

Biliary atresia

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Biliary atresia (BA) is the most common 'surgical' cause of jaundice in infancy.

- **Definition:** Obliterative disorder affecting both intra- and extrahepatic parts of the biliary tree – a *panductular cholangiopathy*
- **Surgery:** Radical resection of all affected extrahepatic ducts and a reconstruction anastomosing a Roux loop to the denuded porta hepatis – a *Kasai portoenterostomy* (KPE)
- **Outcome:** Long-term survival without the need for transplantation in ~50% of infants and children

6.1 HISTORICAL ASPECTS

In 1891, *John Thomson* from Edinburgh described an infant dying from liver failure secondary to congenital biliary obstruction and reviewed other possible cases described previously [1] (Figure 6.1). Further cases were described during the early twentieth century that had restoration of bile flow following conventional biliary anastomosis, but this remained exceptional and the outlook for the vast majority was dismal.

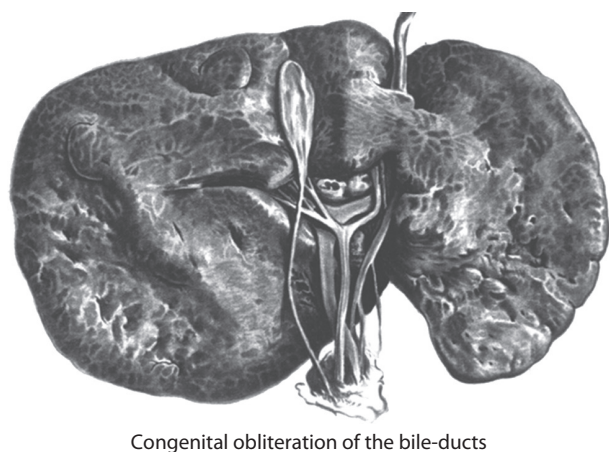
During the 1950s and 1960s, *Morio Kasai*, a Japanese surgeon, developed a more radical approach to the dissection of the porta hepatis exposing residual bile ductules that were microscopic yet patent [2]. This operation (portoenterostomy) resulted in increasing numbers of infants who had restoration of adequate bile flow and long-term survival.

The first liver transplant was performed in Denver, Colorado, by *Thomas Starzl* in March 1963 on a 3-year-old boy who had been born with BA [3]. Unfortunately, the child died on the operating table, but it ushered in the first wave of transplant programmes throughout the world. However, lack of effective immunosuppression led to their suspension until the 1980s, when, with the discovery of cyclosporine, it became a practical option for children in whom a portoenterostomy was unsuccessful or where severe complications of chronic liver disease developed.

6.2 INCIDENCE AND EPIDEMIOLOGY

BA remains a rare disease with a frequency in the United Kingdom, North America and Europe varying from 1 in 15,000 to 1 in 20,000 live births [4–7]. Within the United Kingdom, we have shown significant regional variation, probably due to differences within various racial groups [4] (Figure 6.1). The highest reported incidence is from Taiwan [8], with about 1 in 5000 live births. One of the obvious characteristics of BA is its aetiological heterogeneity, and this to some extent makes interpretation of epidemiology difficult. For instance, the most common variant defined by other features is known as the *biliary atresia splenic malformation* (BASM) syndrome. This accounts consistently for about 10%–15% of North American and European series, whereas in Chinese and Japanese series it is exceptionally uncommon [9].

A seasonal prevalence for the winter months has been suggested in some small series [7], but not in the larger national ones [4,5]. Beyond racial variation, no other factors have been incriminated, although there is a slight female preponderance in most large series [5,8,9]. This is particularly evident for those with so-called *developmental BA* [4]. Interestingly, this female predominance is even more marked in those with choledochal malformation. The reason is unclear.



Congenital obliteration of the bile-ducts

Figure 6.1 Facsimile reproduction from *Edinburgh Medical Journal* of John Thompson's original case of 'congenital biliary obstruction'.

6.3 PHENOTYPIC CLASSIFICATION

The cause of BA is not clear in most cases, and there is much speculation as to the importance of certain factors without much in the way of observable evidence. We have tried to develop a classification based more on observable traits and evidence rather than assumption – as the older simplistic division into 'embryonic' versus 'perinatal' was.

We can therefore recognise four variants, within which there is a high degree of clinical homogeneity, and thus a consistent aetiological mechanism arises as a result.

6.3.1 Biliary atresia splenic malformation syndrome (see Chapter 4)

This syndrome encompasses BA, splenic anomalies (usually polysplenia), vascular anomalies (usually preduodenal portal vein and absence of vena cava), visceral asymmetry (usually situs inversus) and cardiac anomalies (Table 6.1 and Figure 6.2).

For these peculiar anomalies to occur together, there must have been some insult operating at a critical point during embryonic development [11–13]. Our clinical series strongly suggested a much higher incidence of early

Table 6.1 Recognised anomalies in the BASM syndrome

Abnormality	Frequency (%)
Polysplenia/double spleen	98–95
Asplenia	2–5
Situs inversus	50
Predudodenal portal vein	45
Malrotation	30
Cardiac anomalies	25
Absent inferior vena cava	50–70
Annular pancreas	10
Asplenia	2–5
Immotile cilia syndrome	1

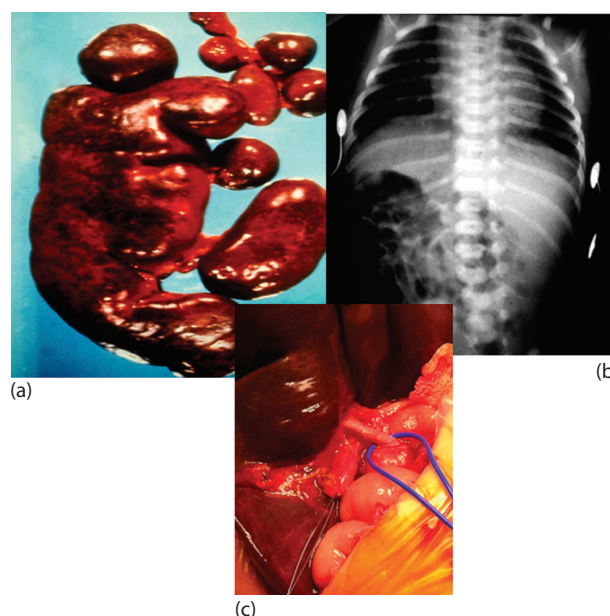


Figure 6.2 BASM syndrome. Typically, infants will have polysplenia (a), situs inversus (b) and a preduodenal portal vein (c).

trimester problems in those where the offspring had BASM (vs. otherwise isolated BA), including a marked association with *maternal diabetes* and possibly *in vitro fertilisation* [11,12]. The formation of the extrahepatic duct occurs from 20 to 38 days, in tandem with key events in the formation of the heart, spleen, determination of situs and so forth. At operation, these infants typically have no common bile duct (CBD); a tiny, atrophic gallbladder; and no evidence of inflammatory response. The liver is also usually symmetrical, whatever the nature of the abdominal situs. Furthermore, despite the protracted timeline, the liver parenchyma appears entirely normal at birth [14].

