Review Article

After Two Centuries Biliary Atresia Remains the Darkest Chapter in Pediatric Hepatology

A-Kader HH[1]*, Feerick J[1] and Rodriguez-Davalos M[2]

[1]*Department of Pediatrics, The University of Arizona, USA*
[2]*Department of Surgery, Yale University School of Medicine, USA*

Abstract

Two centuries after Professor John Burns, of the Department of Surgery, University of Glasgow referred to biliary atresia in his text book the etiology of the obliterative process remains a mystery. We still lack a complete understanding of the pathogenesis of the disorder, which hurdled our efforts to develop preventive and therapeutic measures. Several genetic, immune, viral, toxic and vascular etiologies have been proposed without conclusive evidence. Early recognition and prompt intervention are imperative in order to prevent rapid progressive damage to the liver. Although liver transplantation has been proposed as a primary therapy, the Kasai procedure (hepatoportoenterostomy remains the most reasonable initial approach. Biliary atresia is the most common indication for liver transplantation in the pediatric age group accounting for at least 50% of all transplants.

HISTORY

The first reference to the clinical features of biliary atresia (BA) dates back to 1810 when Professor John Burns, of the Department of Surgery, University of Glasgow wrote the following in his textbook: "The Principals of Midwifery, Including the Diseases of Women and Children" [1]: The jaundice of infants, is a disease attended with great danger, especially if it appears very soon after birth, and the stools evince a deficiency of bile; for we have then reason to apprehend, some incurable state, of the biliary apparatus".

Fatal neonatal jaundice cases associated with atrophic and absent gall bladder were reported by Cursham [2] in 1840 and West in 1852 respectively [3]. In 1892 Thompson reported 49 cases of neonatal jaundice associated with malformation of the biliary tract which were classified into 4 groups. In the first group there was no passage from the liver to the small intestine despite patency of the gall bladder and cystic duct. In the second group a passage was present from the liver to the duodenum in the absence of cystic duct and gall bladder. In the third group (most common) both cystic and hepatic ducts were obliterated. In the

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fourth group the obliteration was distal to the junction of the cystic and hepatic ducts [4-6].

In 1893 Holmes presented a case of neonatal cholestasis in a 7 weeks old infant who died 8 weeks later. The patient had atrophic gall bladder, obliterated cystic and common bile ducts and anomalous hepatic ducts draining into a small globular structure. In 1901 Rolleston reported a case of congenital obliteration of the bile duct associated with hepatic cirrhosis [7]. In 1916 Holmes reviewed the literature which included 120 cases and estimated that at least 16% of the cases could be relieved by anastomosis, introducing for the first time the concept of correctable and non-correctable BA [8].

In 1935 Ladd reported a series of 45 patients with congenital obstruction of the bile ducts and suggested that patients with this disorder can be divided into seven groups [9]: (1) Cases in which there are no extrahepatic ducts. (2) Cases in which there is an atresia of the hepatic ducts. (3) Cases in which there is an atresia of the common duct. (4) Cases in which the gallbladder is represented by a moderate sized cyst not connected with the common duct and in which there may or may not be any common or hepatic ducts. (5) Cases in which the gallbladder connects directly with the duodenum but in which there are no other extrahepatic ducts. (6) Cases in which there is stenosis of the common bile duct plugged with inspissated bile causing complete obstruction. (7) Cases in which there is narrowing of the common duct causing partial obstruction. Ladd recommended that surgical correction should be attempted before the age of 4 months before they develop fatal complications [10].

Gross described the experience of Boston Children's of 147 infants with BA. 27 of these patients had biliary structures amenable to surgical anastomosis. Only 12 patients cleared their jaundice following the surgery, while 15 infants died. All the 119 patients with uncorrectable lesions died after having a protracted course characterized by jaundice, emaciation, ascites, infection and hemorrhage [11].

Prior to the introduction of hepatoportoenterostomy, the non-correctable type of BA was considered incurable. Surgeons used to close the abdomen in the absence of patency of the extrahepatic bile ducts. Several procedures have been tried to establish bile flow and relieve the jaundice in these patients including the creation of artificial bile duct [12], hepatic lymphatic drainage to the jejunum [13] and intrahepatic cholangiojejunostomy with partial hepatectomy [14]. However, none of these procedures proved to be successful despite mild improvement in serum bilirubin. The frustration of theses attempts has led Willis J Potts in 1959 to state that: "Congenital atresia of the bile ducts is the darkest chapter in pediatric surgery" [15].

In 1955 Dr. Katsura made an incision in the porta hepatis and placed the duodenum over the area in a 72 days old girl with non-correctable BA. Following surgery bile flow was established and jaundice cleared [16]. The great discovery was made by Dr. Morio Kasai who found internal biliary fistula between the intrahepatic bile ducts and the small bowel at gross and microscopic examination [17]. The fact that bile was able to force its way into the small bowel gave Kasai a great hint to establish an anastomosis between the small bowel and the porta hepatis. To be successful such anastomosis has to be made at the area where these patent bile ducts are present. The first case of planned hepatoportoenterostomy was published in the Japanese language in 1959 [18] and after that in the German and the English literature in1966 [19,20]. Several modifications in the surgical technique have been made in order to decrease the incidence of ascending cholangitis which is a common complication following the procedure [21].

Embryology

Hepatic development begins in the third week of gestation and continues through the fetal life. However, structural and functional maturation continues after birth [21]. Two buds arise from the junction between the foregut and midgut during the fourth week of gestation. The ventral pancreatic primordium, gives rise to the ventral pancreas and hepatic diverticulum (Figure 1). The hepatic diverticulum grows into ventral mesogastrium and passes through it into the septum transversum, a mesodermal plate that separates the pericardial and peritoneal cavities. The hepatic diverticulum divides into a larger cranial part called pars hepatica, and smaller caudal segment (pars cystica). The cranial part develops into the liver parenchyma and the intrahepatic and extrahepatic biliary tracts while the caudal part will form the gallbladder and the cystic duct. The second bud, the dorsal pancreatic primordium, gives rise to the dorsal pancreas and the pancreatic duct. After rotating, the ventral pancreas fuses with the dorsal pancreas in a position behind the duodenum.

