Biliary Atresia: New Developments

28

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28.1 Introduction

Biliary atresia (BA) is an idiopathic neonatal hepatobiliary disease characterized by progressive fibrosing obstruction of the intra- and extrahepatic biliary tree [1]. Although there have been some changes in modern management, its principles have been largely unchanged since the 1980s involving an initial attempt at restoration of bile flow with the Kasai portoenterostomy (KPE), and if this is unsuccessful or complications ensue, then liver transplantation is offered [2–7]. Nowadays, long-term survival with a normal life is possible with either KPE or a functioning liver transplant, in most centres, for more than 90% of patients [1–3]. Here, we review the recent advances in basic research and clinical progress in these diseases, as well as the diagnostic assessment and therapeutic approach.

28.1.1 Epidemiology and Burden of Disease

The incidence of BA varies dramatically according to geography, with the highest rates being reported from Taiwan, Japan and China (1 in 5–10,000 live births) [2–5]. In the UK, Europe and North America, the incidence ranges from about 1 in 15–20,000 [2, 4]. Although rare, BA is the most common cause of severe chronic progressive liver disease in childhood and is still the leading indication for liver transplantation in childhood (about 50%) [5, 6]. This disproportion can be gauged by considering that in the United States, $77 million (2003 figures) is spent annually on paediatric liver transplantation-related costs, i.e. about 2% of total healthcare expenditures for only 0.0006% of the entire paediatric population [5].

28.1.2 Macroscopic Classification

The Japanese classification of BA describes the macroscopic appearance of the extrahepatic ducts and is based on the level of the most proximal obstruction of the extrahepatic biliary tree [1, 7] (Fig. 28.1):

- Type 1 (5%): level of common bile duct (CBD) and often associated with a cyst which therefore should contain bile.
- Type 2 (2%): level of common hepatic duct (CHD). Transection of the proximal porta hepatis should show both right and left ducts with bile present.
- Type 3 (>90%): Transection of the porta hepatis should not show any remnant bile ducts, as these if present are microscopic. Typically there is a solid dense fibro-inflammatory

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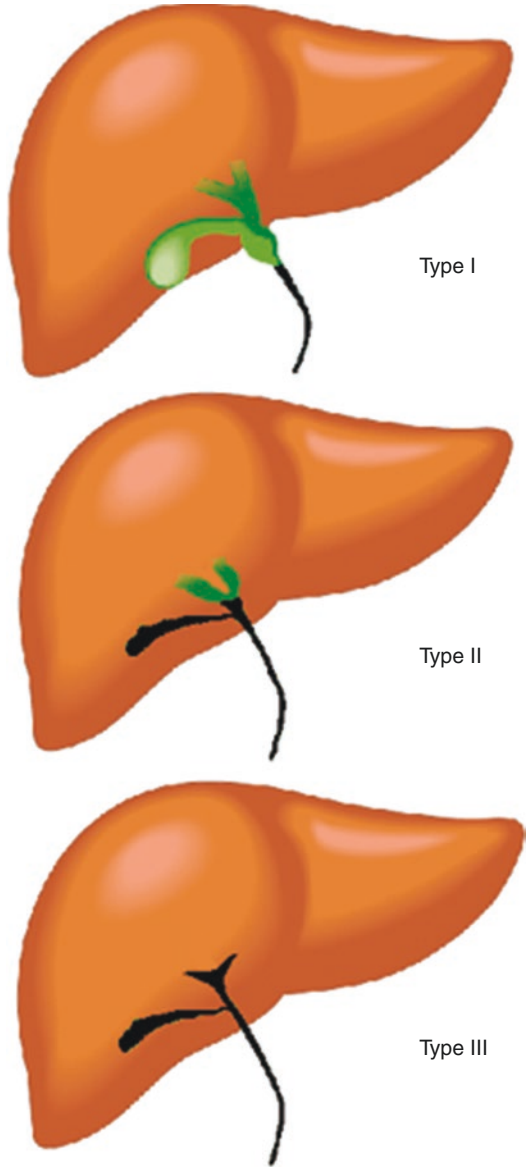

Fig. 28.1 The Japanese classification of biliary atresia

proximal remnant at the porta hepatis. The distal duct may be atrophic, absent or relatively well preserved, if so, usually in connection with a mucus-filled gallbladder.

Intrahepatic bile ducts are always non-dilated and if visualized (rarely) are grossly abnormal with perhaps a myriad of ductules coalescing at the porta hepatis.

28.1.3 Aetiopathogenesis and Phenotypic Classification

The true aetiology of BA is unknown, although developmental and infective hypotheses have been suggested and fashions change [1, 2, 8]. Certainly, BA is not a single uniform disease and at least four different variants with a different pathological background are identifiable from clinical observation alone (Fig. 28.2).