BASM is the variant that seems most likely to have an underlying genetic defect, although it is not a straightforward Mendelian* one. Mutations in the *CFC-1* gene (Ch2q 21.1 loci) were found in 50% of infants with BASM in one French study, but the same pattern was observed in a high proportion of normal controls as well [15]. The gene itself encodes for CRYPTIC protein, which is related to heterotaxy† and cardiac anomalies (e.g. transposition of the great vessels and double-outlet right ventricle), and may also have a role in mesoderm and neural patterning during gastrulation.

A smaller number of infants with BASM have immotile cilia syndrome (Kartagener's‡ syndrome), which provides

* Gregor Mendel (1822–1884), Augustinian friar who, using pea plants, identified the genetic concepts of dominance, recession and so forth.

† Heterotaxy – abnormal states of visceral position or movement; also situs ambiguus.

‡ Manes Kartagener (1897–1975), Austrian physician, described a syndrome of bronchiectasis, sinusitis and situs inversus in 1933.

an interesting speculation about mechanism. Dysfunctional cilia could be incriminated in determination of visceral situs, but how ciliary dysfunction interacts with the developing biliary tree is not known. Normally, only rats and squirrel monkeys have ciliated intrahepatic bile ducts, although there may be chemosensory cilia on cholangiocytes in humans.

There are other syndromic associations which are not within the BASM spectrum. Thus, a relationship with the *cat eye syndrome* has been reported characterised by coloboma, anorectal atresia and chromosome 22 aneuploidy [16].

Finally, other more common congenital abnormalities, such as *oesophageal atresia*, *jejunal atresia* and *anorectal malformations*, arise more commonly than would be expected by chance in infants with otherwise isolated BA.

6.3.2 Cystic biliary atresia

This subtype accounts for about 10% of all BA cases and is caused by extrahepatic cystic formation in an otherwise obliterated biliary tract. The cyst may be filled with bile or mucus depending on the degree of preservation of the connection with the intrahepatic ducts. The largest can be detected antenatally. In our series [17], 50% were detected between 18 and 20 weeks' gestation at maternal antenatal ultrasound (US) screening. It is important that this type of BA is not confused postnatally with an early-obstructing choledochal malformation, and precise diagnosis can only be confirmed at surgery with a cholangiogram. Various patterns of intrahepatic ducts can be recognised, including that of a grossly abnormal, irregular, pruned tree, or it can have a cloud-like appearance caused by multiple interconnections of the filamentous intrahepatic biliary ductules (Figure 6.3). There does not appear to be any ethnic or genetic predilection, but there is undoubtedly a better outcome following KPE [17,18].

6.3.3 Cytomegalovirus-associated biliary atresia

The proposal that viruses may be responsible for numerous infantile cholestatic conditions is attributed to an American

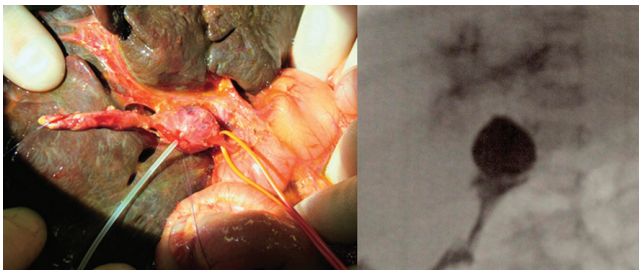


Figure 6.3 Cystic BA. Left: Operative image with cannulated cyst. Note the solid, atrophic gallbladder and string-like distal CBD. Right: Cholangiogram showing cyst and 'cloud-like' appearance of the primitive intrahepatic ducts.

pathologist, Benjamin Landing,* working in the 1960s. Since then, a number of candidate viruses have been suggested that may trigger bile duct injury in some way. The earliest focus was on reovirus Type 3, and serological studies seemed to show an increased frequency of positivity in affected infants compared with those with neonatal hepatitis [19]. Other viruses suggested included human papillomavirus, Epstein–Barr virus, cytomegalovirus (CMV) and rotavirus [20].

More recent work has been based on identification of viral nucleic acid in the principal target organ of the liver and biliary tree. For instance, the Hannover group looked at 74 infants with BA and screened for a panel of 11 viruses using RNA and DNA profiling [21]. A minority of BA infants (42%) showed some evidence of intrahepatic viral RNA or DNA (33% reovirus, 11% CMV). This group, however, concluded that viruses were not 'main players' in the aetiology of BA, but were merely a secondary phenomenon and did not influence prognosis in any way [21,22].

Fischler et al. from Sweden [23] first showed a higher prevalence of anti-CMV antibodies in the mothers of BA infants and higher serum CMV immunoglobulin M (IgM) levels in infants with BA. They also described greater amounts of immunoglobulin deposits on the canalicular membrane of the hepatocytes in infants with BA with ongoing CMV infection. Our focus has been on CMV as a possible aetiological candidate. This is a double-stranded DNA virus of the Herpesviridae family that can infect biliary epithelial cells and hepatocytes and occasionally, but certainly not commonly, where CMV inclusion bodies can be seen.

In our recently published clinical study of 210 infants with BA, 20 (9.5%) of the patients were CMV IgM +ve at the time of presentation [24]. CMV +ve infants were characterised by late presentation, more deranged biochemical derangement and a non-Caucasian origin. They also scored higher for a range of semiquantitative inflammatory and fibrotic scores on liver histology, even when corrected for age. Interestingly, using anti-CMV immunohistochemistry staining, we could find no evidence of the actual virus at the time of surgery in any of those identified. We also looked at the various T cell subsets in a further cross-sectional study based on putative underlying aetiology in 37 infants and showed that those who were CMV IgM +ve were of the predominantly Th-1 (Tbet) subtype compared with both BASM and isolated BA groups [25]. Brindley et al. have shown that there appears to be a specific T cell profile suggestive of prior exposure to CMV in about half of their American infants with BA, together with defects in peripheral blood Treg cells, which might have allowed early exposure [26].

What was clearly different in our CMV IgM +ve infants was their outcome (Figure 6.4). They had much less effect from KPE than those with isolated BA, and this translated into markedly reduced survival [24]. There is a potential for antiviral therapy in addition to surgery for these infants, and we have started using adjuvant ganciclovir, although

* Benjamin Harrison Landing (1920–2000), American pathologist.

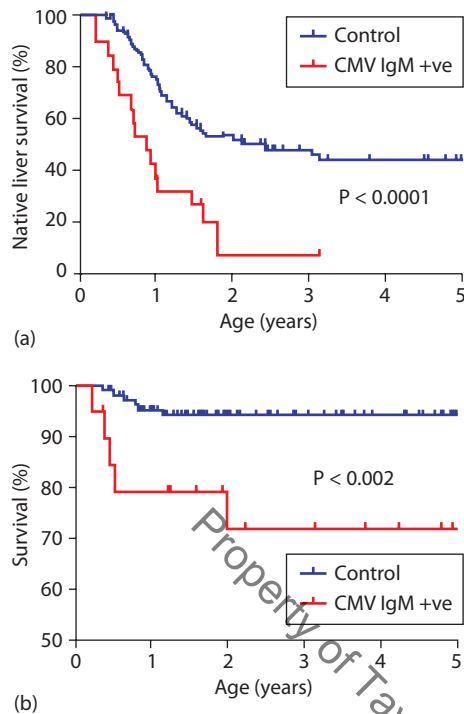


Figure 6.4 Influence of CMV – King’s College Hospital experience (2004–2011). Native liver survival (a) and survival (b) for infants with BA – CMV IgM +ve ($n = 20$) vs. CMV IgM –ve ($n = 111$).

there are no convincing studies which have been published to date.

