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REVIEW

Transitional care for patients with surgical pediatric hepatobiliary disease: Choledochal cysts and biliary atresia

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on behalf of the American Academy of Pediatrics Section on Surgery's Delivery of Surgical Care Committee

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Abstract

Choledochal cysts (CDCs) and biliary atresia (BA) are rare pediatric hepatobiliary anomalies that require surgical intervention due to increased risk of malignancy and liver failure, respectively. The underlying disease and operative procedures place patients at risk for long-term complications, which may continue to affect them into adulthood. Lack of a transitional care model in the health-care system potentiates the challenges they will face following aging out of their pediatric providers' care. We sought to elucidate the long-term complications and challenges patients with CDCs and BA face, review the current literature regarding transitioning care, and propose guidelines aiding adult providers in continued care and surveillance of these patients. A literature review was performed to assess short-term and long-term complications after surgery and the current standards for transitioning care in patients with a history of CDCs and BA. While transitional programs exist for patients with other gastrointestinal diseases, there are few that focus on CDCs or BA. Generally, authors encourage medical record transmission from pediatric to adult providers, ensuring accuracy of information and compliance with treatment plans. Patients with CDCs are at risk for developing biliary malignancies, cholangitis, and anastomotic strictures after resection. Patients with BA develop progressive liver failure, necessitating transplantation. There are no consensus guidelines regarding timing of follow up for these patients. Based on the best available evidence, we propose a schema for long-term surveillance.

Introduction

Choledochal cysts (CDCs) and biliary atresia (BA) are rare hepatobiliary anomalies presenting in childhood that require surgical intervention. The underlying disease and operative procedures these patients must undergo place them at risk for long-term complications that may continue to affect them into adulthood.

As survival for surgically correctable congenital diseases improves, focus has shifted toward long-term outcomes and transitioning care from pediatric to adult providers. In 2002, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Physicians published a treatise laying the framework for safe, comprehensive, and coordinated transitions of care to the adult setting for pediatric patients with complex medical problems.[1] The fields of pediatric cardiac surgery and neurosurgery have previously demonstrated improved outcomes for patients who undergo a structured transitional care program.[2] However, little has been written about transitioning care for pediatric general surgery patients. The Delivery of Surgical Care Committee of the American Academy of Pediatrics Section on Surgery has identified the need for developing and disseminating transition of care programs for patients with general surgical diseases as they age out of the pediatric care setting.[3]

There have been generalized guidelines proposed to help guide the transition of care for children with special health care needs.[4] Recently, reports have been published on transitioning care of patients after surgical therapy for anorectal malformation, Hirschsprung disease, and obesity.[5–7] Challenges encountered during the process include patient and parent reliance on the protective environment provided by pediatric care systems resulting in a reluctance to engage in the transition process, insurance coverage, and lack of uniformity in care. With these barriers in mind, comprehensive care plans incorporating a multidisciplinary team with assessment of multidimensional needs have been proposed.[6]

A similar assessment has not been performed for patients who have undergone repair of CDCs and BA. The lack of a transition of care model for these patients potentiates the challenges they will face as they age out of their pediatric providers' care. Therefore, we sought to elucidate the long-term complications and challenges patients with surgically significant pediatric hepatobiliary disease face, review the current literature in regard to transitioning their care to adult providers, and propose guidelines to aid their adult

providers in the continued care and surveillance needed in this patient population.

Choledochal cysts

Background. Choledochal cysts are rare congenital dilatations of various segments of the intra-hepatic and/or extrahepatic biliary tract. They affect about 1 in 100 000–150 000 live births in Western populations and up to 1 in 1000 live birth in Japan with a 3–4:1 female to male distribution.[8,9] The majority (75–85%) of CDCs are identified within the first decade of life, especially as the number diagnosed prenatally during ultrasound exams increases.[10,11] The classic presentation is the triad of jaundice, a palpable right upper quadrant mass, and abdominal pain. However, these symptoms are seen together in only about 20% of patients. Most patients typically present with one or two of the symptoms. Children have been found to present most commonly with jaundice while adults typically present with abdominal pain.[12]

Choledochal cysts are classified into five types with several subtypes based on the Todani classification (Fig. 1).[9,11] Type I cysts are the most common (50–80%) and involve cystic dilation of segments or the entire common bile duct (CBD). They predominate in the pediatric population.[12] Type II CDCs (2%) are diverticulae of the CBD with no associated dilatation of the biliary tree. Type III cysts (choledochoceles) (1.4–4.5%) are cystic dilations of the intraduodenal or intrapancreatic bile duct. Type IV CDCs (15–35%) involve dilation of multiple intra-hepatic and/or extrahepatic bile ducts. They tend to present more often in adults. Type V CDCs (20%) (Caroli's disease) involve multiple intra-hepatic cysts with associated hepatic fibrosis.[9,10]