During the fourth week of gestation buds of epithelial cells (hepatoblasts) grow into the mesoderm of the septum transversum giving rise to thick anastomotic cords (muralium multiplex) which will entangle the sinusoidal networks arising from tributaries of the vitelline vein [22]. The continuing development of sinusoidal network will result in thinning out of hepatocytes cords attaining the adult single-cord pattern at five years of age [23-25].
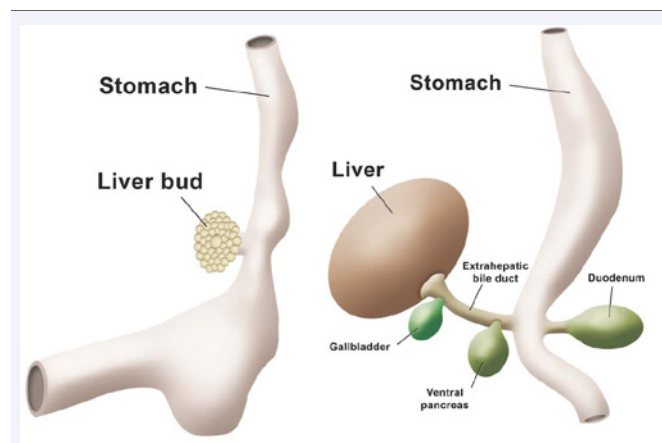
Figure 1 Illustration of normal embryology of the hepatobiliary structure. Development of ventral and dorsal buds at the junction foregut/midgut happens around the 4th week of gestation. The ventral pancreas originates from the ventral primordium. After rotation, it fuses with the dorsal pancreas in a retroduodenal location. The cranial part of the hepatic diverticulum develops into the liver parenchyma and the caudal part becomes the gall bladder and cystic duct. Modified with permission.

The development of intrahepatic bile ducts follows remodeling of the ductal plate which occurs secondary to outgrowth of mesenchyme separating it from the hepatocytes limiting plate and resorption of the excess ductal structures [26,27]. Although bile formation starts at 5-9 weeks of gestation and bile secretion at 12 weeks of gestation the canalicular transport and bile excretory process are not fully mature at birth [28].

The extrahepatic biliary tree continues developing for up to 8 weeks of gestation. The extrahepatic biliary tree is patent from the start which argues against the theory that extrahepatic bile duct atresia results from failure of recanalization of the common bile duct [25].

The intralobular biliary radicles extend from the hepatic lobules to the portal spaces. The perilobular bile ducts assemble toward the right and left hepatic ducts. The common hepatic duct converges with the cystic duct originating from the gallbladder forming the common bile duct.

Classification

Three major variants of BA have been described (Figure 2). In the first type there is patency of the proximal extrahepatic bile ducts with atresia of the distal bile duct. This variant which presents in only 7% of the cases has been termed correctable BA [29]. The second type is seen in 15% of the cases and is characterized by atresia of the common hepatic duct at different levels. In some cases there is patency of the gallbladder, cystic duct and the common bile duct. In the third type (the most common variant) there is nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum. The type of BA does not change the corrective surgery except in the second type where the patent gall bladder and bile ducts can be used as biliary conduit. The proximal patent ducts in the first type are usually excised at the hilum as they are usually diseased.

About 10% of the cases of BA (up to 20% in some Japanese and South Asian series) have a distinct cystic component [30,31]. This type of biliary atresia develops during the prenatal life [32] and has a better prognosis particularly with early surgery. These cysts can be confused with choledochal cysts. However, in cystic biliary atresia there is absence of epithelial lining and it can be differentiated from choledochal cysts by intraoperative cholangiography due to the lack of communication with the intrahepatic bile ducts.

BA can be also classified based on the presence or absence of associated anomalies into three categories:
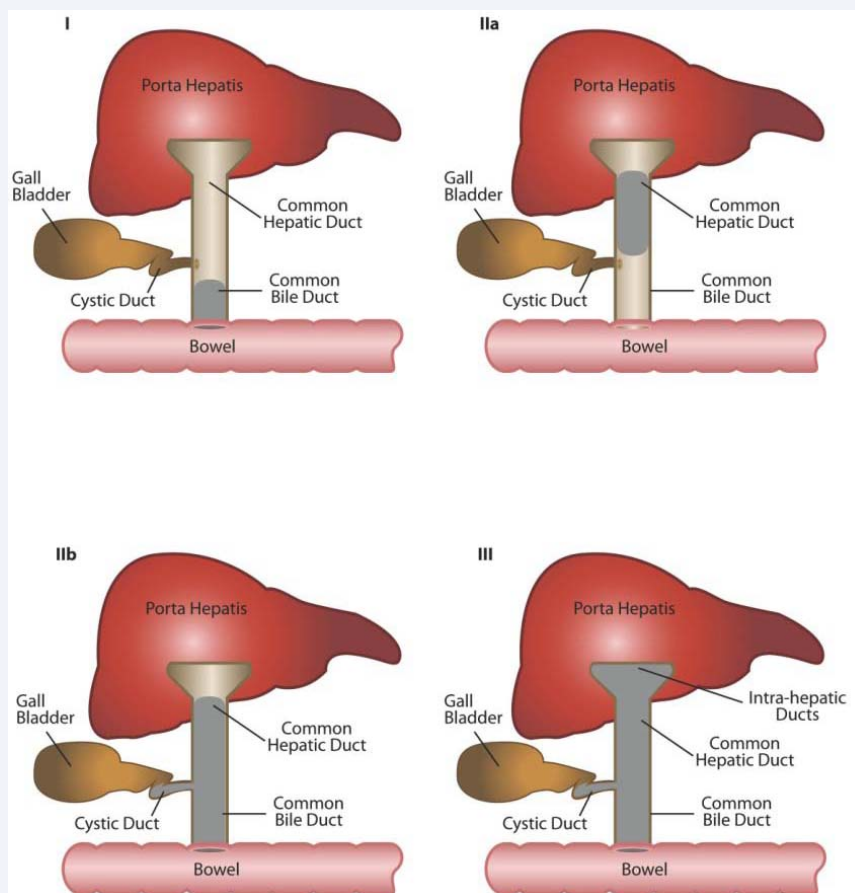
Figure 2 Classification of biliary atresia according to the area of involvement (gray-colored). Type I is characterized by patency of the proximal extrahepatic bile ducts with atresia of the distal bile duct. In type IIa there is atresia of the common hepatic duct. Type IIb is atresia of the cystic duct, common bile duct and hepatic duct. In the type III there is nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum.

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• BA not associated with other anomalies or malformations. This type is also known as perinatal atresia and affects around 70% of biliary atresia patients [33,34]. The patients are not jaundiced at birth. An evolving process develops during the first two months with progressive jaundice and acholic stools.

• BA associated with laterality malformation. This type is also known as Biliary Atresia Splenic Malformation (BASM) syndrome. This type is seen in 10-15% of biliary atresia patients. Associated laterality malformations include situs inversus, malrotation, asplenia or polyspleina, interrupted inferior vena cava and congenital heart disease. BASM syndrome is characterized by poor outcome compared to the perinatal type [35,36].

• BA associated with other congenital malformations such as choledochal cysts, kidney anomalies and cardiac defects [37-39]. This type affects the remaining 10-15% of the patients.