The mechanism by which CMV may work is still very much open to debate in the clinical situation, but it seems more rational in the animal models (Figure 6.5). Thus,

it is possible that the virus acts as a trigger, activating an immune-mediated destructive process during the immediate perinatal period. In mice, this is facilitated by a reduction in regulatory T cells (Tregs) and the inflammatory cascade [27–29].

6.3.4 Isolated biliary atresia

This is the largest group for which there is actually no clear aetiological mechanism at work.

It may still be a developmental problem, but it must have later onset in fetal life than those with BASM, as no other system or organ is affected. One hypothesis is that as the intra- and extrahepatic bile ducts develop from different sources with differing timescales, linkage must occur to provide for luminal bile duct patency from the canalicular membrane to the duodenum. This is achieved at 10–12 weeks of gestation, and if disturbed, perhaps BA is one consequence (‘interface’ BA). For example, in a histological study by Tan et al. [30], sections of the porta of normal fetuses at 12 weeks’ gestation were compared with porta hepatis resections from infants with BA. These proved to be remarkably similar, suggesting developmental arrest. Alternatively, bile ducts may form completely normally in the first trimester, but obliteration occurs at some later stage, possibly even postnatally. This may be associated with a possible ‘neonatal hepatitis’-type picture, or postnatal destruction of the extrahepatic biliary tree could occur secondary to an ischaemic insult affecting the bile ducts or following a bile duct perforation. However, in these cases the intrahepatic ductules dilate, which does not occur in ‘true’ BA cases.

There are other more circumstantial pieces of evidence suggesting a prenatal origin of even isolated BA. Thus,

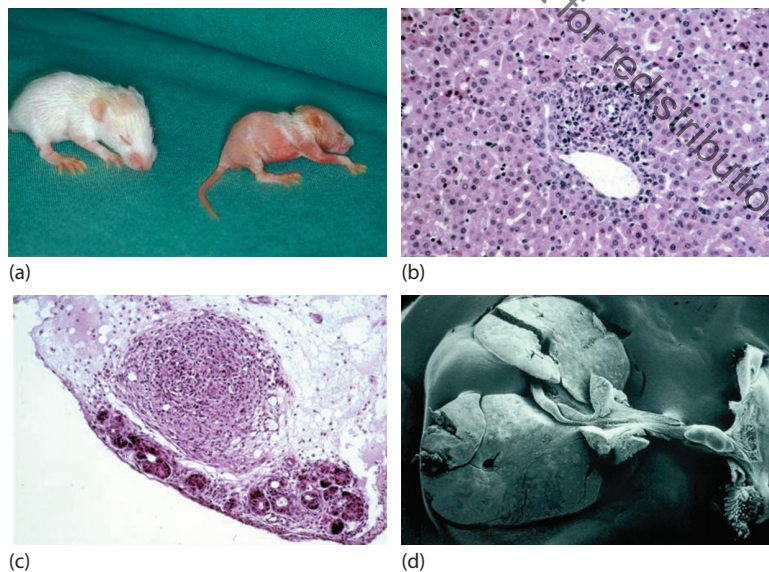


Figure 6.5 Animal models. The usual model involves perinatal administration of rhesus Rotavirus to a susceptible strain of BALB/c mice. The affected offspring develop jaundice (a) due to intrahepatic inflammation (b) and extrahepatic biliary obliteration (c). (d) Scanning electron microscopy shows a small gallbladder and a vanishing CBD. There is only a narrow window perinatally where this can happen, and it can be prevented by maternal vaccination [28]. (Reproduced with permission from Petersen C, Davenport M, *Orphanet Journal of Rare Disease* 2013, 8: 128. doi: 10.1186/1750-1172-8-128.)

studies have found low levels of the hepatic-specific enzyme γ -glutamyl transpeptidase (γ -GT) in amniotic fluid in the second trimester levels in infants who later turned out to have BA [31]. Mushtaq et al. [32] measured bile acids in the Guthrie blood spot (taken in the first days of life) in an attempt to find a screening test for BA. Just over three-fourths (77%) of 61 infants who later proved to have BA had elevated total bile acids (>97th percentile, 33 $\mu\text{mol/L}$). More recently, Harpreet et al. from Texas [33] retrospectively identified split bilirubin values in 31 infants with BA obtained when they were <48 h old (about half their overall cohort with BA). All were abnormal and significantly higher than controls. These disparate studies strongly imply that the cause of the cholestasis is fully established at birth in more than half of infants with what we have been labelling as isolated BA – making even those ‘developmental’ BA.

There are other less well-developed hypotheses on aetiology, including maternal microchimerism (Box 6.1) [34,35] and a recently developed one based on an environmental toxin, biliatresone, identified in sheep and cattle [13,36] (Box 6.2).

BOX 6.1: Maternal microchimerism

A novel mechanism of immune damage has been recently suggested based on the observation that male BA infants have a threefold increase in maternal origin cells in their livers (38). These were later shown to be maternal origin chimeric CD8+ T cells and CD45 NK cells and appear capable of initiating immune cholangiolar damage (39). This phenomenon has been termed *maternal microchimerism*.

BOX 6.2: Australia to the zebrafish

As a result of the hot summer of 1963, the water level in the *Burrinjuck Dam* (New South Wales, Australia) fell, exposing the foreshore and an abnormal proliferation of the *red crumbweed* (*Dysphania glomulifera*). Sheep had been allowed to graze here, and during the next lambing season, it became apparent that a huge proportion of the lambs had developed BA. This phenomenon was repeated during subsequent years, and occasionally affected cattle as well.

Peter Windsor, an Australian veterinary surgeon, collected the weed and passed it on to Michael Pack in Philadelphia, who isolated what was believed to be the toxic isoflavonoid component and named it *biliatresone* (36). This was tested in a zebrafish model and found to target and damage their developing bile ducts and gallbladder. Whether it is a genuine cause in human BA remains unknown, but there are plants related to the red crumbweed already in the human diet, including chard and the beetroot.

We currently think of BA as a final common pathway or phenotype with a number of different causative factors (aetiological heterogeneity) (Figure 6.6). Some of these may be *developmental* (i.e. cystic BA and BASM) and include some in the isolated group. Others may be perinatal in origin and related to viral damage, although our CMV work would suggest a figure of only around 10%. Another factor which might be important, although difficult to prove, is a possible genetic susceptibility to BA – *ADD3* has been suggested in some Chinese infants.

