INTRODUCTION

Definition

Biliary atresia is a destructive inflammatory obliterative cholangiopathy of neonates that affects varying lengths of both intrahepatic and extra hepatic bile ducts (**Figure** 1). No analogous pathological process exists in older children or adults. If untreated, progressive liver cirrhosis leads to death by the age of two years.(1)

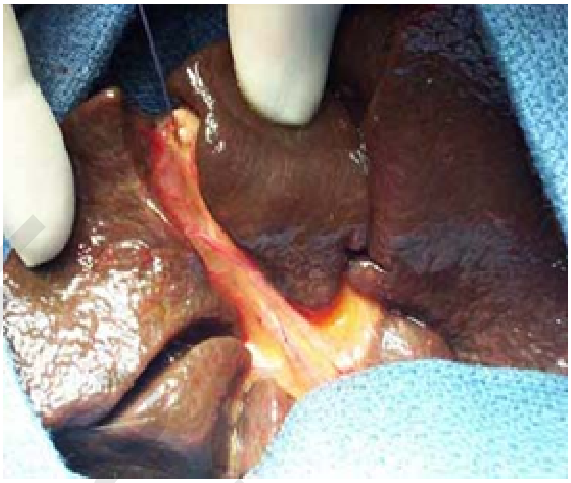


Figure 1: Operative view of complete extra-hepatic biliary atresia.(2)

Incidence

Biliary atresia presents in the neonatal period. The reported incidence of it in several European countries varies between 1/14,000 and 1/20,000 Live births.(3)

In the Pacific Ocean area, the incidence is described to be as high as 1/2,400 live births. The reasons for this high incidence have not been described yet. It represents the most frequent reason for liver transplantation in childhood accounting for more than 50% of pediatric liver transplantation. Even when bile flow is established, variable liver fibrosis, cirrhosis, portal hypertension, and liver failure may still occur. Biliary atresia occurs with slight female predominance.(4)

History

Looking at the problem of biliary atresia from the vantage point of 30 years' experience with the lesion, it has been found that the jaundiced baby who had no extra hepatic bile duct has been the most disappointing patient for the surgeon in the whole spectrum of lesions theoretically correctable by a surgical procedure.(5)

The last 20 years have seen a significant improvement in the prognosis of patients with biliary atresia because of the sequential employment of two major surgical techniques; portoenterostomy and liver transplantation. There have been significant advances in the management of complications of chronic cholestasis and in some complications of cirrhosis.(6)

The first description of biliary atresia was made by ***J. Burke*** in 1817. In 1916 ***Holmes*** introduced in a review of literature the concept of correctable and non-correctable types of disease. ***Ladd*** reported the first successful surgery for the correctable type in 1928. In 1953, ***Gross*** documented that extra hepatic biliary atresia was the most common condition causing obstructive jaundice in the first month of life, and that most patients had the non-correctable type of disease. In the late 1950s, ***Morio Kasai*** reported the presence of patent biliary channels at the portahepatis in young infants with biliary atresia. He postulated that by exposing these channels through radical excision of the atretic extra hepatic biliary remnants then effective drainage of bile could be possible in some cases, especially if such surgery was performed within 8 weeks of birth. Although Kasai portoenterostomy became accepted as the standard initial operation for biliary atresia, this disease remains the foremost indication for liver transplantation in infants and children.(7)

Increased experience with hepatic portoenterostomy revealed that the intrahepatic component of ductal pathology is of great importance in determining prognosis. Liver transplantation was presented by ***Starzl et al***. in 1963 as optional therapy for patients in whom hepatic portoenterostomy was unsuccessful.(8)

In Japan, Kasai's work with patients with biliary atresia began to challenge these concepts. In 1955, he noted that when the extra hepatic biliary tract excised to the hilum, bile flow from the portahepatis occurred. Over the next several years, he devised a procedure in which the structures in the portahepatis were drained via a Roux-en-Y jejunal limb. Although his operation had undergone numerous modifications, Kasai's lasting contribution to the surgical treatment of biliary atresia was the realization that the occluded extra hepatic ductal system could be isolated and dissected to the portahepatis and that a functional enteric anastomosis could potentially be constructed to drain the biliary remnants at portahepatis.(9)

Embryology

❖ Hepatobiliary embryology

The liver primordium appears in the middle of the third week of gestation as an outgrowth of the endodermal epithelium at the distal end of the foregut (**Figure 2**).The hepatic diverticulum divides into two parts: pars hepatica (larger cranial part; primordium of the liver) and pars cystica (smaller ventral invagination; primordium of the gall bladder).(10,11)

The pars hepatica consists of rapidly proliferating cells that penetrate the septum transversum, that is; the mesodermal plate between the pericardial cavity and the stalk of the yolk sac (**Figure 3**). While hepatic cells continue to penetrate the septum, the connection between the hepatic diverticulum and the foregut (duodenum) narrows, forming the bile duct. The pars cystica vacuolates, expands and the stalk becomes the cystic duct. This structure is initially hollow, then solid (by proliferation of epithelial lining), and lastly recanalization occurs by vacuolation of this expanded epithelium. There are several opinions as to whether the duct has a solid phase or remains patent throughout development.(11,12)

During further development, epithelial liver cords intermingle with the vitelline and umbilical veins, which form hepatic sinusoids. Liver cords differentiate into the hepatic

parenchyma (liver cells) and form the lining of the biliary ducts. Hematopoietic cells, Kupffer cells, and connective tissue cells are derived from mesoderm of the septum transversum.(13)

When liver cells invade the entire septum transversum, the organ bulges caudally into the abdominal cavity. The mesoderm of the septum transversum lying between the liver and the foregut and between the liver and ventral abdominal wall become membranous, forming the lesser omentum and falciform ligament, respectively. Together, forming the peritoneal connection between the foregut and the ventral abdominal wall, they are known as the ventral mesogastrium. Mesoderm on the surface of the liver differentiates into visceral peritoneum except on its cranial surface. In this region, the liver remains in contact with the rest of the original septum transversum. This portion of the septum, which consists of densely packed mesoderm, will form the central tendon of the diaphragm. The surface of the liver that is in contact with the future diaphragm is never covered by peritoneum; it is the bare area of the liver. In the 10^{th} week of development the weight of the liver is approximately10% of the total body weight. Although this may be attributed partly to the large number of sinusoids, another important factor is its hematopoietic function as large nests of proliferating cells, which produce red and white blood cells, lie between hepatic cells and walls of the vessels. This activity gradually subsides during the last 2 months of gestation, and only small hematopoietic islands remain at birth. The weight of the liver is then only 5% of the total body weight. Another important function of the liver begins at approximately the 12^{th} week of gestation, when bile is formed by hepatic cells. Meanwhile, since the gall bladder and cystic duct have developed and the cystic duct has joined the hepatic duct to form the bile duct, bile can enter the gastrointestinal tract. As a result, the intestinal contents take on a dark green color. Because of positional changes of the duodenum, the entrance of the bile duct gradually shifts from its initial anterior position to a posterior one, and consequently, the bile duct passes behind the duodenum.(14)

❖ Molecular regulation of liver induction

All of the foregut endoderm has the potential to express liver-specific genes and to differentiate into liver tissue. However, this expression is blocked by factors produced by surrounding tissues, including ectoderm, non-cardiac mesoderm, and particularly the notochord. The action of these inhibitors is blocked in the prospective hepatic region by fibroblast growth factors (FGFs) secreted by cardiac mesoderm. Thus, the cardiac mesoderm “instructs” the gut endoderm to express liver specific genes by suppressing an inhibitory factor of these similar genes. Once this “instruction” is received, cells in the liver field differentiate into hepatocytes and biliary cell lineages, a process that is at least partially regulated by hepatocyte nuclear transcription factors (HNF3and 4).(15)

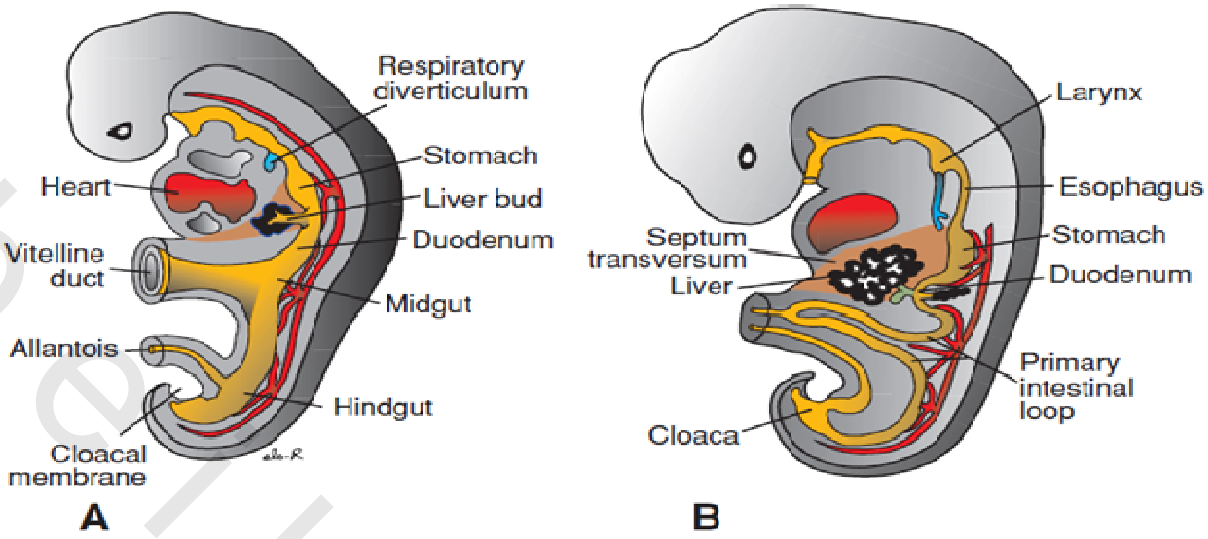


Figure 2: Embryogenesis of hepatobiliary system 1.

A. 25 day, 3-mm embryo showing the primitive GIT and the liver bud.**B.** 32 day, 5-mm embryo showing the epithelial liver cords penetrate the mesenchyme of the septum transversum.[14]

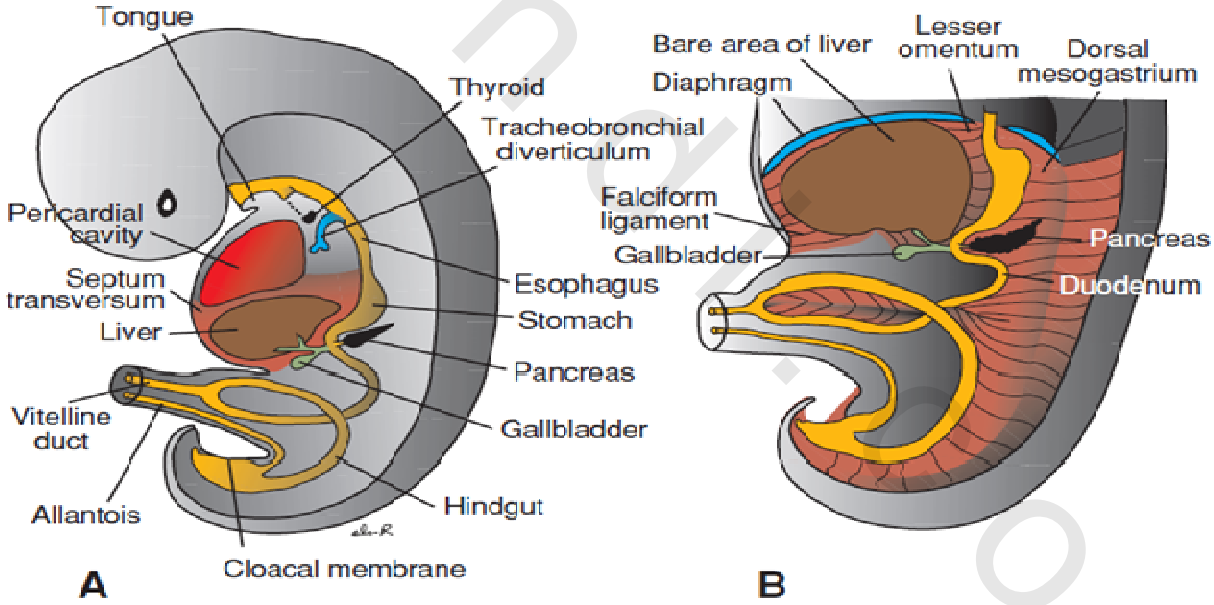


Figure 3: Embryogenesis of hepatobiliary system 2.