- Syndromic BA, typically the biliary atresia splenic malformation syndrome, but there are others such as the cat eye syndrome [9, 10]
- Cystic BA [11]
- Cytomegalovirus (CMV) IgM + ve BA [12]

The others, for which we use the term "isolated BA", lack any real clue to their aetiology and account for the majority of cases.

"Developmental" BA is a term used to include patients with BASM and cystic BA, where the onset is certainly during prenatal life and evident at the time of birth and usually where there is the clear female predominance.

28.1.4 Development of the Extrahepatic Bile Ducts

The extrahepatic bile duct begins as a diverticulum from the duodenum around 20 days' gestation. It is enveloped by the amorphous hepatic primordium and forms its own diverticulum—the gallbladder. Throughout this phase, ending about 45 days, it retains a lumen. It is lined by cholangiocytes expressing transcription factors common to the pancreas and duodenum (e.g. PDX-1, PROX-1, HNF-6) [1, 13]. This is occurring parallel with key changes in visceral rotation, cardiac and splenic development and evolution of the portal and inferior vena cava. Bile duct maldevelopment at this stage could explain the *biliary atresia splenic malformation (BASM) syndrome*, a subset noted in 10% of European BA cases and that encompasses splenic malformation (usually polysplenia), situs inversus, malrotation, absence of the inferior vena cava and a preduodenal portal

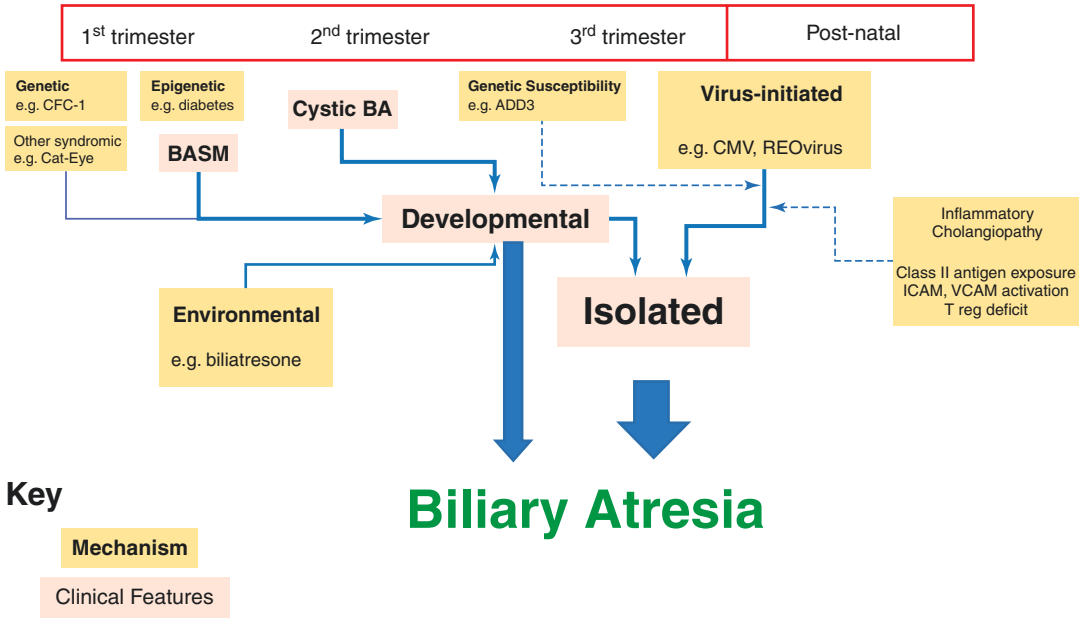

Fig. 28.2 Possible aetiological pathways in biliary atresia

vein [10]. Some of these infants seem to come from an abnormal intrauterine environment (e.g. maternal diabetes and thyrotoxicosis).

Postnatally, infants with BASM have absence of the CBD, an atrophic gallbladder and a normal appearing liver at the time of birth [10, 14]. Mutations in the CFC-1 gene, encoding for CRYPTIC protein which is also related to disorders of heterotaxy and cardiac anomalies, at least in mice, have been identified in 50% of a French series of infants with BASM [15].

28.1.5 Cystic BA

Cystic BA accounts for about 10% of cases and is caused by extrahepatic cyst formation in an otherwise obliterated biliary tract [11]. The cyst may be filled by mucus or bile and can be detected antenatally. Cystic BA may lead to diagnostic confusion with early obstructed cystic choledochal malformation though both need urgent exploration. We speculate that this variant occurs relatively late in gestation beyond the period of initial bile production at 12 weeks with at least in some luminal integrity between intrahepatic and extrahepatic systems. These infants also have a better outcome following surgery, probably because of this more mature intrahepatic bile system [6, 11].