6.4 PATHOGENESIS

BA is an *occlusive panductular cholangiopathy*, which in most infants is probably present at birth (contentious). Progression of the condition results in cholestasis, hepatic fibrosis and ultimately cirrhosis. The histological appearance of the liver is characterised by portal tract oedema, bile duct plugging and proliferation, a small cell infiltrate and occasionally giant cell formation. The immunohistochemical appearance is characterised by abnormal expression of Class II antigens in about one-third and cytokines such as intercellular adhesion molecule (ICAM) (predominantly on the biliary epithelium) and vascular cell adhesion molecule (VCAM) (predominantly on the sinusoidal endothelium) [37–39]. There is also an infiltration of activated CD4 +ve lymphocytes and CD56 +ve natural killer (NK) cells. Most studies suggest polarisation with a predominantly Th1 and Th17 effector profile [25]. Infiltrating portal macrophages and Kupffer* cell activation may also be prominent in some cases, both acting as antigen-presenting cells and ensuring the continuation of the chronic inflammatory process.

There is a systemic response to hepatobiliary inflammation which can be detected as increased levels of cellular adhesion molecules (sICAM and sVCAM) and pro-inflammatory cytokines such as interleukin-2 (IL-2), tumour necrosis factor- α (TNF- α) and IL-18 [40]. Those quoted remain high postsurgery and continue to rise up until at least 4 months after surgery.

The Japanese classification is used in most centres throughout the world (Figure 6.7) to describe the macroscopic appearance of the extrahepatic ducts. It is based on the level of the most proximal obstruction:

- *Type 1 (5%)*: CBD, often associated with a cyst which therefore should contain bile. The gallbladder should also contain bile.
- *Type 2 (2%)*: Common hepatic duct. Transection of the most proximal porta hepatis should show both right and left ducts to contain bile.
- *Type 3 (>90%)*: Transection of the porta hepatis should not show any remnant bile ducts – these being microscopic (Figure 6.8). Subdivided on the basis of the distal remnants into (1) patent CBD and usually mucocele of

* Karl Wilhelm von Kupffer (1829–1902), German anatomist.

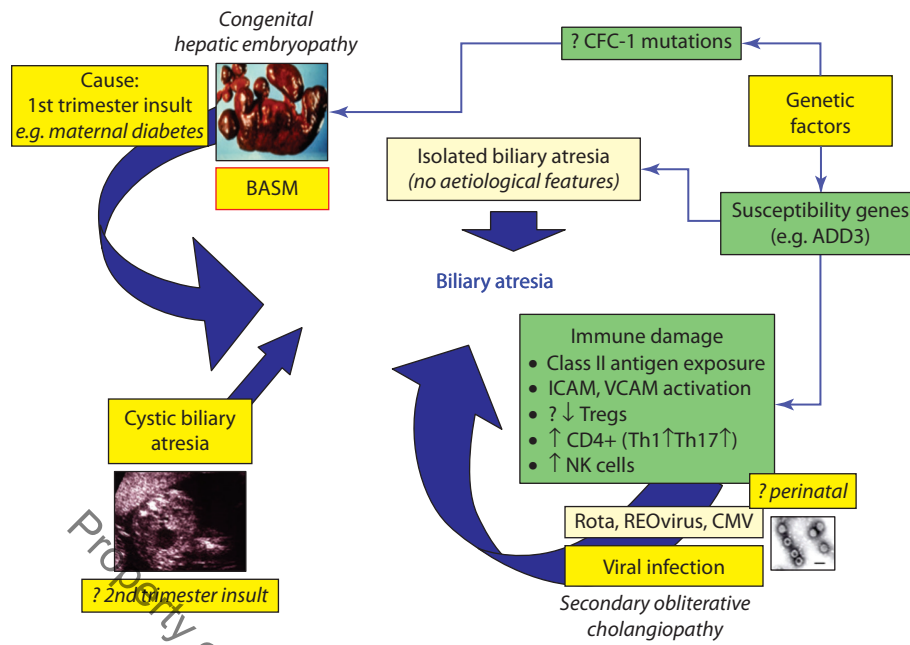


Figure 6.6 Aetiology of BA – aetiological heterogeneity.

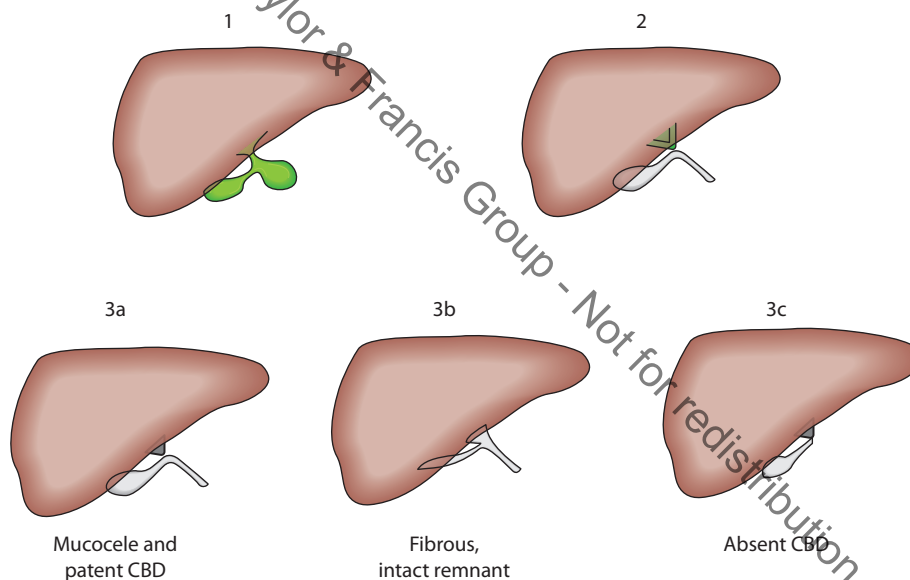


Figure 6.7 Classification of BA. Obstruction at the level of the CBD (Type 1), at the level of the common hepatic duct (Type 2) and involving the whole of the extrahepatic biliary tree (Type 3). Type 3 can be subdivided according to the state of the distal duct (a, b or c).

gallbladder, (2) intact but obliterated distal ducts and (3) absent CBD and usually atrophic gallbladder.

6.5 CLINICAL FEATURES

Infants with BA invariably have a conjugated jaundice, dark urine and pale, acholic stools. When asked, these signs are usually discernible from the time of birth. Birth weight and gestational age are usually normal for both those with BASM and those with isolated BA, and initially infants feed apparently normally, although their weight gain is subnormal [4].

The liver is usually enlarged and firm, and in older infants (>10 weeks), there may be ascites or splenomegaly, indicating portal hypertension.