A. 36 day, 9-mm embryo showing liver expansion caudally into the abdominal cavity. **B.** A slightly older embryo showing the falciform ligament extending between the liver and the anterior abdominal wall, the lesser omentum between the liver and the foregut and the bare area of the liver.[12]

Normal anatomy of biliary system

❖ Intrahepatic biliary anatomy

The right and left hemi livers are drained by the right and the left hepatic ducts, whereas the dorsal lobe (caudate lobe) is drained by several ducts that join both the right and left hepatic ducts. The intrahepatic ducts are tributaries of the corresponding major hepatic ducts, which form part of the major portal triads that penetrate the liver, invaginating the Glisson capsule at the hilum. Bile ducts usually are located above the corresponding portal branches, whereas hepatic arterial branches are situated inferior to the veins. Each branch of the intrahepatic portal veins corresponds to one or two bile duct tributaries that join to form the right and left hepatic ductal systems, converging at the liver hilum to constitute the common hepatic duct. The umbilical fissure divides the left liver, passing between segment III and segment IV, where it may be bridged by a tongue of liver tissue. The ligamentum teres passes through the umbilical fissure to join the left branch of the portal vein (**Figure 4**).[16]

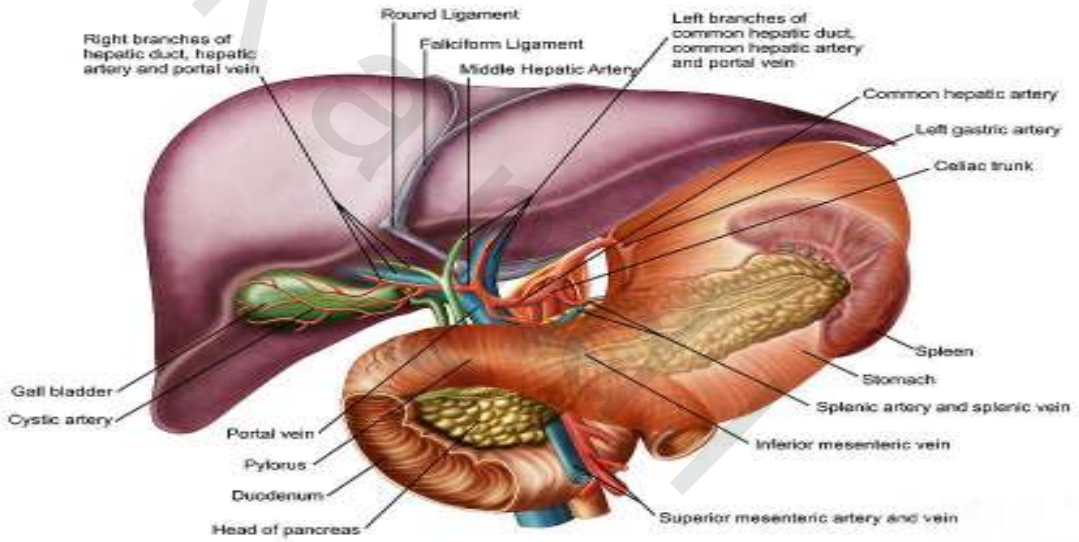


Figure 4: Liver anatomy.[15]

The left hepatic duct drains the three segments; II, III, and IV that constitute the left liver (**Figure 5**). The duct that drains segment III is located slightly behind the left horn of the umbilical recess. It is joined by the tributary from segment IV b to form the left duct, which is similarly joined by the duct of segment II and the duct of segment IV a, where the left branch of the portal vein turns forward and caudally. The left hepatic duct traverses beneath the left liver at the base of segment IV, just above and behind the left branch of the portal vein; it crosses the anterior edge of that vein and joins the right hepatic duct to constitute the hepatic ductal confluence. In its transverse portion, it receives one to three small branches from segment IV.[16]

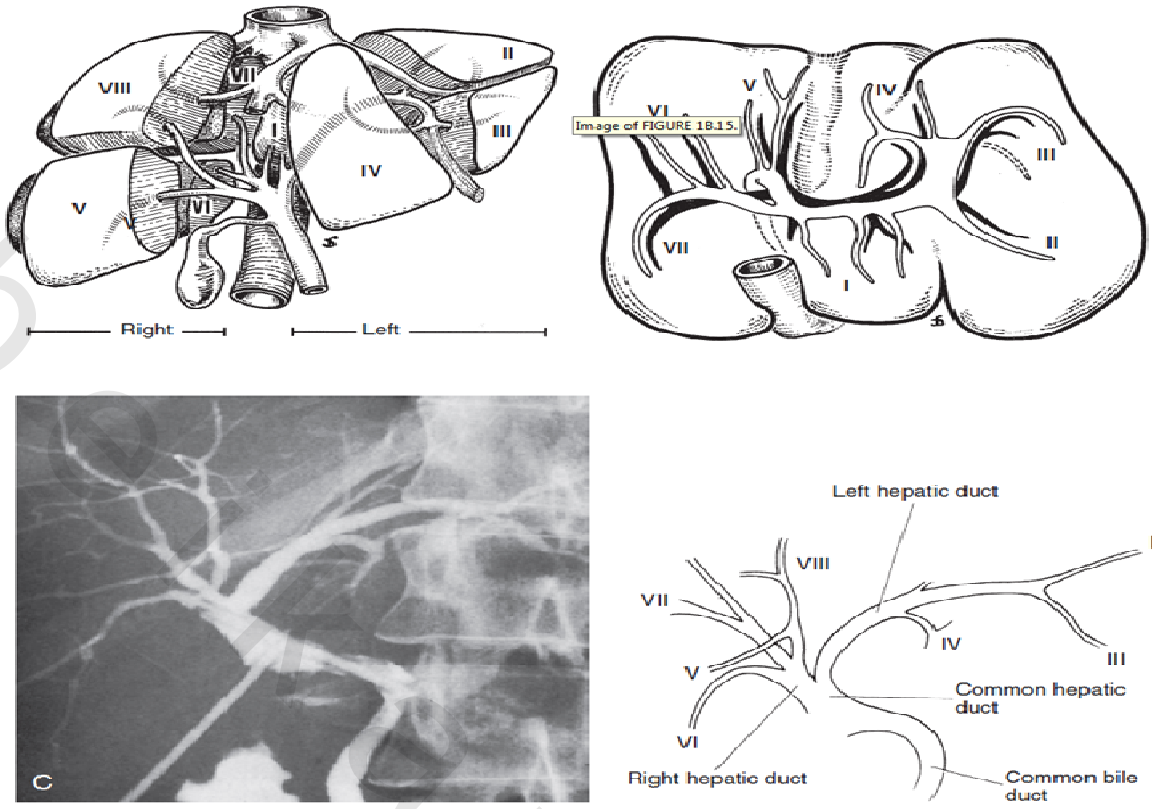


Figure 5: Biliary drainage**.**

A: Biliary drainage of the two functional hemilivers. **B:** Inferior aspect of the liver. The biliary tract is represented in black, and the portal branches are represented in white **C:** T-tube cholangiogram shows the most common arrangement of hepatic ducts.[17]

Figure 6: Biliary and vascular anatomy of the right liver.

A: The horizontal course of the posterior sectoral duct and the vertical course of the anterior sectoral duct. **B:** Trans-tubal cholangiogram shows a common normal variant: the right posterior sectoral duct drains into the left hepatic duct. In this case, the posterior duct is anterior to the posterior sectoral duct.[18]

The right hepatic duct drains segments V, VI, VII, and VIII and arises from the junction of two main sectoral duct tributaries. The posterior or lateral duct and the anterior or medial duct are each accompanied by a corresponding vein. The right posterior sectoral duct has an almost horizontal course and constitutes the confluence of the ducts of segments VI and VII. The duct then runs to join the right anterior sectoral duct, as it descends in a vertical manner. The right anterior sectoral duct is formed by the confluence of the ducts draining segments V and VIII. Its main trunk is located to the left of the right anterior sectoral branch of the portal vein, which pursues an ascending course. The junction of these two main right biliary channels usually occurs above the right branch of the portal vein (**Figure 6**). The right hepatic duct is short and joins the left hepatic duct to constitute the confluence lying in front of the right portal vein and forming the common hepatic duct.[16]

The caudate lobe (segment I) has its own biliary drainage. The caudate lobe is divided into right and left portions and a caudate process.[19]

❖ Extrahepatic biliary and vascular anatomy

The extra hepatic bile ducts are represented by the extra hepatic segments of the right and left hepatic ducts, joining to form the biliary confluence and the main biliary channel draining to the duodenum. The accessory biliary apparatus, which constitutes a reservoir, comprises the gallbladder and cystic duct. The confluence of the right and left hepatic ducts occurs to the right of the hilar fissure of the liver, anterior to the portal venous bifurcation and overlying the origin of the right branch of the portal vein. The extra hepatic segment of the right duct is short, but the left duct is longer. The biliary confluence is separated from the posterior aspect of the quadrate lobe of the liver by the hila plate, which is the fusion of connective tissue enclosing the biliary and vascular elements with the Glisson capsule. Because of the absence of any vascular interposition, it is possible to open the connective tissue constituting the hilar plate at the inferior border of the quadrate lobe and, by elevating this plate; the exposure of the biliary confluence and left hepatic duct can be achieved.[20]

❖ Main bile duct and sphincter of Oddi

The diameter of the main bile duct and is about 6 mm and it's divided into two portions: the upper part is called the common hepatic duct and is situated above the cystic duct, which joins it to form the lower portion which is the common bile duct. The common duct courses downward anterior to the portal vein, in the free edge of the lesser omentum; it is closely applied to the hepatic artery, which runs upward on its left, giving rise to the right branch of the hepatic artery, which crosses the main bile duct usually posteriorly, although in about 20% of cases, it crosses anteriorly. The cystic artery, arising from the right branch of the hepatic artery, may cross the common hepatic duct posteriorly or anteriorly.[18]

The common hepatic duct constitutes the left border of the triangle of Calot, the other corners of which were originally described as the cystic duct below and the cystic artery above. However, the commonly accepted working definition of the triangle of Calot recognizes the inferior surface of the right lobe of the liver as the upper border and the cystic duct as the lower border. Dissection of the triangle of Calot is of key significance during cholecystectomy, because the cystic artery usually runs in this triangle, often the

right branch of the hepatic artery, and occasionally a bile duct, which should be displayed before cholecystectomy. If there is a replaced or accessory common or right hepatic artery, it usually runs behind the cystic duct to enter the triangle of Calot.[18]

At its lower extra hepatic portion, the common bile duct traverses the posterior aspect of the pancreas, running in a groove or a tunnel. The retro pancreatic portion of the common bile duct approaches the second portion of the duodenum obliquely, accompanied by the terminal part of the pancreatic duct of Wirsung.[18]

❖ Gall bladder and cystic duct

The gallbladder is a reservoir located on the undersurface of the right lobe of the liver, within the cystic fossa; it is separated from the hepatic parenchyma by the cystic plate, which is composed of connective tissue closely applied to the Glisson capsule and elongating the hilar plate. Sometimes the gallbladder is deeply embedded in the liver, but occasionally it develops on a mesenteric attachment and may be susceptible to volvulus. The gallbladder varies in size and consists of a fundus, a body, and a neck. The tip of the fundus usually, but not always, reaches the free edge of the liver and is closely applied to the cystic plate. The neck of the gallbladder makes an angle with the fundus and creates the Hartmann pouch, which may obscure the common hepatic duct and constitute a real danger point during cholecystectomy.[18]

The cystic duct arises from the neck or infundibulum of the gallbladder and extends to join the common hepatic duct. Its lumen usually measures about 1 to 3 mm, and its length varies, depending on the type of union with the common hepatic duct. The mucosa of the cystic duct is arranged in spiral folds known as the valves of Heister. Although the cystic duct joins the common hepatic duct in its supraduodenal segment in 80% of cases, it may extend downward to the retro duodenal or retro pancreatic area. Occasionally, the cystic duct may join the right hepatic duct or a right hepatic sectoral duct.[21]