28.1.6 Cytomegalovirus-Associated BA

In 1974, Benjamin Landing proposed that BA could be caused by the effects of a virus [16]. Since then DNA and RNA from a range of candidate viruses (e.g. reovirus, rotavirus and CMV) have been isolated from clinical cases although not consistently so [17, 18].

One of the candidates, CMV, is a double-stranded DNA virus from the *Herpesviridae* family that has the capability to infect and injure bile duct epithelia, and serological evidence of infection in the infant (CMV IgM + ve) has been shown in up to 50% of BA patients in some Chinese series [12, 17–19]. Nevertheless, whether the biliary damage is related to a direct cytopathic effect of the virus or to secondary autoimmune reaction triggered by viral exposure still remains unclear. Patients with CMV IgM + ve BA (about 10% of cases in our series) showed several

distinct clinical and histological features compared to CMV IgM-ve BA infants such as an older age at KPE, a greater degree of splenomegaly and a greater degree of inflammation and fibrosis in the liver even if age-matched [12]; further quantification of the T cell infiltrate also suggested a Th-1 predominance [19]. These patients have also a poor outcome in terms of response to KPE and a higher mortality compared to those who were CMV IgM-ve [12, 20, 21].

28.1.7 Isolated BA

Whatever remains, termed "isolated BA", lack any real clue to their aetiology, though its onset must be after those with BASM given the lack of other affected systems [3]. We also know that formation of the intrahepatic bile duct system only begins beyond about 7 weeks gestation and has to be essentially complete and linking with the extrahepatic bile ducts at the porta hepatis by 12 weeks [13]. One obvious speculation is that this linkage phase is incomplete—so-called "interface" BA.

Alternatively there is normal formation of a functional duct system but later obliteration as a secondary phenomenon.

28.2 Cellular Kinetics and Inflammation

In about 40% of cases of BA (possibly with the exception of BASM), there is a marked inflammatory process with mononuclear cell infiltrate and expression of a variety of adhesion molecules on intrahepatic biliary and vascular surfaces [1, 22]. The immunohistochemical appearance is characterized by abnormal expression of Class II antigens and cytokines such as intercellular adhesion molecule (ICAM), predominantly on the biliary epithelium, and vascular cell adhesion molecule (VCAM), predominantly on the sinusoidal endothelium [22]. There is also an infiltration of activated CD4 + ve lymphocytes and CD56 + ve natural killer (NK) cells. Most studies suggest polarization with a predominantly Th1 and Th17 effector profile [19]. This systemic response to hepatobiliary inflammation can be detected as increased levels of cellular adhesion molecules (ICAM and VCAM) and pro-inflammatory cytokines such as interleukin-2 (IL-2), IL-18 and tumour necrosis factor-α (TNF-α) [23].

28.2.1 Initiators of Cholangiopathy

A number of extrinsic factors have at one time been suggested as triggers to the inflammatory process whereby the end product is bile duct damage and obliteration. Viruses, particularly CMV, may play a role but other mechanisms have been suggested. Thus recently a toxin has been isolated and named biliatresone for its property of causing either damage or developmental arrest. Figure 28.3 illustrates the story behind this piece of biological detective work.

28.3 Clinical Features

Antenatal detection of those with cystic BA (<10%) is possible on the maternal ultrasound scan, usually between 18 and 22 weeks' gestation [11, 24]. For the remaining patients, the disease is usually suspected soon after birth with persistent conjugated jaundice, acholic stools and dark urine in an otherwise healthy neonate. Most infants eventually demonstrate a degree of failure to thrive due to reduced fat absorption, and certainly fat-soluble vitamin deficiency is common (A, D, E and K) [25]. Liver fibrosis and cirrhosis are secondary features which depend on the age of the child, whilst ascites and hepatosplenomegaly are not usually seen until after about 3 months [1].