Pathogenesis

BA is an idiopathic inflammatory obliterative disorder characterized by complete occlusion of part of or the entire intra and extrahepatic biliary tree. It is still unknown if BA results from developmental anomaly of the bile ducts or it is the end-result of a necroinflammatory process of undefined etiology leading to fibrosis and ultimately cirrhosis.

Patients with the common perinatal form, develop jaundice 3 to 4 weeks after birth. Bile duct remnants are usually found in the porta hepatis, and there is absence of associated congenital anomalies. BA is the most common indication of liver transplantation in the pediatric age group as 50% and 80% of biliary atresia patients undergo transplantation by age 2 and 20 respectively [40].

The etiology of the obliterative process associated with biliary atresia remains obscure. The leakage of bile acids induces an inflammatory process in the bile ducts and triggers protracted inflammation and obliteration of the distal bile ducts. However, the pathogenesis of biliary atresia cannot be explained solely by the toxic effects of bile acids as the obliterative process continues despite the establishment of bile flow following the Kasai procedure. BA most likely results from an array of causes including defective morphogenesis, vascular malformation, viral infection or immune-mediated mechanisms which may happen prenatally or during the early postnatal period.

It has been suggested that an abnormality in the immune or inflammatory response may be involved in the pathogenesis of BA. The theory is that a viral or toxic insult can result in the appearance of new antigens on the surface of bile duct epithelium. These antigens can be recognized by circulating T lymphocytes in the proper genetically determined immunologic milieu (e.g., major histocompatibility molecules) triggering a cellular immune injury leading to inflammation and fibrosis of bile ducts [41].

A significantly high frequency of HLA-B12, haplotypes A9-B5 and A28-B35, and their disequilibrium in patients was reported by Silvera et al. [42] in patients with BA. However, these results could not be replicated in a study from Spain [43]. On the other hand, HLA-DR was expressed by the bile duct epithelium in 11 of 16 liver specimens of patients with BA in a Japanese study by Nakada et al. [44]. In the same study HLA-DR was not expressed in

liver specimens from 6 patients with congenital biliary dilatation. In addition, HLA-A33, -B44 and -DR6 were frequently expressed in the blood of patients with BA and their families.

In a study in 18 Egyptian children with BA without extrahepatic congenital malformations by A-Kader et al. [45] there was a significant increased frequency of both B8 and DR3 (83.3% and 94.4% respectively) in patients with BA compared with 6.5% and 14.9% in the general population, respectively. Ten patients had the B8/DR3 haplotype which suggests that genetic factors may play a role in susceptibility to BA.

There are several similarities between primary sclerosing cholangitis (PSC) and idiopathic infantile obstructive cholangiopathies. Both disorders may arise from a progressive inflammatory process that may lead to either stricture formation or luminal obliteration [46]. HLA B8 and DR3 haplotypes are often found in inflammatory bowel disease with concomitant PSC. Additionally, the relative risk of PSC developing in a patient with ulcerative colitis possessing the HLA-B8/DR3 haplotype is increased 10-fold [47].

CFC1 gene mutations have been associated with BASM syndrome. CGC1 gene analysis in 10 patients with polysplenia syndrome showed that the heterozygous transition c.433G>A (Ala145Thr) located in exon 5 was identified in 5 patients, with a twice-higher frequency than in control patients which suggests that heterozygous CFC1 mutation may represent a genetic predisposition to BASM syndrome [48].

Mutations of human jagged 1 (JAG1) gene are responsible for Alagille syndrome. Kohsaka et al. [49] examined the JAG1 mutation in patients with BA. In 102 cases of BA, 9 missense mutations were detected, including 2 intrafamilial expressions in the propositus and an aunt of one family. These mutations were all missense and sporadic except for those of this particular family. The JAG1 gene mutations were generally found in severely ill patients subjected to liver transplantation at less than 5 years of age, which suggests that the JAG1 gene abnormality may be an aggravating factor in BA.

Mutations involving the inversion gene (inv) in chromosome 4 are known to result in anomalous development of the hepatobiliary system in mice [50,51]. The role of the mutations has been investigated in humans with biliary atresia. The inv gene is not likely to be involved in the fetal cases since no consistent mutations in the inv gene were reported in patients with BA, including those with BASM syndrome [52,53].

Another suggested modifier is heterozygosity for alpha-one-antitrypsin (A1AT) deficiency, the most common genetic cause of liver disease. Campbell et al [54] reported a significantly higher frequency of A1AT heterozygosity in children with BA compared to the normal population. In these patients, the presence of non-M alleles was associated with a rapid progression of disease and earlier need for transplantation, implicating A1AT heterozygosity as a potential contributor to disease severity. Larger studies, however, are necessary to confirm this finding.

Histological features similar to ductal plate malformation (DPM) disease have been reported in fetal type BA [55], suggesting that abnormalities in hepatocyte growth factor or

other defects in intracellular adhesion systems might be involved in the pathogenesis of fetal BA. In a report by Hinds only one patient out of nine children diagnosed with BA in utero had BASM syndrome and none of the nine subjects had features suggesting DPM [56]. Tan et al. [57] hypothesized that BA may arise from failure of the ductal plate structure remodeling between 11 and 13 weeks of gestation resulting in the materialization of fragile mesenchymal cuff around the developing hilar bile ducts, which could potentially be predisposed to break at the instigation of bile flow around the 12th-week of gestation.

Garcia-Barceló el al [58] carried out a genome-wide association study (GWAS) in order to identify BA susceptibility loci. The author's genotyped nearly 500,000 single-nucleotide polymorphisms (SNPs) in 200 Chinese patients with BA and 481 ethnically matched control subjects. The 10 most BA-associated SNPs from the GWAS were genotyped in an independent set of 124 BA and 90 control subjects. A strong association was found for rs17095355 on10q24, downstream XPNPEP1, a gene known to be involved in the metabolism of inflammatory mediators.

In a recent study, Cui et al [59] searched for copy number variants that were increased among 61 patients with BA and 5088 controls and observed a statistically significant increase in deletions at 2q37.3 in patients with BA that resulted in deletion of 1 copy of GPC1, which encodes glypican-1 heparan sulfate proteoglycan that regulates Hedgehog signaling pathway and inflammation. Biliary developmental defects in Zebra fish also resulted from gene knockdown of GPC1. Therefore, GPC1 seems to be a BA susceptibility gene. In addition Hedgehog signaling pathway appears to be involved in the pathogenesis of BA.

Portal tract mononuclear cell infiltrate observed in the liver of patients with BA proposes a primary inflammatory process resulting in bile duct obstruction. The literature has concentrated on a possible role for viral infection as well as immune mechanisms in the pathogenesis of BA.