❖ Bile duct blood supply

The bile duct may be divided into three segments: hilar, supraduodenal, and retro pancreatic (lower common bile duct). The blood supply of the supraduodenal duct is essentially axial. Most vessels to the supraduodenal duct arise from the superior pancreaticoduodenal artery, the right branch of the hepatic artery, the cystic artery, the gastroduodenal artery, and the retro duodenal artery. On average, eight small arteries, each measuring about 0.3 mm in diameter, supply the supraduodenal duct. The most important of these vessels run along the lateral borders of the duct and have been called the 3 o'clock and 9 o'clock arteries. Of the blood vessels vascularizing the supraduodenal duct, 60% run upward from the major inferior vessels, and only 38% of arteries run downward, originating from the right branch of the hepatic artery and other vessels. Only 2% of the arterial supply is non-axial, arising directly from the main trunk of the hepatic artery, as it courses up parallel to the main biliary channel. The hilar ducts receive a copious supply of arterial blood from surrounding vessels, forming a rich network on the surface of the ducts in continuity with the plexus around the supraduodenal duct. The source of blood supply to the retro pancreatic common bile duct is from the retro duodenal artery (Posterior pancreatico-duodenal artery), which provides multiple small vessels running around the duct to form a mural plexus (**Figure 10**).[18]

The veins draining the bile ducts are satellites to the corresponding described arteries, draining into 3 o'clock and 9 o'clock veins along the lateral borders of the common biliary channel. Veins draining the gallbladder empty into this venous system, not directly into the portal vein, and the biliary tree seems to have its own portal venous pathway to the liver.[18]

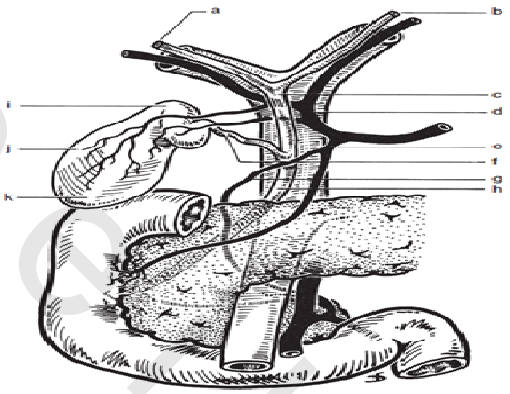


Figure 7: Biliary anatomy**.**

Right hepatic duct (a); left hepatic duct (b); common hepatic duct (c); hepatic artery (d); gastroduodenal artery (e); cystic duct (f); retroduodenal artery (g); common bile duct (h); neck of the gall bladder (i); body of the gall bladder (j); fundus of the gall bladder (k).[18]

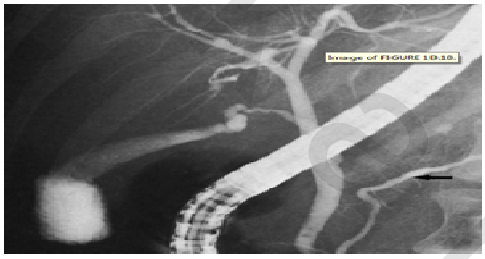


Figure 8: ERCP in biliary atresia. Endoscopic retrograde choledochopancreatogram showing the pancreatic duct (arrow), gallbladder, and biliary tree.[18]

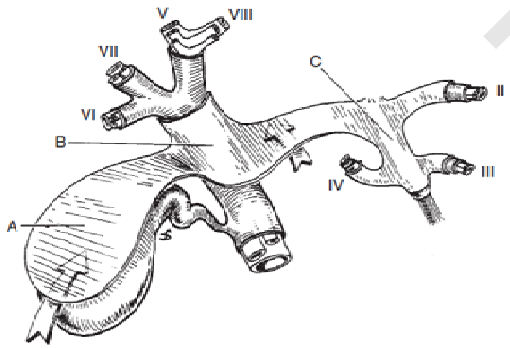


Figure 9: Anatomy of the plate system.

A: The cystic plate above the gall bladder. **B**: The hilar plate above the biliary confluence and at the base of the quadrate lobe. C: The umbilical plate above the umbilical portion of the portal vein. Large, curving arrows indicate the plane of dissection of the cystic plate during cholecystectomy and of the hilar plate during approaches to the left hepatic duct.[18]

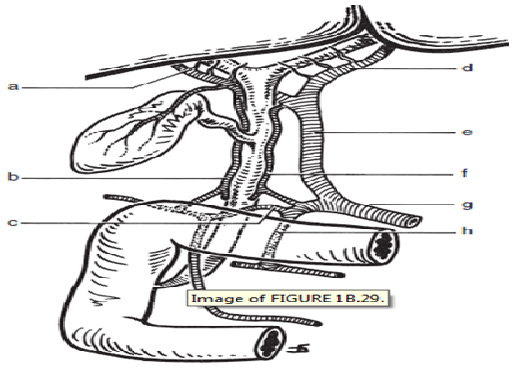


Figure 10: The bile duct blood supply. Right branch of the hepatic artery (a); 9 o'clock artery (b); retro duodenal artery (c); left branch of the hepatic artery (d); hepatic artery (e); 3 o'clock artery (f); common hepatic artery (g); gastroduodenal artery (h).[22]

Pathophysiology of serum bilirubin

Bilirubin is produced in the reticulo-endothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contribute in its production.[23,24] (**Figure 11**)

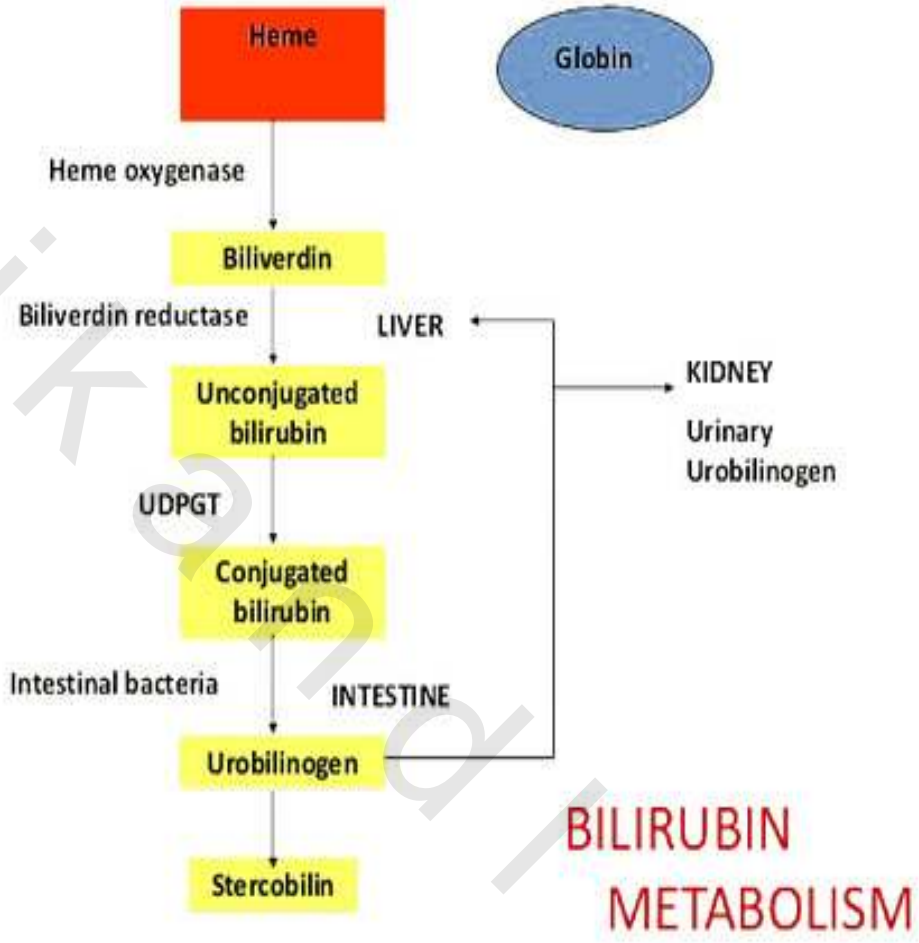


Figure 11: Bilirubin metabolism

Pathology of extra-hepatic biliary atresia

Longitudinal studies have shown the progressive nature of the pathological changes in biliary atresia even with surgical therapy.

❖ Gross pathology

The extra hepatic ductal system usually shows fibrous obliteration of the common and hepatic ductal structures with an absent or atretic gallbladder. The gallbladder may contain white bile (clear mucous) with no pigment. In severe cases, the liver is dark green in color, congested, enlarged and firm in texture. Nodular changes in the hepatic capsule consistent with the development of cirrhosis.[25]

❖ Microscopic pathology

1. Intrahepatic changes

Characteristic pathologic findings in biliary atresia include portal tract edema, bile duct proliferation, portal and periductal inflammation, and associated areas of hepatic cell injury. In typical cases, ductular reaction is prominent and consists of a proliferation of small; inter-anastomosing ductules located at the periphery of the portal tracts. This finding represents the most consistent indicator of the presence of a biliary obstructive process and has repeatedly been shown to be a key feature of biliary atresia. Additional histologic findings within the liver parenchyma include bile duct plugs, giant cell proliferation, haemosiderin deposition, and increased hematopoietic activity.[26]

Extensive proliferation of the bile ductules within the portal tracts is one of the crucial pathognomonic findings for biliary atresia. However, this can also be seen in other hepatic disease processes. The origin of these newly formed bile ductules appear to be from hepatocytes positioned around the ductal plate. Increased and unregulated cell proliferation of the bile ducts is believed to be responsible for this observation. Abnormal biliary epithelial cell expression of Fas ligand and other markers of apoptosis have been noted in liver specimens from patients with biliary atresia. In addition to the proliferation of bile ductules, abnormalities of the larger intrahepatic bile ducts are found. Specifically, a paucity of interlobular ducts or ductopenia is reported (**Figure 12**). Cytokeratin immunostaining for CK 7 and CK 19 subtypes may help in the identification of these ductal structures.[27]

Histologic differentiation of other hepatic disease processes and biliary atresia based on a liver biopsy specimen alone is difficult. Mononuclear cellular infiltrate within the hepatic parenchyma, giant cell transformation, ductular proliferation, and ductopenia are also seen in neonatal hepatitis, alpha-1 antitrypsin deficiency, TPN-induced cholestasis, and the syndromic and non-syndromic forms of intrahepatic bile duct paucity (Alagille's syndrome).[28]