28.3.1 Diagnostic Assessment

Liver biochemistry is non-specific and shows a conjugated hyperbilirubinemia, slightly raised transaminases (AST and ALT) and significantly raised γ-glutamyl transpeptidase (GGT). Protein and albumin levels are usually normal. The

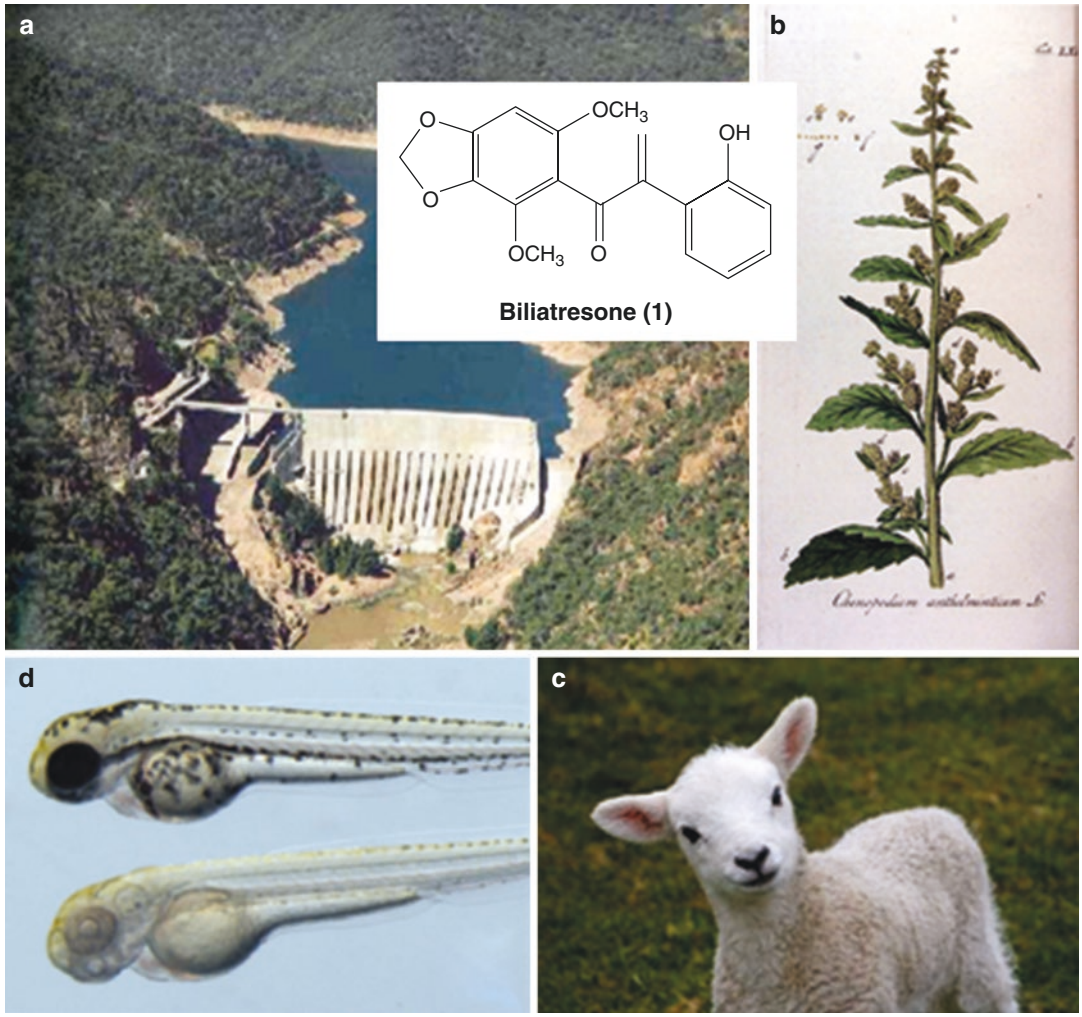

Fig. 28.3 The Biliatresone story: In 1964 in the area surrounding the Burrinjuck Dam in New South Wales, Australia (**a**), the silt foreshores of the dam became exposed by declining water levels causing abnormal colonization by a particular weed termed the red crumbweed (*Dysphania glomulifera* subsp. *glomulifera*) (**b**). This area was then used as grazing land by local farmers and lambs (**c**) subsequently born were affected by BA-like pathology. An isoflavonoid isolated in extracts of the Red Crumbweed, now known as Biliatresone, has been clearly demonstrated to cause biliary maldevelopment in Zebrafish larvae model (**d**). *Picture reproduced with permission from reference* 13

AST-to-platelet ratio index (APRi) can also be calculated and has been used as a surrogate marker of liver fibrosis in larger studies even predicting native liver survival [26, 27].

Abdominal ultrasound is a key investigation in other possible surgical diagnoses characterized by intrahepatic or common bile duct dilatation (e.g. choledocal malformation, inspissated bile syndrome). Actual positive signs of BA are less specific though may include evidence of an atrophic gallbladder or the so-called triangular cord sign, representing the appearance of the solid proximal biliary remnant in front of the bifurcation of the portal vein.