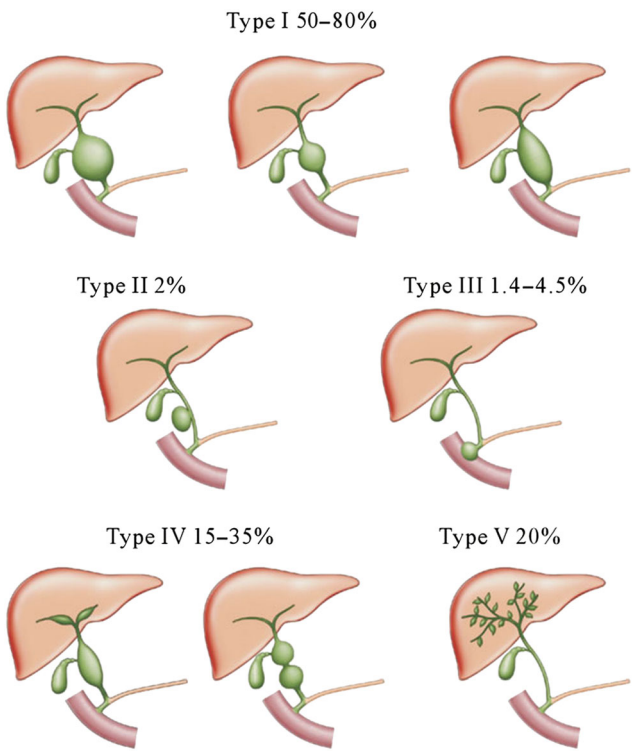

Figure 1 Todani classification of choledochal cysts.[11] Type Ia: dilation of the entire common bile duct (CBD), Ib: dilation of a segment of the CBD, Ic: fusiform dilation of the CBD. Type II: diverticulum of the CBD. Type III intraduodenal or intrapancreatic bile duct cystic dilation. Type IV: dilation of multiple intraand/or extrahepatic bile ducts (type IVa) or multiple extrahepatic bile ducts only (type IVb). Type V: multiple intra-hepatic cysts with associated hepatic fibrosis. Reprinted with permission from Open Journal of Gastroenterology. [Color figure can be viewed at wileyonlinelibrary.com]

Choledochal cysts are thought to arise due to an anomalous pancreaticobiliary junction with a long common channel, leading to reflux of pancreatic secretions into the biliary tract with resultant injury and cyst formation.[8,9] If left untreated, CDCs have a high risk of malignant transformation. The risk is low in childhood but can increase to as high as 20–40% in adulthood.[12,13] Associated malignancies include adenocarcinoma, anaplastic carcinoma, undifferentiated cancers, and squamous cell carcinoma.[9] CDC-associated cholangiocarcinoma has a very poor prognosis. Its incidence is increased in patients with CDCs and presents 10–15 years earlier than the general population.[9,11] Patients who undergo resection of CDC-associated cholangiocarcinoma have 50% survival 2 years after surgical resection, 25% survival 3 years after surgery, with no survivors 4 years postoperatively.[14,15]

In order to prevent malignant transformation, standard surgical treatment is to perform complete cyst excision with biliary diversion through hepaticoenterostomy (either through Roux-en-Y jejunal reconstruction or hepaticoduodenostomy) in uncomplicated types I and IV CDCs. Surgical therapy involves diverticulectomy or simple cyst resection for type II cysts; endoscopic sphincterotomy, sphincteroplasty with or without cyst excision, or operative marsupialization of type III cysts; and segmental resection *versus* liver transplantation for type V cysts.[8,16,17] Goals of surgery include separation of the biliary and pancreatic duct systems to prevent mixing of biliary and pancreatic secretions and removal of extrahepatic pre-malignant tissue.[16,18]

Complicated CDCs may have an altered presentation and require other treatments depending upon the presentation.[19] Examples of complicated CDCs include cysts associated with acute cholangitis, spontaneous perforation, portal hypertension, hepatolithiasis, and pancreatitis. Lal and colleagues found that patients with complicated CDCs were more likely to have postoperative complications, hepatolithiasis, and require reoperation for a stricture at the hepaticojejunostomy. These patients were more likely to undergo preoperative biliary drainage and have definitive surgery several months later.[19]