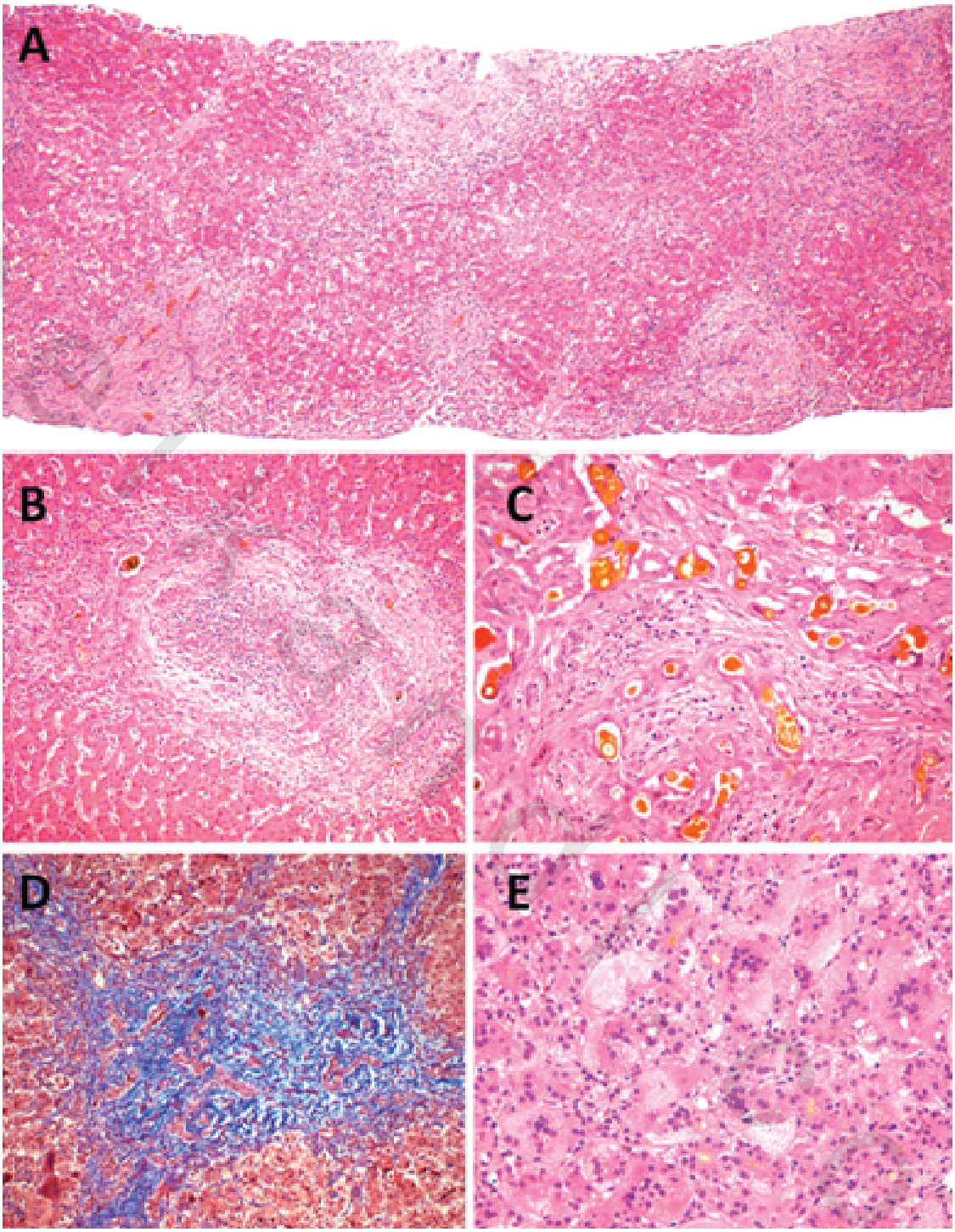


Figure 12: Typical histopathologic features of biliary atresia.

A: Low-power image showing multiple markedly expanded portal tracts. **B:** Expanded portal tract with mild inflammation, edema, prominent ductular reaction, and focal ductular bile plugs. **C:** Ductular reaction with prominent ductular bile plugs. **D:** Portal-based fibrotic expansion as well as presence of fibrous septa. **E:** Prominent cholestasis with giant cell transformation.[29]

Histologic examination of livers with advanced disease shows evidence of progressive micronodular cirrhosis with bridging fibrosis between portal tracts, as well as portal destruction. Beyond 6 months of age, the ductular proliferation in the portal tracts disappears and is replaced by collagen deposition.[29]

2. Extra-hepatic duct system

Histologic studies of resected extra hepatic ductal specimens have shown that ductal involvement with the disease process is quite variable. In some cases, the common bile duct will be completely obliterated with a fibrotic reaction and very little evidence of inflammation. In other patients, there may be one or more duct like structures patent within the fibrous tract to the portahepatis. The lumens of these structures are variable in size, often 30 to 80 μm in diameter. The epithelial cell lining is usually destroyed in this circumstance, and inflammatory cell infiltrates are present in the surrounding connective tissue. A third group consists of specimens in which microscopic ductular structures with lumens greater than 100μm in diameter are found. The epithelial cell lining may be partially intact, but the surrounding tissues demonstrate fibrosis and mononuclear cell infiltrates. Ductal size and structure have been reported to correlate with bile flow following surgical correction, but this has been a point of considerable controversy and questionable clinical import.[30]

Classification of biliary atresia

❖ Morphological classification

The disease is classified according to the level of most proximal biliary obstruction. Japanese and Anglo-Saxon classification described 3 main types: (**Figure 13**)

A. Type I: This comprises about 5% of cases and has luminal patency down to the common bile duct (often associated with a proximal cystic element).

B. Type II: This comprises about 2% of cases and has patency to the level of the common hepatic duct. It can be subdivided into;
(a) Subtype in which the cystic and common ducts are patent
(b) Subtype in which the cystic and common ducts are obliterated

C. Type III: This comprises the majority of patients (about > 90%) in whom the most proximal part of the extra hepatic biliary tract within the portahepatis is entirely solid. Nonetheless, even in type **III** cases, residual but microscopic biliary ductules (of varying size and number) retain continuity with the intrahepatic biliary system.[31]

❖ Surgical classification

The disease could be classified according to surgical intervention into:

A. Correctable: Both of type **I** and type **II** are known as surgically correctable

B. Un-correctable: The more common type **III** is known as surgically non-correctable and is in need for biliary-enteric anastomosis.

In intra-hepatic biliary atresia the extra hepatic ducts may be present or absent. The mechanism of intrahepatic atresia remains obscure and the condition is as yet non-correctable. It requires early liver transplantation.[32]

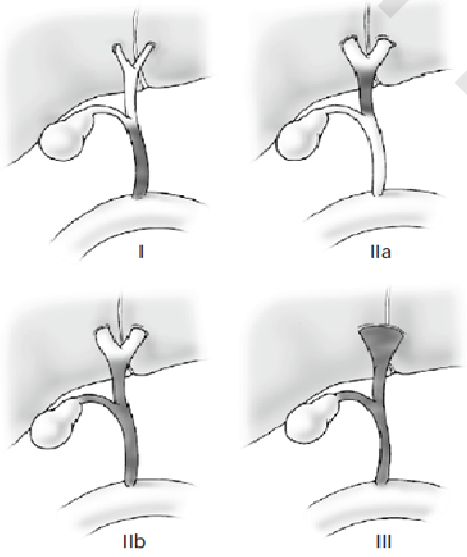
Type I: Occlusion of common bile duct		**Type IIa:** Obliteration of common hepatic duct
Type IIb: Obliteration of common bile duct, hepatic and cystic ducts, with cystic dilatation of ducts at the portahepatis, and no gallbladder involvement		**Type III**: Obliteration of common, hepatic, and cystic ducts without anastomosable ducts at portahepatis

Figure 13: Morphologic classification of biliary atresia. [33]

❖ Clinical classification

Although most textbooks usually discuss in terms of only two variants; embryonic and perinatal, this is far too simplistic so it's preferred to use more verifiably descriptive names with less assumption on cause. Thus, there are probably at least four clinical variants which can be defined.

A. Biliary atresia and other congenital malformations (Fetal/Embryonic): 10-35%

These are infants with BA who have other congenital anomalies. They can be further sub-divided into three groups;

i. Biliary Atresia Splenic Malformation(BASM) syndrome:[34]

These might include splenic malformation (usually polysplenia, but also asplenia and double spleen), disorders of visceral symmetry (e.g. situs inversus and malrotation), malformations of the intra-abdominal veins (e.g. absent inferior vena cava, preduodenal portal vein) and cardiac anomalies. These infants are usually girls, and some seem to develop from an abnormal intrauterine environment (e.g. maternal diabetes, maternal thyrotoxicosis). It is almost certain that their bile duct pathology occurs at the same time as their other developmental anomalies (i.e. during the embryonic phase of organ development, perhaps at 5-6 weeks of gestation) and therefore at the time that the hepatic diverticulum is pushing into the mesenchyme of the pre-hepatic septum transversum. This is well before any intrahepatic duct system has developed (7-10 weeks) and at operation concurs with the observation that the extra hepatic biliary tree is often atrophic with little inflammation and there is usually absence of the common bile duct. Surprisingly, given this timeline the liver parenchyma at the time of birth is actually normal.[35,36]

ii. Biliary atresia with other distinct syndromes:

There is a second group of infants, also with BA, who have other features of other distinct syndromes. The example for this is the so-called cat-eye syndrome(coloboma, ano-rectal atresia etc.) and in this chromosomal aneuploidy (Ch 22) has been shown.[37]

iii. Biliary atresia with non-syndromic congenital anomalies:

In this type, infants with BA have non-syndromic congenital anomalies such as esophageal atresia, jejunal atresia, ano-rectal atresia etc. but none of the peculiar anomalies listed above and for which we have no convincing genetic explanation.

B. Isolated biliary atresia(Postnatal): This is the largest clinical grouping (65-90%):[38]

The initial hypothesis was that these infants also had a developmental problem of their bile ducts. The timing of onset must be later than the syndromic groups as no other system appeared abnormal and perhaps at one of the key stages in biliary development–the juxtaposition of the intrahepatic and extra hepatic bile ducts. Both elements have different origins, develop along separate lines from different structures and biliary continuity is only established by 10-12 weeks gestation. Many hypotheses suggest that even isolated biliary atresia might be a form of 1st trimester arrested development for whatever reason.[39]

The alternate hypothesis is that such infants once had a completely formed intact biliary tree but that obliteration occurs as a secondary, indeed perinatal, phenomenon. The clinical evidence supporting a patent bile duct system and then obliteration is difficult to obtain.[40,41]

C. Cystic biliary atresia

The extra hepatic component of BA is usually characterized by atrophy or absence (particularly in BASM) or by inflammatory obliteration of an intact tree. However, in about 10% of cases, cyst formation (bile or mucus) can occur, and may lead to diagnostic confusion with early obstructed cystic choledochal malformation. Cholangiography at surgery invariably shows that the intrahepatic ducts are grossly abnormal with irregularity and pruning if there is preservation of a tree-like pattern or a cloud-like appearance caused by multiple interconnections of filamentous intrahepatic biliary ductules.[42]

Such infants belong within the biliary atresia spectrum family and should be termed cystic biliary atresia (CBA). They don't seem to have any racial, genetic or epidemiological peculiarities but what is clear is that they are observable on antenatal ultrasound scanning–if looked for at least 18-20 weeks of gestation. They also have a better outcome following surgery, probably because of better quality of luminal continuity with those intrahepatic ducts.[42]

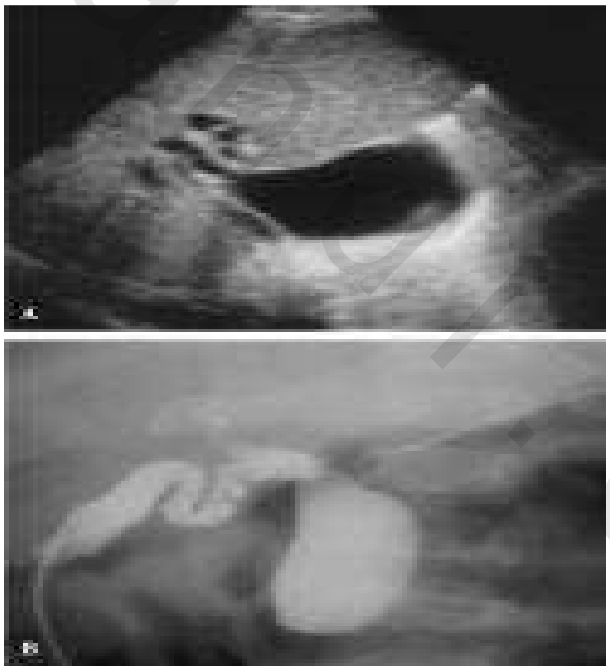


Figure 14: Cystic biliary atresia**.**

A: Oblique sonogram demonstrates a large cystic structure in the portahepatis. **B:** Intraoperative cholangiogram demonstrates filling of the cyst and mildly dilated intrahepatic ducts but no communication with the duodenum. Reproduced with permission from BC Decker, 2000.[43,44]

D. Viral associated biliary atresia:

The last and perhaps most controversial clinical variant is that of viral-associated BA–. This may be associated with REO virus type 3 or more with group C rotavirus (positive in 50% of BA infants) and cytomegalovirus.[45]

Pathogenesis

❖ Theories

There are three explanations which may explain biliary atresia:

1. Recanalization of the solid cords of epithelium may fail. This developmental arrest of the duct system occurs in the sixth prenatal week.(46)
2. The epithelium may fail to proliferate fast enough to keep up with the elongation of the ducts during the fifth week. The ducts become attenuated and finally break, resulting in a complete loss of ductal continuity.(47)
3. Late prenatal or early postnatal inflammatory liver disease can result in fibrosis of part or all of the duct system which is presumably well-formed.(48)

As the biliary tract cannot transport bile to the intestine, bile is retained in the liver (known as stasis) and results in cirrhosis of the liver. Proliferation of the small bile ductules occurs, and peribiliary fibroblasts become activated. These "reactive" biliary epithelial cells in cholestasis, unlike normal condition, produce and secrete various cytokines such as CCL-2 or MCP-1, Tumor necrosis factor (TNF), Interleukin-6 (IL-6), TGF-beta, Endothelin (ET), and nitric oxide (NO). Among these, TGF-beta is the most important profibrogenic cytokine that can be seen in liver fibrosis in chronic cholestasis. During the chronic activation of biliary epithelium and progressive fibrosis, affected patients eventually show signs and symptoms of portal hypertension (esophagogastric varix bleeding, hypersplenism, hepatorenal syndrome (HRS), hepatopulmonary syndrome (HPS). The latter two syndromes are essentially caused by systemic mediators that maintain the body within the hyperdynamic states.(41)

❖ Molecular deficit in biliary atresia

A possible association with the gene GPC1 which encodes a glypican 1-a heparan sulfate proteoglycan has been reported. This gene is located on the long arm of chromosome 2 (2q37). This gene is involved in the regulation of the gene Hedgehog and also of inflammation. The Hedgehog signaling pathway is a signaling pathway that transmits information to embryonic cells required for proper development. Different parts of the embryo have different concentrations of hedgehog signaling proteins. In addition to the association of mutations in the gene and the abnormally low levels of this protein in human cases, knock out mutants in zebra fish develop similar lesions in the liver. Hedgehog inhibitors ameliorate the features in the mutated fish and the addition of hedgehog to normal fish produce lesions.(49)

Diagnosis of biliary atresia

A high index of suspicion is the key in making a diagnosis of BA because surgical treatment by the age of two months has clearly been shown to improve the likelihood of establishing bile flow and to prevent the development of irreversible biliary cirrhosis. However, if jaundice is detected beyond two weeks of age, diagnostic evaluation is warranted, and the detection of conjugated hyperbilirubinemia always indicates the presence of significant hepatobiliary disease (**Figure 17**).[29]

Because clinical differentiation among the various causes of neonatal cholestasis is impossible, diagnostic evaluation must identify anatomic or obstructive causes of jaundice such as biliary atresia, choledochal cyst, or spontaneous bile duct perforation. Non-surgical causes of neonatal jaundice are numerous and include infectious, metabolic, genetic, and toxic etiologies beyond the scope of this chapter.[29]

❖ Antenatal diagnosis

Biliary atresia may be suspected prenatally, when a cystic structure is observed in the portahepatis. In this condition; further investigations must be performed rapidly after birth, in order to distinguish a choledochal cyst, which does not require immediate intervention, from the cystic form of BA, which calls for urgent surgical treatment.[50]

❖ Clinical picture

A. History

In the case of biliary atresia, most infants are full-term, although a higher incidence of low birth weight may be observed. Appetite, growth, and weight gain may be normal.

- **Jaundice**:

Following birth, almost every infant experiences some degree of hyperbilirubinemia. This is generally physiological and resolves over time.[51]

Any of the following features characterize pathological jaundice in which accurate investigations and follow up are mandatory:

1) Clinical jaundice appearing in the first 24 hours or after 14 days of life.
2) Increase in the level of total bilirubin by more than 0.5 mg/dL/ hour.
3) Total bilirubin more than 19.5 mg/dL.
4) Direct bilirubin more than 2.0 mg/dL.

In biliary atresia, direct hyperbilirubinemia is always an abnormal finding and may be present from birth in the fetal/embryonic form. However, in the more common postnatal form, physiologic jaundice frequently merges into conjugated hyperbilirubinemia.[52]

- **Stool:**

Stools may not be completely acholic but have a pale green or light yellow color and become acholic during first few weeks of life.[52]

- **Urine:**

The urine is dark in colour.[52]

B. Physical examination

Physical findings do not identify all cases of biliary atresia as there are no findings pathognomonic for this disorder. Infants with biliary atresia are typically full term and may manifest normal growth and weight gain during the first few weeks of life. Hepatomegaly may be present early, and the liver is often firm or hard in consistency. splenomegaly is common, and an enlarging spleen suggests progressive cirrhosis with portal hypertension.[52]

C. Complications

The majority of complications in BA patients are medical and they are usually severe and often represent indications for LT. Growth retardation in association with fat soluble vitamin deficiency may also develop because fat soluble vitamins A, D, E and K can only dissolve in fat –which isn't absorbed in this condition- so that they cannot be absorbed properly. Although itching may also develop, it doesn't develop in all jaundiced patients.[53]

1) Portal hypertension

Elevated portal venous pressure can be detected in virtually all infants at the time of the Kasai operation. However, whether it persists or regresses depends on the degree of the established fibrosis and, most importantly, the response to surgery.[54]

The age at first hemorrhage is typically approximately 2 to 3 years, and it manifests as sudden hematemesis and melena from rupture of an esophageal varix. Ectopic intestinal variceal bleeding may also occur, usually in an older child with relatively normal liver function.[55]

The initial treatment of bleeding varices is supportive, with restoration of blood volume and correction of platelet deficiency and any coagulopathy. Drugs such as octreotide, or more recently terlipressin, may be used to reduce portal venous pressure.[55]

Banding has become the most efficacious technique to control varices, although it may be limited by patient size. For infants and small children, endoscopic sclerotherapy is still effective, using sclerosants such as ethanolamine or sodium tetradecyl sulfate. Even with various pharmacologic and endoscopic alternatives, sometimes the only mean of variceal control is the Sengstaken tube or equivalent pattern tube. Trans-jugular intrahepatic portosystemic shunt (TIPS) as a method of acutely reducing portal hypertension is also possible in children with BA, but it should be regarded only as a "bridge" to transplantation, and it is not widely available.[56]

2) Hepatopulmonary Syndrome and Portopulmonary Hypertension:

Hepatopulmonary syndrome (HPS) develops due to shunting across the pulmonary vascular bed, likely caused by failure to deactivate vasoactive substances, possibly endothelin-1, by the damaged liver. Patients with HPS have higher levels of exhaled nitric oxide, presumably the final link in this chain. It is more commonly seen in those patients

with BASM, suggesting a congenital element, and it can occur even in those who are anicteric.[18]

It's characterized by cyanosis, hypoxia, and clubbing with significant hypoxia not improving with increasing ambient oxygen by arterial blood gas estimation. Radionuclide lung scans with macro aggregated tagged albumin can be used to quantify the degree of shunting which can range from 4% to 50%.[18]

Portopulmonary hypertension is much less common and may share the same underlying vascular mechanism as HPS. Although it is often silent and perhaps only detected because of cardiomegaly on a chest radiograph, it can be a cause of sudden death and is associated with systolic pulmonary arterial pressure greater than 40 mm Hg.[18]

Although no real therapy is available for the pulmonary vascular anomaly, it is a definite indication for liver transplantation and is usually reversible, albeit with an increased risk of complications.[18]

3) Liver Malignancy

The cirrhotic liver of treated BA is potentially premalignant. It's rarely reported due to the relatively small number of long-term survivors, but perhaps it implies only a moderate risk. Malignant changes may include hepatocellular carcinoma or cholangiocarcinoma, but more benign changes, such as focal nodular hyperplasia, may also occur. Although the youngest reported case was diagnosed in a patient 10 months old, but most cases are seen during later childhood or adolescence as a nodule or mass on routine US screening of the liver. Because of the risk for malignant change, serum α-fetoprotein levels should probably be a part of the routine follow-up for such children, although clearly in some patients, these levels will still be normal. Treatment is by liver transplantation.[57]

❖ Investigations of biliary atresia

A. Laboratory

➔ **Serum bilirubin:**

Total serum bilirubin levels are typically in the range of 6 to 12 mg/dL, with a direct component of 50% or more of the total. However, hyperbilirubinemia greater than 2 mg/dL with a direct component greater than 20% of the total is suspicious and should be investigated.

➔ **Liver enzymes test: (ALT,AST,GGT,ALP)**

Liver enzymes may be moderately elevated.[58]

B. Radiology

i. US abdomen

Sonography is the most commonly used noninvasive radiological investigation for the preoperative diagnosis of BA. Ultrasonography is useful in the initial evaluation of neonatal cholestasis, although it is not diagnostic for biliary atresia.[59]

➔ **The triangular cord sign** [60]

The triangular cord sign at the portahepatis is one of the direct and specific objective criteria for BA. It's a circumscribed, focal, triangular or tubular echogenic density more than 3 mm thick located cranial to the portal vein bifurcation corresponding to fibrosis of the extra hepatic biliary system.[60]

➔ **Gall bladder ghost triad** [61]

- ► Gallbladder length less than 1.9 cm
- ► Thin or indistinct gallbladder wall
- ► Irregular and lobular contour.[62]

However the triangular cord sign is a more useful sonographic finding for diagnosing biliary atresia than gallbladder length and contraction.[61]

➔ **Absence of gall bladder contraction:**

The absence of gallbladder contraction is only suggestive of biliary atresia, as 20% of children with biliary atresia have normal gallbladder contraction. Furthermore, the absence of gallbladder contraction is seen in children with cholestasis due to other causes.[61]

➔ **Vascular changes:**

There is an increased right hepatic artery (RHA) diameter and RHA-diameter to portal-vein-diameter ratio (RHA/PV).[63]

➔ **Hepatomegaly:**

The degree of hepatomegaly and heterogeneous echogenicity of liver parenchymal periportal echo are positively correlated to liver fibrosis, which is able to indicate duration and prognosis of BA and provide reliable clinical evidence for choosing operation opportunity.(63)

➔ **Differential diagnosis of cholestasis**

Ultrasonography is important in evaluating the common bile duct for choledochal cyst abnormalities or choledocholithiasis, and in determining the presence of polysplenia syndrome.(60)

➔ **Intrahepatic biliary dilatation**

Although dilatation of the intrahepatic bile duct occurs infrequently, it suggests biliary atresia when present.(63)

➔ **Associated anomalies**

Other congenital anomalies may be present in children with biliary atresia; in particular situs inversus and polysplenia. Also central biliary cysts and choledochal cysts may be associated with biliary atresia and are well depicted on sonograms.(44)

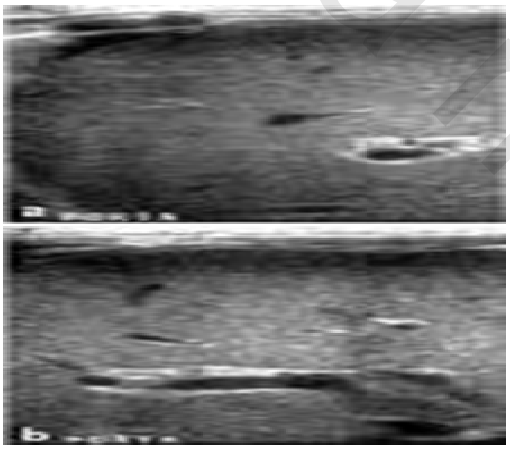


Figure 15: Triangular cord sign **(TC sign)**. Reproduced with permission from Tan Kendrick AP et al, 2003.(60)