Low intestinal bile salt levels interrupt vitamin K absorption, leading to a coagulopathy and raised international normalised ratio (INR) levels. Bleeding may therefore be a presenting feature, before the underlying biliary pathology is recognised. Sometimes this is relatively trivial, such as persistent bleeding of the umbilical stump, but it can be serious and catastrophic with an intracerebral haemorrhage. Vitamin D levels are also low due to the same mechanism

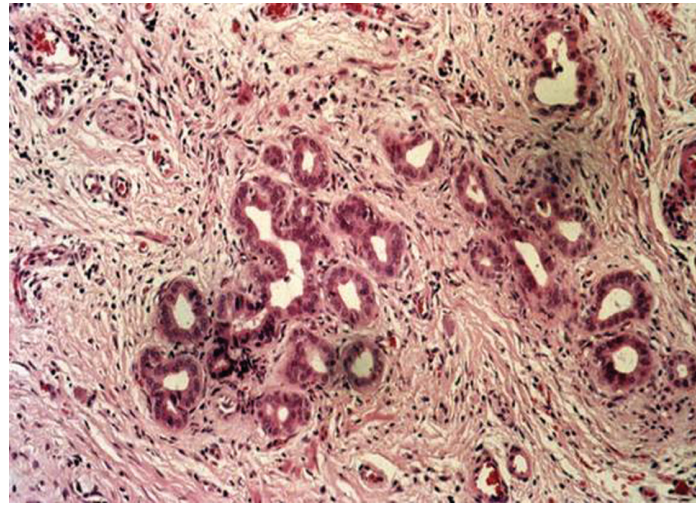


Figure 6.8 Histological appearance of transected porta hepatis in Type 3 BA showing preservation of multiple biliary ductules.

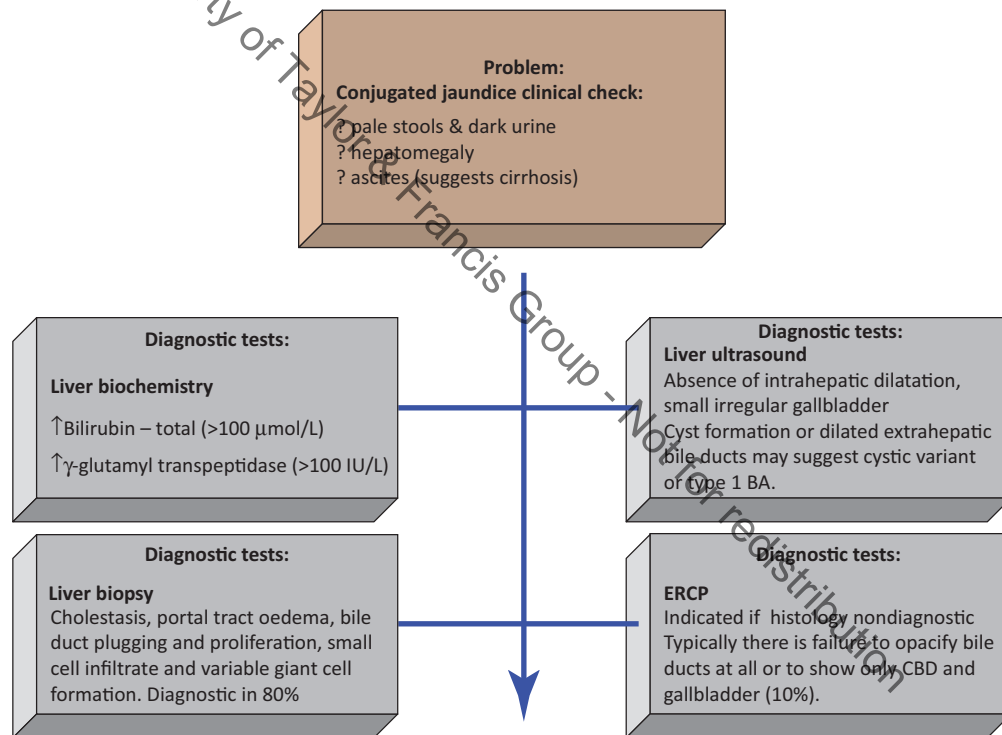


Figure 6.9 Diagnostic approach to infants with conjugated jaundice.

and can even be very low in the United Kingdom and especially in those of Asian ancestry.

The algorithm and investigation strategy at King's College Hospital is given in Figure 6.9. The blood biochemistry shows a raised total and conjugated bilirubin (also known as the direct fraction, referring back to the original van den Bergh* test reaction), with usually high levels of

γ-GT (<200 IU/L) and raised levels of aminotransferases such as aspartate aminotransferase (AST)/alanine aminotransferase (ALT).

An accurate diagnosis of BA may be established preoperatively in about 80%–90% of cases. In our institution, this is achieved by exclusion of various medical causes of conjugated jaundice (e.g. α-1-antitrypsin deficiency), and a combination of ultrasonography and percutaneous liver biopsy. The former is relatively nonspecific, but if it does show intrahepatic bile duct dilatation then this will not be BA. Dilatation more suggestive of the other less common surgical causes such as choledochal malformation,

* Hijmans van den Bergh (1869–1843), Dutch clinician. He discovered (in 1918) that the reaction of a diazo reagent with bilirubin produces a measurably coloured product alone (direct, conjugated) or with the addition of alcohol (indirect, unconjugated).

Table 6.2 ‘Surgical’ causes of conjugated jaundice in infancy

Diagnosis	Percentage of cases
Biliary atresia	80%
Choledochal cyst	10%
Inspissated bile syndrome	5%
Spontaneous perforation of bile duct	<2%
Tumours, lymph node enlargement	<2%
Gallstones	<2%

inspissated bile syndrome and the rare spontaneous perforation of the bile duct (Table 6.2). Percutaneous biopsy is accurate in about 85% of cases, and for those not quite meeting histological criteria, then cholangiography is required. In an increasing number of specialist centres, including our own, endoscopic retrograde cholangiopancreatography (ERCP) would be the next step [41,42]. Other centres have used duodenal aspiration, looking for bile and radioisotope scans documenting failure of bile excretion.

6.6 SURGERY: KASAI PORTOENTEROSTOMY (FIGURES 6.10 AND 6.11)

For most infants with BA, an attempt should be made to restore bile flow with a KPE. There is a dearth of preoperative predictors of success, including the age at surgery, and none with absolute discrimination. The groups which do have a worse prognosis are those coming to surgery at >100 days of age, those with other malformations [12] those with CMV IgM +ve BA [23], while infants with cystic BA [17] and low AST to Platelet Ratio Index (APRI) values [43,44] have a better outlook.

Because of the lack of absolute predictive factors, primary liver transplantation should probably only be considered for those with overt clinical features of cirrhosis (e.g. obvious ascites), US evidence of cirrhosis (parenchymal heterogeneity) and liver failure (increasing INR and decreasing albumin). This group should only form <5% of all those treated [45].

The technical features of the operation are illustrated in Box 6.3. Complete resection of all biliary remnants should be the object in all morphological types, including those with cystic change, even when there may be an obvious patent proximal duct. In my practice, frozen section analysis, formerly used to confirm patent ductules, is not necessary, as it should not be possible to resect any further biliary tissue anyhow. We have also found that a straightforward Roux loop reconstruction is all that is required. There is no advantage to the creation of mucosal valves or stomas in the loop, which in any case do not reduce postoperative cholangitis and may make a subsequent transplant dissection more hazardous.