The proposed role for viral infection in BA is based on the identification of lymphocytes in the connective tissue of the porta hepatis in BA patients [60], the seasonal clustering of BA and the fact that BA can be induced in in experimental animals with viral infection [61]. Viral infection can conceivably induce a progressive, immune-mediated fibroinflammatory obliterative disorder [62-64].

Several viruses have been investigated for a possible role in the pathogenesis of BA including hepatitis A and B viruses [65], hepatitis C virus [66], cytomegalovirus [67-70], human papilloma virus [71], and human herpes viruses [67]. However, none of these studies provided conclusive evidence.

Many investigators believe that reovirus type 3 (Reo-3) is the most likely infectious cause of biliary atresia based on studies in experimental models. The hepatobiliary histologic lesions of human newborns with biliary atresia have been compared to those induced in weanling mice by Reo-3. In a study by Bangaru et al [72] two of 12 babies had elevated and rising neutralizing titers to Reo-3 during the course of their illness with BA. The authors have also shown that hepatobiliary murine pathology is not the property of a single viral gene. There are also reports that show lack of correlation between infection with Reo-3 and extrahepatic biliary atresia or neonatal hepatitis [73].

Glaser [74] reported that 62% of babies with BA and 52% of infants with idiopathic neonatal hepatitis have Reo-3 antibodies. Although serum antireovirus antibodies were not consistently detected in infants with BA, this may be due of passively transferred maternal anti-reovirus antibodies. Brown et al [75] reported that Reo-3 antigens were not detected in the hepatobiliary tissues of 19 infants (18 with BA, one with neonatal hepatitis). Similarly, Steele et al [76] detected the presence of reoviral RNA only once in a single patient sample in a study which included 14 with BA, 20 with idiopathic neonatal hepatitis, and 16 age-matched controls.

Interest in Rotavirus as a possible infectious etiology originates from the observation that infection in weanling mice results in bile duct and liver damage similar to that observed in BA [77-79]. In a mouse model, oral vaccination against Rotavirus prevented most rhesus rotavirus-induced BA, which suggests a possible approach for prophylaxis against BA [80].

On the other hand, in a large study seventy-four liver biopsies (taken during Kasai portoenterostomy) were screened by polymerase chain reaction for the common human hepatotropic viruses including DNA viruses (herpes simplex virus, Epstein-Barr virus, varicella zoster virus, cytomegalovirus, adenovirus, parvovirus B19 and polyoma BK) and RNA viruses (enteroviruses, rotavirus and Reo-3). In addition Mx protein expression which has been shown to be significantly up-regulated during viral infections was assessed by immunohistochemistry. Virus DNA/RNA was found in less than half of the biopsies. A limited number presented with double infection. The majority of the liver biopsies showed expression of Mx proteins in hepatocytes, bile ducts and epithelium. The authors concluded that although the inflammatory response in the livers of BA patients mimicked that observed during viral infections the known hepatotropic viruses do not play a major role in the etiology and progression of BA [81].

The immune process which persists after clearance of the viral antigens mimics the response seen in humans as shown by Narayanaswamy et al [82] who reported that the early circulating inflammatory process in BA is persistent, progressive and involves a non-polarized T cell, macrophage and cell adhesion molecule response only partially ameliorated by the Kasai procedure. Mack et al. [83] have shown that adoptive transfer of the T cells from RRV-diseased mice into naïve syngeneic severe combined immunodeficiency (SCID) recipients mice resulted in bile duct-specific inflammation. This induction of bile duct pathology occurred in the absence of detectable viruses, indicating a definite response to bile duct autoantigens.

In a report by Davenport et al [84] CD4+ lymphocytes and CD56+ (NK cells) predominated in the liver of infants with BA as compared with controls. In addition, the expression of the macrophage marker (CD68) within the liver and biliary remnants and reduction of ICAM-1 expression on infiltrating cells in the biliary remnants appear to be associated with a better postoperative prognosis. Another support for an antigen-driven cellular immune response is the observation of up-regulation

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of CD4 T-helper 1 (Th1) cytokine encoding genes, and down-regulation of genes encoding Th2 cytokines as reported by Bezerra et al [85].

Lu et al [86] have identified autoantibodies against α-enolase in the Rhesus Rotavirus (RRV)-induced mouse model of BA; and in serum samples from patients, suggesting a role of humoral autoimmunity in the pathogenesis of BA. The cross-reactivity between an anti-enolase antibody and RRV proteins suggests that molecular mimicry might activate humoral autoimmunity in BA patients. Although circulating autoantibodies, including antineutrophil cytoplasmic antibodies (ANCA) and antibodies directed to α-enolase and vimentin were reported in patients with BA proposing a role of Th2 in the pathogenesis of BA [87,88]. However, ANCA could not be found in another study in Egyptian children [89].

Maternal microchimerism may play a role the pathogenesis of BA. Suskind et al [90] demonstrated maternal microchimerism in patients with BA, suggesting that engrafted maternal lymphocytes may induce graft-versus-host disease (GvHD) resulting in BA. Kobayashi et al. [91] using maternal anti-HLA antibody, in the hepatocytes and bile duct epithelia in BA demonstrated maternal microchimerism.

In a study by Muraji et al [92] significantly larger numbers of maternal XX+ cells were found in the portal area and sinusoids of patients with BA compared to controls. In the same study phenotypic analyses of XX+ cells, CD8+ T cells, CD45+ cells, and cytokeratin-positive cells were found with significantly higher numbers and among total CD8+ T cells in comparison to controls. Whether these maternal cells may function as maternal effector T lymphocytes, or targets or bystanders is not clear. Muraji has suggested that the first hit may be due to GvHD interaction by engrafted maternal effector T lymphocytes and the secondary effects result from maternal chimeric effector T lymphocytes (e.g., GvHD interaction) or targets (e.g. HvGD interaction) [93]. However, since 2-way maternofetal cell trafficking is a common observation, the presence of maternal microchimerism by itself does is not a definite proof for its etiological role in the pathogenesis of BA.

Vasculopathy has been also proposed as a contributing factor in the pathogenesis of BA. Ho et al [94] reported the histological features of the extrahepatic hepatic biliary tree as well as a wedge liver biopsy in 11 patients with BA (ultrasonography of the hepatic artery at the porta hepatis was also done in 5 of the 11 patients). Arteriopathy manifesting as hyperplasia and hypertrophy of the hepatic arteries was reported in all cases affecting the arteries from the trunk of the common hepatic artery to its peripheral branches supplying the entire biliary tree. However, it is not clear if these effects are the cause or the result of the disorder.