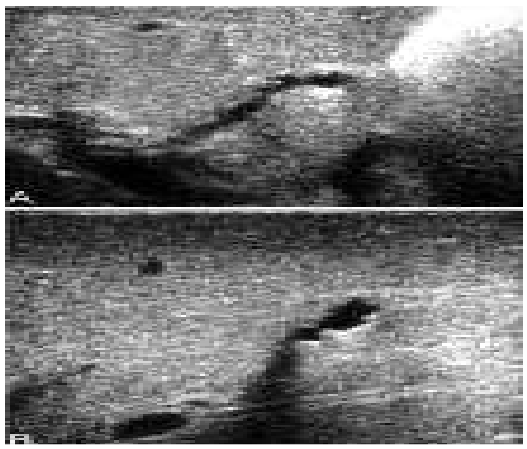


Figure 16: Gallbladder ghost triad. Reproduced with permission from Tan Kendrick et al, 2003.(58)

ii. Hepatobiliary scintigraphy

Nuclear imaging or hepatobiliary scintigraphy is commonly employed to differentiate obstructive from parenchymal causes of jaundice. After intravenous injection of the ^{99m}technetium-labeled iminodiacetic acid tracer, it is taken up in the liver with subsequent visualization of the isotope in the intestine excluding biliary atresia. It's time consuming as phenobarbital administration for up to 5 days is used to enhance the sensitivity of the test. Patients should not have had barium studies within the 48 hours preceding hepatobiliary scintigraphy. If a barium study has been performed in this time frame, an abdominal radiograph may be indicated to make sure the bowel is clear of barium, a high density material that can result in artifacts.(64)

Only the excretion of radioisotope in the duodenum rules out BA. Thus non-excretion of the radioisotope neither confirms nor rules out the diagnosis of BA. Several factors, however, may limit the effectiveness of hepatobiliary scintigraphy. For example, severe neonatal hepatitis may result in decreased hepatic radiotracer uptake and therefore decreased excretion into the bowel. Also, because biliary atresia may be an evolving process, excretion of radiotracer into the gastrointestinal tract may be seen in children with biliary atresia in the early stages of the disease. Furthermore, reliability of the test diminishes with serum bilirubin levels greater than 10 mg/dL. Lack of appearance of the isotope in the intestine has specificity for biliary atresia of only 50% to 75% because severe intrahepatic cholestasis and paucity syndrome may yield similar non-visualization results.(65)

iii. MRCP

MRCP is a reliable non-invasive imaging technique for the diagnosis of BA. It has been reported that a small GB by MRCP can be considered highly suggestive of BA. Periportal thickening in the MRCP image seems to represent periportal fibrosis on histologic examination and increased sonographic echo in the periportal area. MRCP is more expensive than hepatobiliary scintigraphy and not available in all hospitals.(66,67)

iv. ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) was also used to diagnose biliary atresia. However, it remains clinically impractical because of the specialized equipment and training required to perform the procedure successfully.(68)

v. Intraoperative cholangiogram

This test is scheduled when the diagnosis of biliary atresia is likely. During this procedure, a contrast dye is injected into the gallbladder while the flow of dye is monitored. If there is no flow of contrast into the extra hepatic biliary ducts, a diagnosis of biliary atresia is confirmed and a Kasai procedure is performed at that time.(25)

Recently, laparoscopic-assisted cholangiography had been used to accurately display the anatomic structure of the biliary tree with minimal surgical intervention.(52)

C. Liver biopsy

The most definitive test for establishing the diagnosis of biliary atresia is the liver biopsy obtained percutaneously as a part of the initial evaluation of the jaundiced infant or at the time of abdominal exploration in conjunction with an operative cholangiogram.(69)

With an experienced pathologist, a percutaneous liver biopsy has a diagnostic accuracy of greater than 80-90%.(70)

Ductular proliferation, bile plugs and intracellular bile pigments emerged as the best indicators of BA while multinucleate giant cellular transformation and portal cellular infiltration were seen in neonatal hepatitis. It's recommended doing pre-laparotomy liver biopsy for all suspected cases of BA to decrease the frequency of negative laparotomy to achieve cost benefit with reduced morbidity.(71)

If the liver biopsy is obtained at the time of laparotomy, frozen section analysis of the specimen is required. The differential diagnosis includes alpha-1-antitrypsin deficiency, Alagille syndrome, non-syndromic paucity of interlobular bile ducts, cystic fibrosis, and total parenteral nutrition (TPN)-induced cholestasis; all of which may have similar-appearing hepatic histology on frozen section analysis. If the diagnosis is uncertain on frozen section biopsy and the cholangiogram is non-diagnostic, the operation should be terminated. A definitive portoenterostomy procedure can be performed subsequently if the diagnosis is confirmed with permanent sections and special staining studies if necessary.(52)

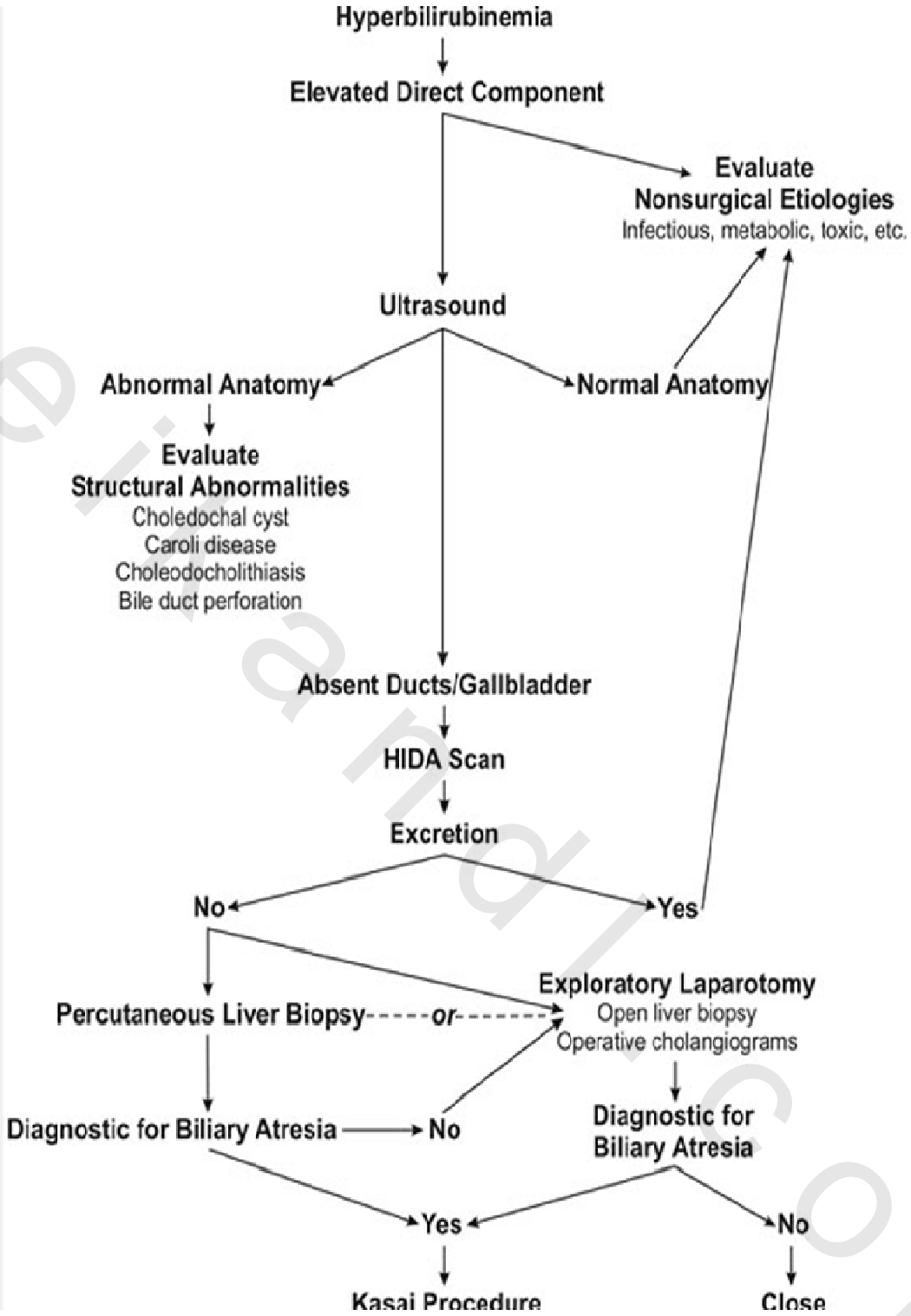


Figure 17: Diagnosis of jaundiced neonate**.**

Diagnostic algorithm for jaundiced neonate with suspected biliary atresia. Iminodiacetic acid (IDA). From Principles and Practice of Pediatric Surgery.[52]

❖ Differential diagnosis of biliary atresia

Table 1: Differential diagnosis of biliary atresia.[28,52,72]

Hepatic	**Congenital infections:** Echovirus, Coxsackievirus, Reovirus, Cytomegalovirus, Rubella virus, Herpes virus, Varicella virus, hepatitis B virus, Syphilis, Toxoplasmosis, Listeriosis, Tuberculosis.
	Metabolic disorders: Galactosemia, Tyrosinemia, Hereditary fructose intolerance, Alpha-1 antitrypsin deficiency, Cystic fibrosis, Hypopituitarism, Bile acid synthesis defect.
	Storage disorders: Gaucher's disease, Niemann- Pick disease, Neonatal iron storage disease, Glycogen storage disease
	Genetic disorders: Alagille syndrome, Down syndrome, Turner syndrome, Zellweger syndrome, Aagenaes syndrome
	Familial cholestatic disorders: Byler syndrome, BSEP deficiency, FIC 1 deficiency, MDR 3 deficiency
	Miscellaneous disorders: Idiopathic neonatal hepatitis, Nonsyndromic paucity of interlobular bile ducts, Congenital hepatic fibrosis, Inspissated bile syndrome, Total parenteral nutrition-associated cholestasis, Ischemia-reperfusion injury, Histiocytosis X, Sepsis
Extra-hepatic	Caroli's syndrome, Neonatal sclerosing cholangitis, Choledochal cyst, Spontaneous perforation of the common bile duct, Extrinsic bile duct compression (tumor), Choledocholithiasis, Bile duct stenosis

Treatment of biliary atresia

1. The correctable type

Only about 10 to 20% of the patients with biliary atresia have an extra hepatic bile duct large enough to perform a mucosa-to-mucosa anastomosis with the intestine. These cases of correctable-type can undergo hepatico-enterostomy.(18)

2. The un-correctable type

The remaining patients, about 85 to 90%, do not have any bile duct amenable to a conventional anastomosis. For these non-correctable types, hepatic portoenterostomy should be performed. It was first described by ***Morio Kasai*** in 1959.(9)

There have been numerous subsequent modifications, but the success of this operation remains critically dependent on a meticulous dissection of the portahepatis and its subsequent anastomosis to a Roux-en-Y limb of jejunum.(9)

The Kasai procedure combined with biliary stents may be also appropriate for adult patients with hilar biliary stricture that cannot be managed by standard surgical methods.(73)

A. Preoperative preparation:

As to preoperative management, in addition to the routine preoperative care for abdominal surgery, vitamin K, 1~2 mg/kg/day, is usually given for several days before surgery. The bowel is prepared with tobramycin sulfate and metronidazole orally, at a dose of 10 mg/kg/day, each starting 36 hour before operation. Early discontinuation of oral feeding and enema are properly enforced. Blood is cross matched, and preoperative broad spectrum antibiotics are administered.(18)

