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'Looking at the problem of biliary atresia from the vantage point of 30 years’ experience with the lesion, we can say with certainty that the jaundiced baby who has had no extrahepatic bile duct has been the most disappointing patient for the surgeon in the whole realm of lesions theoretically correctable by a surgical procedure.'

After early descriptions in the 18th and 19th centuries, surgical results were first reported in the early 20th century, and prior to the 1950s, survival of infants with biliary atresia was rare, the natural sequence being the development of cirrhosis with death from intractable liver failure.

In the 1960s, an undercredited physicist from Harvard, Thomas Kuhn, wrote his book The Structure of Scientific Revolutions wherein he introduces the world to ‘paradigms’ and ‘paradigm shifts’. Two physicians have revolutionised the management and long-term survival of infants with biliary atresia, these being Morio Kasai and Thomas Starzl. Their interventions, the Kasai portoenterostomy and liver transplantation, respectively, represent ‘paradigm shifts’ in the management of biliary atresia, converting a uniformly fatal condition to one with a survival rate in excess of 80%.

Prior to Kuhn’s 1962 book, science was considered a ‘rational endeavour in which knowledge is achieved through painstaking, day-to-day accumulation of data, facts, and minor discoveries’; Kuhn referred to this traditional approach as ‘normal science’. By comparison with Kasai and Starzl, and without minimising their exemplary contributions, perhaps the work of other researchers on the pathophysiology, advances in surgical technique, choleretics, steroids and antibiotics, are just ‘normal science’?

Whatever one feels about people’s respective contributions to this spectrum of progress, this special supplement of the South African Medical Journal will hopefully provide useful insights into this enigmatic disease – from presentation, investigation and confirmation of diagnosis; through operative technique and perioperative care; and when this ‘fails’, empowering you as the clinician to care for your patient, hopefully bridging them to liver transplantation and ongoing survival.

J A Loveland
Department of Paediatric Surgery
Chris Hans Bangwanath Academic Hospital
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand
Johannesburg
loveland@wol.co.za

Maximising Kasai portoenterostomy in the treatment of biliary atresia: Medical and surgical options

A Grieve, M Davenport

Biliary atresia (BA) remains one of the most challenging conditions in paediatric surgery. It has several possible causes, resulting in a range of different clinical scenarios. The current therapeutic approach is almost entirely surgical with an initial attempt to restore bile flow and preserve the native liver using a Kasai-type portoenterostomy. Liver transplantation (cadaveric or living donor) is usually reserved for failure or for infants presenting late with end-stage cirrhosis. The role of adjuvant medical therapy is unclear and evidence of benefit is lacking. Nonetheless, the use of post-operative steroids, prophylactic antibiotics and choleretic agents such as ursodeoxycholic acid is common. Ideally, the entire pathway should be complementary and seamless with few infants dying of end-stage liver disease or uncorrectable associated congenital malformations. Experience from high-volume centres suggests that clearance of jaundice can be achieved in 50 - 60% of infants, with 10-year native liver and real survival rates of 45% and 90%, respectively.

Ladd described his experience of operating on newborn infants with surgical jaundice at Boston Children's Hospital. Although it is unclear how many of his cases had genuine biliary atresia (BA), his results were remarkable, with 6/11 cases draining bile. Unfortunately, later reports identified most cases of BA as ‘uncorrectable’, with an inevitable dismal outcome despite many desperate surgical manoeuvres. Those surgical pioneers recognised that no matter how high the level of biliary dissection, it was not possible to identify any bile-containing structure to fashion any kind of conventional biliary anastomosis.

Kasai published his first report in the Japanese surgical journal Shujitsu in 1959. He recognised, albeit accidentally, that the apparently solid proximal biliary remnant contained microscopic biliary channels which retained a communication with the intrahepatic bile duct system. Therefore, if enough of these could be exposed in the porta hepatis and be drained into a Roux loop, then sufficient bile flow could be restored and jaundice would recede.

The results in ‘uncorrectable’ BA were greeted with scepticism in the West, and it was not until the 1970s that the procedure was taken up by institutions in the USA and western Europe. Our experience with the Kasai procedure at King’s College Hospital dates from this era. Nevertheless, what Kasai performed in the 1950s and 1960s is not necessarily what we would recognise today. His original technique, while reaching the surgical plane flush with the liver capsule, does not attempt to go beyond a fairly narrow oval within the bifurcation of the portal vein (5 mm diameter), and uses a short Roux loop (25 - 30 cm) with a relatively crude anastomosis (5/0 surgical catgut). Later, authors sought to increase the area exposed by dissecting into the Rex fossa around the umbilical point (junction with left portal vein) and around the bifurcation of the right vascular pedicle. This more extended approach leaves a denuded area approaching 20 x 10 mm, to be incorporated into a longer (40 - 50 cm) Roux loop (Fig. 1).

The only other element of the operation which changed, but was subsequently reverted to the original, was the design and configuration of the Roux loop. It became fashionable to open the loop to the skin as a stoma and then re-feed the bile back in again in an attempt to reduce the incidence of post-operative cholangitis. Other modifications with the same objective included the creation of ‘valves’ within the loop. Despite initial acceptance of theoretical benefit, neither manoeuvre has any advantage to the standard long Roux-en-Y limb. About 20% of cases have a patent common bile duct and gallbladder, leading to a mucocele, which can be used as the conduit with the transected porta hepatis (i.e. a portocholecystostomy). This abolishes the risk of cholangitis, but bile drainage is more tenuous and a much higher revision rate leads to failure. Efforts to use the appendix as a conduit have also been discarded with time.
The advent of minimally invasive surgery and laparoscopic techniques probably reached its apogee with a successful laparoscopic Kasai portoenterostomy (KPE) by a Brazilian team in 2002. Several small-series case reports followed, together with a prospective trial from Hannover, Germany. Most pioneers came to recognise that, while possible, the laparoscopic technique was sufficiently different to lead to poorer outcomes. Isolated centres in China, Japan and South America still offer this technique, but most larger centres have reverted.

What would constitute an open radical extended KPE today? The principles include a radical dissection within the porta hepatis to separate the proximal biliary remnant (and any lymphatic efferents) from the right and left portal vein and the hepatic arteries. Usually, small veins from the confluence of the portal vein are divided, exposing the caudate lobe as the posterior limit. The Rex fossa on the left side can be opened by dividing the isthmus of liver tissue connecting segments III and IV exposing the junction of umbilical vein with left portal vein. This triangular, pyramidal biliary remnant is then transected flush with the capsule, starting in the gallbladder fossa. It extends on the right side to incorporate a small triangular area between the anterior and posterior right vascular pedicle and on the left to the umbilical point. Controversy remains as to how best to expose the porta hepatis to achieve these goals. Since the 1970s, the large centres in London and Paris have advocated dislocation of the liver outside of the abdominal cavity by dividing the ligaments. Others advocate division of the left triangular ligament, extracting only the left lobe to achieve a similar objective. Others leave the liver within the peritoneal cavity, but sling the vascular pedicles to aid portal dissection.

KPE, as described here, should be associated with clearance of jaundice (to normal) in 50 - 60% of infants.

**Key variables in outcome**

BA should not be considered a single disease entity with a predictable natural history and stereotypical response to surgery. This aetiological heterogeneity is complex and our broad classification which seeks to categorise syndromic BA and cystic BA as examples of developmental diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis, with evidence of benefit. It appears to increase cholestasis, with protection of cholangiocytes and hepatocytes. A crossover trial from France assessed the effect of UDCA (25 mg/kg/day in 3 divided doses) on liver function in children more than 1 year post KPE in a discontinuation/re-introduction fashion. Sixteen children with BA all cleared their jaundice. Six months after ceasing UDCA treatment, 1 child worsened clinically with recurrence of jaundice, and all but 2 had significant worsening of their liver enzymes. On UDCA re-introduction, their biochemistry improved.

**Peri-operative regimens**

Given adequate uncomplicated surgery exposing enough ductules, the question is: can more be done to improve the chances of eventual success? Medical management and perhaps pharmacology may help in 4 potential areas.

**Bile drainage**

Change of stool colour is evident in most cases in the first week post KPE; failure is inevitable if this does not occur. While the early return and degree of bile flow is related to anatomical factors evident and only correctable at surgery, there may be a role for other choleretic agents.

The efficacy of corticosteroids, which have been used for over 30 years post KPE, remains unknown. Despite this, about 50% of infants with BA treated in the United States of America receive post-operative steroids. The problem is one of scale: BA is rare and few centres see more than 5 new cases per year. This is compounded by surgeon and disease variation, leaving only small cohorts to analyse. A meta-analysis failed to find evidence of effect. A randomised placebo-controlled trial from 2 centres in the United Kingdom retrospectively reviewed low-dose prednisolone treatment (starting at 2 mg/kg/day) in 73 infants. The study showed early biochemical benefit (reduced 1-month bilirubin), but no effect on ultimate outcome (need for transplantation, etc.). Further evidence from one of the centres using a higher dose of prednisolone (5 mg/kg/day) showed continued biochemical benefit, resulting in an increased proportion clearing jaundice (Table 1).

Ursodeoxycholic acid (UDCA) has been used in adult cholestatic diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis, with evidence of benefit. It appears to increase cholestasis, with protection of cholangiocytes and hepatocytes. A crossover trial from France assessed the effect of UDCA (25 mg/kg/day in 3 divided doses) on liver function in children more than 1 year post KPE in a discontinuation/re-introduction fashion. Sixteen children with BA all cleared their jaundice. Six months after ceasing UDCA treatment, 1 child worsened clinically with recurrence of jaundice, and all but 2 had significant worsening of their liver enzymes. On UDCA re-introduction, their biochemistry improved.

**Prevention and treatment of cholangitis**

Cholangitis may occur in children with some restoration of bile flow, typically in the first 2 years post KPE. Early use of potent intravenous (IV) antibiotics effective against gram-negative organisms remains the
agreed first-line treatment, but there is controversy about the value of any published prophylactic regimen. Some centres insert a Hickman line and administer IV antibiotic for 4 - 6 months, while others do not administer anything.3

### Limitation of hepatic fibrosis
Unlike many cholestatic conditions presenting in infancy, BA is characterised by relatively early aggressive hepatic fibrosis and, ultimately, cirrhosis that leads to life-threatening portal hypertension and the early need for transplantation.36,37 Modulation of this biological process would have immense benefit, but seems elusive and far distant. Asian centres routinely prescribe the Chinese herb Inchniko-to, claimed benefits include inhibition of apoptosis and liver fibrosis,6,38 but real evidence of benefit remains unpublished.

### Nutritional management
BA infants are nutritionally compromised with deficits in protein metabolism, low muscle and liver stores of glycogen, obvious fat malabsorption, key deficiencies in fat-soluble vitamins (D, A, K and E) and, if cirrhotic, low serum and storage levels of zinc and selenium. Medical and dietetic attendants must maximise nutritional potential and maintain normal growth and development with sub-optimal liver and bile flow. This usually involves changing to a more appropriate formula (e.g. Caprilon (Nutricia)) with higher medium triglyceride levels) and regular parenteral vitamin supplementation. Early initiation of overnight naso-gastric feeding also helps to maintain effective calorie/ protein intake, which becomes crucial in the failing liver listed for transplantation, where outcome is directly related to nutritional status.37

### Benchmark of outcomes in BA
KPE remains an important element in the strategic management of the infant with BA. In historical series, it was the only solution available. The Sendai (Japan) series reflecting Kasi's experience is a good example of surgical evolution.24 This showed 10-year survival rates of 10% for the first 63 patients treated from 1953 to 1967, 27% for 44 cases from 1968 to 1972, and 48% for 61 cases from 1973 to 1977. In addition, not all were jaundice-free, with major problems with cholestasis and portal hypertension. By comparison, in our recent experience in England and Wales, where liver transplantation is available to all regardless of status or income, overall 10-year survival was about 90% with native liver survival of 46%.39 Over 95% of those with their own livers are jaundice-free and have a good expectation of normal life. In England and Wales over the past 12 years, resources and expertise have been concentrated, which is probably the most important aspect of maximising KPE potential.