Long-term postoperative complications occur between 5% and 30% of cases.[20–26] The most common complications include anastomotic stricture, bile duct stenosis, bile duct stones, intrahepatic calculus formation, cholangitis, pancreatitis, and malignant transformation of remnant cystic tissue. Formation of intrahepatic stones and cholangitis is thought to arise due to bile stasis. The incidence of pancreatitis decreases from 88% to $\leq$ 10% after CDC resection.[11] Pancreatitis and pancreatic stones are believed to be caused by remnant intrapancreatic cystic tissue and pancreatic ductal anomalies.[22] Post-operative malignant risk due to remnant cystic tissue or subclinical disease occurs in 0.7% to 6% of patients, placing them at continued increased risk of carcinoma compared with the general population.[18] Types IV and V CDCs are at especially high risk for malignant transformation due to their intrahepatic (non-resectable) components. It is recommended that

the extrahepatic bile duct be resected near the level of the pancreatobiliary junction with a wide hepaticoenterostomy at the hilum of the liver to avoid these complications.[22] Development of biliary cancer following choledochal cyst resection, cholangitis, and intrahepatic stones have been noted predominantly in types I and IV-A cysts in several studies.[12,15,22,27]

Proposed timeline: From birth to transition/transfer. Children with CDCs are typically diagnosed within the first decade of life. Providers and parents should be monitoring for short-term postoperative outcomes such as wound infection, hernia formation, anastomotic/bile leak, bowel obstruction, ileus, and perforation. These patients should continue to be followed for long-term complications such as anastomotic stricture, bile duct stenosis, bile duct stones, intrahepatic stone formation, and malignant transformation of any remnant cyst tissue. They should have follow up with their pediatric surgeon in the immediate postoperative phase for weeks to months, then on a yearly basis as needed. One should have a low threshold for re-evaluation should the patient present with abdominal pain or jaundice.

As these patients age into adulthood (around ages 18–21), their care will need to be transitioned to adult-focused providers (Table 1). Planning for the transition will need to be carried out on a case by case basis due to variability in patient complications. Unless there are suspected long-term complications, it is unlikely they will need to follow up with an adult surgeon at that point in time. During the transition process, stakeholders will need to be involved to ensure optimal care and follow up for the patient. Stakeholders include the patient's primary care provider, pediatric surgeon, and pediatric gastroenterologist. During the transition, the patient's internal medicine or family medicine physician should be given a detailed description of the patient's diagnosis, operative interventions, and long-term postoperative complication risk. This will allow them to develop a differential diagnosis specific to that patient's altered anatomy and physiology. They will likely need to establish care with an adult gastroenterologist for follow up on at least a yearly basis, especially if they have known long-term postoperative complications.

Literature review on transition of care. Unfortunately, there is currently very limited literature regarding transitional care for patients with CDCs. Elli *et al*. propose transition of care recommendations for patients with chronic liver disease, which include BA, Alagille's syndrome, Alpha-1 antitrypsin deficiency, and liver transplantation.[28] While CDCs are not included in their evaluated population, the authors' recommendations remain generalizable and can be applied to this cohort. These recommendations include beginning the transition process between ages 16 and 18 years, informing and including the patient in the transition process and coordinating combined visits between pediatric and adult providers (specifically gastroenterologists) over several visits within a 12-month period. This process will ensure a thorough transmission of information and compliance with treatment plans during the transition.

Table 1 Stakeholders list for CDCs (i.e. who should comprise the medical home for patients with CDCs transitioning to adult care providers)

Pediatric	Adult
Primary care provider (i.e. pediatrician or family medicine physician)	Primary care provider (internist or family medicine physician)
Pediatric gastroenterologist	Adult gastroenterologist
Pediatric surgeon	
Specialist for associated congenital anomalies (geneticist, cardiologist, if applicable)	

CDCs, choledochal cysts.

In regard to guidelines for continued follow up after the immediate transition period, there remains little uniformity. Several studies have followed patients after surgical excision for as long as 35 years to better evaluate postoperative complications. Ono *et al*. followed 56 children with CDCs who underwent total resection of the extrahepatic bile duct and hepaticojejunostomy for a mean of 17 (10–27) years. Although 96% of patients survived to follow up and 89% of patients were symptom-free, they found six patients with late postoperative complications including persistent dilatation of intrahepatic bile ducts, recurrent abdominal pain, repeated cholangitis, intrahepatic lithiasis, and cholangiocarcinoma. They recommend long-term surveillance, especially in those with dilatation of the intrahepatic bile ducts or biliary stones.[22] Shimamura *et al*. reported a case of intrahepatic cholangiocarcinoma developing 34 years after excision of a type IV-A CDC.[23] They endorse careful long-term follow up to detect new lesions at an early stage, especially in type IV-A patients with dilated intrahepatic bile ducts. Chijiiwa *et al*. and She *et al*. followed patients for 18 and 30 years, respectively. They also recommend long-term follow up without specific recommendations for duration and follow-up testing.[21,24]

