REVIEW

Medical management of 'failing' Kasai portoenterostomy

N Hadzic

The only effective treatment for 'failing' Kasai portoenterostomy is liver transplantation (LT). However, to maximise a patient's chances to achieve the proclaimed >95% survival with sequential surgical management, medical follow-up and treatment must be planned carefully. This includes routine fat-soluble vitamin supplementation with choleretics, aggressive nutritional support, regular ultrasonography, optimal general paediatric care, and psychological support for the family once complications arise. Careful timing of LT is of critical importance, although recent trends include earlier consideration of LT in children with biliary atresia. This management can only be offered through centralised, specialised national services. Due to its ramifications in paediatric surgery, dietetics, metabolic, social, adolescent and transplantation medicine, paediatric hepatology is a fine example of patient care that is genuinely multidisciplinary.

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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.[1] 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 gastro-intestinal bleeding and synthetic liver failure, between 6 and 12 months of age, with survival unlikely beyond 15 - 18 months.[1,2] 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.[3] Centralised medical management and sequential surgical options usually provide long-term survival with good quality of life for about 95% of these children.[4] 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.

Professor Nedim Hadzic has been a leading paediatric hepatologist in arguably the world's busiest Paediatric Liver Unit, at King's College, London, UK, since 1994. He trained at the University Children's Hospital in Sarajevo, Bosnia-Herzegovina, and the Institute of Child Health/Great Ormond Street Hospital, London. His research interests include biliary atresia, alpha-1-antitrypsin deficiency, liver involvement in primary immunodeficiencies and haematopoietic stem cell transplantation, auto-immune liver disease and liver transplantation. His publication record includes more than 130 articles in international journals and 12 book chapters. He is frequently invited to lecture nationally and internationally. In 2012 he was awarded a personal Chair in Paediatric Hepatology at King's College Medical School, University of London.

Corresponding author: *N Hadzic (nedim.hadzic@kcl.ac.uk)*

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.[5] 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.[5] 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

Table 1. Indications for LT in children with BA

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

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

Table 2. Fat-soluble vitamin supplementation in chronic cholestasis

Vitamin	Supplementation	Dose
Vitamin K	Phytomenadione	Injection (2 mg/0.2 ml) (can be given orally)
	Menadiol	Tablet (10 mg) Infants: 1 mg/day Children: 5 - 10 mg/day
Vitamin E	Alpha-tocopheryl acetate	Oral (age 1 month - 18 years) 2 - 20 mg/kg/day Intramuscular 10 mg/kg/month
Vitamin D	Cholecalciferol (vitamin D_3)	Oral solution (3 000 units/ml) 1 - 12 years: 10 000 - 25 000 units/day 12 - 18 years: 10 000 - 40 000 units/day
	Alfacalcidol	Oral drops (2 µg/ml): >20 kg: 15 - 30 ng/kg/day; > 20 kg: 250 - 500 ng/day Children (aged 12 - 18 years): 250 - 500 ng/day
	Ergocalciferol (vitamin D_2)	Intramuscular injection (300 000 units/ml) 30 000 - 60 000 units/month
Vitamin A	Retinol	Oral solution (150 000 units/ml) 5 000 units/day Injection (50 000 units/ml) 50 000 units/month

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.[6] 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.

Nutritional interventions include special medium-chain triglyceride-based milk formulas, which do not require bile salts for effective intestinal absorption. These formulas are often constituted in more concentrated, smaller volumes to counteract the mechanical effects of PHT in these children. The next step in nutritional management is naso-gastric feeding (either partial at the end of each feed or continuous overnight). The effects are often dramatic on nutritional condition, neurological development and the number of infections, and occasionally on symptoms such as jaundice and

itching.[8,9] 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 infectious complications and septicaemias, which could be life-threatening in end-stage CLD. Optimising nutritional status prior to LT appears to have a beneficial effect on outcome.[4] Successful LT usually reverts the nutritional difficulties within weeks after the operation, making further supplementation unnecessary.[9]