6.6.1 Operative problems

Is it BA? The diagnosis is uncommonly a problem at laparotomy. Biliary hypoplasia and neonatal hepatitis should be considered if there is bile in a normal-appearing gallbladder. Here, the cholangiogram can be difficult to interpret as the ducts are small and the key feature is to document communication to intrahepatic ducts. But if there is bile, then it cannot be Type 2 or 3 BA, and in most cases of Type 1 BA, there should be an obvious cyst.

BASM syndrome? The operator should probably stand on the left side of infants with situs inversus. Extra care is needed to preserve the exposed preduodenal portal vein and avoid kinking and so forth. The biliary appearance is usually different and resembles an upside-down octopus, with an absent CBD and little inflammatory change. Formation of a Roux loop with malrotated bowel needs extra care to avoid large mesenteric gaps, predisposing to internal hernia.

Is there ascites? A moderate degree of ascites is common, and in most KPE, no drain need be used. Consideration should be given to a drain if this is excessive. Fluid from the drain will need to be replaced with albumin solution until it diminishes. In any case, it should be removed at 7–10 days; otherwise, it will form an ascitic fistula.

Is there bleeding? Significant portal hypertension may lead to venous collateralisation around the porta, rendering dissection difficult. Bipolar diathermy is the principal method of haemostasis. The transected portal plate should not, however, be diathermied at all to avoid bile ductule damage. Bleeding from this source invariably stops with pressure alone.

6.6.2 Surgical controversies

6.6.2.1 SURGICAL EXPERTISE

This is not a simple operation and is rarely performed in general paediatric surgical practice. Studies looking at experience of the centre (by implication, the surgeon carrying out the procedure) have shown significant differences in outcome between low-flow and high-flow centres. For instance, 5-year native liver survival was 61% in UK high-volume centres during the 1990s compared with 14% in low-volume centres [45]. The obvious solution to this problem is to maximise centre experience and concentrate patients – which is what has been achieved in England and Wales since 1999 with the designation of three distinctly funded units. Results have suggested an improvement in national outcome compared with both historical experience [44,46,47] and national results from the European mainland [48–51], Canada [52] and Japan [53]. It is noteworthy that there are no national outcome statistics from the United States [17,54]. This centralisation approach is probably only possible in densely populated countries where surgical care is provided largely from a monopolistic institution such as the British National Health Service. A similar system has now been adopted in Switzerland [49], Finland [6] and Denmark [50].

BOX 6.3: Operative steps – the Kasai portoenterostomy**Incision**

- Right-sided, muscle cutting to cross midline.

Confirm diagnosis

- By inspection (no bile or only clear mucus in gallbladder).
- Equivocal features indicate the need for *operative cholangiogram* – purse string through gallbladder (~4 fg feeding tube).
- Presence of other anomalies, for example, polysplenia, preduodenal portal vein and situs; absent IVC.
- Assess degree of liver damage – Overt cirrhosis? Degree of portal hypertension?

Mobilisation of liver

- Divide falciform ligament and left triangular ligaments only.
- Deliver and evert liver into wound.

Porta hepatis dissection

- Mobilise gallbladder and identify hepatic arteries with sling around distal CBD. Divide CBD between ligatures and then dissect bile duct remnants towards porta hepatis.
- Mobilisation of duct remnants from bifurcation of portal vein. Ligation of small veins (5/0 vicryl) supplying porta and part of caudate lobe.
- The right-side dissection should show the *bifurcation into anterior and posterior vascular pedicles*.
- The left side dissection is facilitated by dividing the spur of the liver tissue linking segments IV and III to allow the origin of the umbilical vein from the left portal vein to be displayed (*Recess of Rex*).
- The resulting pyramidal cone of remnant bile ducts should measure at least 2 cm in diameter from right to left.
- Sharp dissection using combination of blade and curved sharp-pointed scissors at transition between remnants and liver at the level of the capsule. It is pointless to dissect into liver parenchyma. Any residual tissue should be almost transparent.

Roux Loop Preparation

- Measurement of length of Roux loop ~40–50 cm (antimesenteric).
- Division of jejunum ~5–10 cm from duodenojejunal flexure – GIA linear stapler.
- End-to-side *enteroenterostomy* (using single-layer 5/0 PDS or Endo GIA stapler).
- Creation of mesocolic window to right of middle colic artery.

Portoenterostomy

- Ensure Roux loop has adequate length to reach porta without tension.
- Portoenterostomy (using 6/0 PDS®), placing back row first untied and ‘parachuting’ loop down to porta when complete. Avoid placing sutures in extreme right or left of porta hepatis, but use adventia on surrounding vessels instead. Complete anterior row.
- Close mesocolic window around Roux loop.

Wound closure

- Layered ‘watertight’ repair using 2/0 or 3/0 Vicryl®.
- Subcuticular 5/0 PDS®.

6.6.2.2 STATE OF THE NATIVE LIVER

BA is not simply a mechanical biliary obstruction, but in most, there is also a major intrahepatic inflammatory process as described above, leading to fibrosis and ultimately cirrhosis. It is axiomatic that the longer an obstructed liver is left alone, then the more severe the fibroinflammatory process within the organ, leading to detrimental metabolic derangements, coagulopathy, portal hypertension and a

diminishing synthetic liver reserve. It should therefore be obvious that the earlier the surgery, the better the outcome, and indeed, the concept of a cut-off then emerged (60 days, 80 days, etc.) [55]. Obvious maybe, but actually difficult to prove in reality. In many large series (particularly where a number of institutions were involved), no real effect of age (within reason) was discernible [17,45] (Figure 6.12). The most recent study from our institution [56] using



Figure 6.10 Operative photograph of KPE showing initial mobilisation of liver from abdominal cavity.

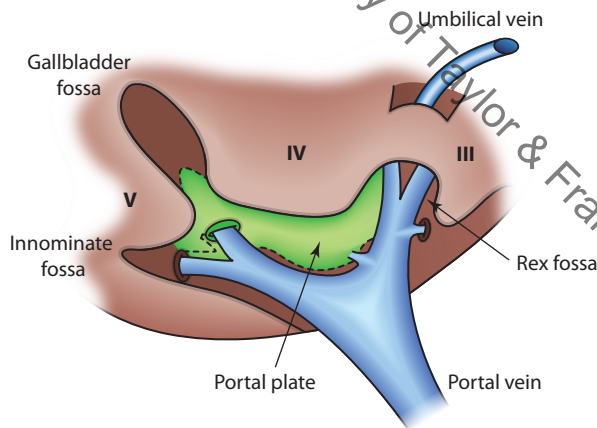


Figure 6.11 Schematic diagram of the area within porta hepatis to be resected.