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Table 1. Single surgeon experience (2000 - 2011) with 145 infants (aged <70 days at time of KPE) with isolated BA*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Clearance of jaundice (&lt;20 μmol/l)</th>
<th>Not cleared (&gt;20 μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No steroid</td>
<td>45 (49.4)</td>
<td>46 (50.6)</td>
</tr>
<tr>
<td>Low† (starting 2 mg/kg/day)</td>
<td>11 (61.1)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>High† (starting 5 mg/kg/day)</td>
<td>24 (66.6)</td>
<td>12 (23.4)</td>
</tr>
</tbody>
</table>

KPE = Kasai portoenterostomy; BA = biliary atresia.*

---

Biliary atresia (BA), a progressive chronic cholangiopathy affecting 1/8 000 - 1/17 000 live births, is the most common cause of chronic liver disease (CLD) in children and a considerable burden for public health resources. In contrast to its complex and contentious aetiology, the natural history of BA is much better defined. Affected children begin developing life-threatening CLD complications, such as gastrointestinal bleeding and synthetic liver failure, between 6 and 12 months of age, with survival unlikely beyond 15 - 18 months.\(^2\) BA is by far the most common indication for liver transplantation (LT) in children, with reported 1- and 5-year patient survival rates of between 85% and 95% in the majority of experienced centres.\(^2,3\)

The primary LT approach for infants who present timely with BA has been discouraged.\(^1\) Centralised medical management and sequential surgical options usually provide long-term survival with good quality of life for about 95% of these children.\(^1\) However, the morbidity and mortality for these complex procedures are not insignificant and will never be completely removed, despite advances in their management. The deferral of LT has many surgical and medical advantages, including the size of the older recipients, exposure to a far broader deceased donor organ pool, completion of immunisation schedules, longer exposure with seroconversion to community infections, and better psychological preparation. Complex pathways of care must be developed to enable these children to achieve good medical progress, with minimal complications and appropriate neurological, intellectual and social development, and maximal integration into society.

**What is failed Kasai portoenterostomy?**
Kasai portoenterostomy (KPE) procedure aims to restore bile flow, which is the main prerequisite for the loss of clinical jaundice. The surgical success of KPE is conventionally defined as complete normalisation of serum bilirubin at either 6 or 12 months of age.\(^1\) Normal stool pigmentation is often seen in these children, although this could be associated with inadequate bile flow and persistent jaundice. Failure to achieve clearance of jaundice (i.e. early ‘failed’ KPE) mimics the natural history of BA and represents an early indication for LT, similar to primary LT due to a late referral or undiagnosed BA.

However, the clearance of jaundice does not necessarily equate with the absence of CLD complications (for categorisation see Table 1), although many complications overlap in clinical practice. The most common indications for considering LT in children with BA are abdominal distension secondary to synthetic function failure (ascites) and recurrent gastro-intestinal bleeding.

**Non-surgical management after KPE**
Children with partially successful KPE must be monitored 3-monthly with abdominal ultrasound to assess: (i) arterial flow (hepatic artery resistance index); (ii) the progression of splenomegaly; and (iii) the development of focal lesions. Most focal lesions are non-vascularised regenerative nodules (nodular regenerative hyperplasia) within cirrhotic livers, but about 1 - 2% of BA children develop hepatocellular carcinoma (HCC), which could also be an incidental finding at the time of LT.\(^1\) To delineate the lesion, additional axial imaging with magnetic resonance imaging (MRI) or multiphase contrast computed tomography (CT) is often required. Malignancies are not always associated with elevated alpha-fetoprotein, but 6-monthly monitoring, at least, is recommended.\(^1\) In addition to standard biochemical markers of liver function, serum levels of fat-soluble vitamins, calcium, phosphate and alkaline phosphatase should be assessed during routine clinic visits.

There is little scientific evidence for the long-term benefits of pharmacological treatment in BA. The use of steroids in the immediate post-operative period is discussed elsewhere. Choleretic medications, such as ursodeoxycholic acid (UDCA), phenobarbitone or low-dose rifampicin, are often used. Cholestyramine can be helpful for clearing jaundice in the early post-operative stages, but its interference with the
gastro-intestinal absorption of other nutrients outweighs its medium- to long-term benefits.

**Nutritional care after KPE**
The supportive role of adequate nutrition after corrective surgery for BA cannot be overemphasised.4 Children with BA become malnourished for multiple and overlapping reasons, including increased energy expenditure, poor bile-flow-related malabsorption, chronic enteropathy secondary to portal hypertension (PHT), and relative restriction in physical activity.7 Their nutritional assessment should include detailed anthropometry (mid-arm circumference, skin-fold thickness and head circumference) and height, as simple weight monitoring could be misleading due to progressive hepatosplenomegaly and fluid retention. Regular supplementation with fat-soluble vitamins (A, D, E and K) should be established. If failure of routine oral supplementation is detected due to prematurity, severe cholestasis, poor medication adherence, dark skin colour or any other reason, then more aggressive parenteral regimens with monthly intramuscular injections should be introduced. Standard and enhanced supplementation schedules practised at our centre are summarised in Table 2.

### Table 1. Indications for LT in children with BA

<table>
<thead>
<tr>
<th>Complications of PHT</th>
<th>Gastro-intestinal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent cholangitis</td>
</tr>
<tr>
<td></td>
<td>Hepatopulmonary syndrome</td>
</tr>
<tr>
<td>Failure of liver synthetic function</td>
<td>Worsening coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Intractable ascites</td>
</tr>
<tr>
<td></td>
<td>Spontaneous bacterial peritonitis</td>
</tr>
<tr>
<td>Nutritional difficulties</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td></td>
<td>Fat-soluble vitamin deficiencies</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Failing to achieve developmental milestones in infancy</td>
</tr>
<tr>
<td></td>
<td>Motor difficulties secondary to PHT</td>
</tr>
<tr>
<td></td>
<td>Delayed puberty</td>
</tr>
<tr>
<td></td>
<td>Chronic encephalopathy</td>
</tr>
<tr>
<td>Miscellaneous CLD complications</td>
<td>Intractable pruritus</td>
</tr>
<tr>
<td></td>
<td>Development of focal lesion, suspected hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Osteoarthropathy</td>
</tr>
<tr>
<td></td>
<td>Poor quality of life</td>
</tr>
</tbody>
</table>

LT = liver transplantation; BA = biliary atresia; PHT = portal hypertension; CLD = chronic liver disease.

### Table 2. Fat-soluble vitamin supplementation in chronic cholestasis

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Supplementation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>Phytomenadione</td>
<td>Injection (2 mg/0.2 ml) (can be given orally)</td>
</tr>
<tr>
<td></td>
<td>Menadione</td>
<td>Tablet (10 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infants: 1 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 5 - 10 mg/day</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Alpha-tocopheryl acetate</td>
<td>Oral (age 1 month - 18 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 - 20 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/kg/month</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Cholecalciferol (vitamin D₃)</td>
<td>Oral solution (3 000 units/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - 12 years: 10 000 - 25 000 units/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 - 18 years: 10 000 - 40 000 units/day</td>
</tr>
<tr>
<td></td>
<td>Alfacalcidol</td>
<td>Oral drops (2 µg/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;20 kg: 15 - 30 ng/kg/day; &gt;20 kg: 250 - 500 ng/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children (aged 12 - 18 years): 250 - 500 ng/kg/day</td>
</tr>
<tr>
<td></td>
<td>Ergocalciferol (vitamin D₂)</td>
<td>Intramuscular injection (300 000 units/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 000 - 60 000 units/month</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Retinol</td>
<td>Oral solution (150 000 units/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 000 units/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection (50 000 units/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 000 units/month</td>
</tr>
</tbody>
</table>
itching. The patients' families usually have no difficulty managing infusion pumps and specialised formulas at home.

Percutaneous endoscopic gastrostomy (PEG) feeding, which has a clear role in managing other forms of nutritional difficulties in childhood, is best avoided in children with CLD. Most of these children have PHT, which often becomes more significant with PEG insertion, leading to worsening of the existing PHT and often to peristomal varices and associated complications. In all forms of nutritional support, it is important to maintain a regular oral intake (no matter how small) during infancy. Failure to do so could lead to ongoing behavioural feeding difficulties, which are very resistant to management, even after successful LT.

Total parenteral nutrition (TPN) is rarely required in children with end-stage CLD secondary to BA. Presently, such patients should be listed for LT before becoming severely malnourished. TPN also aggravates jaundice and possibly increases the risk of vascular access-related infections and sepsicaemias, which could be life-threatening in end-stage CLD. Optimising nutritional status prior to LT appears to have a beneficial effect on outcome. Successful LT usually reverts the nutritional difficulties within weeks after the operation, making further supplementation unnecessary.

Symptomatic management

The most challenging cases for medical management post-KPE include children who have not completely cleared their jaundice, but do not yet qualify for LT. Common problems include nose bleeding, easy bruising, itching, tiredness and lack of concentration, with suboptimal academic achievements. Fat-soluble vitamin supplementation, including vitamin K, is all that can be arranged for the coagulopathy, with occasional additional parenteral vitamin K (10 mg) during intercurrent infections, if required. With significant splenomegaly, there is anecdotal evidence of a potential risk for rupture following direct abdominal trauma, but the real risks are difficult to quantify. We typically recommend that children with splenomegaly and platelet counts <100x10^7/L avoid contact sports. In some countries, protective shields for the spleen are recommended; however, this is not our practice.

Chronic pruritus, secondary to abnormal bile flow and retention of pruritogenic chemicals, including bile acids, usually heralds decompensation of the liver disease. This symptom is usually not as severe as in other conditions such as progressive familial intrahepatic cholestasis or Alagille syndrome. To alleviate the itching, we recommend UDCA (20 mg/kg/day) and rifampicin (up to 10 mg/kg/day), before attempting antihistamines such as alimemazine, opiates (naltrexone) or serotonin-antagonists (ondansetron). Failure to control the itching associated with BA with these medications is a definite indication for LT; further, more aggressive anti-pruritic measures are not justified.

Re-emergence of jaundice after KPE

After KPE, the remodelled biliary substitute has very little or no bile flow and retention of pruritogenic chemicals, including bile acids, usually heralds decompensation of the liver disease. This symptom is usually not as severe as in other conditions such as progressive familial intrahepatic cholestasis or Alagille syndrome. To alleviate the itching, we recommend UDCA (20 mg/kg/day) and rifampicin (up to 10 mg/kg/day), before attempting antihistamines such as alimemazine, opiates (naltrexone) or serotonin-antagonists (ondansetron). Failure to control the itching associated with BA with these medications is a definite indication for LT; further, more aggressive anti-pruritic measures are not justified.

Management of PHT

Children with BA almost inevitably develop chronic biliary disease, which often leads to PHT and associated complications. Some children may have subclinical disease with no splenomegaly, but most will have firm hepatomegaly and splenic enlargement, often mirrored by hypersplenism and pancytopenia. PHT with a syndromic form of BA (BA splenic malformation (BASM)) is more difficult to monitor clinically. These children appear to be far more prone to developing hepatopulmonary syndrome (HPS) and may be presented for LT consideration through that pathogenic scenario.

Standard measures to control PHT in children with all forms of CLD, including BA, include upper and lower gastro-intestinal endoscopy with variceal banding or sclerotherapy, when indicated. The stools of children with BA are often positive for occult blood, particularly in the first several months after initial surgery. However, any sudden drop in haemoglobin or haematocrit is an indication for endoscopy, irrespective of whether it has been associated with haematemesis, haematochezia or melaena. Some children with PHT develop anorectal varices which also occasionally require sclerotherapy. Exceptionally, additional tests such as barium contrast studies, Meckel's scintigraphy or haemolytic screening are required. Our centre does not perform elective surveillance endoscopies in children with BA due to reliable clinical follow-up based on non-invasive markers (platelet count, portal vein and hepatic artery flows, and hepatic artery resistance on Doppler ultrasound). Furthermore, there are logistical difficulties in scoping all children with BA and anecdotal evidence of triggering gastro-intestinal bleeding following endoscopic intervention. The role of propranolol in primary prevention and post-bleeding management of oesophageal varices in childhood remains controversial. Monthly infusions of slow-release octreotide could be considered for gastro-intestinal bleeding from an unidentified source, or for patients not amenable to conventional endoscopy. Shunt options, sometimes considered for non-cirrhotic forms of PHT, are contra-indicated in BA due to the possibility of developing dramatic post-operative encephalopathy. The development of abdominal distension and ascites is a harbinger of terminal hepatic decompensation. Combinations of spironolactone (up to 8 mg/kg/day), albumin infusions and sodium restriction could induce short-term recompensation, but the next...
step should be consideration for LT. It is important to rule out spontaneous bacterial peritonitis by diagnostic paracentesis and to consider antibiotic prophylaxis (ciprofloxacin or norfloxacin) until LT, if cytology suggests >300 cells/ml of aspirate. Tolvaptan, a selective vasopressin V2-receptor antagonist, is the novel oral medication which is increasingly used in hypertensive and euvolemic hyponatraemia.18

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is a rare complication of intrahepatic PHT which leads to chronic intrapulmonary vasodilatation and abnormal alveolar-arterial oxygenation.15 HPT pathogenesis is related to overproduction of vasodilators such as nitric oxide and carbon-monoxide in CLD.19 Although seen in all forms of cirrhotic CLD and in congenital vascular malformations such as Abernethy syndrome, the highest prevalence of HPS is in BA, particularly BASM.14

HPS diagnosis is made by a combination of clinical features, such as peripheral and lip cyanosis, chronic fatigue, exertional dyspnoea and clubbing, associated with arterial hypoxaemia and increased intrapulmonary shunting (usually above 6 - 8% threshold) on technetium-labelled macro-aggregated scintigraphy. Echocardiography should always be performed to exclude cardiac pathology and the development of primary pulmonary hypertension; bubble contrast echocardiography in adults is more valuable than in children to discriminate intracardiac shunting. Orthodeoxia, a drop in oxygen saturation associated with vertical posture, is characteristically present in HPS, but not in porto-pulmonary hypertension, which is much more serious, but thankfully a much less common complication of PHT in childhood.15

Children with BA must be monitored for the development of HPS as it represents a prompt indication for LT; delaying LT could considerably reduce their chances for a successful post-operative outcome. Such patients soon become oxygen-dependent and often remain so for several weeks or even months after LT. In the early transplant era, this complication was a contra-indication for surgery, but increased awareness and meticulous peri-operative and postoperative care have contributed to these children having similar risks and outcomes compared with their peers transplanted for other elective indications.