Radioisotope hepatobiliary imaging should show absence of biliary excretion in BA but is non-specific [28]. In the UK and North America, percutaneous liver biopsy is popular and has a

positive predictive value of >90% and typically shows the histological features of "large-duct obstruction", i.e. oedematous expansion of the portal areas, ductular proliferation, bile plugs and portal fibrosis [29]. There is in some a marked inflammatory aspect with infiltration of activated mononuclear cells, such as CD4+ T cells and NK cells. As the disease progresses, then monocytes/macrophages also appear with progressive bridging fibrosis between portal areas [1].

Sometimes, direct cholangiography has to be performed to prove (or disprove) the diagnosis. This can be performed using endoscopic retrograde cholangiopancreatography (ERCP) or at laparoscopy or indeed via a small incision directly over the gallbladder.

28.4 Screening for BA

Population screening programmes for BA are based on the provision of stool colour cards to parents of newborns in order to identify acholic stools and have been in use Japan [30], Taiwan [31], Switzerland [32] and Canada [33]. A large-scale prospective study which enrolled more than 6000 Canadian families demonstrated the practicality and cost-effectiveness of the stool colour card [33], even if this success may be more limited in countries without routine 30-day-old well-child visits for review of the stool colour card [34]. Recently, a pilot study on a mobile application that utilizes a smartphone's camera and colour recognition software to analyse an infant's stool in the perinatal period (PoopMD©) showed that it may have value as a tool to help parents identify acholic stools and provide guidance as to whether additional evaluation with their paediatrician is indicated [35].

28.5 Management

Following confirmation of the diagnosis, it is important to consider how far advanced the disease is. Primary liver transplant is uncommon in Western series (<2% in the UK) and could be an option in some countries, but it should probably only be a consideration in those presenting late (>100 days) or with obvious cirrhosis, ascites and portal hypertension and liver failure (increasing INR and decreasing albumin). For the remainder a KPE is indicated as attempt to retain the native liver.

28.5.1 "Maximally Invasive" Surgery

Conventional open portoenterostomy, first described by Japanese surgeon Morio Kasai in 1957, still represents the gold standard of treatment. The key part of the procedure is the dissection at the level of the portal plate. Our practice is to exteriorize the liver on the abdominal wall by division of the left triangular and falciform ligaments. The gallbladder is then mobilized from its bed and the distal CBD divided and then dissected back towards the porta hepatis (Fig. 28.4). Division of small veins from the back of the portal confluence to the porta plate facilitates downwards traction of the portal vein and exposes the caudate lobe. On the left side, there is often an isthmus of liver parenchyma (from segment III to IV) which may need division by coagulation diathermy to open up the recessus of Rex (where the umbilical vein becomes the left portal vein). On the right side, the division of the right vascular pedicle into anterior and posterior branches should be visualized. The "width" of the transected portal plate should extend from this bifurcation into Rouviere's fossa on the extreme right to the point where the left portal vein gives off its first branches to segment IV. A 40–45-cm retrocolic Roux-en-Y loop should be constructed. The jejunojejunostomy lies about 10 cms from the ligament of Treitz and can be stapled or sutured. The proximal anastomosis must be wide (~2 cms) and typically end-to-side.

28.5.2 "Minimally Invasive" Surgery

During the early years of the new century, there was a brief flirtation with the concept of the