The authors recommend continuing long-term follow up for this population due to the risk of developing complications (such as anastomotic biliary stricture) and malignant transformation in any remnant cystic tissue left behind after surgery. Consensus guidelines for follow-up frequency, laboratory testing, and surveillance imaging do not exist. Some have suggested performing yearly liver function tests (LFTs) and right upper quadrant ultrasounds.[16] Wiseman *et al*. follow their adult patients post-resection with a liver function panel every 4 months for 2 years, then every 6 months for 5 years. They also use annual ultrasound for 5 years as surveillance in their adult patients postoperatively.[26] Nishayama *et al*. recommend lifelong semiannual follow up with computed tomography (CT) scans and CA 19-9 levels in high risk patients, such as patients with postoperative dilated biliary ducts, intrahepatic biliary stones, and anastomotic strictures.[27] They recommend annual ultrasounds for low risk patients who do not demonstrate any high-risk features.

Based on our review of the current literature, the authors recommend the following surveillance plan for adults who had CDC excision as children without any risk factors: annual ultrasounds and hepatic function panel (with fractionated bilirubin and alkaline phosphatase) and γ-glutamyltransferase (GGT) levels. These patients include children who underwent resection of type I CDCs with complete resection of the cyst leaving no known residual anatomic abnormalities and patients with type II CDCs who had cyst excision. Patients with type III CDCs, which

have also been noted to have a low risk of malignant transformation, may also be monitored annually.[17] Types IV and V cysts require closer surveillance. They have a higher risk of having remnant cystic tissue, especially types IVa and V cysts due to their intrahepatic components, leading to increased risk of malignant transformation. These patients should be followed by a gastroenterologist with consideration for surveillance every 6–12 months with ultrasound, hepatic function panel, GGT, and CA 19-9 levels. Elevation in these levels would suggest an obstructed biliary system that should warrant further work-up. In addition, should an abnormality be found on ultrasound, such as biliary ductal dilatation or a mass, cross-sectional imaging with CT or magnetic resonance imaging scans can be used to better define biliary anatomy. Those with known dilated biliary ducts, intrahepatic biliary stones, or anastomotic strictures should have surveillance every 6–12 months with imaging (US with consideration for cross-sectional imaging [CT or magnetic resonance imaging]), LFTs, GGT, and CA 19-9 levels. This is particularly important for types I and IV cysts following wide resection of the extrahepatic biliary tree and hepaticoenterostomy (either hepaticojejunostomy or hepaticoduodenostomy). These patients have the highest risk for anastomosis-related complications that may lead to strictures or obstruction of the biliary system. A low threshold should prompt further evaluation should these patients present with abdominal pain, jaundice, or elevated LFTs. Surveillance should begin no later than 15 years post-excision and will be lifelong as the risk of developing cholangiocarcinoma increases with age.[24] It should be noted that the efficacy of screening for malignancy is unknown at present (Table 2).

Future research directions. Current research has compared reconstructive techniques (hepaticojejunostomy *vs* hepaticoduodenostomy) after CDC excision.[29–32] Historically, reconstruction with hepaticoduodenostomy was thought to lead to increased rates postoperative complications, gastritis and gastric cancer (presumably from bile reflux), and biliary cancers.[18] Therefore, wide hepaticojejunostomy was the preferred reconstructive method. More recently, there has been a trend, particularly in regions of the world with a higher incidence of CDCs, to utilize minimally invasive techniques. Hepaticoduodenostomy is easier to perform laparoscopically. Consequently, there is a resurgence in this technique.

Research has also focused on outcomes after laparoscopic-assisted CDC excision. Shen *et al*. performed a meta-analysis comparing laparoscopic *versus* open cyst excision with Roux-en-Y hepaticojejunostomy.[33] They found longer operative time but less blood loss and shorter hospital stay compared with open surgery. They conclude that laparoscopic surgery is a feasible, safe choice for CDC excision. Ng *et al*. reported no complications in their laparoscopic group compared with cases of pancreatitis, cholangitis, and hypertrophic scarring seen postoperatively in their patients who underwent open surgery at 35-months follow up.[34]

As noted earlier, laparoscopic hepaticoduodenostomy is being espoused by some minimally invasive surgeons as a safe option. Yeung *et al*. evaluated short-term outcomes between laparoscopic hepaticojejunostomy and hepaticoduodenostomy in their review of 31 patients.[35] They saw better outcomes in the patients that had hepaticoduodenostomy for their biliary reconstruction with no postoperative events of cholangitis or reoperation compared with 5% developing cholangitis and 25% undergoing reoperation after hepaticojejunostomy.