Social issues

Any chronic illness represents a dramatic burden on family life. Numerous studies suggest that disrupted family dynamics result in a significantly higher prevalence of marital problems, divorces and alcoholism.20 Many children with BA develop psychological problems, including lack of self-confidence, suboptimal academic achievements, risk behaviour, rebellion against dominieering parents, and so forth,16,21 most of which peak during adolescence. Furthermore, siblings often feel neglected due to the ongoing attention directed to the child with BA. Consideration for living-related LT can often help address some of these conflicts, but its long-term consequences remain unknown.

Preparation for liver transplantation

All children should be managed in anticipation of future LT following KPE, although it may never be required.17 They should be given routine and extended vaccines such as pneumococcus and meningococcus type C (particularly relevant to the BASM subgroup), varicella zoster (VZ) and hepatitis A and B, if not already part of the local immunisation schedule. VZ vaccine is worth emphasising, as frequent chicken pox contacts in the community after LT may warrant the repeated use of expensive VZ immunoglobulins in non-immune immunosuppressed patients. It would be interesting to see whether the routine rotavirus vaccine recently introduced in some countries would affect the prevalence of BA, as this virus has been implicated in some experimental BA models and a few geographical clusters.

In our experience, there are broadly two peak periods for consideration of LT in BA in childhood. The first is in infancy, where LT is a life-saving procedure and the living-related option with use of the left lobe segmental graft from a parent is relatively straightforward. The bonus of this early operation is the lack of active memory of the illness and the surgery for the patient. This, however, may eventually result in increased management adherence problems during adolescence. The second is the peri-pubertal period, when suboptimal liver function could lead to stunted growth, delayed puberty, and eventual full-blown decompensation of CLD. The living-related option then becomes more challenging, as these children would probably need a larger right lobe graft. However, this is usually outweighed by the advantages of deferring LT.

References


Most difficult hepatobiliary (HPB) problems in infancy and childhood result from pathological anatomical/mechanical derangements; therefore, surgery on the liver and bile ducts depends on a detailed understanding of liver structure, function and repair response to injury or disease.¹ Most importantly, the surgeon should be aware of the very diverse range of anatomical variations. Perhaps key to improving the outcome of paediatric HPB surgery is centralised management and associating this with a paediatric liver transplant programme, which adds expertise and, frequently, the added benefit of adult HPB surgical input to paediatric surgical care. This has been performed in the United Kingdom (UK) with excellent measurable benefit.²,³

Biliary atresia
Portoenterostomy

The surgery for biliary atresia (BA), initially proposed by Kasai in 1959, has seen little change, although numerous modifications have been proposed.⁴ There is now remarkable consensus over most aspects of the surgery, but less in the role of the use of steroids, prophylactic sterilisation, minimally invasive open surgery (not laparoscopy), a high starting dose, short course and early taper steroid protocols, antibiotic prophylaxis and choleretic agents and the prevention and treatment of cholangitis. With a combination of early surgery, pre-surgery gut antibiotics, choleretic agents and the prevention and treatment of injury or disease,² most importantly, the surgeon should be aware of the very diverse range of anatomical variations. Perhaps key to improved outcomes in paediatric HPB surgery is centralised management and associating this with a paediatric liver transplant programme, which adds expertise and, frequently, the added benefit of adult HPB surgical input to paediatric surgical care. This has been performed in the United Kingdom (UK) with excellent measurable benefit.²,³

Solving difficult hepatobiliary problems in children
A J W Millar

Corresponding author: A J W Millar (alastair.millar@uct.ac.za)
is best performed using super-cut curved scissors, commencing on the left lateral aspect. Bleeding from the cut surface of the portal plate should be minimal. Traction sutures placed in the caudate lobe may facilitate exposure. A complete resection of the extrahepatic biliary tree is advisable in all types of BA, except for the uncommon case in which there is a significant remnant of patent bile duct in the porta hepatis. Biliary continuity should be restored using the Roux limb, which is anastomosed to the transected tissue in the porta hepatis as a portoenterostomy with continuous or interrupted 5/0 absorbable sutures. The posterior layer of sutures should be placed well clear of the transected portal plate and the lateral and anterior layer should be placed superficially in Glisson's capsule. The operation must be completed by ensuring that the defects in the mesentery are sutured closed and the Roux limb lies appropriately without twisting. Various types of valves have been advocated (mucosal flap and intussusception valves), but there is no strong evidence for their efficacy. A drain is unnecessary. In some BA cases, operative cholangiography may show a patent lower common bile duct in continuity with the gallbladder, with the atretic process restricted to the common hepatic and hepatic ducts. Reconstruction of the biliary tract using the gallbladder (portocholecystostomy) after resection of the remnants of the bile ducts has been suggested to be effective in preventing post-operative cholangitis. However, obstructive post-operative complications are frequent with this technique and it has largely been abandoned.

**Post-operative care and long-term complications**

Antibiotics are administered intravenously (IV) in the immediate post-operative period and replaced by oral antibiotic prophylaxis after the return of bowel activity. This can be continued for the first year according to protocol. Choleretics (cholestyramine, ursodeoxycholic acid (10 mg/kg/dose twice daily) and phenobarbitone (5 mg/kg/dose nocte)) and vitamins A, D, E, and K are also prescribed for at least 1 year. Ranitidine (1 mg/kg/dose 3 times daily) is administered for gastric protection for the duration of the course of steroids. Steroids have been recommended on the basis that they may reduce scar tissue formation and improve bile flow after portoenterostomy; no controlled trials have confirmed or refuted their efficacy, although observational evidence supports their use. Dose, time of treatment initiation and duration vary widely; prospective trials are in progress to define best practice.

The best available evidence suggests that a short course of initial high-dose steroid (4 - 5 mg/kg/day) with rapid tapering is the most effective:

- Steroids (an optional 2-week course): e.g. 20 mg methylprednisolone (IV) on day 1, decreasing to 2.5 - 5 mg/day, followed by 5 mg prednisolone (oral) daily for 1 week
- Antibiotics (IV) for 5 days: gentamicin (2.5 mg/kg/dose) 3 times daily (levels needed) and amoxicillin (25 mg/kg/dose) 3 times daily
- Antibiotic prophylaxis (started on post-operative day 6): ceftazidime (12.5 mg/kg/dose) twice daily for 1 month, or ciprofloxacin (5 - 10 mg/kg/dose) twice daily (oral) with extended prophylaxis (od) dose.

Complications of portoenterostomy include: ascending bacterial cholangitis, cirrhosis, portal hypertension, metabolic and nutritional consequences of cholestasis, intrahepatic cyst formation, hepatopulmonary syndrome, pulmonary hypertension, and malignant change in the liver (rare).

**Ascending bacterial cholangitis**

This serious complication is most common in the first year following portoenterostomy. Episodes of infection occur in approximately 40 - 50% of the infants, most commonly in those who have achieved at least some degree of bile flow. The complication, characterised by worsening jaundice, fever and acholic stools, is diagnosed by blood culture, percutaneous liver biopsy or aspiration blood culture. A wide range of causative organisms may be identified, including *Escherichia coli*, *Proteus* and *Klebsiella* species, but suspected cases must be treated early and empirically with broad-spectrum antibiotics (e.g. cefazidime, amoxicillin, ciprofloxacin and gentamicin or piperacillin and amikacin), before the detailed results of investigations are available.

Several operative modifications have been made to Kasai's original portoenterostomy to reduce the incidence of cholangitis, including diversion stomas and the formation of anti-reflux valves in the limb of the Roux loop. Despite the theoretical benefits of such modifications, in practice they confer little additional benefit, and equally good results are obtained from the use of a long Roux loop.

Cholangitis may occur some years after portoenterostomy in children with otherwise good liver function. In such cases, partial obstruction of the Roux loop, perhaps secondary to an adhesion or twist in the loop, must be excluded, as this can be relieved by surgery. Percutaneous trans-hepatic cholangiography (PTC) and radionuclide hepatic imaging are essential to identifying the site of the obstruction in these cases. Prolonged antibiotic prophylaxis may be unnecessary, particularly if there is no obstruction of the Roux loop. If cholangitis recurs frequently despite these measures and with deteriorating liver function, then liver transplantation should be considered.

**Results**

Several variables have been studied to predict the effectiveness of portoenterostomy; some derived from peri-operative data, e.g. age at surgery, macroscopic appearance of the bile ducts, microscopic analysis of the resected specimen, and liver histopathology. The extent of histological abnormality (degree of fibrosis) at the time of surgery may indicate a poorer prognosis, but this finding has not been consistent. The degree of portal hypertension at the time of the procedure is correlated with a shorter time to requiring liver transplantation, reflecting liver pathophysiology in a more functional way.

Although disputed, the surgeon's experience has also been implicated as an important prognostic factor. In a personal series of patients operated on at a mean age of 52 days over a 3.5-year period (2004 - 2007), clearance of jaundice was achieved in 23/29 of patients operated on at a mean age of 52 days over a 3.5-year period (2004 - 2007), clearance of jaundice was achieved in 23/29 cases (79%). Perhaps more importantly, improved outcome has been associated with greater centre caseload (and consequently, greater experience), and better communication between major centres and peripheral units. The age at which surgery is performed is the single most widely quoted prognostic variable, although some have shown little relationship in infants aged <10 weeks. However, in infants older than 100 days at the time of portoenterostomy, uncorrected atresia of the bile ducts results in progressive intrahepatic disease and a clear detrimental effect of age on survival has been demonstrated. In summary, the post-operative volume of bile flow is probably related to the size of bile ductules at the porta hepatis, while the long-term quality of survival in those with adequate bile flow depends on the severity of secondary liver damage at the time of surgery and the incidence and severity of post-operative cholangitis.