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 experience 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 $<100x10^9$/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, opiate- (naltrexone) or serotonin-antagonists (ondansetron).[10] 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 peristalsis, which is a physiological deterrent for microbial invasion of the biliary system. The bile is sterile under normal circumstances. The most common infectious complication in children with BA is ascending cholangitis (AC), which is often caused by intestinal micro-organisms.[11] This clinical syndrome has no firmly defined diagnostic criteria and is probably over-diagnosed. Clinically, affected children develop sudden fevers (up to 39 - 40°C), with jaundice, pale stools and darker urine. The latter is variable and could be related to dehydration.

AC typically occurs in children who have practically cleared jaundice; those with poor bile flow usually develop different, more dramatic CLD complications. The additional inflammation of the biliary system could worsen chronic post-KPE histological changes in the liver.[11] To minimise the added damage, standard recommendations include the aggressive use of intravenous antibiotics in all children after KPE who develop pyrexia that is unresponsive to paracetamol for longer than 24 hours. Blood cultures are usually negative, but treatment should be given for at least 48 hours after the fever has subsided. AC can be recurrent and occasionally necessitates liver tissue culture and prolonged rotating courses of broad-spectrum antibiotics with good biliary excretion and minimal hepatotoxicity (e.g. ciprofloxacin, co-amoxiclav, co-trimoxazole or cephalosporins). Failure to control AC episodes may indicate a deep-seated chronic biliary infection and represent a *bona fide* indication for LT.

Occasionally, children with BA develop sudden jaundice with no systemic symptoms. In such children, ultrasonography plays a limited role and hepatobiliary scintigraphy is indicated to assess biliary excretion and possible mechanical problems with bile flow. These children could benefit exceptionally from surgical exploration and refashioning of the Roux-en-Y loop,[12] consequently avoiding early LT. More frequently, the late-onset jaundice represents a sign of incipient hepatic decompensation and heralds urgent consideration for LT.

Management of PHT

Children with BA almost inevitably develop chronic biliary disease, which often leads to PHT and associated complications.[13] Some children may have subclinical disease with no splenomegaly, but most will have firm hepatomegaly and splenic enlargement, often mirrored by hypersplenism and pancytopenia.[13] PHT with a syndromic form of BA (BA splenic malformation (BASM)) is more difficult to monitor clinically.[14] These children appear to be far more prone to developing hepatopulmonary syndrome (HPS)[14] and may be presented for LT consideration through that pathogenic scenario.[15]

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.[16] 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.[17] 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 hypervolaemic and euvolaemic 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 tehnetium-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 post-operative 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 domineering parents, and so forth,[21,22] 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.[13] 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.