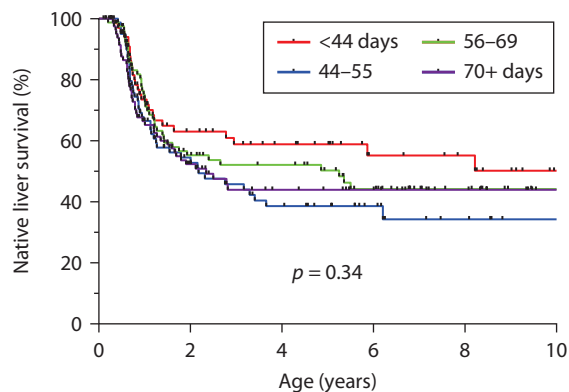


Figure 6.12 Effect of age at KPE. England and Wales data. Infants with isolated BA ($n = 318$) were divided by age at surgery. There was no difference overall ($X^2 = 3.3$, $p = 0.34$) or for trend ($X^2 = 0.87$, $p = 0.35$). Specifically, there was no difference between two outermost curves ($X^2 = 2.1$, $p = 0.15$). (From Davenport M, et al., *Journal of Pediatric Surgery* 2011, **46**: 1689–1694.)

age-cohort analysis and rigorous outcome measures showed clearly that the age effect was most obvious and statistically significant in those infants who could be considered to have *developmental* BA; that is, they had either BASM or cystic BA – variants where the biliary obstruction almost certainly is present long before birth. In the isolated BA group, there was no significant variation in *early* outcome (clearance of jaundice or need for transplant before 2 years) at ages up to and beyond 100 days.

6.6.2.3 ADJUVANT POSTOPERATIVE THERAPY

In an operation where even in the best hands failure is likely in up to half, surgeons become increasingly interested in anything which can improve outcome. Some adopt a nihilistic approach and blame the patients for their lack of biliary ductules and simply await the transplantation. Others will load the postoperative protocol with corticosteroids, ursodeoxycholic acid, antibiotics, vitamin supplements, nutritional supplements and so forth. Other more esoteric medications have also been used, such as colchicine and the Chinese herb Inchinko-to [57]. Evidence of real efficacy for any of the foregoing is lacking.

Postoperative corticosteroids have been the subject of a number of studies since first described in anecdotal form in the 1980s. As is usual, early published studies were largely positive but small-scale and completely uncontrolled [58], with a later larger study from Hannover, Germany, showing no benefit from a high-dose regimen [59]. The first randomised placebo-controlled trial from London and Leeds (two of the three English centres) did show significant early biochemical benefit (reduced serum bilirubin) but no statistical difference in the need for transplant and ultimately clearance of jaundice using a low dose of oral prednisolone (2 mg/kg/day) for 1 month postoperatively [60]. A follow-up study from London using a higher initial dose (5 mg/kg/day) given in open-label format again confirmed this biochemical benefit, but now also showed a statistically significant increase in the proportion who had cleared their jaundice from 52% to 67% [61]. The randomised placebo-controlled START trial carried out in 14 North American centres on 140 infants using a similar dose of steroid showed no statistically significant difference but still had an increase in clearance from 49% to 59% [62]. Age at KPE does appear to be important in terms of the effectiveness of steroids [61,63], and the American trial had a much higher proportion of those who were >70 days than the English one.

6.6.2.4 ROLE OF LAPAROSCOPY (SEE CHAPTER 8)

There is no doubt that instrument technology and surgical enthusiasm have driven change in many areas such that gallbladders are now rarely removed as an open procedure. The first laparoscopic Kasai procedures were reported in 2002 by surgeons from Brazil [64]. Although indubitably a surgical tour de force, it is unclear what benefits it might have in BA beyond the obvious cosmetic one. The only really important outcome in BA is simply restoration of bile flow and subsequent clearance of jaundice – no more and no

less. It is probable that the key to this is an assiduous portal dissection, proximal biliary resection and high clean portal plate transection with exposure of the maximum possible biliary ductules to drain into a jejunal Roux loop, although my colleague Dr. Yamataka disputes this (see Chapter 8). This is more difficult laparoscopically (despite magnification and robotic technology), and the published results have been only occasionally comparable in terms of meaningful outcome [65].

Consensus opinion from the main paediatric endosurgery organisations (e.g. International Pediatric Endosurgery Group [IPEG] Cannes 2008) suggests that the Kasai is probably an operation too far, although only time will really tell. Certainly, some pioneers in the field have now reverted to the traditional open operation [65].

6.6.3 Outcome and results of the Kasai portoenterostomy

The earliest measurable outcome is clearance of jaundice (although to what level is arguable). Recently reported clearance rates to normal bilirubin values (e.g. $<20 \mu\text{mol/L}$) within 6 months in large, typically multicentre series have varied from 27% to 57% [46–49,53], with translation into a 5- (or 4-) year native liver survival of 37%–52% for the most recent cohorts [45,48] (Table 6.3).

Uncorrected biliary occlusion causes progressive intra-hepatic disease, and the longer this is allowed to persist, the more irreversible it becomes. It is likely that the degree of restoration of bile flow, and hence survival with a native liver, is related to the number and area of the residual bile ductules at the porta, while the long-term quality of that

survival is dependent on the severity of sustained liver damage.

Although this operation has been performed for at least 30 years in Japan, there are still few detailed long-term studies of its survivors [66]. Single-centre series from France [67], the United States [68–72] and the United Kingdom [10] suggest that about 30%–45% of the children may survive to reach 10 years of age with their native liver intact.

BA is still the most common indication for liver transplantation during childhood and was initially used for older survivors of the Kasai operation with life-threatening complications (e.g. variceal bleeding and chronic liver failure). However, with increasing experience in transplantation, early liver replacement has been undertaken in infants who have no response to portoenterostomy. There are no absolute medical or anatomical contraindications to transplantation in BA, but timing of the operation can still be difficult and waiting times due to organ donor shortages may be prolonged [72,73].

During the transplant renaissance of the 1980s, it was suggested that more transplant operations should be performed as primary procedures during infancy rather than following a Kasai operation, irrespective of age, liver function and so forth. However, this approach ignores the potential for long-term survival with a native liver in a high proportion of the children and underestimates the potential mortality and morbidity of the transplant procedure itself. In those countries where liver transplantation is a 'safe' option, primary liver transplantation should be considered for those infants with a delayed presentation (e.g. >100 days of age), together with evidence of established cirrhosis (e.g. ascites and splenomegaly).

Table 6.3 National outcomes in biliary atresia

	Period	n	Age at Kasai (D) (median/mean)	Clearance jaundice (%)	4- to 5-year native liver survival	4- to 5-year true survival
Centralised Series						
England and Wales (45)	1999–2009	443	54	56%	46	90
Decentralised National Series						
France (48)	2003–2009	329	59	33%–39% ^a	33–39 ^a	85–92 ^a
Swiss (49)	1994–2004	48	59	n/a	37	91
Netherlands (51)	1987–2008	214	214	n/a	46	73
Canada (52)	1996–2002	150	55	n/a	39%	82
Multicentre, Not National						
United States (54)	1997–2000	104	61 ^a	~40% ^b	n/a	n/a
North America (18)	2004–2010	159	62	46	n/a	n/a
National Asian						
Japan (53)	89–98	1381	65	57–62 ^c	52–62 ^d	70–78 ^d

^a Range.

^b Estimate.

^c Level of 'clearance' not strictly defined.

^d Range including Kasai variants.