Approximately 70 - 80% of infants show evidence of bile flow after surgery, which is adequate to ensure survival to 5 years of age in >65% of cases, reducing the need for paediatric liver transplantation. Furthermore, series from Japan, France, the USA and the UK suggest that 30 - 40% of paediatric patients survive to 10 years of age with their native liver intact following portoenterostomy, although approximately 40% have abnormal results on liver function tests. In a French series, 23% (63/212) of patients who underwent

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portointerostomy between 1968 and 1983 were alive with their native liver intact 20 years after surgery, although all but 2 had signs of cirrhosis.17

**Choledochal cysts**

Total cyst excision has been the treatment of choice for decades. A cholangiogram is performed if the anatomy of the cyst has not been defined pre-operatively with ultrasound, computed tomography or magnetic resonance cholangiopancreatography. A sample of bile should be taken for amylase, lipase and culture testing. The extrahepatic cyst must be excised completely, keeping to the relatively avascular plane just deep to the peritoneum. Distal excision should be complete down to the level of the pancreatic duct junction, which can be confirmed endoscopically using a choledochoscope or, if not available, a paediatric cystoscope in the case of fusiform cysts with pancreaticobiliary malunion. A vessel loop passed around the cyst is useful to lift it clear of the portal vein. The proximal anastomosis should ideally be at the level of the right and left hepatic duct confluence, without leaving a cuff of residual cyst. The cyst should not be excised too high in the porta hepatis, as it is easy to cut off the cyst above the entrance of the right and left hepatic ducts into the cyst. Extending the width of the anastomosis by incising along the left hepatic duct, which usually lies outside of the liver, avoids stenosis.18 Roux-en-Y biliary enteric drainage is the preferred route, as long-term bile reflux gastritis occurs in up to 25% of cases where a hepatico-duodenostomy has been performed. Minimally invasive techniques are popular in Asia where choledochal cysts are more commonly seen; the simpler hepatico-duodenostomy procedure appears to be favoured.19,20

**Foregut atresia and biliary anomalies**

These anomalies, noted with increasing frequency, include the hepatocystic duct where the common hepatic or right hepatic duct inserts into the gallbladder, choledochal cysts, stenosis and choledochocole.21

**Portal hypertension**

The meso-Rex shunt, first described by de Ville de Goyet22 using an autologous internal jugular vein graft, is now the preferred method of treatment for portal cavernoma.23 There have been several further technical innovations including use of the coronary vein, inferior mesenteric vein and spliced saphenous veins when the jugular vein is not available. Selective shunts are preferred if the Rex vein is not patent (30% of cases) and oesophageal varices are not controlled by banding or sclerotherapy. Outcomes are excellent, with long-term vein patency in nearly all cases, and good evidence of restoration of hepatic nutrition, with increased liver growth, resolution of the cavernoma and biliopathy, a reduction in spleen size, and an added bonus of improved intellectual performance.24-27

**Budd-Chiari syndrome**

This rare but devastating disease, which may be associated with a thrombophilic diathesis or anatomical web, can be managed in the early stages with trans-jugal stenting. The Senning hepato-atrial patch operation is less commonly used, but can be successful. If liver cirrhosis is established, then transplantation is indicated.20,28

**Hepatic vascular tumours and malformations**

Glucose transporter-1 (GLUT-1)-negative infantile haemangiomas may not respond to propranolol and steroids. If the infant is small and unstable due to cardiac failure, thrombocytopenia and/or jaundice, then hepatic artery ligation may be a simpler, effective and indeed less invasive intervention than embolisation. Laparoscopic occlusion of the main feeding arteries is also effective. Transplantation has been used as a last resort in a few cases.29

**Tumour surgery**

Extending the limits of hepatic resection has become a fine art.30-32 Perhaps in some cases this is a bridge too far, as ill-advised and poorly conducted extended hepatic resections may lead to early post-operative liver failure and/or the necessity for emergency liver transplantation. Also, transplantation after local recurrence following resection has a poorer outcome. Good surgical exposure is achieved by a large subcostal incision, which can be extended to the xiphisternum in the midline, and by using one of the self-retaining retractor systems. Intra-operative ultrasound can define the exact relationship between the area to be resected and the major venous anatomy. Obstructed and dilated bile ducts can be cut flush with the residual cut surface of the liver and drained with a Roux-en-Y hepaticojejunostomy.33 If the extrahepatic bile ducts are to be preserved, it is essential to ensure that arterial supply has not been compromised. Infow occlusion (Pringle) is routine and it is wise to have control of the inferior vena cava above and below the liver prior to commencing resection. Occasionally, total vascular exclusion is useful to control bleeding. Many technical aids are available for parenchymal transaction, but personal preference is for non-stick bipolar diathermy and titanium haemostatic clips. Topical haemostatic agents can help with ooze, and the Argon beam coagulator helps with haemostasis over a large cut section, but the Argon is a ‘luxury’ in my opinion. A vascular stapler for the hepatic veins is particularly useful in larger children. The key to successful resection is to mobilise the liver fully off the retrohepatic inferior vena cava and subsequently define and control the vascular inflow and the hepatic venous outflow to the sector(s) to be resected. Great care should be taken to ligate or clip the venous connections from segments 8 and 1 to avoid bleeding from the cava or under-surface of the liver. Low central venous pressure helps to minimise blood loss. Further ‘tips and tricks’: (i) taking too much liver and leaving a remnant at risk for ‘small-for-size’ syndrome can be avoided by pre-operative portal vein embolisation/ligation, allowing for growth of the proposed liver remnant prior to resection; (ii) avoid hepatic congestion by ensuring that there is no hepatic venous outflow obstruction from torsion/kinking of the residual liver remnant; and (iii) reduce inflow perfusion with somatostatin infusion, splenic artery ligation and even temporary partial porto-systemic shunting. In the post-operative period, management includes medical support for the liver with infusion of fresh-frozen plasma to maintain haemostasis and protein C levels and N-acetyl cysteine infusion as prophylaxis against metabolic liver failure. Where the hepatic veins are involved by tumour, a ‘proximal’ hepatectomy can be performed safely if sufficiently large accessory right hepatic Baer’s vein(s) are draining the residual liver into the inferior vena cava.34 Ex vivo perfusion and bench surgery have also been performed successfully for the rare benign tumour involving the cavo-hepatic confluence.


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REVIEW
Selection and work-up for liver transplantation
M Zuckermann, J A Loveland

The evaluation of the liver transplantation candidate is intended to confirm the indication for transplantation, determine the severity of disease, exclude contra-indications, optimise pre-transplantation care and candidate condition, and educate the patient and family on post-procedure expectations. This article is intended as a guide for the appropriate selection and work-up of patients for liver transplantation.

Candidate evaluation
The primary goal of evaluating patients for liver transplantation (LT) is to identify appropriate candidates and establish a pre-transplantation plan. Prospective patients must first be referred to a transplantation centre for evaluation and, if deemed suitable, for work-up, with a view to being listed for transplantation. South Africa has centres offering LT in Johannesburg and Cape Town. Typically, referred patients are evaluated by a clinician, and further evaluations and tests are performed before the patient is discussed at a multidisciplinary transplantation meeting. Initiating the referral early in the course of disease facilitates improved outcomes, by allowing earlier LT before the establishment of end-stage disease. It is also well described that patients awaiting transplantation (and their families) demonstrate better psychological adaptation when the entire spectrum of issues is approached by a multidisciplinary clinical team.1 It is not uncommon for children to exhibit behavioural problems, depression, poor social adaptation and non-compliance after transplantation, which can be moderated by early counselling after referral.2

Purpose and policy
Organ availability is the rate-limiting step regarding successful transplantation and a reduction in waiting-list mortality. This is particularly applicable in centres that do not have related living donor programmes, but rely solely on deceased donor organs. Consequently, the decision-making and selection process must be transparent, and a consistent set of evidence-based criteria must be applied to determine whether selection for transplantation is appropriate.

Indications
Borne out by our experience, approximately 50% of paediatric patients requiring LT have biliary atresia.2 However, the indications for LT fall into 5 major categories of liver disease: (i) cholestatic diseases; (ii) metabolic disorders; (iii) fulminant liver failure; (iv) auto-immune hepatitis; and (v) liver tumours.

General listing criteria
Infants and children should be listed for LT when there is evidence that hepatic decompensation has occurred, is imminent, or is inevitable based on the natural history of the disease. Clinical end-points that determine suitability for transplantation may include one or more of the following: severe cholestasis; portal hypertension with/without variceal bleeding; multiple episodes of ascending cholangitis; failure of hepatic synthetic function; malnutrition and failure to thrive; intractable ascites; encephalopathy; unacceptably poor quality of life due to liver disease; and life-threatening complications of stable liver disease, such as hepatopulmonary syndrome.

Pre-LT assessment and work-up
The first step in evaluating a potential candidate for LT is to determine the severity and prognosis of the liver disease. A subjective clinical assessment is undertaken together with an objective assessment including comprehensive laboratory and radiological evaluations. The aim of this is to: (i) identify contra-indications that would either exclude LT, require discussion on a case-by-case basis or could be optimised; (ii) identify comorbidities or psychosocial factors that reduce the expectation of successful LT; and (iii) determine the wishes of the patient and family regarding LT.1,3 This in-depth assessment determines the suitability of the patient for potential listing, allowing better allocation of resources and, ideally, optimising the survival rate of LT recipients.

Current contra-indications in children include: non-resectable extrahepatic malignancy; concomitant end-stage organ failure that cannot be corrected by combined transplantation; uncontrollable sepsis; and irreversible serious neurological damage.

Once transplantation is considered, a specially trained multidisciplinary clinical team meets with the patient and family to assess suitability for LT and to provide further counselling. The team usually includes: a hepatologist; a transplant surgeon; a cardiologist; a pulmonologist; an anaesthesiologist; transplantation co-ordinators and nursing staff; a psychiatrist and/or psychologist; a physiotherapist; a dietician; and a social worker.

The general work-up is as follows, although specific additional testing may be performed on a case-by-case basis:

• Biochemistry
  • Full blood count and grouping
  • Qualitative liver function tests, including synthetic function (albumin and international normalised ratio (INR))
  • Urea and electrolytes, with urine microscopy, culture and sensitivities
  • Alpha-fetoprotein
  • Vitamins A, E and D
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• Serology: hepatitis A, B, C, varicella, HIV, cytomegalovirus, Epstein-Barr virus, herpes simplex virus (HSV) and measles.

• Radiology
  • Chest X-ray – abdominal ultrasound (Duplex Doppler), looking specifically at: patency of portal vein with direction of flow; presence of ascites; vascular anatomy of coeliac axis, including hepatic artery resistance index; splenic size; and additional indicators of portal hypertension
  • Magnetic resonance angiography, or angiography if vascular anatomy is uncertain (to be discussed with the surgeons).

• Cardiology
  • Electrocardiogram and echocardiogram.
  • Respiratory
    • Cough swab or tracheal aspirate for acid-fast bacilli and culture
    • Oxygen saturations
    • Respiratory function tests in selected patients.

• Anthropometry
• Immunisation record
• Dental review
• Assessment of the severity of liver disease
  • Upper gastro-intestinal endoscopy (if there is evidence of variceal bleeding)
  • Liver biopsy to assess hepatic architecture
  • Calculation of paediatric hepatology score (Paediatric End-Stage Liver Disease (PELD) score – see below).

Listing of candidates
On completion of the work-up, the patient and results are considered by the candidate's selection committee for a decision regarding suitability for LT. This committee consists of the listed multidisciplinary team and may include the patient’s primary care physician. While the structure of this committee may vary substantially between centres, the process is uniform and primarily involves inductive reasoning to review suitability for LT and possible reasons for exclusion. The latter include systemic comorbidities, patients being ‘not sick enough’ or ‘too sick’ and other psychosocial barriers. There is scant information on the quality of life of paediatric LT recipients and their families. Results suggest that psychological support should be made available to both, before and after the operation. Particular attention should be paid to the partners of related living donors and the siblings of affected children to minimise secondary phenomena including marital difficulties, sibling neglect, and other psychological problems before and after LT.

The following questions are posed to the committee before listing a patient for LT:
  • Does the patient need LT as therapy for disease?
  • Have the indications and contra-indications been assessed properly?
  • What is the surgical risk?
  • Is the patient's medical condition such to allow tolerance of the procedure and post-operative course?
  • What are the chances of recurrent disease affecting graft and patient survival?

Prioritisation
The allocation criteria for a resource as scarce as a donor liver became crucial in 1999 when it was shown that waiting time – a previous listing criterion – constituted a poor predictor of pre-transplant mortality. An allocation score centred on objective parameters and based on continuous scale measuring of the severity of end-stage liver disease was required. The liver allocation system, implemented by the Organ Procurement Transplantation Network in the USA in 2002, is based primarily on the severity of liver disease, assessed by the Model for End-stage Liver Disease (MELD) for adults and PELD for paediatric patients with chronic liver disease.6,7 The system employs risk determination based on a 3-month pre-transplantation assessment, and quantifies the risk of death within the 3 months post transplantation (the higher the score, the higher the mortality). The PELD model, based on analyses of data from the Studies of Pediatric Liver Transplantation (SPLIT), has been shown retrospectively to be predictive of waiting list mortality in paediatric patients. The PELD score, derived from bilirubin, albumin, INR, growth failure and patient age when first placed on the waiting list, may be calculated with a tool available on the United Network for Organ Sharing (UNOS) website.8

This system is a step towards a more precise and accountable means of ranking patients and may contribute to reduced waiting times and pre-transplantation mortality among children with advanced liver disease – rather than allocating organs to patients who have waited longer but are more stable. The PELD score has not been proven to be a successful predictor of post-transplantation outcome, but has also not been shown to adversely affect results.7,9,10

Waiting period and pre-transplantation care
Optimising the clinical status of the child on the waiting list is essential, particularly as waiting times are becoming longer and, unfortunately, there are many more potential recipients than donors. Aggressive medical management is often required to treat the major complications of liver failure: intractable ascites; variceal bleeding; and hepatorenal syndrome. The management of malnutrition is the most important contribution of paediatric hepatologists and diabeticians to patient management. Nutrition is one of few variables, known to affect both pre- and post-transplantation outcome, that can be prevented or ameliorated. Better-nourished children have decreased mortality, a lower infection risk and fewer post-operative surgical complications.11,12

Particular attention is also paid to immunisation. If feasible, live vaccines are administered before transplantation (varicella with measles, mumps and rubella, if aged >6 months) and caregivers are given advice on completing other vaccines, such as pneumococcal and hepatitis A and B. Candidates are suspended from the transplantation waiting list for 2 weeks following vaccination with live virus vaccines.