B. Operative procedure

i. Principle of Kasai procedure

The basis of this procedure is that the intrahepatic bile ducts are patent in early infancy and minute bile ducts are present in the cone-shaped fibrous tissue, replacing extra hepatic biliary radicles. In hepatic portojejunostomy, the extra hepatic bile ducts, including fibrous remnants at the portahepatis, are totally removed and bile drainage established by anastomosis of an intestinal conduit to the transected surface at the portahepatis. Microscopic biliary structures at the liver hilus drain bile into the intestinal conduit and, in time, an auto approximation between the intestinal and ductal epithelial elements occurs.(9,74)

ii. Operative steps

Under general anesthesia with tracheal intubation, the patient is placed in the supine position. To ensure a good venous backflow, no padding should be placed behind the baby's lower thorax at the time of its installation for the operation, as usually done to expose the hilar region. The diagnosis is always confirmed initially through a limited laparotomy through a right subcostal muscle-cutting incision from the costal margin to the

medial border of the left rectus muscle allowing access to the gallbladder (**Figure 18** A). Upon inspection of the abdominal cavity, attention must be paid to other possible anomalies, in particular those associated with the polysplenia syndrome. If a Meckel's diverticulum is present, it should be resected, since it increases the risk of major bleeding later in life, if portal hypertension developed.[18]

a. Intraoperative cholangiogram

The operation starts by examining the gall bladder; (does it contain bile?) and a cholangiogram if needed. It should be obvious that a cholangiogram is not always possible, simply because the gallbladder may not have a lumen. Nonetheless, this is in itself presumptive of the diagnosis. To exclude BA, the cholangiogram should demonstrate proximal intrahepatic ducts. This can be difficult, as contrast preferentially fills the distal duct and duodenum. A small, distal vascular or "bulldog" clamp should promote reflux into the more proximal biliary tree if patent. **(Figure 18 B)**.[18]

b. Mobilization

The liver should be fully mobilized by dividing the falciform, coronary, and triangular ligaments so that the organ can then be everted outside of the abdominal cavity. This allows full exposure of the portahepatis and facilitates dissection **(Figure 18 C)**; this also reduces venous return, so that an increase in intravenous volume support is always needed, together with close communication between surgeon and anesthesiologist.[18]

c. Portal dissection

Initially the gallbladder is mobilized and the distal common bile duct divided, with the dissection consisting of elevation of the proximal pyramidal remnant from the right hepatic artery and bifurcation of portal vein. Small veins to the portahepatis need division to facilitate downward traction of the portal vein and exposure of the posterior part of the portal plate and caudate lobe **(Figure 18 D)**. On the left side, the recessus of Rex, where the umbilical vein joins the left portal vein, should be exposed; an isthmus of liver parenchyma from segment III to IV may need division by coagulation diathermy to achieve this exposure. On the right side, remnant of biliary tissue can be identified almost circumferentially around the right vascular pedicle. The division into right anterior and posterior pedicles should be visualized, and the posterior pedicle's biliary elements should also be incorporated into the subsequent Roux loop.[18]

Excision of biliary remnants flush with the liver capsule is accomplished by use of small-sized round-shaped scissors or a sharp knife through developing a plane between solid white biliary remnant and the underlying liver at the level of the posterior surface of the portal vein **(Figure 18 E, F)**; excising liver parenchyma itself does not seem to improve bile drainage. Hemorrhage from the cut surface of the portahepatis is occasionally considerable. Irrigation with warm saline stops the bleeding, usually within 10 min. Ligation or cautery should not be applied because of the possibility of accidental obliteration of small bile ducts that may be opening on the transected surface. All the denuded area of the portahepatis needs to be incorporated into the Roux loop as the por-toenterostomy. Some authors (***Gittes& Koybayashi***, 2007) have suggested a role for frozen section of the portal plate to determine that the observed ductules are large enough.

Burrowing into liver parenchyma itself seems pointless, possibly because subsequent scarring obliterates any exposed ductules.[18]

d. Roux loop and portoenterostomy

A standard retrocolic Roux loop measuring 40 to 45 cm should be constructed. The jejunojejunostomy should lie about 10 cm from the ligament of Treitz and can be stapled or sutured. The proximal anastomosis must be wide (approximately 2 cm), and as such, an end-to-side tension-free arrangement is preferred. Fine, precise sutures (e.g., 6-0 PDS) at the edge of the portal plate are satisfactory. Remnant ductules are concentrated in the right and left recesses, and it is important that all parts of the transected plate are incorporated **(Figure 18 G, H)**.[18]

An anti-reflux intussusception valve could be constructed by removing three centimeters of the anti-mesenteric half of the seromuscular coat from the biliary limb proximal to the anastomosis. The gastric and biliary limbs are then coapted over the denuded mucosa with sutures along the edges of the incised seromuscular layer. Subsequently, the intussuscepted valve is created in the biliary limb proximal to the spur valve. The vasa recti of the conduit are divided by the width equal to the intestinal diameter. The seromuscular layer of the devascularized intestine is then removed. The denuded segment and an equivalent length of its proximal portion of the intestine are intussuscepted into the distal segment. This valve with fixed with eight to ten interrupted sutures **(Figure 18 I)**.[18]

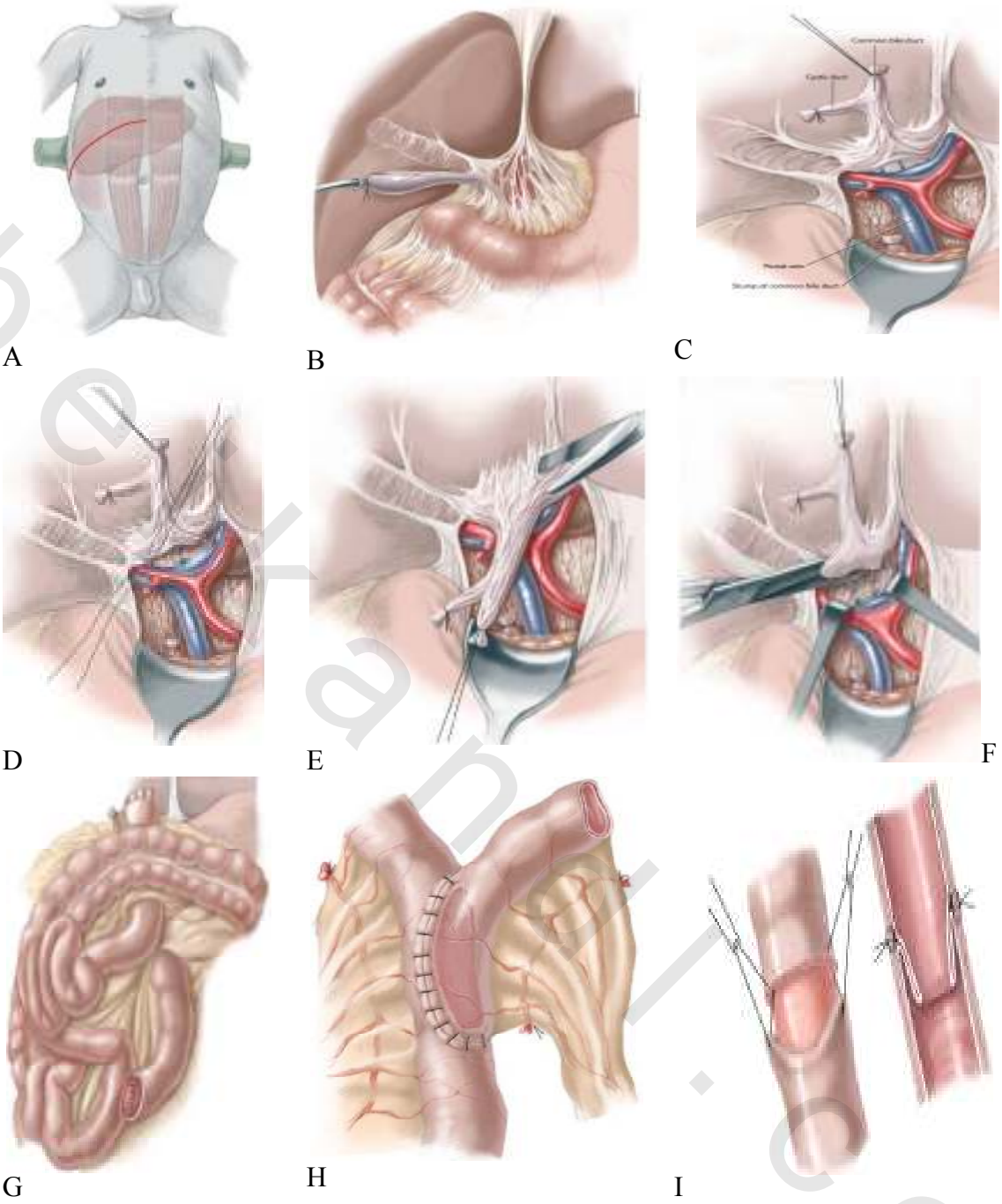


Figure 18: Steps of Kasai.[75]

iii. Modifications of the traditional Kasai procedure

With the objective of achieving better results-that is, longer survival with the native liver- several modifications of the traditional Kasai HPE have been described as in Table 2.

iv. Technical variants of Kasai procedure

Classical Kasai portoenterostomy is always is the right choice for any type of biliary atresia. However, many technical variants of the traditional Kasai HPE are possible, depending on the anatomical pattern of the biliary remnant.[25]

In case of a patent gall bladder with patent proximal bile ducts (i.e., type I or "distal" BA), a cholecystoenterostomy or hepaticoenterostomy can be performed. Also hepatoportocholecystostomy may be carried out, whereby the gallbladder with its artery is mobilized and anastomosed to the nude liver surface of the portahepatis from where the biliary remnant was removed. Construction of hepatoportocholecystostomy, with no direct contact between the portahepatis and the intestine, reduces the risk of postoperative cholangitis. Yet, bile leakage with postoperative biliary ascites due to kinking and obstruction of the cystic and common bile duct is a complication specifically associated with this technique.[25]

In case of the cystic form of BA, where the cyst communicates with the intrahepatic bile ducts, a cystoenterostomy may be an option.[25]

v. Laparotomy versus laparoscopy

The HPE is usually performed via a transverse laparotomy but can also be achieved using laparoscopy, in particular with robotics.[76,77]

Yet, recently discussions have emerged about the evidence based indication of the laparoscopic Kasai operation. In 2011 ***Ure et al.*** reported a prospective study that demonstrated that this approach is indeed technically feasible, but the study was stopped after inclusion of 12 infants subjected to a laparoscopic Kasai, due to a significant lower survival with the native liver compared to children treated by its laparotomy counterpart. Another study failed to detect any benefit of laparoscopic versus conventional HPE, in particular no lower incidence of adhesion formation hence easier subsequent LT, one of the intended goals of the laparoscopic approach. Accordingly, some clinics have completely abandoned the laparoscopic approach for Kasai portoenterosomy.[78,79]

Table 2: Modifications of the traditional Kasai hepato-porto-enterostomy.

a. Wide dissection of the biliary remnant	
Hashimoto modification:	Extension of the lateral dissection into segmental bifurcations of the portal vein, followed by trimming the liver with the CUSA.[80]
Suzuki modification:	Trimming of the segment IV of the liver with the CUSA.[81]
Ando modification:	Better exposure of the biliary remnant, by dividing the ligamentum venosum (Arantius' remnant).[82]
b. Prevention of cholangitis	
• Increasing length of roux-en-y from 50 – 70 cm	
• Anti-reflux valve: (Nakajo modification):	Confection of 2-cm long antireflux valve by invaginating the proximal intestinal portion of the Roux-en-Y limb into its denuded distal portion.[83]
• Kasai II-operation:	Creation of a double-Y, where the proximal part of the Roux-en-Y limb is exteriorized through the abdominal wall; the distal segment is end-to-side anastomosed to this proximal segment for continuity of the bile flow.[84]
• Enteric conduit: ► Sawaguchi modification:	Complete exteriorization of the entire Roux-en-Y limb as a jejunostomy.[85]
► Suruga modification:	Double-barrel ostomy of the Roux-en-Y limb.[86]
► Endo modification:	Anastomosis of an ileocolic conduit to the portahepatis, and exteriorization of the ascending colon as a colostomy including the ileocecal valve.[87]

C. Postoperative care

If Kasai operation succeeded, bile flow is restored, the stools become colored, and jaundice fades. Thus, the natural evolution of BA towards biliary cirrhosis is delayed or even, rarely, altogether prevented, so that Kasai operation may help to postpone liver transplantation until late childhood, adolescence, or even adulthood.[88]

Nasogastric drainage and intravenous fluids are required for 2 to 4 days postoperatively. Antibiotics-intravenous at first and then oral- are given for 1 month. All

these infants, even those clearing their jaundice, have subnormal quantities of intestinal bile and to ameliorate the effects of fat malabsorption, they should have a formula rich in medium-chain triglycerides. Vitamin supplementation is standard, both enteral and parenteral. What is the best postoperative management after portoenterostomy remains unestablished? Different drugs may be administered, but (gold) standardized protocols have not been defined.[89,90]

Barbiturate, cholestyramine, and ursodeoxycholic acid are given to enhance bile flow, and steroids to reduce inflammation. Glucocorticoids stimulate the transcription of genes coding for anti-inflammatory proteins and additionally, steroids appear to have positive pharmacological actions on the bile flow. Yet, the use of this category of drugs remains controversial.[89,90]

D. Postoperative complications

A number of complications can occur following surgical therapy for biliary atresia, and these may have dramatic effects on native liver function and survival.