Toxic insult resulting in biliary atresia has been suggested because of the seasonal clustering reported in some studies. However, a toxic-mediated inflammatory process as a cause for biliary atresia has been strongly suggested following the reports of 3 outbreaks of BA in lambs in Australia in 1964, 1988 and 2007 [95]. The outbreaks happened following draught as the ewes gazed in lands previously submerged and possibly exposed to

toxins during the early stages of pregnancy. The affected animals presented with failure to thrive, jaundice and acholic stools and died within 4 weeks of birth. Autopsy confirmed the presence of BA.

Epidemiology

Biliary atresia is the most common cause of neonatal cholestasis requiring surgical approach and also the most common indication for liver transplantation in the pediatric age group accounting for 50% of pediatric transplant procedures [96]. Around 250 to 400 new cases of biliary atresia are diagnosed every year in the USA with an estimated frequency of 1 in 8000 to 15,000 live births [97]. There is a female predominance and an increased incidence among African-Americans [98]. In a recent report, Rivera et al [99] mapped the international incidence of biliary atresia per thousand live births (Figure 3). Lin et al [100] reported that the incidence of BA negatively correlated with the gross domestic product and marginally negatively correlated with rotavirus vaccine coverage rates.

Increased seasonal variation has been suggested raising the possibility for environmental trigger in the pathogenesis of BA. Significant seasonal variations were reported with increased incidence of BA from August to October [101-109] as well as December to March [106]. Clustering of cases in 1976, 1977, and 1979 was reported in Texas, with a higher incidence from November to January [108]. However, other studies did not validate seasonal clustering [100-105,107,109]. The data regarding a change in the incidence of BA has been also conflicting. An increased incidence over time was suggested in a study by Tiao et al [110]. Contradicting results were reported in other studies [100,109]. An incidence in urban areas as compared with rural areas in New York was reported by Calton et al [104].

Clinical features

Jaundice is usually the first sign of BA and is usually detected any time from birth up to eight weeks of age. It is not uncommon to misdiagnose BA as physiologic or breast milk-associated jaundice as in many patients BA is recognized in full-term thriving babies. Therefore, it is imperative to fractionate bilirubin in any baby with hyperbilirubinemia beyond the age of two weeks.

As the patient gets more cholestatic the urine attains dark color with pale and eventually acholic stools. We usually ask the nursing staff and the family to keep stool samples for us so we can personally examine them. Dark urine resulting from excretion of bilirubin into urine can mix with stools making them look darker in color and sloughing of intestinal epithelium can also provide false coloration to the pale stools. Hepatomegaly is a common finding and with the progression of the disease liver fibrosis and cirrhosis can develop leading to end-stage liver disease with portal hypertension, splenomegaly and ascites. Laboratory studies reveal conjugated hyperbilirubinemia with variable degree of elevated transaminases, gammaglutamyl transferase (GGT) and alkaline phosphatase. Synthetic functions are initially normal prior to the progression of liver disease [111,112].

Diagnosis

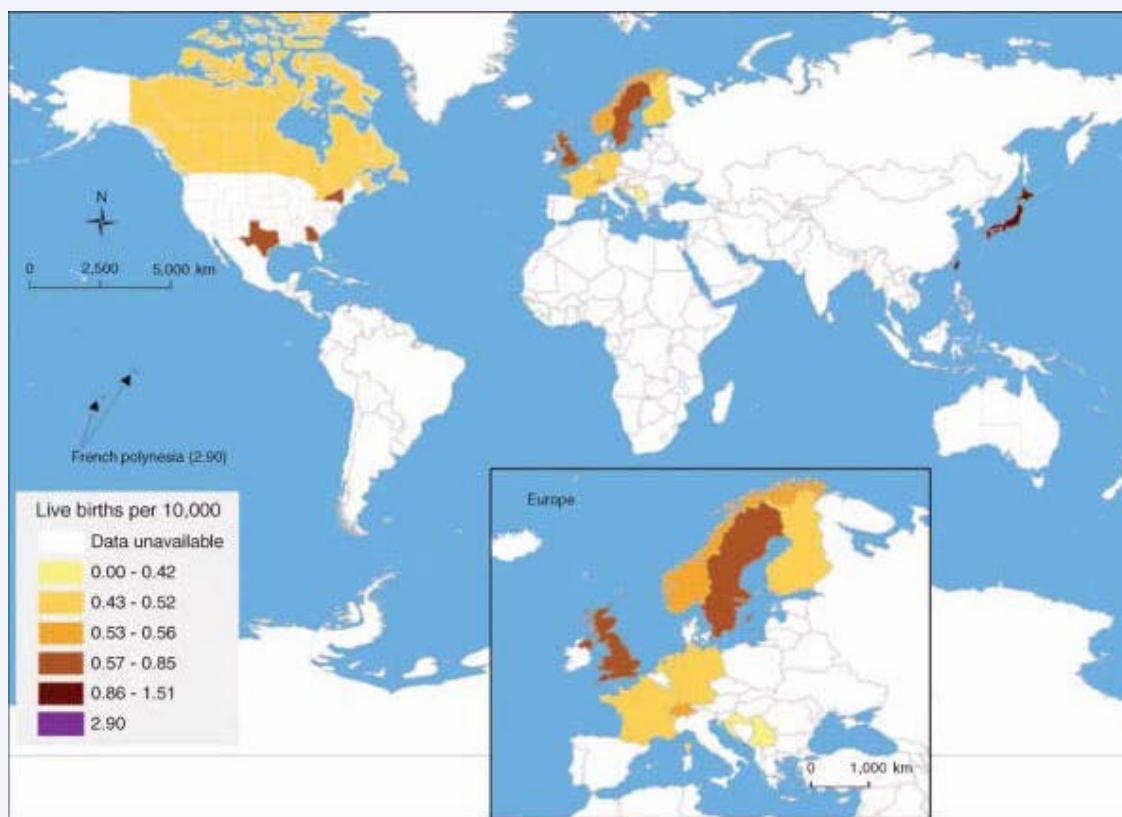The initial evaluation and management of infants presenting

Figure 3 Worldwide incidence quintiles of BA [99]. Printed with permission [99]Jimenez-Rivera, et al. JPGN 2013: 56(4), April 2013, p 344–354.

with neonatal cholestasis can be challenging and must be logical, decisive and cost-effective. The priorities are to exclude treatable infections, manage metabolic diseases and surgically correct BA and choledochal cysts, in a timely manner to prevent progressive damage to the liver.

Ultrasonography (US) is a non-invasive and economic tool which is generally used as the initial diagnostic modality in patients with neonatal hepatobiliary disease. Beside evaluating the hepatobiliary system US can also identify congenital anomalies such as situs inversus and polysplenia which may be associated with BA.