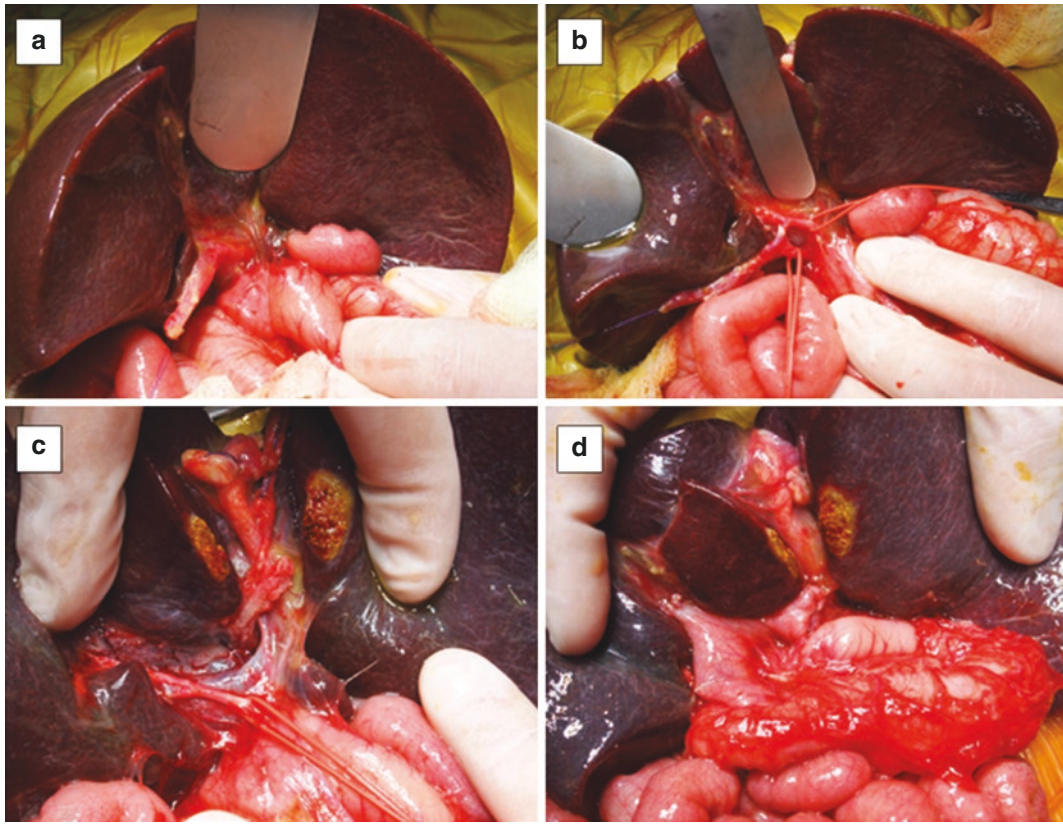

Fig. 28.4 Intraoperative picture of Kasai portoenterostomy. (**a**) Exteriorisation of the liver and exposure of the porta hepatis. (**b**) The gallbladder is then mobilized from its bed and the distal CBD divided and then dissected back towards the porta hepatis. (**c**) Exposure and transection of portal plate. (**d**) Reconstruction with Roux-en-Y loop

laparoscopic Kasai option. This procedure was reported first by a Brazilian team in 2002 [36] and there have been small case series since [37]. It has become apparent that laparoscopic KPE does not offer anything advantageous to the child beyond a better scar. Clinically meaningful results are certainly not better and rarely comparable to open surgery [38]. Two large centres have reverted from laparoscopic to the open operation with restoration of their previous results [38, 39]. A recent systematic review found no significant difference between the laparoscopic and open KPE groups in terms of operative time, early clearance of jaundice and cholangitis, but the rate of 2-year survival with native liver was significantly higher in the open group than in the laparoscopic [40]. This is likely to be because of the difficulties with portal plate dissection using laparoscopic instruments, as delicate dissection and radical resection of all extrahepatic biliary remnants are key features to maximize the results. Laparoscopic KPE is still being practised in a few centres in Japan, but one team at least has reverted to a less extensive dissection and more superficial transection [41, 42].

28.6 Adjuvant Therapy for Biliary Atresia

The success of the operation is gauged by clearance of jaundice (within 6 months), and each centre treating infants with BA will have its own

Table 28.1 Adjuvant postoperative therapy after KPE

Therapy	Rationale
Corticosteroids	Anti-inflammatory effect and choleretic effect
Antibiotics	Decreases risk of ascending cholangitis
UDCA	Establishes bile flow, possible anti-inflammatory action
Ganciclovir/ valganciclovir	Competitive inhibitor of deoxyguanosine triphosphate (dGTP) of CMV
Fat-soluble vitamin supplementation	Restores intrinsic deficiency due to impairment of bile flow
Phenobarbitone	Induces liver microsomal enzymes and thereby increases bile flow
MCT-based formula milk	Effective maintenance of calorie intake, as MCT does not require bile for its absorption in the gastrointestinal tract

Legend: *UDCA* ursodeoxycholic acid, *CMV* cytomegalovirus, *MCT* medium-chain triglyceride

postoperative regimen to try and maximize the restoration of bile flow. Most will include a prolonged period of oral antibiotics, ursodeoxycholic acid, fat-soluble vitamin supplementation, medium-chain triglyceride (MCT)-based formula milk and usually steroids (Table 28.1).

28.6.1 Corticosteroids

Steroids have been used for at least 30 years albeit delivered in an uncontrolled pragmatic fashion [43]. The rationale behind the use of steroids maybe twofold: firstly, there is a pronounced inflammatory element in a proportion of infants with BA, and steroids have many anti-inflammatory properties. Moreover, steroids have a positive choleretic effect which may improve bile flow and keep open the primitive bile ductule-Roux loop connection in the early postoperative phase [44]. There have been two prospective, double-blind, randomized, placebo-controlled trials. The first one used a low dose of prednisolone (2 mg/kg/day) in two English high-volume centres in 73 infants [45]. This showed a statistically significant improvement in early bilirubin levels (especially in the "younger" liver) in the steroid group but did not translate to a reduced need for transplant or improved overall survival. The other study is the START trial [46]; this randomized 140 infants from 14 North American centres to a steroid arm using initially IV methylprednisolone 4 mg/kg/day for the first 3 days followed by oral prednisolone (4 mg/kg/day till the second week, 2 mg/kg × 2 weeks, followed by a tapering protocol over the next 9-week period). Although there was a difference in the clearance of jaundice from 49% in the placebo group to 59% in the steroid group, this did not attain statistical significance. They also did a subgroup analysis of infants <70 days at KPE ($n = 76$) and showed that 72% (28/39) in the steroid group cleared their jaundice compared to 57% (21/37) in the placebo group, unfortunately still not statistically different ($P = 0.36$).

