray, D Byers, LL Christensen, GB Klintmalm: The changing clinical presentation of recurrent primary biliary cirrhosis after liver transplantation. *Transplantation* 76, 1583-1588 (2003)

25. PB Sylvestre, KP Batts, LJ Burgart, JJ Poterucha, RH Wiesner: Recurrence of primary biliary cirrhosis after liver transplantation: Histologic estimate of incidence and natural history. *Liver Transpl* 9, 1086-1093 (2003)

26. DA Jacob, UP. Neumann, M. Bahra, J. Klupp, G. Puhl, R. Neuhaus, J. M. Langrehr: Long-term follow-up after recurrence of primary biliary cirrhosis after liver transplantation in 100 patients. *Clin Transplant* 20, 211-220 (2006)

27. D. Morioka, H. Egawa, M. Kasahara, T. Jo, S. Sakamoto, Y. Ogura, H. Haga, Y. Takada, H. Shimada, K. Tanaka: Impact of human leukocyte antigen mismatching

on outcomes of living donor liver transplantation for primary biliary cirrhosis. *Liver Transpl* 13, 80-90 (2007)

28. R Chapman, J Fevery, A Kalloo, DM Nagorney, KM Boberg, B Shneider, GJ Gores: Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 51, 660-678 (2010)

29. E Bjornsson, R Olsson, A Bergquist, S Lindgren, B Braden, RW Chapman, KM Boberg, P Angulo: The natural history of small-duct primary sclerosing cholangitis. *Gastroenterology* 134, 975-980 (2008)

30. DJ Rea, JK Heimbach, CB Rosen, MG Haddock, SR Alberts, WK Kremers, GJ Gores, DM Nagorney: Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 242, 451-458 (2005)

31. W Graziadei, RH Wiesner, KP Batts, PJ Marotta, NF LaRusso, MK Porayko, JE Hay, GJ Gores, MR Charlton, J Ludwig, JJ Poterucha, JL Steers, RA Krom: Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology* 29, 1050-1056 (1999)

32. E Alabraba, P Nightingale, B Gunson, S Hubscher, S Olliff, D Mirza, J Neuberger: A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. *Liver Transpl* 15, 330-340 (2009)

33. U Broome, A Bergquist: Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. *Semin Liver Dis* 26, 31-41 (2006)

34. MM Claessen, MW Lutgens, HR van Buuren, B Oldenburg, PC Stokkers, CJ van der Woude, DW Hommes, DJ de Jong, G Dijkstra, AA van Bodegraven, PD Siersema, FP Vleggaar: More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. *Inflamm Bowel Dis* 15, 1331-1336 (2009)

35. AVera, S Moledina, B Gunson, S Hubscher, D Mirza, S Olliff, J Neuberger: Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. *Lancet* 360, 1943-1944 (2002)

36.U Khettry, A Keaveny, A Goldar-Najafi, WD Lewis, EA Pomfret, JJ Pomposelli, RL Jenkins, FD Gordon: Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol* 34, 1127-1136 (2003)

37. M Kugelmas, P Spiegelman, MJ Osgood, DA Young, JF Trotter, T Steinberg, ME Wachs, T Bak, I Kam, GT Everson: Different immunosuppressive regimens and recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 9, 727-732 (2003)

38. B Brandsaeter, E Schrumpf, O Bentdal, K Brabrand, HJ Smith, A Abildgaard, OP Clausen, K Bjoro: Recurrent primary sclerosing cholangitis after liver transplantation: a magnetic resonance cholangiography study with analyses of predictive factors. *Liver Transpl* 11, 1361-1369 (2005)

39. E Cholongitas, V Shusang, GV Papatheodoridis, L Marelli, P Manousou, N Rolando, D Patch, K Rolles, B Davidson, AK Burroughs: Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 14, 138-143 (2008)

40. J Alexander, JD Lord, MM Yeh, C Cuevas, R Bakthavatsalam, KV Kowdley: Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 14, 245-251 (2008)