Outcome and graft survival following LT
The overall results of paediatric LT are encouraging. UNOS reported on 9 064 children transplanted between 1997 and 2004, with 1-year patient and graft survival rates of 86% and 78% among children aged 1 – 5 years.14-15 The SPLIT registry report on 1 611 patients showed 1-year patient and graft survival rates of 88% and 82%, respectively.16 Age at diagnosis, severity of illness, and possibly the technical variants of grafts utilised (reduced-size and split grafts), may be associated with increased morbidity and decreased overall survival.17 Ng et al. reported second and third transplantation rates of 12% and 2%, respectively, 5% chronic rejection, and 6% post-transplant lymphoproliferative disease in their paediatric LT cohort.18 Although tests of graft function were preserved in 90% of 5-year survivors in the cohort, one-third of children did not have complete normalisation of liver enzymes, suggesting ongoing graft inflammation.19 Most long-term survivors of paediatric LT retain good graft function, but may have chronic medical conditions and post-
transplantation complications. LT success is determined by more than graft survival rates; ongoing management requires the involvement and commitment of healthcare providers within and beyond transplantation teams.

**Living donor liver transplantation**

Introduced in 1989, living donor liver transplantation (LDLT) has developed as an alternative to deceased donor transplantation, to overcome the critical organ shortage, particularly in Asia. Living donor transplantation in children is common practice worldwide, and achieves results comparable with those performed with deceased donor organs.24 Bilary atresia is an indication for LDLT, and caregivers frequently question the possibility of using this approach early in the course of LT work-up.

LDLT raises several ethical and technical considerations for the donor and recipient; the balance between recipient benefit and the risk of donor morbidity and mortality is central to its justification. Donor safety is of utmost concern. The primary donor selection criterion remains voluntary and informed consent, followed by extensive counselling, work-up and evaluation of donor suitability. Internationally reported donor morbidity rates range from 0% to 67%, depending on the individual definition and recognition of morbidity, which undoubtedly correlates with the experience and volumes of individual centres.25 The donor mortality rate has been estimated to be between 0.1% and 0.3%.

Graft and recipient size matching are important to achieve success outcomes. The metabolic demands of the recipient must be met, providing a sufficient graft size to meet the recipient’s needs without compromising the donor’s safety. The refinement of surgical technique, together with a greater understanding of the anatomical and physiological differences in LDLT when compared with deceased donor LT, has improved outcome.

The proven or potential benefits of LDLT include: a reduction in waiting time (thereby decreasing waiting list mortality); the selection of appropriate timing for transplantation; the superior quality of the donor liver; and significant expansion of the donor pool. Before the addition of a living donor programme to a transplantation unit, the risk-to-benefit ratio, availability of deceased donor organs, infrastructure, and recipient demands must be considered.


Paediatric living donor liver transplantation

J F Botha

Paediatric liver transplantation is a highly effective therapy for children with end-stage liver disease; 1-year survival rates currently exceed 90% and long-term survivors enjoy an almost-normal quality of life. Key to the success of paediatric liver transplantation has been the technical refinement to provide children with suitably sized grafts. Adult-to-paediatric living donor liver transplantation highlights this success and has been instrumental in decreasing waiting list mortality to less than 5%.

Liver transplantation (LT) is the definitive treatment for children with end-stage liver disease (ESLD). The greatest limitation for LT is scarcity of deceased donor organs. This is particularly critical for smaller children (weighing <10 kg). Living donor liver transplantation (LDLT) has emerged over the last 2 decades as a viable alternative option, offering children definitive treatment, reducing their mortality while on the waiting list, and providing adequate long-term graft and patient survival.1 Compared with the whole-size deceased donor graft, LDLT in children presents a greater technical challenge with a greater chance of complications. The shorter vascular pedicles, the orientation and the size mismatch between the vessels of graft and recipient can lead to multiple forms of vascular complications. Graft size can increase the technical challenge and even compromise abdominal wall closure. The presence of a cut surface can lead to bleeding and/or bile leakage, and the size of the bile duct along with its blood supply can compromise adequate biliary drainage. Here I comprehensively review paediatric LDLT and its most recent developments.

Indications
Indications for LT in children include:

- extrahepatic cholestasis, e.g. biliary atresia
- intrahepatic cholestasis, e.g. Alagille syndrome, and progressive familial intrahepatic cholestasis (PFIC) syndromes
- metabolic diseases such as Wilson's disease, alpha 1 antitrypsin deficiency, Crigler-Najjar syndrome, and other inborn errors of metabolism (tyrosinaemia, hyperoxaluria, organic acidemias)
- fulminant hepatic failure
- primary liver tumours, e.g. hepatoblastoma and hepatocellular carcinoma (HCC).

Cholestatic liver diseases
Biliary atresia is the most common indication for LT in children. Typically, most of these children will have undergone a Kasai’s procedure that has failed to establish bile flow, and transplantation is necessitated by the development of secondary biliary cirrhosis.

Metabolic diseases
The group of metabolic diseases accounts for the second most common indication for LT. The metabolic diseases are divided into those associated with structural damage to the liver (Wilson’s, alpha-1 antitrypsin) and those in which the liver is structurally normal and LT is required to replace a life-threatening enzyme deficiency (Crigler-Najjar syndrome, ornithine transcarbamylase deficiency, or hyperoxaluria type 1).

Liver tumours
Non-resectable hepatoblastoma is effectively treated with total hepatectomy and transplantation. HCC is often secondary to other metabolic conditions (e.g. tyrosinaemia) and, if contained within the liver, is also effectively treated with total hepatectomy and transplantation.

Surgery
Thomas Starzl performed the first human LT in a 2-year-old child with biliary atresia 4 decades ago. The patient died in the operating room of uncontrolled haemorrhaging. The evolution of paediatric LT has focused mainly on the refinement of its surgical techniques to counteract the critical shortage of deceased donor organs. This shortage is most profound for children, who require smaller grafts. Given the low number of paediatric donors, up to 50% of children would die while on the waiting list before receiving a transplant. To alleviate the lack of available organs for young recipients, reduced and split deceased LTs were performed in the 1980s. The development of these techniques has almost eliminated waiting list mortality for children. The scarcity of organs has been alleviated also in part by the development of LDLT programmes in various centres worldwide. Eighty per cent of the paediatric deaths caused by liver disease occur in children aged <2 years. LDLT offers several advantages over deceased donation, including: reduced time on the waiting list; procurement under optimal conditions from a healthy donor; a shorter cold ischaemia time; and elective scheduling of the operation.

Donor selection
The typical living donor is a parent or first-degree relative of compatible bloodtype and aged between 18 and 55 years. The donor undergoes thorough medical and psychological evaluation, after which detailed imaging (computed tomography or magnetic resonance imaging) is performed to evaluate the potential graft size, as well as vascular and biliary anatomy. In general, children are well served by receiving a left lateral segment graft. Donor safety is the over-riding concern and has been excellent after left lateral segmentectomy, with a usually quoted donor mortality of 0.02 – 0.05% (a risk approaching that of donating a kidney).
The first LDLT, in which segments 2 and 3 were procured from the mother and transplanted into a child with biliary atresia, was reported in 1988. The procurement usually involves removing the left lateral segment along with the left branch of the portal vein, left hepatic artery and left hepatic vein. The recipient operation is similar to that of implantation of a cadaveric split left graft; the inferior vena cava (IVC) is preserved, the left hepatic vein is anastomosed to the recipient IVC, and the left portal vein of the graft is anastomosed to the main portal vein in the recipient. The arterial anastomosis is slightly more difficult as only the left hepatic artery is available; this is usually anastomosed to the recipient common hepatic artery. The biliary reconstruction is more commonly in the form of a Roux-en-Y, due to the size mismatch and the anatomical position and orientation conferred by the size of the graft.

Biliary atresia leading to cirrhosis is by far the most common cause of ESLD in the paediatric population, accounting for over 50% of the indications for LT. The portal vein in this subset of patients is typically hypo-elastic and narrow, as a result of recurrent cholangitis and previous Kasai’s portoenterostomy. This usually means that the portal vein needs to be dissected back to the splenoportal junction and may require the use of vein grafts. The artery, however, is usually unexpectedly larger for the size of the child, making the arterial anastomosis relatively straightforward. Because children with biliary atresia have usually had prior abdominal surgery, operative blood loss and the risk of enterotomies are higher. Furthermore, there may be associated cardiac and intestinal anomalies that need to be known prior to transplantation so that the best post-operative care can be rendered.

LDLT for the paediatric recipient, especially in smaller children, has led to the development of new surgical techniques to increase the donor pool. Almost all of these techniques use the left lateral segment (segments 2 and 3) for transplantation, but even this graft could be too large for children weighing < 10 kg. Monosegment LT appears to be a satisfactory option for infants weighing < 10 kg. Either segment 2 or 3 can be transplanted with satisfactory results in very small children. LDLT has been widely debated from a societal and ethical point of view and has become an accepted procedure worldwide, especially for paediatric recipients.11,12 Donor mortality and morbidity rates are low following left lateral segment donation, and recipient survival rates are between 80% and 90% at 1 year post transplantation in experienced centres. The good survival rates following LDLT allow transplantation to take place before the onset of life-threatening complications and severe nutritional failure.

Post-operative complications

Primary non-functioning of the liver following transplantation, although rare, is a devastating complication and needs to be recognised early to allow appropriate management and re-transplantation to be offered. Similarly, hepatic artery thrombosis usually also leads to massive hepatic necrosis and allograft failure also necessitating re-transplantation.13 If identified early, arterial reconstruction can be attempted with variable results. Portal vein thrombosis usually does not result in graft loss, but needs to be corrected by thrombectomy and anastomotic revision when detected in the early post-transplant period.14 Left lateral segment grafts in particular are associated with an increased risk of problems with the hepatic venous anastomosis, and can sometimes result in acute Budd-Chiari syndrome; these may be avoided by attention to technique.

Biliary complications occur in 10 - 20% of paediatric LDLT recipients; bile leaks from the cut surface of the liver or the anastomosis are the most common. Drainage is usually required. Cat surface leaks are mostly self-limiting and can be managed conservatively while anastomotic leaks may require re-operation and anastomotic revision. Later on, anastomotic strictures can occur and are usually managed by percutaneous means and occasionally by revision of the anastomosis.

Conclusion

LDLT has been widely debated from a societal and ethical context, and has become an accepted procedure worldwide, especially for paediatric recipients. Donor mortality and morbidity rates are low following left lateral segment donation, and recipient survival rates are between 80% and 90% at 1 year post transplantation in experienced centres. The good survival rates following LDLT allow transplantation to take place before the onset of life-threatening complications and severe nutritional failure.

References


Accepted 17 September 2012.
Liver resections are widely performed in paediatric surgery. Many techniques exist to achieve vascular control, minimise bleeding and complete the parenchymal division.

Methods
Subsequent to institutional approval, a retrospective chart review was conducted of all children (aged ≤18 years) who underwent a liver resection between January 2005 and June 2012 at the two teaching hospitals served by the Department of Paediatric Surgery, University of the Witwatersrand, Johannesburg. Data pertaining to basic demographics, indications for surgery, parenchymal transection techniques, morbidity, mortality and histology were collated.

Results
During the review period, 21 liver resections were performed. Age at surgery ranged from 6 weeks to 11 years. Indications for surgery (Fig. 1) included resections for malignancy (n=18), and benign disease (n=3). Of the resections for malignancy, 9 were for hepatoblastomas, following cisplatinum and doxorubicin neoadjuvant chemotherapy. Type of resection per pathology (Fig. 2) included non-anatomical resections for contiguous disease in 4 patients with Wilms’ tumour, and anatomical resections in the remainder. Notably, all hepatoblastomas in this series occurred in the right liver. One child died after developing acute inflow occlusion of the segment 2,3 liver remnant secondary to torsion. This was recognised immediately after leaving the operating theatre, but re-exploration failed to establish adequate inflow. No bile leaks or other complications were observed.

Conclusion
Care for these patients should be multidisciplinary. High-volume units and access to liver transplantation offer optimal results. No technique is proven superior to the ‘clamp crush’ technique of parenchymal transection. Knowledge of hepatic anatomy is key to minimising morbidity, and surgeons should be familiar with and have the flexibility to use all techniques of vascular control.