Table 2 Choledochal cyst data sheet for parents and providers

Choledochal cysts data sheet
- Definition:
  - Choledochal cysts (CDCs) are rare congenital dilatations of various segments of the intra-hepatic and extrahepatic biliary tract
- Epidemiology:
  - They affect 1 in 100 000–150 000 live births in Western populations and up to 1 in 1000 live births in Japan. The female to male distribution is 3–4:1
  - Majority are identified within the first decade of life.
- Clinical presentation:
  - Right upper quadrant mass, abdominal pain, jaundice, and acholic stools
  - Nonspecific symptoms: nausea, vomiting, fever, weight loss, and pruritus
  - May be seen on prenatal ultrasound
- Risks if left untreated:
  - Cholangiocarcinoma: cancer of the bile ducts, more frequent in types I and IV cysts
  - Ascending cholangitis due to biliary obstruction, rupture, secondary biliary cirrhosis, choledocholithiasis, and pancreatitis.
- Diagnosis:
  - Abdominal ultrasound, cross sectional imaging (CT or MRI/MRCP)
- Management:
  - Surgery: complete excision with wide hepaticojejunostomy or hepaticoduodenostomy to re-establish gastrointestinal tract continuity is recommended for types I and IV. Simple cyst excision is recommended in type II. Type V cysts may need liver transplantation.
- Post-operative complications:
  - Intrahepatic biliary stones, anastomotic stricture, and cholangitis
  - Cholangiocarcinoma: although the risk is reduced by excision, it remains higher than the general populations at 0.7–6% post-excision
- Prognosis:
  - Prognosis is generally very good after CDC excision; however, 5–30% have postoperative complications that require management.
- Follow up:
  - Long-term follow up is recommended because of an increased risk for cholangiocarcinoma and anastomotic biliary stricture. Efficacy for screening is unknown at present.
  - Low risks patients: those with cyst types I, II, or III and without dilated biliary ducts, postoperative complications, or suspicion for residual cystic tissue.
- Consider yearly surveillance
- Labs: LFTs and GGT, consider CA 19-9
- Imaging: right upper quadrant US. MRI or CT if an abnormality is found.
  - High risk patients: those with cyst types IV or V or patients with postoperative dilated biliary ducts, intrahepatic biliary stones, or anastomotic strictures.
- Consider surveillance every 6–12 months to screen for early malignancy in higher risk patients:
- Labs: LFTs, GGT, and CA 19-9
- Imaging: right upper quadrant US with consideration for MRI or CT
- Follow up with gastroenterologist

CT, computed tomography; GGT, γ-glutamyltransferase; LFTs, liver function tests; MRCP, Magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

However, these studies have only compared short and mid-term outcomes between the techniques. There are no data on long-term outcomes and malignancy rates in patients who have undergone laparoscopic surgery. While the existing literature suggests minimally invasive approaches are safe, we do not know if this changes the rate of malignant degeneration. At present, there is no reason to believe the rate of malignancy would be higher after laparoscopic excision so long as care is taken to remove as much abnormal cystic tissue as possible, particularly given that the rate of stricture and cholangitis do not seem to be increased after minimally invasive resection and reconstruction. Similarly, there are no data suggesting that the type of biliary reconstruction (hepaticojejunostomy *vs* hepaticoduodenostomy) should alter the surveillance plan. Providers should be aware of the type of surgery and biliary reconstruction their patients had, particularly if complications arise.

Biliary atresia

Background. Biliary atresia is a progressive obstructive cholangiopathy of unknown etiology. It is characterized by complete obstruction of all or part of the extrahepatic biliary system and is associated with abnormalities of the intrahepatic biliary tree.[36] The incidence of BA in the USA is about 0.73 per 10 000 live births with a slight female predominance.[37] The incidence is lower in some European countries such as France (0.51 per 10 000) but higher in Asia, as in Taiwan (1.23 per 10 000).[38,39] Left untreated, BA is fatal; the only effective treatments are hepatic portoenterostomy (Kasai operation) and liver transplantation.[40] In children, BA is the most common cause of end-stage liver disease and the leading indication for liver transplantation.[41,42] Ultimately, approximately 80% of children with BA will progress to need liver transplantation.

Three distinct groups of patients with BA have been identified.[43] Most patients (group 1, about 85%) have isolated BA without associated major malformations. Group 2 (about 5%) comprises patients with BA and at least one other major malformation (without laterality defects). Patients in Group 3 (10%) have a syndromic form of BA with laterality defects such as situs inversus or intestinal malrotation. Overall, cardiovascular-associated anomalies are most prevalent (16%), followed by gastrointestinal (14%), splenic (7%), and genito-urinary anomalies (5%).