Several US features have been suggested as diagnostic markers for BA. Farrant et al. reported that the absence of gallbladder or the detection of irregular wall or abnormal shape has sensitivity, specificity, and accuracy of 90%, 92.4%, and 91.9%, respectively [113]. The diagnostic accuracy was higher in a study which included 158 infants (35 of whom had BA) using a 13-MHz linear-array probe [114].

The gallbladder ghost triad (gallbladder length <19 mm, lack of a smooth mucosal lining with an indistinct wall, and irregular or lobular contour) was present in 30 of 31 infants with BA in a study by Tan Kendrick et al [115].

US in infants with biliary atresia may detect the triangular cord (TC) sign which is a cone-shaped mass cranial to the bifurcation of the portal vein (Figure 4). The TC sign represents the fibrous remnants at the porta hepatis seen in patients with BA and may be a helpful diagnostic tool in evaluating patients with neonatal cholestasis. Park et al [116] found that the TC sign had a sensitivity of 84% and a specificity of 98% in a study of 79 infants which included 25 patients with BA. However, data regarding the diagnostic accuracy of the TC sign have been conflicting [117-119].

High-frequency ultrasonography (HUS) can provide improved spatial resolution and therefore a better imaging. A recent study reported the sensitivity, specificity, and accuracy of HUS to be superior to conventional ultrasonography and MR cholangio pancreatography [120].

Hepatobiliary scintigraphy is a radionuclide diagnostic imaging study that can be used to evaluate hepatocellular function and patency of the biliary system by tracing bile flow from the liver through the biliary system into the bowel. Sequential images of the liver, biliary tree and gut are obtained. A lack of excretion into the intestines is suggestive of extrahepatic occlusive disorders including BA. Although the uptake may be impaired and delayed in neonatal hepatitis due to poor hepatocellular extraction, excretion into the bowel will eventually occur. Therefore, it is important to obtain a follow-up scan after 24 hours in order to confirm a delayed excretion into the bowel. The administration of phenobarbital (5 mg/kg/day do you give it divided twice daily, or once daily?) for 5 days prior to the scan is usually needed in order to enhance hepatocellular uptake increasing the chances of detecting the tracer excretion into the bowel.

The accuracy of hepatobiliary scintigraphy in differentiating BA from other cholestatic disorders was reported in a meta-

Figure 4 The Triangular cord (circled); a cone-shaped mass cranial to the bifurcation of the portal vein representing the fibrous remnants at the porta hepatis in patients with BA.

analysis of 81 studies using Tc-99 m-labeled immunodiacetic acid (IDA) derivatives. Sensitivity and specificity were 98.7% (range 98.1–99.2%) and 70.4% (range 68.5–72.2%), respectively. The use of radiotracers with high hepatic extraction and adjusting dose according to the weight was associated with increased specificity. Other factors enhancing specificity included the use of hepatic-inducing drugs (such as phenobarbital) and the administration of a booster dose if no excretion was seen in the intestines [121].

Magnetic resonance cholangio pancreatography (MRCP) is a widely accepted method for imaging the biliary system. However, the value of MRCP in the diagnosis of BA has not been established. An accuracy of 82–98%, sensitivity of 90–100%, and specificity of 77–96% has been reported in several studies [122-125].

Liu et al [126] investigated the diagnostic value of three-dimensional MRCP (3D-MRCP) for BA in 190 infants with neonatal cholestasis. The diagnostic accuracy for 3D-MRCP was 70.53%, with sensitivity and specificity of 99.04% and 36.05% respectively. These results challenge the earlier reports and suggest that despite the high sensitivity of 3D-MRCP in diagnosing BA, the test seems to be poorly specific. The ability of 3D-MRCP sequence to accurately visualize the biliary system in newborns and young infants has been studied by Bourliere-Najean et al [127]. The extrahepatic bile duct confluence was seen only in 10 children out of 16 (62.5%) with no hepatobiliary disorder. The visualization was successful in 75% of infants older than 30 days but only in 50% of studied neonates. The authors concluded that normal biliary system may not be consistently visualized in infants younger than 3 months of age using 3D-MRCP, which can be used as an adjunctive screening test but it should be combined with other diagnostic modalities.

Endoscopic retrograde cholangiopancreatography (ERCP) is an alternate diagnostic modality at centers with appropriate equipment and endoscopists skilled in performing this procedure. Multiple reports have shown that ERCP can be safely performed in young subjects and can differentiate BA from other causes of neonatal cholestasis [128-133]. Patients with findings suggesting biliary atresia on ERCP can proceed to intraoperative cholangiogram avoiding further testing and diagnostic delay.

Aabakken et al. were successful in performing ERCP in 20 of 23 patients suspected to have BA with a mean age of 2.4 months and weight of 4.8 Kg [128]. The diagnosis of BA was confirmed in the 6 patients who had findings suggestive of the disorder. Complications were reported in 2 patients including hyperamylasemia and cholangitis. No patient had clinical manifestations of pancreatitis or elevated lipase

ERCP was accomplished in 45 patients with cholestasis while cannulation failed in 3 subjects in a study reported in 48 cholestatic patients under the age of 100 days [129]. Twenty five patients were diagnosed with BA based on ERCP observations. BA was confirmed in 3 of the remaining patients and post ERCP pancreatitis was not reported.

In another report ERCP was performed successfully without complications in 43 of 50 cholestatic infants with a mean age and weight of 69 days and 4.5 kg respectively. Twenty nine patients had ERCP findings suggesting BA and the diagnosis was confirmed by intraoperative cholangiogram [130].

In a retrospective study, which included 104 patients with cholestasis ERCP was successful in 95 subjects. The mean age and weight of the patients was 7 weeks and 4.05 kg respectively. BA was found in 51 children (53.7 %), with sensitivity of 86 % and specificity of 94. No significant complications were reported [131].

Petersen et al [132] reported their experience with ERCP in 140 patients with neonatal cholestasis (mean age: 60 days; weight: 4 kg). ERCP excluded BA in 25% of the cases but the failure rate was 13% due to technical issues. The sensitivity was 92% and specificity was 73%. Four patients presented with temporary elevation of lipase without clinical consequences,

and one suffered from a paralytic ileus for 2 days. The average procedure period was 23 minutes.

The utility of ERCP in evaluating infants and children with pancreaticobiliary disorders, including BA and choledochal cyst was also reported recently by Saito et al [133]. The report included 225 ERCPs which were performed in 220 pediatric patients (median age, 2 years) with an overall success of 96%. (92% in infants and 100% in children> 3 years of age). Among 90 cases suspected to have BA ERCP successfully identified 16 cases (18%) with other diagnosis. Hyperamylasemia developed in 9.4% of the patients. Duodenal perforation occurred in only 1 patient with neonatal hepatitis, who was successfully treated with conservative therapy with the intravenous antibiotics administration.