Department of Paediatric Surgery, Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, Johannesburg
J A Loveland, MB BCH, FCS (SA), Cert Paed Surg
F Krog, MB ChB, MRCS (Ed)
P Beale, MB BCH, FCS (SA)

Corresponding author: J A Loveland (loveland@wol.co.za)
surgical morbidities were documented in the remaining patients. With respect to resection technique, hepatic vascular exclusion (HVE) of the liver was used in 3 cases, and selective vascular inflow control combined with hepatic venous outflow control for the remainder. Parenchymal transection was performed using a surgical blade in the 3 HVE cases, with combinations of the Cavitron Ultra Sonic Aspirator (CUSA), Harmonic Scalpel, and unipolar diathermy for the rest. No patients in our series were considered for transplantation.

Discussion
The regenerative capacity of the liver was first described in ancient times, and dates back to Greek mythology:1 Prometheus, a titan and champion of mankind, stole fire from Zeus and presented it to humans. As punishment, Zeus sentenced Prometheus to eternal torment. He was incarcerated on a rock and each day an eagle was sent to feed on his liver. Fortunately (or unfortunately!) the liver regenerated each night and the eagle returned daily, sentencing Prometheus to eternal torment.

Thankfully, the regenerative capacity of the liver forms the basis of modern hepatobiliary surgery, where in the presence of a non-cirrhotic liver, up to 80% of the liver can safely be resected, relying on this regenerative capacity of the remnant to sustain the patient’s functional requirements.1 Liver resection progress has been significant in the last few decades and pivotal to a better understanding of liver anatomy and physiology.2

Glisson gave the first accurate insights into liver anatomy in Cambridge in 1654 when, after boiling the liver to remove the parenchyma, its vascular system was infused with coloured milk and defined.3 In 1888, Rex challenged conventional division of the liver on the basis of the falciform ligament and described an avascular plane through the liver that extended from the gallbladder fossa to the inferior vena cava (IVC).4 This was supported by Cantlie in 1897.5 Wendell and Haberer were the first surgeons to undertake anatomical resections along this line, today known as the Rex-Cantlie Line, in the beginning of the 20th century.6,7 The early masters of hepatic surgery include Langenbuch, who performed the first elective liver resection in 1888, and William Keen, who described the ‘finger fracture’ technique in 1891.8 To date, no technique has been demonstrated to be superior to this ‘clamp crush’ technique.9 In 1908, Pringle described the temporary compression of the portal triad to control the inflow of blood into the liver.10 This technique is still widely used today. The description of the intrahepatic biliary duct system and vascular tree was refined by Carl-Herman Hjortsjö.11 However, in 1954, Couinaud published his seminal work describing the segmental anatomy of the liver and dividing it into the 8 segments with which we are familiar today.12 To ensure uniform anatomical descriptions of resection, the standardised International Hepato Pancreato Biliary Association (IHPBA) Brisbane 2000 terminology of liver anatomy and resections was published, and reviewed by Strasberg in 2005.13,14

The foremost tool of the modern liver surgeon remains an in-depth knowledge of the anatomy of the liver and, in particular, an awareness of the numerous deviations from normal, particularly with respect to arterial and biliary anatomy.

Concurrent with anatomical advances, anaesthesia – using ether – was introduced by Crawford W Long in the 19th century, and Joseph Lister implemented antiseptic techniques in 1867 after Louis Pasteur noted the dangers of bacteria. Implementing these principles led to major advances in the quest for safe hepatic surgery. Nevertheless, in the 1950s the peri-operative mortality after a right hepatectomy approached 50%. Fifty years later, Belghiti reported on 747 patients who had undergone liver resections during the 1990s with normal parynchema of the remnant, and a mortality rate of 1%.15 Cirrhosis, portal hypertension and steatosis remain the most important risk factors for mortality.16,17 Fortunately, these features are less common in the paediatric population compared with adults.

Previously thought to be a potentially ‘bloody’ operation, anaesthetic techniques focused on maintaining a high central venous pressure (CVP) to counteract blood loss. In reality, a ‘full’ IVC transmits these high pressures to the hepatic veins, actually contributing to more bleeding during the parenchymal transection. Presently, a low CVP approximating 5 mmHg forms the cornerstone of strategies to minimise bleeding. Surgery is divided into 2 distinct phases, pre- and post-transection. Pre-transection, a low CVP should be maintained, minimal intravenous fluids administered, and vasopressors used, if necessary. Post-transection, provided that bleeding is controlled, the patient should be returned to a euvolaemic state.18
A multidisciplinary team approach and high-volume units confer lower morbidity rates and a survival advantage, as clearly demonstrated with the management of biliary atresia.18 Vascular control is used to minimise bleeding during the parenchymal transection. Options include the Pringle manoeuvre, various combinations of inflow and outflow control, and total hepatic isolation/HVE.

The Pringle manoeuvre, where both the common hepatic artery and portal vein are controlled in the hepatoduodenal ligament, has a minimal haemodynamic effect, although the pathological liver does not tolerate it as well as a healthy liver. In this situation, intermittent occlusion is better tolerated. In the normal liver, continuous occlusion of up to 60 minutes is acceptable and 120 minutes of intermittent occlusion is tolerated. Used in isolation, the Pringle manoeuvre does not reduce venous back-bleeding and is not our technique of choice.

Hepatic arterial and portal venous inflow to the segment(s) being resected can be isolated specifically in the porta hepatitis; this is our technique of choice. Ligation of the respective hepatic artery and portal vein can be performed en masse or individually. This maintains normal inflow to the remaining liver segment, while preventing ischaemia and reducing bleeding during the parenchymal transection. This technique is combined with hepatic venous outflow control of the respective hepatic vein at its confluence with the IVC, to control back-bleeding.

Total vascular exclusion involves controlling both the supra- and infrahepatic IVC, as well as temporarily occluding both the common hepatic artery and portal vein in the porta hepatitis (Pringle manoeuvre). Sound knowledge of the hepatic vascular anatomy is mandatory, and it is important to control the direct venous branches between the retrohepatic IVC, the adrenal glands and segment 4 of the liver. It is also essential to perform a manual test clamp prior to formally applying clamps, as 10 - 15% of patients become significantly haemodynamically unstable. HVE is particularly useful in situations where the anaesthetist is unable to lower the CVP and a very high/refractory CVP persists, or where the tumour encroaches in situations where the anaesthetist is unable to lower the CVP and a very high/refractory CVP persists, or where the tumour encroaches on the IVC. The procedure should not last longer than 60 minutes. Whichever preference, the surgeon and anaesthetist must be accomplished in performing all techniques described above, and have the flexibility to use them interchangeably.

Parenchymal transection Numerous techniques and devices have been developed to transect the hepatic parenchyma, including: 'clamp crush', vascular staplers, ultrasound dissection, Hydrojet, tissue-sealing devices and radiofrequency-dissecting sealant. The surgeon should be familiar with the different techniques and devices and should tailor the approach to the different resections performed, as there is no modality proven to be superior in all situations. Randomised controlled studies have compared the different techniques of parenchymal transection, and concluded that there is no superior technique to 'clamp crush'.20,21 The latter is based on the 'finger fracture' technique and consists of a device that crushes the parenchyma, exposing the hepatic vasculature and bile ducts to allow more accurate occlusion.

Role of transplantation Transplantation may be considered if the tumour is not macroscopically resectable, in the absence of metastatic disease. Typical indications include tumours involving all 4 sectors of the liver, or where the residual volume is calculated to be less than 20%; central tumours involving the bifurcation of the main portal vein; significant involvement of the IVC; and recurrent disease after previous resection. Results of primary transplantation are far better than salvage transplantation for recurrent disease after primary resection.

Conclusion There is no doubt that caring for these patients in a multidisciplinary environment is optimal. High-volume units offer the best results and treating these patients in a surgical unit with access to liver transplantation offers a complete solution for all manners of presentation. An indepth knowledge of hepatic anatomy remains key to successful outcomes with minimal morbidity. While our unit prefers to isolate both the inflow and outflow to a specific segment of liver, surgeons should have the flexibility to use all techniques. Total hepatic isolation is recommended where the tumour is adjacent to or involves the IVC, or nestles in close proximity to the left or right portal veins.


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Endoscopic injection sclerotherapy for bleeding varices in children with intrahepatic and extrahepatic portal venous obstruction: Benefit of injection tract embolisation

V L Bandika, E A Goddard, R De Lacey, R A Brown

Background. The outcome of sclerotherapy for bleeding oesophageal varices may be influenced by injection technique. In a previous study at our institution, sclerotherapy was associated with a high re-bleeding rate and oesophageal ulceration. Embolisation of the injection tract was introduced in an attempt to reduce injection-related complications.

Methods. To determine the outcome and effectiveness of injection tract embolisation in reducing injection-related complications, we retrospectively reviewed a series of 59 children who underwent injection sclerotherapy for oesophageal varices (29 for extrahepatic portal vein obstruction (EHPVO) and 30 for intrahepatic disease) in our centre.

Results. Sclerotherapy resulted in variceal eradication in only 11.8% of the children (mean follow-up duration: 38.4 months).

Variceal eradication with sclerotherapy alone was achieved in 20.7% and 3.3% of EHPVO and intrahepatic disease patients, respectively. Injection tract embolisation was successful in reducing the number of complications and re-bleeding rates. Complications that arose included: transient pyrexia (16.7%); deep oesophageal ulcers (6.7%); stricture formation (3.3%); and re-bleeding before variceal sclerosis (23%).

Conclusion. Injection sclerotherapy did not eradicate oesophageal varices in most children. Injection tract embolisation by sclerosant was associated with fewer complications and reduced re-bleeding rates.

Progress has been made in developing newer endoscopic techniques for managing bleeding oesophageal varices which are safer, but pose challenges in terms of availability, cost and operative techniques. Endoscopic variceal band ligation is safer than sclerotherapy, but the diameter of the band applicator makes it impossible to insert the applicator into the small oesophagus of children aged <3 years. Coupled with the success and increased availability of liver transplantation (LT), the successful management of bleeding oesophageal varices in these children is required in preparation for LT or other appropriate surgery.

We aimed to assess whether the use of injection tract embolisation improves the efficacy and safety of sclerotherapy compared with the previously used direct injection method in the management of oesophageal varices where banding is not feasible. We retrospectively evaluated a series of children with bleeding oesophageal varices, treated with sclerotherapy in our centre. We analysed the outcome of endoscopic sclerotherapy performed with injection tract embolisation and its relationship to the underlying aetiology.

Methods

Between 1998 and 2007, 70 children who presented with bleeding oesophageal varices secondary to portal hypertension (41 with intrahepatic conditions and 29 with EHPVO) underwent injection sclerotherapy at Red Cross War Memorial Children’s Hospital. The patients presented with upper gastrointestinal bleeding manifested as haematemesis or malaena. Resuscitation and stabilisation using intravenous fluids, blood, platelets and fresh-frozen plasma transfusions, was performed if required. An infusion of octreotide was administered at 1 - 5 µg/kg in a 5% dextrose solution at 5 ml/hour, in decreasing doses over 4 - 5 days. If these measures failed to arrest upper gastrointestinal bleeding, emergency endoscopy was performed. Failure to arrest bleeding by sclerotherapy was managed by placement of a Sengstaken Blakemore tube (SSBT).

Once stable, patients underwent elective videoscope endoscopy under general anaesthesia. Careful endoscopic assessment of the foregut was performed to identify the site and true cause of bleeding.
Patients with non-variceal upper gastro-intestinal bleeding were excluded from analysis. The extent of oesophageal varices and the presence of gastric varices were documented; 5% ethanolamine oleate was injected as a sclerosant, usually 0.5 - 0.75 ml per injection, at multiple (up to 5) sites paravariceally – enough to produce a visible blanch with mucosal swelling. Injection tract embolisation was performed by continuation of the sclerosant injection using the terminal 0.2 ml as the needle was withdrawn. The number of injections and amount of sclerosant used were noted. Subjects were admitted to a high-care unit following sclerotherapy and monitored for adverse effects. Repeat sclerotherapy was performed at 2-weekly intervals until identified varices were eliminated. Because the recurrence of varices depends on the underlying pathogenesis, further investigations were undertaken to identify the underlying cause of portal hypertension.

Results
The study population comprised 70 children: 29 with EHPVO and 41 with intrahepatic causes of portal hypertension. Eleven children with intrahepatic disease secondary to biliary atresia were not included in the analysis of sclerotherapy details due to missing clinical data, but were included in the analysis of outcome.