Most infants with BA (group 1) are asymptomatic, often jaundice-free at birth, and appear to be thriving until 2 to 6 weeks of life when they develop persistent jaundice, acholic stools, dark urine, and hepatomegaly.[44] Patients in groups 2 and 3 appear jaundiced from birth and do not have an asymptomatic period. On laboratory evaluation, infants with BA have elevated levels of total and direct bilirubin, aspartate aminotransferase, alanine transaminase, and GGT. Ascites and splenomegaly, resulting from portal hypertension, are late findings and not usually seen on initial presentation.

Biliary atresia must be suspected in all newborns in whom jaundice persists after the period of physiologic hyperbilirubinemia (first 2 weeks of life).[44,45] The diagnosis can be delayed because of failure to differentiate jaundice due to liver disease from physiologic jaundice. Fractionation of bilirubin into conjugated (direct) and unconjugated (indirect) portions is necessary in the evaluation of cholestasis. Expeditious work-up is indicated to identify those causes that are amenable to medical or surgical correction. The outcome of infants with BA is inversely correlated to the age at diagnosis and Kasai operation.[46]

The Cholestasis Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has formulated a clinical practice guideline for the diagnostic evaluation of cholestatic jaundice in the infant based on a comprehensive and systematic review of the literature integrated with expert opinion.[47] The most common causes of cholestatic jaundice in the first months of life are BA and idiopathic neonatal hepatitis. Idiopathic neonatal hepatitis accounts for up to 25% of infants with cholestatic jaundice. Alpha-1 antitrypsin deficiency causes another 5% to 15% of cases. The remaining cases are caused by a variety of other disorders, including extrahepatic obstruction from a CBD gallstone or CDC; metabolic disorders such as tyrosinemia, galactosemia, and hypothyroidism; inborn errors of bile acid metabolism; Alagille's syndrome; infection; and other rare disorders.[48]

The Kasai operation involves excision of the extrahepatic biliary remnant with a high portal-plate dissection to maximize exposure of residual bile ductules.[42] Drainage of bile is re-established from the portal plate into a 30–40 cm Roux limb of jejunum. If the Kasai is performed within the first 60 days of life, 70% to 80% of patients demonstrate bile drainage. If performed between 60 and 90 days, 40% to 50% of patients show drainage. After 90 days of life, only 25% of patients will have adequate drainage. If performed later than 120 days of life, $< 20\%$ of infants will effectively drain bile.[46] In a recent French study of 695 patients with BA, survival with native liver was best in children who underwent Kasai in the first 45 days of life.[46] Unfortunately, late diagnosis of BA remains a problem in the USA. The average age at Kasai is 61 days, and 44% of patients still undergo the procedure after 60 days of life.[44]

If successful, the Kasai operation increases the survival of children with BA and consequently postpones subsequent liver transplantation. Authors have reported long-term 20-year survival rates in patients with their native liver. However, most long-term survivors develop complications.[40]

Growth failure is common in patients with BA. Forty percent of patients who underwent liver transplantation had growth failure, which was found to be an independent risk factor for pre-transplant mortality, post-transplant mortality, longer hospital stays, and graft failure.[49] Infants with BA have poor bile flow with subsequent malabsorption issues, poor appetite, and increased energy expenditure. Growth failure after the Kasai operation is associated with increased risk of transplantation or death by 24 months of age.[49]

Cholangitis, thought to be due to bacteria ascending the Roux limb toward the portal plate, occurs in 40–60% of infants with BA within the first 2 years following Kasai operation.[50] Approximately 25% will have multiple episodes of cholangitis that negatively impact transplant-free survival.[50] Because BA is a progressive disease, even with good bile drainage, most patients will develop cirrhosis and portal hypertension.[44] Associated variceal hemorrhage can be fatal. Management of variceal hemorrhage is derived from adult studies and includes sclerotherapy, esophageal band ligation, octreotide, and consideration of therapy with beta-blockers. Children with refractory hemorrhage should be

referred to a center with expertise in portosystemic shunting and/or liver transplantation.

Portal hypertension is associated with ascites in 24% of patients.[50] The presence of ascites is associated with worse outcomes.[51] Ascites can be medically managed, but if intractable, the patient should be evaluated for presence of portal vein thrombosis or the patient should be considered for liver transplantation. Another complications in end-stage liver disease is abnormal right to left intrapulmonary shunting resulting in hypoxia. This complication can be treated with liver transplantation.[44] However, the optimal timing of transplant in relation to the degree of hypoxia remains unclear.