41. J Campsen, MA Zimmerman, JF Trotter, M Wachs, T Bak, T Steinberg, I Kam: Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. *Liver Transpl* 14, 181-185 (2008)

42. BJ Rosenstein, PL Zeitlin: Cystic fibrosis. *Lancet* 351, 277-282 (1998)

43. JA Cohn, TV Strong, MR Picciotto, AC Nairn, FS Collins, JG Fitz: Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. *Gastroenterology* 105, 1857-1864 (1993)

44. JA Dodge, S Morison, PA Lewis, EC Coles, D Geddes, G Russell, JM Littlewood, MT Scott: Incidence, population, and survival of cystic fibrosis in the UK, 1968-95. UK Cystic Fibrosis Survey Management Committee. *Arch Dis Child* 77, 493-496 (1997)

45. JR Yankaskas, BC Marshall, B Sufian, RH Simon, D Rodman: Cystic fibrosis adult care: consensus conference report. *Chest* 125, 1S-39S (2004)

46. O Efrati, A Barak, D Modan-Moses, A Augarten, D Vilozni, D Katznelson, A Szeinberg, J Yahav, Y Bujanover: Liver cirrhosis and portal hypertension in cystic fibrosis. *Eur J Gastroenterol Hepatol* 15, 1073-1078 (2003)

47. C Colombo, MG Apostolo, M Ferrari, M Seia, S Genoni, A Giunta, LP Sereni: Analysis of risk factors for the development of liver disease associated with cystic fibrosis. *J Pediatr* 124, 393-399 (1994)

48. J Feigelson, C Anagnostopoulos, M Poquet, Y Pecau, A Munck, J Navarro: Liver cirrhosis in cystic fibrosis--therapeutic implications and long term follow up. *Arch Dis Child* 68, 653-657 (1993)

49. T Lamireau, S Martin, M Lallier, JE Marcotte, F Alvarez: Liver transplantation for cirrhosis in cystic fibrosis. *Can J Gastroenterol* 20, 475-478 (2006)

50. P Milkiewicz, G Skiba, D Kelly, P Weller, R Bonser, U Gur, D Mirza, J Buckels, D Stableforth, E Elias: Transplantation for cystic fibrosis: outcome following early liver transplantation. *J Gastroenterol Hepatol* 17, 208-213 (2002)

51. V Benseler, GW McCaughan, HJ Schlitt, GA Bishop, DG Bowen, P Bertolino: The liver: a special case in

transplantation tolerance. *Semin Liver Dis* 27, 194-213 (2007)

52. LA Mieles, D Orenstein, L Teperman, L Podesta, B Koneru, TE Starzl: Liver transplantation in cystic fibrosis. *Lancet* 1, 1073 (1989)

53. DR Mack, MD Traystman, JL Colombo, PH Sammut, SS Kaufman, JA Vanderhoof, DL Antonson, RS Markin, BW Shaw, Jr., AN Langnas: Clinical denouement and mutation analysis of patients with cystic fibrosis undergoing liver transplantation for biliary cirrhosis. *J Pediatr* 127, 881-887 (1995)

54. JA Fridell, GJ Bond, GV Mazariegos, DM Orenstein, A Jain, R Sindhi, JD Finder, E Molmenti, J Reyes: Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. *J Pediatr Surg* 38, 1152-1156 (2003)

55. G Noble-Jamieson, N Barnes, N Jamieson, P Friend, R Calne: Liver transplantation for hepatic cirrhosis in cystic fibrosis. *J R Soc Med* 89 Suppl 27, 31-37 (1996)

56. MS Tanner: Liver and biliary problems in cystic fibrosis. *J R Soc Med* 85 Suppl 19, 20-24 (1992)

57. BJ Rosenstein, H Eigen: Risks of alternate-day prednisone in patients with cystic fibrosis. *Pediatrics* 87, 245-246 (1991)

58. MW Konstan, PJ Byard, CL Hoppel, PB Davis: Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 332, 848-854 (1995)

59. R Chavez-Cartaya, M Drage, NV Jamieson, P Friend, G Noble-Jamieson, R Levy, N Barnes, R Calne: Biliary complications in liver transplantation for cystic fibrosis. *Transplant Proc* 31, 2411-2412 (1999)