A follow-up study [47] to the original UK trial examined the use of a high-dose prednisolone cohort (starting at 5 mg/kg/day) and reported the same beneficial biochemical effects (now including a reduction in AST and APRi levels) with a statistically significant higher proportion of those who cleared their jaundice in the steroid groups. Later analysis showed that the key appeared to be the age of the infant at time of KPE [48]. In practice, all three of the English specialist centres (London, Leeds and Birmingham) use high-dose steroids albeit in a variety of regimens.

28.6.2 Ursodeoxycholic Acid (UDCA)

This is widely thought to be beneficial, but only if surgery has already restored bile flow to reasonable levels. UDCA "enriches" bile and has a choleretic effect, increasing hepatic clearance of supposedly toxic endogenous bile acids and may

confer a cytoprotective effect on hepatocytes. There is but a single study which looked at the effect of UDCA on liver function in 16 children >1 year post-KPE how who had resolved their jaundice. Its crossover design looked at UDCA (25 mg/kg/day in three divided doses) in an 18 month period followed by 6 months washout and then resumption. All but two had sustained significant worsening in their liver enzymes that on restarting UDCA reversed [49].

28.6.3 Antiviral Treatment for CMV IgM + ve

Antiviral treatment with intravenous ganciclovir and/or its oral prodrug valganciclovir has been trialled and shown to be well-tolerated and effective in prevention of long-term neurological damage (e.g. hearing loss) in newborns with symptomatic congenital CMV infection [50, 51]. The real potential for antiviral therapy in children with CMV IgM + ve BA (10% of cases) exists, even if no convincing studies have been published to date [20, 21]. In our own unpublished series of 37 consecutive IgM + ve BA patients, the group who received adjuvant antiviral postoperative therapy (9 patients) presented a statistically significant higher clearance of jaundice compared with those who did not receive such treatment (89 vs. 41%).

28.7 Postoperative Complications

The most common problem after KPE is that there is no or ineffective restoration of bile flow; jaundice therefore worsens and end-stage liver disease and cirrhosis beckon. The key in these infants is to prepare the way to a safe liver transplant by strict attention to nutrition, vitamin deficiencies and fluid management. There are some specific complications, which can occur independently of this process though.

28.7.1 Cholangitis

Ascending bacterial cholangitis are relatively common and at least one episode is seen in up to 50% of most large series. The CHiLDREN consortium reviewed 219 long-term survivors and reported an incidence of cholangitis of 17% in the preceding 12 months [52]. The risk is most apparent in the first 2 years post-surgery although the reason for the diminution in risk is obscure, though it could be related to some time-dependent change in local immunologic defence within cholangioles. The key clinical features are pyrexia, worsening jaundice and a change in liver biochemistry. Following blood culture, episodes should be treated aggressively with broad-spectrum intravenous antibiotics effective against Gram–ve organisms (e.g. gentamicin, meropenem, piperacillin/tazobactam) [53].

28.7.2 Portal Hypertension and Oesophageal Varices

Abnormally raised portal venous pressure is seen at the time of KPE in about 70% of BA infants. It is caused by liver fibrosis and correlates with the age at KPE, bilirubin level and ultrasound-measured spleen size [54]. However the initial measured pressure is a poor predictor of outcome either in terms of response to KPE or more surprisingly even in those who will go on to develop varices. About 60% of children who have survived with their native liver beyond 2 years will have definite varices visible at endoscopy, and of these about 20–30% will bleed. Upper gastrointestinal varices take time to develop, and bleeding is unusual before 9 months of age and more usually occurring from 2 to 3 years. Emergency treatment of bleeding varices specifically includes the use of vasopressin or somatostatin analogues and sometimes even a Sengstaken-Blakemore tube. Most can be treated endoscopically with banding or in the very young, injection sclerotherapy [55].

Recently we proposed a new prediction score associated with good specificity and sensibility in the selection of children with clinically significant varices eligible for a screening endoscopy [56]. Some children also develop haemorrhoids and anorectal varices later during childhood [57].