Intrahepatic causes of portal hypertension included: biliary atresia (20); congenital hepatic fibrosis syndromes (3); neonatal hepatitis (1); auto-immune hepatitis (1); Alagille syndrome (1); Langerhans cell histiocytosis (1); and idiopathic cirrhosis (3). Clinico-demographic details are summarised in Table 1.

Regardless of the cause of portal hypertension, all patients had severe enough upper gastro-intestinal bleeding to necessitate a blood transfusion. Mean patient age at first sclerotherapy, presumed to coincide with the age at first episode of upper gastro-intestinal bleeding, was 3 years and 7 months.

Sclerotherapy and octreotide were effective in arresting acute variceal bleeding in 56/59 (94%) patients. SSBT insertion was used in 3 patients, and endoscopic variceal band ligation (EVBL) was performed in 4 of the older patients. No emergency definitive surgical procedure was offered.

Gastric varices were identified in 22/59 (37.3%) patients – slightly more than in the EHPVO group, but not statistically significant. Surprisingly, gastric varices were rarely found to be a cause of upper gastro-intestinal bleeding; no patient had any additional procedure to specifically address bleeding varices in the gastric region of the oesophageal gastric junction. Of interest is that the presence of gastric varices was used as an indication for selecting patients for shunt surgery in EHPVO.

Among children in the intrahepatic disease group, 53.3% had initial or first oesophageal bleeding before age 2 years, compared with 37.9% in the EHPVO group, although this difference was not statistically significant. No significant difference in the number of patients presenting with first variceal bleeding was noted within all the age categories in both groups (p>0.05). In the intrahepatic group, the distribution pattern of age at first variceal bleeding was related to the nature of the underlying disease, modification effect of therapy offered and subsequent course of the disease spectrum.

Sclerotherapy alone was successful in controlling the bleeding from oesophageal varices in 7 (11.9%) patients. However, 2 of these patients with EHPVO presented as re-bleeders after previous variceal sclerosis and were managed by additional sclerotherapy sessions.

Eighteen of 29 (62.1%) EHPVO patients were offered surgical shunts. Meso-Rex shunts were the most favoured, performed on 8

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Table 1. Clinico-demographic details of patients undergoing sclerotherapy

<table>
<thead>
<tr>
<th></th>
<th>EHPVO (N=29)</th>
<th>Intrahepatic disease (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>20:9</td>
<td>10:20</td>
</tr>
<tr>
<td>Age at first sclerotherapy (months), mean (range)</td>
<td>42.6 (9 - 112)</td>
<td>45.0 (7 - 159)</td>
</tr>
<tr>
<td>Number of sclerotherapy sessions, mean Median (range)</td>
<td>6.48</td>
<td>3.73</td>
</tr>
<tr>
<td>Number of injections to variceal sclerosis, mean Median (range)</td>
<td>25.46</td>
<td>16.70</td>
</tr>
<tr>
<td>SSBT</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Co-existent gastric varices</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

EHPVO = extrahepatic portal vein obstruction; SSBT = Sengstaken Blakemore tube.

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Table 2. Complications of the different sclerotherapy injection techniques

<table>
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<tr>
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<th>Study</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Hill and Bowie(^2) (no injection tract embolisation) (N=33) n (%)</td>
</tr>
<tr>
<td>Transient pyrexia</td>
<td>13 (39)</td>
</tr>
<tr>
<td>Deep oesophageal ulcers</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Stricture</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Re-bleeding before variceal sclerosis</td>
<td>12 (36)</td>
</tr>
<tr>
<td>Confirmed sepsis</td>
<td>-</td>
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patients, 2 of whom were post LT. Splanorenal and mesocaval shunts were offered to 6 and 4 patients, respectively.

Eleven patients underwent LT. No definitive procedure was offered to 7 patients who were awaiting donor availability or had a condition excluding them from LT at that time. Nine patients were lost to follow-up. Four deaths were reported, occurring during admission for sclerotherapy; cause of death was not directly related to sclerotherapy or its complications, but to the underlying disease.

Injection tract embolisation was associated with a lower complication rate (Table 2). A larger number of confirmed sepsis cases were reported among intrahepatic disease patients (17/30 (56.7%) compared with 9/29 (31%) EHPVO patients; p=0.067). Organisms cultured included *Escherichia coli*, *Staphylococcus epidermidis*, *Klebsiella* species and *Acinetobacter* species.

**Discussion**

The study cohort had a nearly even distribution of EHPVO and intrahepatic disease as a cause of varices, allowing us to compare modes of sclerotherapy and determine if outcome was influenced by underlying aetiology.

Early portoenterostomy and LT availability have contributed to a higher incidence of children requiring sclerotherapy for intrahepatic portal hypertension compared with the Fill and Bowie study where most patients had EHPVO.

The age of first variceal bleeding in the intrahepatic group was determined by the underlying disease process. In this study, more children with intrahepatic disease than EHPVO bled within the first 2 years of life. The reason for this is the contribution of a delayed diagnosis of biliary atresia in these children. Three patterns of intrahepatic variceal bleeding were also demonstrated: first group (0 - 24 months) – missed biliary atresia; second group (25 - 60 months) – mainly attributable to poorly functioning or failed portoenterostomy; third group (3 - 9 years) – could be explained as a critical point where intrahepatic cholangiopathy effect is maximal and overrides biliary drainage offered by portoenterostomy, and where LT should be considered in children with previously ‘successful’ portoenterostomy. In EHPVO, there was an equal distribution of patients in the first 5 years of life, suggesting an age-independent aetiology.

The results of our study do not support other reports showing sclerotherapy to be successful in both groups in eradicating oesophageal varices (i.e. controlling bleeding without a need for a definitive procedure). Injection tract embolisation with sclerosant was successful in both groups in our study. Only 3/59 (5.1%) children required SSBT placement to arrest variceal bleeding, supporting previous findings.

As in other studies, 3 - 5 sessions of sclerotherapy at 2-weekly intervals were needed to achieve variceal sclerosis. In 7 children who showed variceal eradication with sclerotherapy alone, an additional 2 sessions were required. The amount of sclerosant to cause visible blanch was 0.7 ml/injection, similar to other studies within the range of 0.5 - 1 ml/injection. The mean number of injections per session was 4.27, with a mean of 2.98 ml sclerosant administered per session.

Injection tract embolisation with sclerosant was successful in the overall reduction of complications. Hill and Bowie expressed complication rates as a one-time event which could have overestimated the true occurrence. We appreciate the difficulties in comparison due to difference in presentation of complication rates. Transient pyrexia, stricture, ulcers and re-bleeding before variceal sclerosis were less incident in our study compared with non-tract embolisation in the hospital’s previous series (Table 2). Although the authors of the comparative study attributed the high re-bleeding rates to a high rate of gastric varices, we demonstrated similar high gastric variceal rates but these varices were not implicated as a cause of bleeding. Our high re-bleeding rates might have been due to sluggish bleeding which was erroneously labelled as re-bleeding. Our observed oesophageal stricture rate of 3.3% was lower than in other studies. No statistically significant difference was noted in endoscopy-associated bloodstream infections in either group, but over 50% of patients in the intrahepatic group had sepsis compared with 37% in the EHPVO group. This could be due to a probable bias in selecting patients in the intrahepatic group. The patients with significant liver dysfunction on presentation were not offered sclerotherapy, especially if they were not eligible for LT. Furthermore, more patients in this group died from primary liver disease or were lost to follow-up. The net effect was the selection of patients with portal hypertension from intrinsic liver disease, but without a significant liver dysfunction impairing immunity.

Sclerotherapy was not associated with any mortality. However, some patients in the intrahepatic group died from the primary...
disease before definitive treatment was offered. The higher number of patients lost to follow-up in the intrahepatic group could have been due to patients in this group who were not eligible for LT, and either died at home or sought care from other health facilities.

In conclusion, a similar outcome of sclerotherapy was demonstrated in both groups in our study. Sclerotherapy alone was unsuccessful in controlling oesophageal varices in both groups. However, it was useful in managing acute variceal bleeding and should be offered as an option, particularly in the young patient where endoscopic variceal banding is not technically possible. We now routinely employ injection tract embolisation by sclerosant, which has greatly contributed to reducing sclerotherapy complications.

Acknowledgements. We acknowledge the staff of the Red Cross War Memorial Children’s Hospital for their invaluable contribution to this work.

References

Accepted 25 September 2012.
Lessons from the hepatoblastoma-familial polyposis connection

S W Moore, N Tshifularo, J J Grobbelaar

Background. Approximately one-third of hepatoblastoma (HB) patients have associated congenital abnormalities, but familial recurrence is rare, except in association with familial adenomatous polyposis (FAP). This correlation may be missed if not actively sought, with implications for long-term outcome and management.

Methods. We retrospectively investigated 3 families with an HB-familial polyposis connection, from a cohort of 113 FAP families (1989 - 2010). Data were analysed to assess clinical problem, treatment, complications and management. Long-term morbidity and functional outcome were analysed to identify management difficulties.

Results. Three FAP families (2.65%) had an HB association. In one case, undiagnosed FAP at the time of HB diagnosis was only detected 5 years later, when the mother presented with advanced colorectal carcinoma. A chromosome 5 APC gene mutation (exon 15 codon 793 C>T) was then identified. In a second case, a non-related boy presented with a stage 4 multifocal HB with lung metastases. Genetic studies identified an APC gene mutation (exon 6 codon 232 C>T). Further family investigation showed >20 related FAP patients. A third HB-FAP association was identified in a known FAP family early in the study, prior to the availability of genetic testing.

Conclusion. Although a rare association, a family history of FAP in HB patients is an important hidden connection. Genetic variation may be outside the usual FAP gene site. Identifying families with unknown HB/FAP is important due to long-term management implications and follow-up.

Hepatoblastoma (HB) is the most common primary liver cancer of childhood, accounting for up to 1% of all paediatric malignancies, particularly in the younger child. HB is associated with congenital abnormalities in approximately one-third of patients, suggesting complex genetic and/or epigenetic factors in its pathogenesis. In addition to an association with low birth weight, there are several linked genetic diseases including overgrowth syndromes such as Beckwith-Wiedemann syndrome, chromosomally linked conditions (trisomies 2, 8 and 20) and X-linked Simpson-Golabi-Behmel syndrome, type 1 glycogen storage diseases, Li-Fraumeni syndrome, familial adenomatous polyposis (FAP) and type 1 neurofibromatosis.

Familial recurrence of HB is extremely rare outside of associated adenomatous polyposis coli (APC) families and a causative relationship between HB and interstitial deletions of 5q21.3-q23.3 (the APC gene region) is well known. Consequently, offspring of FAP families have a 750 - 7 500 times higher risk of developing HB. Although 75 - 80% of FAP individuals have APC gene mutations, there is a group with non-typical de novo genetic variation. As a result, the screening of HB patients for APC gene variation in cases of childhood HB without a family HB history remains an open discussion. It appears to be important to identify these high-risk individuals and perform long-term screening to improve their management.

We aimed to investigate HB-FAP gene associations and clinical implications in a South African population.

Methods

Based on available clinical data of 2 known FAP families, a local database of 113 FAP cases (1989 - 2010) was investigated for HB associations. Data were analysed for details of clinical problem, treatment, complications and management. Long-term morbidity and functional outcome were analysed to identify management difficulties.

Results

HB was evident in the offspring of 3/113 known FAP cases (2.65%).

Case 1

A 2-year-old child re-presented after absconding half-way through a course of chemotherapy (cisplatinum and doxorubicin (PLADO)) for a stage 4 HB. Lung metastases were excised and a right hemi-hepatectomy for a localised lesion in the left lobe of the liver (Fig. 1). He has survived into adulthood (22 years) without further HB metastatic events. He presented with rectal bleeding at 14 years of age and a pedunculated adenomatous polyp was identified on colonoscopy and removed. He subsequently developed multiple rectal and colonic polyps, for which a total colectomy was performed. Recurrence of rectal polyps in his rectal stump necessitated revision of the lower rectal stump and fashioning of a pouch. Genetic studies identified an APC gene mutation (exon 6 codon 232 C>T). Further investigation of family history revealed relations to a large well-known FAP mixed-ancestry family with >20 affected patients.

Case 2

A mixed-ancestry male infant in a family without any FAP history was diagnosed with HB in the left liver lobe at 15 months of age. Following 4 courses of PLADO, he underwent a left hepatectomy with successful outcome. Six years later, the boy's 34-year-old mother was diagnosed with advanced colon carcinoma and liver metastases. At surgery, multiple colonic polyps were also noted. The mother and child's APC genes showed the same mutation (exon 15 codon 793 C>T). The patient developed multiple adenomatous polyps, and was successfully treated 15 years later by total colectomy. Two other family members with the same genetic mutation have since been identified and followed up.