60. EP Molmenti, RH Squires, D Nagata, JS Roden, H Molmenti, CG Fasola, C Prestidge, L D'Amico, D Casey, EQ Sanchez, RM Goldstein, MF Levy, M Benser, W McPhail, W Andrews, JA Andersen, GB Klintmalm: Liver transplantation for cholestasis associated with cystic fibrosis in the pediatric population. *Pediatr Transplant* 7, 93-97 (2003)

61. G Noble-Jamieson, J Valente, ND Barnes, PJ Friend, NV Jamieson, A Rasmussen, RY Calne: Liver transplantation for hepatic cirrhosis in cystic fibrosis. *Arch Dis Child* 71, 349-352 (1994)

62. M Davenport: Biliary atresia. *Semin Pediatr Surg* 14, 42-48 (2005)

63. CL Mack, RJ Sokol: Unraveling the pathogenesis and etiology of biliary atresia. *Pediatr Res* 57, 87R-94R (2005)

64. HV Diem, V Evrard, HT Vinh, EM Sokal, M Janssen, JB Otte, R Reding: Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. *Transplantation* 75, 1692-1697 (2003)

65. D Sandler, KS Azarow, RA Superina: The impact of a previous Kasai procedure on liver transplantation for biliary atresia. *J Pediatr Surg* 32, 416-419 (1997)

66. KS Azarow, MJ Phillips, AD Sandler, I Hagerstrand, RA Superina: Biliary atresia: should all patients undergo a portoenterostomy? *J Pediatr Surg* 32, 168-172 (1997)

67. R Ohi, M Ibrahim: Biliary atresia. *Semin Pediatr Surg* 1, 115-124 (1992)

68. JB Otte, GJ de Ville, R Reding, V Hausleithner, E Sokal, C Chardot, B Debande: Sequential treatment of biliary atresia with Kasai portoenterostomy and liver transplantation: a review. *Hepatology* 20, 41S-48S (1994)

69. M Davenport, N Kerkar, G Mieli-Vergani, AP Mowat, ER Howard: Biliary atresia: the King's College Hospital experience (1974-1995). *J Pediatr Surg* 32, 479-485 (1997)

70. J Laurent, F Gauthier, O Bernard, M Hadchouel, M Odievre, J Valayer, D Alagille: Long-term outcome after surgery for biliary atresia. Study of 40 patients surviving for more than 10 years. *Gastroenterology* 99, 1793-1797 (1990)

71. W J Van der Werf, AM D'Alessandro, SJ Knechtle, G Pilli, RM Hoffmann, RH Judd, JS Odorico, AD. Kirk, SC Rayhill, HW Sollinger, M Kalayoglu: Infant pediatric liver transplantation results equal those for older pediatric patients. *J Pediatr Surg* 33, 20-23 (1998)

72. KF Murray, RL Carithers, Jr.: AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 41, 1407-1432 (2005)

73. NR Barshes, TC Lee, R Balkrishnan, SJ Karpen, BA Carter, JA. Goss: Orthotopic liver transplantation for biliary atresia: the U.S. experience. *Liver Transpl* 11, 1193-1200 (2005)

74. EC Utterson, RW Shepherd, RJ Sokol, J Bucuvalas, JC Magee, SV McDiarmid, R Anand: Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 147, 180-185 (2005)

75. L Li, ID Krantz, Y Deng, A Genin, AB Banta, CC Collins, M Qi, BJ Trask, WL Kuo, J Cochran, T Costa, ME Pierpont, EB Rand, DA Piccoli, L Hood, NB Spinner: Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet* 16, 243-251 (1997)

76. EE Sparks, KA Huppert, MA. Brown, MK Washington, SS Huppert: Notch signaling regulates formation of the three-dimensional architecture of intrahepatic bile ducts in mice. *Hepatology* 51, 1391-1400 (2010)