ERCP can be performed with fairly acceptable results in infants suspected to have BA. However, at the time being the role of ERCP in the diagnostic process of BA remains undefined and should be deliberately considered when anatomical information from less-invasive imaging modalities is insufficient [133].

Percutaneous liver biopsy is a fundamental diagnostic tool in the evaluation of neonatal hepatobiliary diseases and may provide reliable discriminatory evidence. Characteristic pathologic features in patients with BA include bile ductular proliferation, the presence of bile plugs, and portal or perilobular edema, inflammatory cell infiltration and fibrosis, with intact hepatic lobular architecture (Figure 5).

Bile duct proliferation results from obstruction of bile flow and aims at reabsorbing and redirecting bile salts back to the portal circulation in order to prevent the stasis of toxic bile salts [134].

The challenging problem in many cases with neonatal hepatobiliary disorder is to distinguish BA from neonatal hepatitis. Portal inflammation and giant cell transformation can be seen in both conditions. However, the characteristic features of neonatal hepatitis include severe, diffuse hepatocellular disease, with distortion of lobular architecture, marked infiltration with inflammatory cells, and focal hepatocellular necrosis with the bile

ductules showing little alteration [112]. BA is an evolving process and therefore an early biopsy may miss the developing lesions. Repeating the liver biopsy in 2-3 weeks after the initial biopsy is not unusual provided that this does not delay the diagnostic process.

The definitive diagnosis of BA is usually made by intraoperative cholangiogram. If no communication is seen between the biliary tree and the small intestine following the injection of a contrast material into the gall bladder the diagnosis is established. However, it is an invasive procedure and requires general anesthesia. Percutaneous transhepatic cholangiography although less-invasive is technically challenging. Another diagnostic modality is ultrasound-guided percutaneous cholecystocholangiography (PCC) . Myers et al. [135]reported their experience with PCC in 9 cholestatic infants with a mean age of 44 days after other diagnostic modalities failed to provide a definitive diagnosis. None of the reported 5 patients with completely opacified biliary tree had BA while 3 of the patients with incomplete opacification of the biliary tree had BA and one had biliary hypoplasia.

Management

After several trials and modifications the Kasai procedure became an established and accepted therapeutic procedure to treat patients with BA. The rationale for the procedure is that the residual minute channels present in the fibrous tissue of the porta hepatis may be in direct continuity with the intrahepatic ductular system. Therefore, transection of the porta hepatis followed by anastomosis of the bowel to the proximal surface of the transection might establish bile flow. If flow is not rapidly established progressive obliteration and cirrhosis ensue. The surgical procedure , Kasai portoenterostomy, is also referred to as a "Roux-en-Y" or a "hepatoportojejunostomy". The Y-shaped passageway formed by the Kasai procedure allows bile to flow from the liver into the intestine. The key for successful hepatoportoenterostomy is early diagnosis and surgical intervention which stresses the importance of increased awareness of the disease. The success rate for establishing good bile flow after the Kasai operation is much higher (90%)
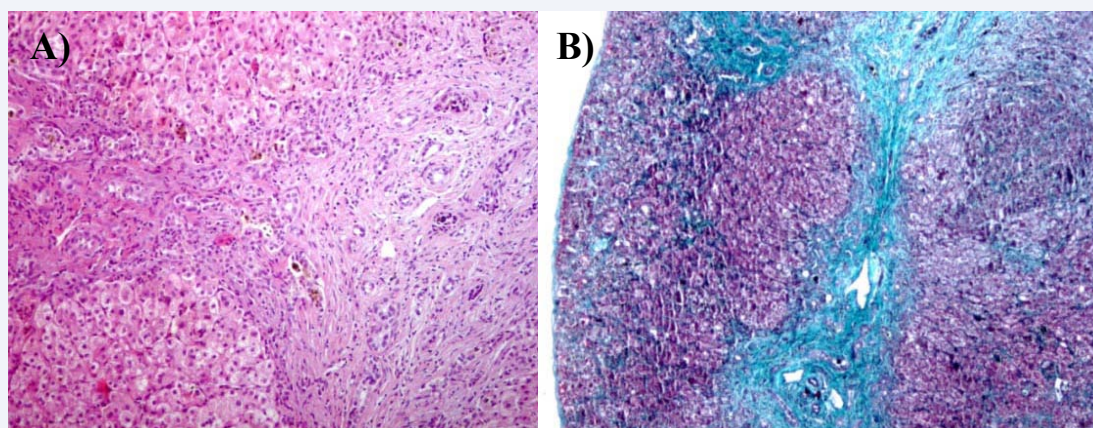

Figure 5 Pathological features of BA.
A. Expanded portal area, bridging fibrosis, and bile ductular proliferation (H&E stain).
B- Bridging fibrosis (Masson Trichrome stain)

if performed before 8 weeks of life. Unfortunately in most patients, a degree of hepatic dysfunction persists. The continuing inflammation of the intrahepatic biliary tree, indicates that BA is not merely an extrahepatic disease but a disorder which involves the entire hepatobiliary system.

Koga et al. have shown that laparoscopic Kasai portoenterostomy (LKPE) can be performed safely and successfully with encouraging outcome [136]. A prospective study looked at survival with the native liver after laparoscopic versus conventional Kasai portoenterostomy in patients with BA. Although laparoscopic Kasai procedure was technically feasible, the study was discontinued due to a lower survival with the native liver after laparoscopic Kasai operation. Patients who had conventional Kasai portoenterostomy had better outcome at follow-up after 24 months than patients who had LKPE [137].

Postoperative management

There is no evidence that supports the routine use of glucocorticoids following the Kasai procedure. In a systematic review and meta-analysis report the jaundice-free rate did not significantly differ between steroid or non-steroid groups, nor did the cholangitis rate. Overall survival ranged from 58% to 95% in the steroid group versus 36% to 96% in the control group. Native liver survival ranged from 30% to 56% in the steroid group and from 31% to 48% in the control group [138-141].

Cholangitis is a very common problem following the Kasai procedure as the vast majority of patients will experience at least one episode during the first two years of life [139-149]. Cholangitis usually happens due to altered anatomy and bacterial stasis at the site of anastomosis and recurrent episodes can lead to liver cirrhosis. Despite the absence of randomized trials most centers will place the patients on prophylactic antibiotics such as trimethoprim/sulfamethoxazole (TMP/SMZ) or neomycin for the first 12 months following hepatoportoenterostomy. In a report by Bu et al.. patients who received prophylaxis with TMP/SMZ or neomycin had lower recurrence rates of cholangitis than those in the control group. There was no difference in the recurrence rates of cholangitis between the TMP/SMZ and neomycin groups. In addition, the survival rates were higher in the TMP/SMZ and neomycin groups compared to control group [150].