28.8 Miscellaneous

Ascites is related to and caused by portal hypertension in part, but there are other contributory factors which include hypoalbuminaemia and hyponatraemia. Conventional treatment includes a low-salt diet, fluid restriction and the use of diuretics particularly spironolactone. Often seen in settings of malnutrition, consideration should be given to nasogastric feeding to try and increase calorie and protein intake.

Hepatopulmonary syndrome (HPS) may develop even in anicteric children, especially in those with BASM. The exact mechanism of HPS is still unknown, even though it may be a manifestation of preexisting congenital vascular anomaly. HPS can be diagnosed using arterial blood gas estimation with and without inspired oxygen, and typically hypoxia is worse in the standing position (platypnea). This complication is usually resistant to conventional therapy, and liver transplantation appears to be the only specific treatment.

Malignant change involving both cholangiocarcinoma and hepatocellular carcinoma (HCC) has been reported in children post-KPE [58]. It is related to the underlying cirrhosis of most of the long-term survivors. Surveillance using regular serum alpha-fetoprotein levels and ultrasound are helpful but not absolute markers of the malignant change, and suspicious nodules should be thoroughly investigated with magnetic resonance imaging (MRI) or computed tomography (CT) and biopsy.

28.9 Outcome and Results

In order to allow meaningful comparison between series, it is important to use reproducible outcome measures which accurately reflect performance and effective management of BA.

These are:

- *Clearance of jaundice* to a preset level (typically ≤20 μmol/L in Europe and < 1.5 mg/dl in North America). This is influenced by type of BA, age at surgery, the experience of the surgeon and the nature of the surgery performed. A clearance rate higher than 50% should be expected in experienced surgeons operating on infants <70 days of age.
- *Actuarial native liver survival* (end-points of death and liver transplant). This is influenced mostly by clearance of jaundice rate but also by postoperative complications and quality of medical follow-up. Obviously, increased access to transplantation and softening of the indications will reduce the native liver survival over time.
- *Actuarial true survival* (end-point death). This reflects on not only the success of the original operation but also access and safety of the transplant procedure and minimization of postoperative risk. The burden of associated anomalies, mainly cardiac, should be also considered.

Centralization of the resources has been the single most important public health measure and has changed the outcome of BA. Since 1999, the treatment of BA has been centralized to three centres in England and Wales (London, Birmingham and Leeds), and the benchmark study of outcome following this centralization has allowed publication of key national statistics. In this cohort of 424 patients who underwent KPE from 1999 to 2010, clearance of jaundice was achieved in 55%, with a 5- and 10-year native liver survival estimated in 47% and 43%, respectively [6]. Following this English experience, encouraging results were achieved in smaller countries such as Finland [59] and Denmark [60] and Switzerland [61]. The only constraint is geography such as in the relatively low population density countries such as Canada [62] and Australia [63]. Published national outcomes are given in Table 28.2. Essentially if your country is not listed, then its outcomes will be worse. The recently launched online registry "bard-online" (www.bard-online.com) might aid

Table 28.2 National outcomes in Biliary Atresia

	Period	*N*	Age at KPE, days (mean/median)	Clearance of Jaundice[a]	4- to 5-year native liver survival	4- to 5-year true survival
Centralized national series						
England and Wales [6]	1999–2009	443	54	56%	46%	90%
Finland [59]	1987–2010	72	64	75%	75%[b]	92%[b]
Decentralized national series						
France [64]	2003–2009	329	59	33–39%	33–39%	85–92%
Swiss [61]	1994–2004	48	59	39.5%	37%	91%
Netherlands [65]	1987–2008	214	59	38%	46%	73%
Canada [62]	1992–2002	230	64	n/a	39%	83%
Germany [66]	2001–2005	183	57	18%	20%	83%
Multicentre, not National						
USA [67]	1997–2000	104	54	55%	46%	89%
Italy[c]	2001–2005	59	78	51%	38%	87%
National Asia						
Japan [68]	1989–1998	1381	65	57–62%	52–62%	70–78%

[a]Clearance of jaundice variably defined
[b]Outcome at 2 years after KPE
[c]Unpublished data from Italian Survey on BA including patients from five centres (Brescia, Bergamo, Modena, Naples and Rome) (Alberti D, personal communication)
n/a: not available

in the collection of multinational data, including from countries without registries [69].

28.10 Conclusions

Origins of BA are mysterious, its diagnosis contentious, and its outcome uncertain. The future will see improvements in understanding the basis for this enigmatic disease, but it is noteworthy that all currently successful treatments have been surgical. Nowadays, long-term survival with a normal life is possible with KPE or a functioning liver transplantation for more than 90% of patients which is *incroyable* compared to the equivalent statistic of around 10% widely held as the norm in the 1970s.

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