Cirrhosis can predispose a patient to the development of hepatocellular carcinoma (HCC). HCC has been reported in children with BA.[44] Serum alpha-fetoprotein (AFP) levels have been elevated in almost all HCC patients with BA.[44] Cholangiocarcinoma has also been reported. Because early identification of any malignancy is crucial to outcome, screening children with BA and cirrhosis with ultrasound and AFP levels is recommended. At this point, there is no standard of care for timing of surveillance.

Proposed timeline: From birth to transition/transfer. Patients born with BA can survive for more than 20 years with their native liver after the Kasai operation. Most patients eventually develop complications such as cholangitis, portal hypertension, gastrointestinal bleeding, and hepatobiliary malignancies. Ultimately, the majority of patients with BA will require liver transplantation. Lifelong follow up is needed in these patients, so that complications can be identified, and optimal treatment can be initiated.

Until the age of 18, patients with BA are generally managed by pediatricians, pediatric gastroenterologists, and/or pediatric surgeons (Table 3). If they have already undergone liver transplantation, transplant surgeons and transplant hepatologists may be involved in the care team. After age 18, these patients are referred to and managed by gastroenterologists. It is therefore important that adult gastroenterologists be aware that long-term survivors of the Kasai operation with native liver may develop complications such as recurrent cholangitis, portal hypertension, and malignancies. Liver transplantation should be considered early to avoid liver-related mortality.[40]

Table 3 Stakeholders list for BA (i.e. who should comprise the medical home for patients with CDCs transitioning to adult care providers).

Pediatric	Adult
Primary care provider (i.e. pediatrician or family medicine physician)	Primary care provider (internist or family medicine physician)
Pediatric gastroenterologist (consider pediatric hepatology expertise)	Gastroenterologist (consider hepatology expertise)
Transplant hepatologist†	Transplant hepatologist†
Pediatric general surgeon	+/− Adult general surgeon (consider hepatobiliary surgical expertise) if complications require surgical management
Transplant surgeon†	Transplant surgeon†
Specialist for associated congenital anomalies (geneticist, cardiologist)	

†If patient has undergone or is being considered for liver transplantation. BA, biliary atresia; CDCs, choledochal cysts.

Literature review on transition of care. Patients with BA require close long-term follow up for progressive liver disease. Of long-term survivors of BA after the Kasai operation, a fraction of patients retain normal liver function, while most are in a state of compensated cirrhosis.[51,52] Some have reported between 20% and 40% 20-year survival rates in patients with their native liver.[40] Shinkai *et al*. found that at age 20, nearly half of the adult survivors had already developed liver cirrhosis and its sequelae.[53] Episodes of cholangitis and gastrointestinal bleeding occurred after 20 years of age in 37% and 17% of the adult patients, respectively. About 20% of these adult patients died of liver failure or underwent living-related partial liver transplantation in their 20s.

Hepatocellular carcinoma is an uncommon but reported complication in children with BA. In almost all the reported cases, serum AFP levels have been elevated.[44] Surveillance for HCC in adults with cirrhosis is becoming an accepted standard of care with serial ultrasound and serum AFP measurement every 6 months. A similar standard of care does not exist for children. Shneider *et al*. suggest considering surveillance in those children with BA who survive with their native liver into adolescence.[54] Other tumors such as focal nodular hyperplasia, hepatoblastoma, and cholangiocarcinoma have been described.[55] In a retrospective review of 157 children over an 18-year period following Kasai operation, Yoon *et al*. found 8% developed new hepatic tumors. Malignant lesions were found in 23% (two HCC and one cholangiocarcinoma). Of HCC cases in BA found in the literature, 20% developed within the first year of life and 68% occurred in children younger than 10 years. Approximately half of the HCCs were incidentally detected in the explanted liver at transplantation or at autopsy. The authors recommended screening with AFP levels and regular imaging studies, but specifics regarding frequency and duration of testing were not discussed.

Lykavieris *et al*. recommend lifelong follow up for BA patients after the Kasai operation.[36] They emphasize that the Kasai operation cannot be considered a cure for the disease. BA is not restricted to the extrahepatic bile ducts, so even children in whom the Kasai operation has been successful display abnormalities of the intrahepatic biliary tree, including stenosis and dilatation. This leads to ongoing cholestasis that further aggravates the cirrhosis already present in most of the children at the time of portoenterostomy. It can also lead to bile duct damage due to bacterial cholangitis. Early detection of portal hypertension and liver cancer is important. In their review of 20-year survivors with native liver after the Kasai operation, 70% developed portal hypertension. The authors do not provide specific recommendations regarding how follow up should be conducted.