➔ **Medical complications:**

The majority of complications in BA patients are medical. This includes portal hypertension with all of its sequlae (splenomegaly, ascites and encephalopathy). Without exception they are severe and often represent indications for LT.[31]

➔ **Surgical Complications**

1. Non-Specific

Surgical complications are rare after a traditional HPE. They comprise the standard complications of abdominal surgery, including adhesive ileus, wound dehiscence, anastomotic intestinal leak, or intussusception at the foot point of the Roux-en-Y limb, as well as internal hernia. Bleeding from the portahepatis or bile leakage from the hilar anastomosis may also occur but, again, is rare.[91]

2. Specific

1) **Non-functioning portoenterostomy***:*

The most common complication is that the portoenterostomy does not work, and therefore it will have no effect on restoration of bile flow, and jaundice will worsen and lead to end-stage liver disease. For these infants, transplantation is required for survival, typically within the first 2 years of life.[79]

2) Cholangitis

❖ Cause:

Cholangitis is presumed to occur by bacterial ascent from the Roux loop via patent biliary ductules. It is therefore uncommon in those who have no effect from Kasai surgery. Nonetheless, it may occur in 30% to 50% and is most frequent within a year of surgery. Cholestasis is the main risk factor for cholangitis, and all patients with biliary atresia have very small ducts.[92]

❖ Presesntation:

Clinically, cholangitis is characterized by worsening jaundice, fever, and acholic stools and in some cases severe sepsis requiring resuscitation and intensive care. The diagnosis may be confirmed by blood culture or by percutaneous liver biopsy. Sometimes recurrent cholangitis may be problematic, which can be associated with intrahepatic cyst formation, presumably acting as a bacterial nidus.(93)

❖ Treatment:

It is important to treat suspected cases early with broad-spectrum antibiotics effective against gram-negative organisms (e.g., ceftazidime, amoxycillin, piperacillin). Most patients respond to prolonged antibiotic prophylaxis, either with intravenous broad-spectrum antibiotics via an indwelling vascular access device or with oral non-absorbable antibiotics (e.g., neomycin).If stools became acholic, a pulse of corticosteroids is useful. If cholangitis still recurs despite these measures, liver transplantation should be considered.(93)

❖ Effect of cholangitis on prognosis:

The prognosis of extra hepatic biliary atresia (EHBA) depends first on the progression of the basically existing disease and second on the development of preoperative existing alterations of hepatic structure. In addition there are postoperative complications which have essential influence on the prognosis of the disease. In this context ascending cholangitis causes a very important problem for children who have undergone a portoenterostomy. Both the organism and the frequency of cholangitis may play a part. In addition the frequency of cholangitis is also an important factor; the more the episodes of cholangitis the greater the probability of cirrhosis.(94)

3) Late-presenting cholangitis and Roux loop obstruction

Late-onset cholangitis is an uncommon complication after the Kasai operation for biliary atresia. Long-term survivors of the Kasai portoenterostomy for biliary atresia with immediate deterioration in liver function warrant investigation for possible Roux loop obstruction. And resolution of the obstruction allows preservation of their native liver. Percutaneous transhepatic cholangiography and radionuclide hepatic imaging may be useful for the diagnosis.(95)

4) Intrahepatic biliary cavities:

Intrahepatic biliary cysts, solitary or multiple, may appear even after a successful Kasai operation in about 20% of cases. Some of these cysts can contribute to recurrent cholangitis and affect morbidity and mortality. Treatment, particularly in cases complicated by cholangitis, consists of percutaneous transhepatic cholangio-drainage, as well as, less frequently used, local alcohol injections, or, in cases where permanent drainage is necessary, internal intestinal drainage with a cystenterostomy. In severe cases it may be an indication for LT.(96)

5) Cessation of bile flow

Loss of fecal bile pigment in a patient with a well-functioning portoenterostomy is an ominous sign. Prompt re-establishment of bile flow is imperative to avoid liver damage. Parents should be encouraged to report changes in stool color or signs of cholangitis.(97)

If cessation of bile flow occurs, a pulse of corticosteroids is tried because corticosteroids both augment bile flow and reduce inflammation. If bile flow is not re-established, corticosteroids are stopped and preparation for reoperation is taken. However, multiple attempts at reoperation are not useful and increase the technical difficulties for subsequent transplantation.(97)

E. Redo surgery

The following 3 categories of patients with extra hepatic biliary atresia should be considered for re exploration following a Kasai or modified Kasai portoenterostomy:

- ► Infants who become jaundiced after an initial anicteric phase postoperatively.
- ► Infants with favorable hepatic and biliary duct remnant histology at initial operation, who do not successfully drain bile.
- ► Infants who may have had an inadequate initial surgery.(98)

F. Liver transplantation for biliary atresia

If Kasai operation is not successful, that is, no restoration of bile flow is achieved, and/or medical complications of biliary cirrhosis appear, even if jaundice has subsided, liver transplantation is indicated. A high hepatic artery resistance index measured on doppler ultrasonography is an indication for relatively urgent transplantation. Most transplantation for biliary atresia patients are performed in the first or second year of life. BA represents about half of the indications for LT in childhood. LT should not be deferred too long once it becomes apparent that it will be required, since timing of LT not only affects survival, but may also influence neurodevelopmental outcome.(99)

The dramatic improvement in survival with the use of cyclosporin and tacrolimus immunosuppression after liver transplantation raises the question of transplantation becoming a more conventional form of surgical treatment for biliary atresia. The donor supply is always a problem, alleviated to some extent by reduced-size liver transplantation. Despite the debate over whether hepatic portoenterostomy or primary liver transplantation should be performed as the initial surgical procedure for biliary atresia, the consensus among pediatric surgeons all over the world is that hepatic portoenterostomy is still the most reasonable first choice. However, liver transplantation plays an important role in the long-term management of biliary atresia.(100)

Nutritional support before transplantation and, reciprocally, performance of transplantation before malnutrition develops may reduce developmental delays. The goal of the LT is to offer a normal life to these children, allowing for normal physical, intellectual, psychological, sexual, and social development.(25)

There are two sources for a liver graft

A. **Cadaveric donor:** the graft usually derives from an adult donor, and the left lobe (segments II and III) or the left liver (segments II, III, and IV) are used after in situ

or ex situ splitting of the whole liver. Pediatric donors are much less frequent, but in those cases the whole liver can be transplanted.

B. **Living-related donor**: usually the donor is a close relative, in most cases one of the parents. A left lobectomy is generally performed to transplant segments II and segment III. Morbidity of the lobectomy performed in the donor is not negligible, reaching 10%.[25]

Outcome of patients with biliary atresia

Before Kasai operation was developed, most children with BA died before the age of two. The worldwide diffusion of Kasai HPE in the 1970s considerably changed the prognosis of this disease, yet many children still die from the complications of biliary cirrhosis. Only after the introduction of LT in the 1980s did the outcome of BA patients dramatically improve, so that survival now reaches 90% in industrialized countries.[101]

❖ Overall survival

Overall survival of BA patients (i.e. patients after Kasai only, or Kasai and subsequent LT, or primary LT) has dramatically improved since the implementation of pediatric LT. Not only surgical innovations but primarily medical advances nowadays allow a more positive prognosis for pediatric patients.[25]

❖ Survival with native liver

In Western countries short term clearance of jaundice can be achieved with Kasai HPE in approximately 50 to 60% of children. This is closely related to the widely used outcome measure for patients with BA, that is, the survival with native liver (SNL).[102]

As a general rule, half of BA patients need LT in the first two years of life, one-third of patients can survive with their native liver up to the age of ten years, and one fourth up to twenty years. Yet, even if some patients treated for biliary atresia will survive into adulthood with their native liver, they will commonly present with secondary biliary disease including cholangitis and portal hypertension.[103]

Prognostic factors of the outcome of biliary atresia

Several prognostic factors of Kasai operation have been related to the short-term results of this procedure. Among them are many that are non-modifiable which affect prognosis directly. Other prognostic factors of BA are related to the organization of care for these patients and therefore are improvable or modifiable.[104]

A. Non-modifiable risk factors

1. Anatomy of the biliary remnant; type of BA

More favorable situations encompass a patent gallbladder and/or cystic dilatation of the extra-hepatic bile duct (type II), or BA restricted to the common bile duct (type I).[105]

Agenesis of intrahepatic bile ducts which is rare has the worst prognosis. It results possibly from primary agenesis of the hepatic diverticulum and requires liver transplantation, even before portoenterostomy.[106]

2. Histology of the liver at the time of operation

Bridging fibrosis at the time of Kasai HPE is associated with worse outcome.[105]

3. Association of BA with polysplenia syndrome

Patients with embryonic atresia especially polysplenia syndrome seem to have a worse prognosis when compared to those with the perinatal form of the disease. The unsatisfactory outcome of children submitted to Kasai portoenterostomy at an age less than 30 days probably reflects the different pathogenesis of embryonic or fetal atresia.(107)

4. Portal pressure at the time of operation

BA patients with elevated portal pressure at the time of Kasai operation (>15 cmH_2O) have lower chances of success of this procedure and a higher risk of developing portal hypertension, even if bilirubin levels are normalized after surgery.(54)

B. Modifiable risk factors

1. Case Load

As with other challenging operations, the case load of the center performing portoenterostomy seems to influence greatly the outcome of the intervention, that is, survival with native liver.(88)

2. Age of patient at Kasai operation.

The age of the patient when the HPE is performed has been repeatedly demonstrated to influence SNL in large series; short-term results of Kasai portoenterostomy are better when it is done early, that is, at the latest by the end of the third month of life, with clear evidence that the earlier the operation, the better the outcome. Syndromic BA, that is, "developmental" BA, exhibits an even worse outcome if operated in late. Although some reports failed to establish a parallel between early intervention and success of Kasai HPE, their conclusions were likely flawed owing to insufficient numbers of patients. The earlier the diagnosis of BA, the later LT is required.(108)

3. Accessibility of liver transplant

The timing for transplantation and the patient's nutritional status influence the post-transplant outcome. Improvements in transplantation techniques and the appropriate referral of patients allow for a striking increase in the survival rate.(109)

Newborn Screening

In order to improve outcome of BA patients, that is, to reduce the need for early LTs in these children, and last but not least, to save non-negligible resources of the national public health system, measures must be taken towards an early diagnosis of BA. If a BA child can be maintained in good health for longer with its own liver, that is, if LT can be delayed after infancy and early childhood, it not only lessens the risks of the LT procedure itself, but also the frequency of post-transplant medical complications often met in childhood, such as Epstein-Barr virus primary infection in the immunosuppressed child and the ground for a life threatening post-transplant Lymph Proliferative Disorder. If pediatric LTs were prevented, this would also lead to significant financial savings. Many screening programs for BA have been proposed, such as early measurement of serum bile acid , serum direct bilirubin, serum Apo C-II and III proteins, urinary sulfated bile acid,

and fecal bilirubin and fat; however, none has been put into practice extensively, due to both cost and technical complexity.[110]

A much simpler method, based on the detection of neonatal cholestasis through examination of the baby's stool color, represents an extremely attractive alternative; pale grey-pigmented stool is readily identified in 95.2% of children with BA in early infancy. Such screening, which can rely on the use of a very simple stool color card, is easy and inexpensive. Both the parents and the pediatrician can easily detect pathologic stool pigmentation by confronting the baby's feces with color indicators on the card; an examination that optimally should be performed during the first month of life in order to have enough time for confirming the diagnosis and performing an early portoenterostomy. The first concept of routine screening of newborns for BA using a stool color card was initiated in Japan in the early 1990s, introduced nationwide in Taiwan in the early 2000s, and is now also available in Switzerland. The stool color card was thus proven to be a simple, noninvasive, efficient, low-cost, and applicable mass screening method for early diagnosis and management of BA, hence an ideal mean to help identify a devastating disease, that, if not treated early in life, inexorably leads to the need to overly precocious and risky LT in infancy, secondarily depriving the community of most precious organs for transplantation. The benefit of this BA screening program is thus not only paramount for the child and his family, but also for society in general.[111–113]