Over the last three decades cephalosporins have been used for the treatment of ascending cholangitis sometimes combined with aminoglycosides. However, the efficacy of cefoperazone in the treatment of cholangitis post-Kasai's operation has been declining which pressed the need for a more effective first-line empirical antibiotic. In 2004, meropenem was introduced as a suitable candidate [151]. Further research is needed to define the first-line therapeutic option. The use of a short-term "blast" of steroid to augment bile flow has been reported to augment antibiotic treatment of refractory cholangitis in patients with BA [152].

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid, which has been used in patients with a variety of liver diseases. Enrichment of the bile acid pool with a hydrophilic bile acid will displace the hydrophobic toxic bile acids. UDCA can prevent mitochondrial damage by stabilizing the membranes and decreasing the release of free radicals. UDCA is commonly used in patients with BA in a dose of 15-30 mg/kg/day. In a small randomized trial which included 28 patients with BA following the Kasai procedure patients receiving high-dose steroids, ursodeoxycholic acid, and intravenous antibiotics had an accelerated clearance of jaundice [150]. UDCA can also relieve pruritus which is a devastating symptom of cholestasis.

Rifampin has also been reported to relieve pruritus in patients with cholestasis. In an open trial, 24 children with cholestasis including 13 patients with BA with severe pruritus that had not responded adequately to ursodeoxycholic acid, diphenhydramine, or phenobarbital were treated with rifampin, 10 mg/kg per day in two divided doses. Complete and partial reliefs of pruritus were seen in 10 patients and 12 patients respectively while 2 children had no response. The treatment was also associated with reduction of gamma-glutamyl transpeptidase [153].

Patients with BA commonly suffer from growth failure due to increased requirements, decreased intake and malabsorption. The presences of chronic liver disease increase the nutritional and caloric requirements. It is recommended to provide 150% of the usual recommended daily caloric needs in order to maintain an adequate and steady growth. Patients on breast feeding my benefit from fortifying the breast milk while formula-fed babies need concentrated formulas and supplements such as glucose polymers or medium-chain triglycerides (MCT) oil. MCT oil is the preferred form of oil since it does not require micellar solubilization. Nasogastric tube feedings may be needed to achieve the nutritional goals but gastrostomy tube placement is discouraged as patients with BA may develop portal hypertension and gastric varices.

Patients with BA and chronic cholestasis are at increased risk for fat-soluble vitamins (A, K, E and D) deficiency. The deficiency can be exacerbated by the use of bile acid-binders such as cholestyramine which is commonly used to relieve pruritus.

Serum vitamin A concentration can be maintained at normal levels by administering 10,000-15,000 IU/day as oral Aquasol A. Degenerative neuromuscular syndrome secondary to vitamin E deficiency, usually presents as ataxic gait, can develop in patients with chronic cholestasis and can be reversed with early recognition and oral α-tocopherol supplementation (50-400 IU/day). In some patients with severe malabsorption a higher dose (up to 1000 IU/day) or the oral administration of d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) may be necessary. Monitoring the serum level and the ratio of serum vitamin E to total serum lipids is essential.

Patients with BA and chronic cholestasis are also maintained on Vitamins D (5,000-8,000 IU/day of D2 or 3-5 μg/kg/day of 25-hydroxycholecalciferol) as well as vitamin K administered provided as a water-soluble derivative of menadione (2.5-5.0 mg every other day) [39].

Twice the usual recommended daily doses of water-soluble vitamins as well as micronutrient supplementation (calcium, phosphate and zinc) are usually advised in patients with chronic cholestasis [154,155].

With the progression of liver disease patients with chronic cholestasis may develop portal hypertension and consequently ascites, esophageal varices and variceal hemorrhage. The

presence of ascites is always a risk factor for the development of spontaneous bacterial peritonitis (SBP) and should be always suspected in the presence of any unusual symptoms or signs. Patients with ascites should restrict sodium intake to 1-2 mEq/kg/day. Fluid restriction is not necessary if the patient has adequate urine output. Spironolactone (3-5 mg/kg/day in 3-4 divided doses) is the diuretic of choice. If spironolactone alone does not control ascites, other diuretic such as thiazide or furosemide may be added. Tense ascites can be safely relieved with paracentesis and intravenous albumin infusion followed by furosemide intravenously.

Patients with portal hypertension may develop variceal hemorrhage and hypersplenism. It is important to ascertain the cause of gastrointestinal (GI) bleeding because episodes of GI bleeding in patients with chronic liver disease may result from other causes such as gastritis or peptic ulcers. Swallowing blood from upper airway lesions may also present as GI hemorrhage especially in patients with coagulopathy. Patients with variceal bleeding may develop blood volume depletion requiring blood transfusion. It is important to avoid over-transfusion, as well as rapid blood transfusion which can induce further variceal bleeding. Endoscopic sclerotherapy or variceal band ligation are usually used in the management of bleeding esophageal varices. Variceal band ligation in children is a safe and effective technique that achieves variceal eradication more quickly, with a lower rebleeding rate and fewer complications compared with sclerotherapy [156].

At the time being there is no general recommendation for surveillance endoscopy for varices or primary prophylaxis of variceal hemorrhage [157].

The long-term prognosis for patients with BA is variable. Survival with the native liver ranges from 30%-55%, 30%-40% and 20%-40% at 5, 10 and 20 years respectively [158-167]. Although patients with BA can survive more than twenty years without transplantation, the majority of these patients will have manifestations of chronic liver disease [168].

Unfortunately the majority of patients with BA will require liver transplantation. Although liver transplantation has been suggested as a primary approach for the management of patients with BA, at the time being, hepatoportoenterostomy remains to be the most reasonable initial approach. As long as the patient is in a stable condition it is wise to defer transplantation allowing the patient to continue to gain weight and grow, increasing the chances of a successful liver transplant. Infants and children can receive a cadaveric organ or a segment of a living-related donor. Liver transplantation can be more challenging in patients who underwent multiple revisions of the hepatoportoenterostomy and those with BASM syndrome because of possible extensive dissection and vascular reconstruction in these patients.

The survival rates following liver transplantation continues to improve. In the USA the **one-year** patient and liver-graft survival rates following liver transplant are 92.1% and 83.6%, respectively in patients with BA [169]. In international series, long-term survival is approximately 70 to 80 percent at both 5 and 10 years post liver transplantation [170-172].

Finally, despite the major strides made in the field of pediatric hepatology and despite the fact that we have known BA for two centuries, BA continues to be the darkest chapter in pediatric hepatology. The development of innovative preventive and therapeutic modalities is hurdled by the lack of complete understanding of the pathogenesis of the disease. More collaborative research is needed in order to unravel the mystery of this disorder.

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