1. Hadzic N. Biliary atresia. In: Jara P, ed. Liver diseases in children. International Hepatology Updates. Barcelona: Permanyer Publications, 2009.
2. Shneider BL, Mazariegos GV. Biliary atresia: a transplant perspective. Liver Transplant 2007;13:1482-1495. [http://dx.doi.org/10.1002/lt.21303]
3. Shneider BL, Brown MB, Haber B, et al. Biliary Atresia Research Consortium. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. J Pediatr 2006;148:467-474. [http://dx.doi.org/10.1016/j.jpeds.2005.12.054]
4. Utterson EC, Shepherd RW, Sokol RJ, et al. Split Research Group. Biliary atresia: Clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. J Pediatr 2005;147:180-185. [http://dx.doi.org/10.1016/j.jpeds.2005.04.073]
5. Hadžić N, Quaglia A, Portmann B, et al. Hepatocellular carcinoma in biliary atresia: King's College Hospital experience. J Pediatr 2011;159:617-622. [http://dx.doi.org/10.1016/j.jpeds.2011.03.004]
6. Pierro A, Koletzko B, Carnielli V, et al. Resting energy expenditure is increased in infants and children with extrahepatic biliary atresia. J Pediatr Surg 1989;24:534-538.
7. Holt RI, Miell JP, Jones JS, Mieli-Vergani G, Baker AJ. Nasogastric feeding enhances nutritional status in paediatric liver disease but does not alter circulating levels of IGF-I and IGF binding proteins. Clin Endocrinol (Oxf) 2000;52:217-224.
8. DeRusso PA, Ye W, Shepherd R, et al. Biliary Atresia Research Consortium. Growth failure and outcomes in infants with biliary atresia: A report from the Biliary Atresia Research Consortium. Hepatology 2007;46:1632-1638. [http://dx.doi.org/10.1002/hep.21923]
9. Holt RI, Broide E, Buchanan CR, et al. Orthotopic liver transplantation reverses the adverse nutritional changes of end-stage liver disease in children. Am J Clin Nutr 1997;65:534-542.
10. Cynamon HA, Andres JM, Iafrate RP. Rifampin relieves pruritus in children with cholestatic liver disease. Gastroenterol 1990;98:1013-1016.
11. Ernest van Heurn LW, Saing H, Tam PK. Cholangitis after hepatic portoenterostomy for biliary atresia: A multivariate analysis of risk factors. J Pediatr 2003;142:566-571. [http://dx.doi.org/10.1067/mpd.2003.195]
12. Houben C, Phelan S, Davenport M. Late-presenting cholangitis and Roux loop obstruction after Kasai portoenterostomy for biliary atresia. J Pediatr Surg 2006;41:1159-1164. [http://dx.doi.org/10.1016/j.jpedsurg.2006.01.066]
13. Hadzic N, Tizzard S, Davenport M, Singer J, Howard ER, Mieli-Vergani G. Long term outcome of biliary atresia; is chronic liver disease inevitable? J Pediatr Gastroenterol Nutr 2003;37:430-433.
14. Davenport M, Tizzard SA, Mieli-Vergani G, Hadzic N. Biliary atresia splenic malformation syndrome: a 28 year single center experience. J Pediatr 2006;149:393-400. [http://dx.doi.org/10.1016/j.jpeds.2006.05.030]
15. Barbé T, Losay J, Grimon G, et al. Pulmonary arteriovenous shunting in children with liver disease. J Pediatr 1995;126:571-579.
16. Ling SC, Walters T, McKiernan PJ, Schwarz KB, Garcia-Tsao G, Shneider BL. Primary prophylaxis of variceal hemorrhage in children with portal hypertension: A framework for future research. J Pediatr Gastroenterol Nutr 2011;52:254-261. [http://dx.doi.org/10.1097/MPG.0b013e318205993a]
17. O'Meara M, Cicalese MP, Hadzic N, Mieli-Vergani G. Successful use of long-acting octreotide for intractable chronic gastrointestinal bleeding in children (submitted for publication).
18. Zhang J, Fallon MB. Hepatopulmonary syndrome: update on pathogenesis and clinical features. Nat Rev Gastroenterol Hepatol 2012 (in press). [http://dx.doi.org/10.1038/nrgastro.2012.123]
19. Schrier RW, Gross P, Gheorghiade M, et al. SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-2112. [http://dx.doi.org/10.1056/NEJMoa065181]
20. Alonso EM, Neighbors K, Mattson C, et al. Functional outcomes of pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2003;37:155-160.
21. Caudle SE, Katzenstein JM, Karpen SJ, McLin VA. Language and motor skills are impaired in infants with biliary atresia before transplantation. J Pediatr 2010;156:936-940. [http://dx.doi.org/10.1016/j.jpeds.2009.12.014]
22. Alonso EM, Neighbors K, Barton FB, et al. Studies of Pediatric Liver Transplant Research Group. Health-related quality of life and family function following pediatric liver transplantation. Liver Transpl 2008;14:460-468. [http://dx.doi.org/10.1002/lt.21352]

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