Division of Paediatric Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town
S W Moore, MB ChB, FRCS (ED), MD
N Tshifularo, MB ChB, FCS (SA), FCPaed Surg (SA)
Pathology Research Laboratory and National Health Laboratory Service, Stellenbosch University, Tygerberg, Cape Town
J J Grobbelaar, MSc (Genetics)

Corresponding author: S W Moore (sww@sun.ac.za)
in segments 5, 6 and 7 of the liver following chemotherapy.

Fig. 1. Abdominal computed tomography (CT) scan showing a calcified hepatoblastoma in segments 5, 6 and 7 of the liver following chemotherapy.

Case 3
A male infant, born to a known FAP family, was diagnosed and successfully treated for HB early in the study, prior to the availability of genetic testing. The patient never developed further features of FAP and there was no familial recurrence.

Discussion
HB is a well-known embryonal tumour, with recognised genetic associations to several cancer predisposition syndromes including FAP. Family histories are uncommon in these, with the exception of familial FAP,1 as shown in this study. The incidence of FAP in association with HB, identified in 3/113 FAP families (2.65%), was lower than a previous report of 8/93 (8.6%) HB families.12

There are several lessons from this study. Firstly, although the genetic links between HB and FAP are well established, it is a reminder to clinicians of this rare, possibly hidden link. Secondly, the clinical identification of associated FAP in our first case benefitted the patient and led to the identification of a whole family at high risk of cancer. Thirdly, from the second case, a full history in patients with HB should include a family history of HB. A timely genetic analysis for FAP in the child with HB would have benefited the mother who developed a more important link than previously thought in understanding the basis of the site of APC mutation has proven difficult, as no significant correlation between the site of mutation detected in those with or without HB has been demonstrated.13 The nature of the HB-associated APC mutations, however, appears variable, as shown in 2 families in this study where the APC mutation sites lay outside the loss-of-heterozygosity (LOH)-associated region for colorectal FAP (i.e. codons 1285 - 1 378),14,15 in keeping with previous reports.1,15

From a molecular perspective, these genetic associations may be a more important link than previously thought in understanding the oncogenesis of liver tumours such as HB. Chromosomal variations occur frequently in HB, having been reported in up to 88% of cases in a genome profiling study.16 The most likely candidate genes identified thus far are CTNNB1 (catenin, beta-1-catenin)17 and insulin-like growth factor II (IGF2) tumour suppressor at locus 11p15.18 In addition, more than 85% of HBs show accumulation of β-catenin which indicates an activated Wingless-type (Wnt) pathway.19 Beta-catenin mutations that play a key role in liver development, regeneration and oncogenesis, are found in 50 - 90% of HB tumours.20 However, multiple deletion or point mutations frequent in chromosomes 1q, 2 (or 2q), 8, 17q, and 20 have been described in HB, as well as losses in chromosomes 4q and 11q, and high-grade amplifications at 7q34, 14q11.2, and 11q22.2.21 The HB-related Beckwith-Wiedemann syndrome is also associated with the dysregulation and LOH of imprinted genes at chromosome 11p15.5.22 This subgroup is of considerable interest due to the location of the IGF2 and H19 genes within this region,23 indicating complex genetic/epigenetic associations of the imprinted 11p15 region in the pathogenesis of HB and other related tumours.24,25

The link to FAP is important because of the high risk of developing HB in families with germline APC gene abnormalities. This risk is 750 - 5 000 times higher than in the general population,26,27 as well as the risk of other tumours occurring in familial cancer genes. The question as to whether specific APC gene mutations are more likely to be associated with HB remains open. In both cases tested genetically in this series, the APC gene mutation lay outside the usual FAP site on chromosome 5 (viz. family 1, part of a 20-strong known FAP ancestry: exon 6 codon 232 C>T; family 2: exon 15 codon 793 C>T). The significance of this is unknown, but it suggests that those associated with HB may relate to other sites on the gene.

Understanding the link between FAP and HB may, therefore, be of the utmost importance to patient evaluation and follow-up. Screening for APC gene mutations in infants with HB, although difficult, facilitates genetic counselling and an estimation of risk, owing to an autosomal dominant hereditary pattern.28 We agree that the presence of HB-risk APC mutations justifies HB screening in neonates born to gene carriers.29

References

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Biliary atresia (BA) is a neonatal cholestatic jaundice which results from obstruction of the extrahepatic biliary system due to destructive inflammation of unknown aetiology. It occurs in 1/5 - 1/8 000 live births in Asia and 1/18 - 1/20 000 children in Europe. Apart from this difference in incidence, no ethnic differences have been demonstrated. However, females appear to carry a slightly higher BA risk. BA affects variable lengths of the extrahepatic system and, if untreated, most patients die of biliary cirrhosis before their second birthday due to liver failure. Recognised subtypes include an embryonic form (BA splenic malformation (BASM)) associated with other congenital anomalies, as well as at least 3 other subtypes (isolated BA, a cystic variety; and cytomegalovirus (CMV)-IgM-positive BA). If treated timeously by surgical drainage (Kasai procedure), approximately 40 - 55% of affected children can clear their jaundice to normal values and expect at least a 5-year native liver survival. BA is the leading cause of end-stage liver disease in children, leading to significant mortality and morbidity; therefore, research into potential causes would improve results, and possibly prevention.

The aetiology of BA is unknown, but it is generally agreed to be attributed to multifactorial prenatal and perinatal insults to the developing biliary tree. Research points towards a viral-initiating factor in predisposed individuals, which initiates an antigen-antibody reaction that causes inflammatory targeting of the extrahepatic (and possibly intrahepatic) bile ducts. This mechanism is of particular interest in patients with impaired immunity (e.g. HIV-infected).

CMV is related to biliary disease in infants, being cholestatic in its own right, and has been implicated in intrahepatic bile destruction and duct paucity, as a potential causative factor. Patients with IgM-CMV-positivity appear to suffer progressive liver damage, suggesting that the virus may promote ongoing sclerosis in the biliary tree, consequently affecting outcome.

We aimed: (i) to detect CMV infection rates and baseline characteristics of infants with BA over 10 years (2001 - 2011); and (ii) to investigate the effect of perinatal CMV infection in BA and compare the outcomes of CMV-IgM-positive children with non-exposed children with cholestatic jaundice.

**Methods**

We performed a retrospective review of hospital records of patients with cholestatic jaundice, referred to the Paediatric Surgical Unit of Tygerberg Hospital from 2001 to 2011 (Table 1). Data were anonymously collated and stored in a Microsoft Excel database. Patients were categorised into 2 groups: those with and those without BA (non-BA), and were compared in terms of CMV infection. CMV testing results were derived from laboratory results or patient records. Fisher's exact and/or chi-squared statistical tests for significance were performed where necessary.

**Table 1. Causes of cholestatic jaundice in a cohort of 74 patients**

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>39 (27 evaluable)</td>
</tr>
<tr>
<td>Non-biliary atresia</td>
<td>34 (31 evaluable)</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>10</td>
</tr>
<tr>
<td>Choleodochal cyst</td>
<td>9</td>
</tr>
<tr>
<td>Viral enterocolitis</td>
<td>5</td>
</tr>
<tr>
<td>HIV hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>Gallstones</td>
<td>1</td>
</tr>
<tr>
<td>Auto-immune</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2</td>
</tr>
</tbody>
</table>
applicable. A p-value <0.05 was regarded as statistically significant. Ethical approval of the study was granted (S12/02/061) by the ethics review committee of Stellenbosch University. Research was conducted according to guidelines outlined in the Declaration of Helsinki. Patient anonymity and confidentiality were protected.

Results
Of the 74 patients investigated, 39 (52%) had BA and 35 had other causes of surgical hepatobiliary disease (Table 1); 27 (69%) BA patients and 31 (89%) non-BA patients were reviewed following the exclusion of 12 BA patients and 4 non-BA patients due to lack of sufficient data. Twenty-one (78%) BA patients had CMV positivity (IgM/IgG) on testing; 20 were IgM-positive, whereas 8 non-BA cholestatic jaundiced patients were IgM-positive (p<0.01). Two (7.5%) of 27 BA infants were HIV-exposed (born to HIV-positive mothers), whereas 7 (35%) of the non-BA group were HIV-positive (p<0.01). Both HIV-exposed BA infants were CMV-IgM-positive. Long-term outcomes of the 21 CMV-positive BA patients (non-HIV exposed) included 3 deaths and a higher rate of severe early liver damage, suggesting a poorer outcome in CMV-affected patients.

Discussion
The surgical causes of prolonged neonatal jaundice include BA, hypoplasia of bile ducts, inspissated bile ducts, choledochal cysts and spontaneous biliary duct perforation. BA remains the most common neonatal cholestatic disorder and is characterised histologically by complete obliteration of the lumen of all, or part, of the extrahepatic biliary tree.

Although the cause of BA is unknown and many theories as to its aetiology exist, it is generally agreed that it is attributed to multifactorial pre- and postnatal insults to the developing biliary tree.1,7,10,11 Current aetiology theories include viral infections, including human CMV; immune dysregulation; auto-immune mechanisms; vascular lesions; defective morphogenesis (including inherited mutations of laterality genes, somatic mutations, and modifier genes); and toxin exposure.4 A study showing a seasonal clustering of children presenting with BA supports an infective aetiological factor.4 Although multiple factors are involved in the targeting of the developing biliary tree, the correlation between viral infections and BA suggests the possibility that the viral infection initiates an inflammatory auto-immune process which results in the ductal sclerosis seen in the condition.11 Current information suggests that this is based on antibody-mediated inflammation (probably virally induced) which leads to progressive biliary sclerosis.4

Histological observations in the porta hepatis and liver samples of children with BA provide further support of a possible link between BA and a viral infection.9 Viruses currently identified as potential aetiologic agents include CMV, reovirus, and herpes simplex virus, among others.12 Although there appears to be a correlation between CMV infection and BA, the significance must still be determined due to the small cohort studied thus far.6,5,7,9,11,12

Human CMV infection is a strong candidate, being cholestatic in its own right.9,10 It has also been associated with intrahepatic bile duct destruction and ductal paucity, indicating a possible role in the pathogenesis and progression of extrahepatic BA.12 In addition, when related to BA, CMV-IgM-positive patients appear to have greater liver damage, consequently affecting outcome deleteriously.7,8,9,10

Although no unequivocal link has been established between BA and CMV infection, there appears to be a fairly strong correlation between the two, as demonstrated by our study. CMV is a slow replicating virus from the herpes family, infecting only as many as 1% of all neonates in developed countries, but demonstrating up to 90% IgG-positivity in developing countries.9 Only 5 - 10% of infected infants have typical CMV inclusion disease with symptoms of hepatosplenomegaly, jaundice and petechiae; a further 5% having subclinical disease. Consequently, the vast majority of exposed babies are asymptomatic. The South African population has a high background CMV infection rate in pregnant women (M Anderson, personal communication); in this context, it is therefore difficult to determine when CMV infection is the unequivocal cause of BA. Nevertheless, there appears to be a connection to BA in countries with low CMV community prevalence.2

A principal difficulty in making the connection between these entities is that no single test is 100% sensitive and/or specific for CMV infection.1,9,13,14 Serology, CMV quantitative polymerase chain reaction (qPCR), immunohistochemistry and histology have been unable to confirm a possible role of CMV in BA aetiology. De Tomasso et al.9 describe a low accuracy of serological tests for detecting active CMV infection, with no correlation between the CMV-positive qPCR and histopathological changes reported by others.1,3,11 Our study, however, reinforces a probable correlation.

Some information suggests a worse outcome in CMV-affected patients.6 Hill et al.14 have shown a connection to CMV Th1 and Th17 cell infiltrates which affects BA prognosis. This raises the possibility that CMV infection might not only be a causative factor, but may promote ongoing biliary tree sclerosis.1,6,10

The presence of co-morbidities such as HIV raises interesting possibilities in the antigen-antibody hypothesis of BA aetiology. This is of particular interest in areas of high HIV prevalence, such as sub-Saharan Africa, and is probably explained by the fact that some non-BA patients with neonatal hepatitis on biopsy were subsequently shown to be HIV-related. Our results, however, demonstrate that HIV exposure did not preclude the occurrence of BA in at least 2 cases. Recent evidence indicates that an interaction between HIV infection and other environmental factors such as CMV co-infection accelerates immune system deterioration.10 On the other hand, should an antigen-antibody be important in the aetiology of BA, impaired immunity, such as HIV, may influence BA type and/or outcome. As such, this connection warrants further study.

Conclusion
Our results suggest a correlation between CMV exposure, infection and surgical hepatobiliary disease, including an effect on BA outcome. HIV positivity does not preclude BA; a relationship that requires further investigation.

References

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