77. D Krantz, RP Colliton, A Genin, EB Rand, L Li, DA Piccoli, NB Spinner: Spectrum and frequency of jagged1 (JAG1) mutations in Alagille syndrome patients and their families. *Am J Hum Genet* 62, 1361-1369 (1998)

78. D Alagille, M Odievre, M Gautier, JP Dommergues: Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *J Pediatr* 86, 63-71 (1975)

79. D Krantz, DA Piccoli, NB Spinner: Alagille syndrome. *J Med Genet* 34, 152-157 (1997)

80. KM Emerick, EB Rand, E Goldmuntz, ID Krantz, NB Spinner, DA Piccoli: Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 29, 822-829 (1999)

81. SA Shulman, JS Hyams, R Gunta, RM Greenstein, SB Cassidy: Arteriohepatic dysplasia (Alagille syndrome): extreme variability among affected family members. *Am J Med Genet* 19, 325-332 (1984)

82. C Englert, E Grabhorn, M Burdelski, R Ganschow: Liver transplantation in children with Alagille syndrome: indications and outcome. *Pediatr Transplant* 10, 154-158 (2006)

83. P Mattei, D von Allmen, D Piccoli, E Rand: Relief of intractable pruritus in Alagille syndrome by partial external biliary diversion. *J Pediatr Surg* 41, 104-107 (2006)

84. BM Kamath, KB Schwarz, N Hadzic: Alagille syndrome and liver transplantation. *J Pediatr Gastroenterol Nutr* 50, 11-15 (2010)

85. M Kasahara, T Kiuchi, Y Inomata, K Uryuhara, S Sakamoto, T Ito, Y Fujimoto, Y Ogura, F Oike, K Tanaka: Living-related liver transplantation for Alagille syndrome. *Transplantation* 75, 2147-2150 (2003)

86. E Jacquemin: Progressive familial intrahepatic cholestasis. Genetic basis and treatment. *Clin Liver Dis* 4, 753-763 (2000)

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

88. SW van Mil, LW Klomp, LN Bull, RH Houwen: FIC1 disease: a spectrum of intrahepatic cholestatic disorders. *Semin Liver Dis* 21, 535-544 (2001)

89. P Ujhazy, D Ortiz, S Misra, S Li, J Moseley, H Jones, IM Arias: Familial intrahepatic cholestasis 1: studies of localization and function. *Hepatology* 34, 768-775 (2001)

90. P Lykavieris, S van Mil, D Cresteil, M Fabre, M Hadchouel, L Klomp, O Bernard, E Jacquemin: 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* 39, 447-452 (2003)

91. PF Whitington, GL Whitington: Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. *Gastroenterology* 95, 130-136 (1988)

92. C Kurbegov, KD Setchell, JE Haas, GW Mierau, M Narkewicz, JD Bancroft, F Karrer, RJ Sokol: Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile. *Gastroenterology* 125, 1227-1234 (2003)

93. M Hollands, FJ Rivera-Pedrogo, R Gonzalez-Vallina, O Loret-de-Mola, M Nahmad, CA Burnweit: Ileal exclusion for Byler's disease: an alternative surgical approach with promising early results for pruritus. *J Pediatr Surg* 33, 220-224 (1998)

94. SS Strautnieks, LN Bull, AS Knisely, SA Kocoshis, N Dahl, H Arnell, E Sokal, K Dahan, S Childs, V Ling, MS Tanner, AF Kagalwalla, A Nemeth, J Pawlowska, A Baker, G Mieli-Vergani, NB Freimer, RM Gardiner, RJ Thompson: A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nat Genet* 20, 233-238 (1998)

95. SS Strautnieks, JA Byrne, L Pawlikowska, D Cebecauerova, A Rayner, L Dutton, Y Meier, A Antoniou, B Stieger, H Arnell, F Ozcay, HF Al-Hussaini, AF Bassas, HJ Verkade, B Fischler, A Nemeth, R Kotalova, BL Shneider, J Cielecka-Kuszyk, P McClean, PF Whitington, E Sokal, M Jirsa, SH Wali, I Jankowska, J Pawlowska, G Mieli-Vergani, AS Knisely, LN. Bull, RJ Thompson: Severe bile salt export pump deficiency: 82 different ABCB11 mutations in 109 families. *Gastroenterology* 134, 1203-1214 (2008)