6.7 COMPLICATIONS (TABLE 6.4)

Early portoenterostomy failure (~20%) will be evident with increasingly severe jaundice, persistence of pale stools and the onset of end-stage liver failure. All such children require urgent evaluation for transplantation, and this should be available by the end of their first year of life.

In the remaining children, there will be some degree of chronic liver disease, at least histologically, and normal liver biochemistry and absence of any clinical features of liver disease are found in only ~15% of a larger series. Typically, hepatomegaly and marginal elevation of liver enzymes can be found, but others will have signs of more overt liver damage, such as ascites, intermittent jaundice, ascending cholangitis, failure to thrive and portal hypertension.

6.7.1 Ascending bacterial cholangitis

Cholangitis occurs most commonly in the year following primary surgery. It is recorded in about 40%–50% of cases in most series and almost always occurs in children with at least some degree of bile flow, not in those who show no response to KPE and early failure [10,74]. Clinically, it is characterised by worsening jaundice, fever and acholic stools. The diagnosis may be confirmed by blood culture or by percutaneous liver biopsy, but it is important to treat suspected cases early with broad-spectrum antibiotics effective against Gram-negative organisms (e.g. ceftazidime, amoxicillin and piperacillin). Sometimes, recurrent cholangitis may be problematic and consideration should be given to prolonged antibiotic prophylaxis using either intravenous broad-spectrum antibiotics or oral nonabsorbable antibiotics (e.g. neomycin). In the older child, US should also be done looking for the presence of ‘bile lakes’. In some, if large and localised, these can be drained into the Roux loop or occasionally externally using percutaneous radiological techniques. If, despite these measures, cholangitis recurs frequently, then liver transplantation should be considered.

Sometimes, cholangitis occurs some years after the portoenterostomy procedure in children with otherwise good liver function. It is important in these cases to exclude a mechanical Roux loop obstruction, as corrective surgery is relatively simple [75]. Percutaneous transhepatic

cholangiography and radionuclide hepatic imaging may be useful in diagnosis here, and the newer techniques of Roux loop enteroscopy may also have a role.

6.7.2 Portal hypertension (see Chapters 23 and 25)

An abnormal increase in portal venous pressure has been demonstrated in virtually all infants at the time of the Kasai operation [76]. Subsequent portal hypertension, however, depends on both the degree of established fibrosis and, most importantly, the response to surgery. About 60% of children who survive to 2 years will have endoscopic evidence of oesophageal varices, although only approximately half of those will ever bleed. The severity and degree of the varices themselves are not related to the original degree of liver fibrosis [77] as assessed in a liver biopsy or, in a newer biochemical surrogate, such as the APRI or clinical prediction rule [43,78], to the number of episodes of cholangitis. Endoscopic surveillance of the upper gastrointestinal tract in children with treated BA has been suggested from about the age of 2 years because of this unpredictability of variceal formation [79,80].

The age at first bleed has been about 2–3 years and is manifest by sudden haematemesis and melaena. The initial treatment of bleeding varices is supportive with restoration of blood volume and correction of platelet deficiency and any coagulopathy. Drugs such as the somatostatin derivative octreotide may also be used to reduce portal venous pressure. Endoscopic sclerotherapy has been the mainstay of treatment [81] using sclerosants such as ethanolamine or sodium tetradecyl sulphate, although for older children, variceal banding is now a better alternative [82]. Treatment should be initiated as soon as practical and is repeated as necessary to control and obliterate the varices. Emergency use of a Sengstaken tube may be required for control of severe bleeding (see Chapter 23).

An innovation which is increasingly used in adults with bleeding oesophageal varices is the interventional radiological procedure transjugular intrahepatic portosystemic shunt (TIPS). It has been reported in an infant with portal hypertension due to BA as a temporary measure or ‘bridge’ to transplantation [83], and perhaps will be used increasingly in the future.

Some children develop anorectal varices later during childhood [84]. These children almost always have already

Table 6.4 Specific complications following portoenterostomy

		Features	Management
Ascending cholangitis		↑ Jaundice, pyrexia	Antibiotic (e.g. Tazocin® and gentamicin)
Portal hypertension	Ascites	↑ Abdominal distension, hydrocele, hernias	Spironolactone, ascitic tap
	Oesophageal varices	Gastrointestinal bleeding, anaemia	Endoscopy with sclerotherapy or banding (size dependent)
Hepatopulmonary syndrome		Cyanosis	Liver transplant
End-stage liver failure		↑ Jaundice, malnutrition, ↑ INR, ↓ albumin, sepsis	Correction of nutritional depletion (e.g. nasogastric feeding), liver transplant

undergone treatment for oesophageal varices, and it simply reflects another site of portosystemic anastomosis. These can be treated by sclerotherapy (with oily phenol) or again banding.

6.7.3 Metabolic consequences of cholestasis after Kasai portoenterostomy

Virtually all infants at presentation will have diminished plasma levels of *vitamin D*, which is even more impaired in those with Asian or Afro-Caribbean family origins (unpublished observation). Postoperatively, because of impaired intestinal absorption of calcium and phosphate and despite regular oral supplementation of vitamin D, their levels will increase, but for most, they will remain subnormal. Rickets and pathological fractures are uncommonly seen, but changes in bone density on investigation (densitometry) can be evident and the threat remains [85].

Other fat-soluble vitamin malabsorption may be seen [85], and typically these children will have a vitamin K-dependent coagulopathy. These problems usually respond to oral vitamin D supplementation, but parenteral administration may be needed. The role of vitamin E malabsorption is unclear. Certainly, long-term vitamin E deficiency in cholestatic syndromes has been reported in association with certain neurological sequelae, such as abnormal eye movements.

Copper and zinc metabolism may be abnormal in post-KPE children [68]. High serum copper and low serum zinc levels have been reported in children with persisting cholestasis and in some that have cleared their jaundice [86,87]. The clinical consequences of this are uncertain.

6.7.4 Miscellaneous complications

Intrapulmonary shunting and hypoxia may develop even in anicteric children following KPE and constitutes the *hepatopulmonary syndrome* [88]. The mechanism for this is unknown, although it appears to be more common in those children with BASM, and therefore may be a manifestation of a preexisting congenital vascular anomaly. It can be diagnosed using arterial blood gas estimation \pm inspired oxygen, and typically, the hypoxia is worse in the standing position (*platypnea*). Specific ventilation or perfusion radionuclide lung scans are able to quantify the degree of shunting. This complication is resistant to conventional therapy, and liver transplantation appears to be the only specific treatment, although it is associated with significant morbidity and mortality [88].

Malignant change (both cholangiocarcinoma and hepatocellular carcinoma [HCC]) in the liver of post-Kasai children has been reported [89], which is perhaps not surprising given the underlying cirrhosis of most of the long-term survivors. A recent review from King's College Hospital of four cases of HCC remains the largest series and suggested an incidence of about 1% [90]. The median age at presentation

of the HCC was just over 2 years of age, and all were cured by transplantation. Surveillance using serial α -fetoprotein levels (although they still could be normal) and serial US should be offered for survivors, even in those who have cleared their jaundice.

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