96. S Knisely, SS Strautnieks, Y Meier, B Stieger, JA Byrne, BC Portmann, LN Bull, L Pawlikowska, B Bilezikci, F Ozcay, A Laszlo, L Tiszlavicz, L Moore, J Raftos, H Arnell, B Fischler, A Nemeth, N Papadogiannakis, J Cielecka-Kuszyk, I Jankowska, J Pawlowska, H Melin-Aldana, KM Emerick, PF Whitington, G Mieli-Vergani, RJ Thompson: Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. *Hepatology* 44, 478-486 (2006)

97. O Scheimann, SS Strautnieks, AS Knisely, JA Byrne, RJ Thompson, MJ Finegold: Mutations in bile salt export pump (ABCB11) in two children with progressive familial intrahepatic cholestasis and cholangiocarcinoma. *J Pediatr* 150, 556-559 (2007)

98. Davit-Spraul, M Fabre, S Branchereau, C Baussan, E Gonzales, B Stieger, O Bernard, E Jacquemin: 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* 51, 1645-1655 (2010)

99. G Maggiore, E Gonzales, M Sciveres, MJ Redon, B Grosse, B Stieger, A Davit-Spraul, M Fabre, E Jacquemin: Relapsing features of bile salt export pump deficiency after liver transplantation in two patients with progressive familial intrahepatic cholestasis type 2. *J Hepatol* 53, 981-986 (2010)

100. V Keitel, M Burdelski, Z Vojnisek, L Schmitt, D Haussinger, R Kubitz: De novo bile salt transporter antibodies as a possible cause of recurrent graft failure after liver transplantation: a novel mechanism of cholestasis. *Hepatology* 50, 510-517 (2009)

101. P Jara, L Hierro, P Martinez-Fernandez, R Alvarez-Doforno, F Yanez, MC Diaz, C Camarena, V la De, E Frauca, G Munoz-Bartolo, M Lopez-Santamaria, J Larrauri, L Alvarez: Recurrence of bile salt export pump deficiency after liver transplantation. *N Engl J Med* 361, 1359-1367 (2009)

102. E Jacquemin: Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. *Semin Liver Dis* 21, 551-562 (2001)

103. E Jacquemin, JM De Vree, D Cresteil, EM Sokal, E Sturm, M Dumont, GL Scheffer, M Paul, M Burdelski, PJ Bosma, O Bernard, M Hadchouel, RP Elferink: The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood. *Gastroenterology* 120, 1448-1458 (2001)

104. E Jacquemin, D Hermans, A Myara, D Habes, D Debray, M Hadchouel, EM Sokal, O Bernard: Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. *Hepatology* 25, 519-523 (1997)

105. L Cutillo, M Najimi, F Smets, M Janssen, R Reding, GJ de Ville, EM Sokal: Safety of living-related liver transplantation for progressive familial intrahepatic cholestasis. *Pediatr Transplant* 10, 570-574 (2006)

Abbreviations: LTx: liver transplantation; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; AMA: M2 antimitochondrial antibody; MELD: Model of End Stage Liver Disease; INR: International Normalized Ratio; ELTR: European Liver Transplant Registry; UK: United Kingdom; HLA: human leukocyte antigen; IBD: inflammatory bowel disease; UC: ulcerative colitis; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; CCA: cholangiocarcinoma; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; BA: biliary atresia; AS: Alagille syndrome; PFIC: progressive familial intrahepatic cholestasis; ATP8B1: ATPase class I type 8B; BSEP: bile salt export pump; MDR3: Class III Multidrug Resistance

Key Words: Liver Transplantation, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Cystic Fibrosis, Biliary Atresia, Alagille Syndrome, Progressive Familial Intrahepatic Cholestasis, Byler Disease, Bile Salt Export Pump Disease, MDR3 disease, Review

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