In a Dutch cohort of 106 patients with BA between 1977 and 1988, 27% survived for 20 years without transplantation.[56] Overall, 20-year survival with and without transplantation was 43%. Fifty-two patients died without liver transplantation mainly because the technique was not available to small children at the time. Of the 28 20-year survivors, half had elevated bilirubin and

transaminases; half had experienced one or more episodes of cholangitis. Half also had signs of portal hypertension. Most (80%) had either clinical or ultrasonographic signs of cirrhosis. Two had a stable liver adenoma. None had elevated AFP levels. Of the patients who survived to age 20 with their native liver, 20% (six of 28) did not have abnormal liver biochemistries, signs of cirrhosis, or portal hypertension; the oldest patient was 28 years old. Whether a small portion of patients can be considered cured after the Kasai operation remains to be determined. The authors argued that all survivors should have regular ultrasounds at 6 to 12-month intervals to screen for tumors until the true prevalence of tumors in BA is known and the efficacy of surveillance can be assessed.

In a recent review of long-term outcomes in BA, Kelay and Davenport echo the recommendation for required lifelong monitoring for these patients.[57] As management of these patients continues to improve, they are surviving into their teens and adulthood. The oldest survivor known with their native liver is 60 years old.[57] However, as discussed earlier, these patients carry the burden of their condition for the rest of their lives. In order to attain quality of life, minimize poor long-term outcomes, and improve survival, these patients should be part of a multidisciplinary program that allows for a smooth transition of care into the adult setting. This program will also set the groundwork for continued surveillance for the rest of their lives (Table 4).

Future research directions. Many areas of neonatal cholestasis and BA would benefit from further research. Improved understanding of the etiology and pathogenesis of BA might allow for new medications to delay or halt disease progression.[44] Research to develop new choleretic medications and improved cholangitis treatment after the Kasai operation could prevent ongoing bile duct damage. Future research into the subtypes of BA could determine whether they are associated with unique predispositions, etiologies, and outcomes.[43]

More robust screening programs and care regionalization to experienced centers might allow for earlier detection and improved outcomes with better long-term success of the Kasai operation.[43,45] Initiatives to educate parents and pediatricians, including

Table 4 Biliary atresia data sheet for parents and providers

Biliary atresia data sheet
- Definition:
  - Biliary atresia (BA) is a rare progressive obstructive cholangiopathy of unknown cause characterized by complete obstruction of all or part of the extrahepatic biliary system associated with concomitant abnormalities of the intrahepatic biliary tree
- Epidemiology:
  - Affects ~1:10 000–20 000 depending on the location. The female to male distribution is 1.4:1
  - Most patients are identified within the first 2–3 months of life.
- Clinical presentation:
  - Jaundice and acholic stools
  - Dark urine, enlarged liver, and failure to thrive
- Risks if left untreated:
  - Cirrhosis, portal hypertension, failure to thrive, liver failure, and death
- Diagnosis:
  - Laboratory tests including fractionated bilirubin, hepatic function, and coagulation profiles
  - Abdominal ultrasound: absence of gall bladder suggestive of BA
  - Hepatobiliary scintigraphy (HIDA): of variable utility; may be suggestive of BA or help rule out BA
  - Percutaneous or operative liver biopsy: can be highly suggestive of BA; next best diagnostic test after cholangiogram
  - Percutaneous or operative cholangiogram: gold standard
- Management:
  - Kasai operation (portoenterostomy): excision of the extrahepatic biliary remnant with a high portal-plate dissection allows drainage of bile from the portal plate into a Roux limb of jejunum.
  - Liver transplantation (primary or after a failed Kasai operation)
- Post-operative complications:
  - Cholangitis, portal hypertension, ascites, pruritus, growth failure, and progressive liver failure
  - Hepatobiliary malignancies: hepatocellular carcinoma (HCC), cholangiocarcinoma, and hepatoblastoma
- Prognosis:
  - Outcomes are best if the Kasai operation is performed within the first 60 days of life.
  - Two thirds will have re-established bile flow after the Kasai operation. Of these patients, half will have long-term biliary drainage, while the other half will progress to liver transplantation within 20 years.
  - One third will require early transplantation after failed Kasai procedure.
  - Most patients will eventually require liver transplantation.
- Follow-up:
  - Long-term follow up is recommended because of the risk of progressive liver failure with concomitant cirrhosis, portal hypertension, and hepatobiliary cancers.
  - Hepatic function tests and right upper quadrant ultrasounds every 6–12 months (for life) to screen for progressive liver failure and tumor development.
  - Alpha-fetoprotein levels should be followed in older survivors with their native liver to screen for HCC.

using stool color cards to make the determination of acholic stool more objective have been developed to speed the time to diagnosis. Apart from the age at detection and the timing of the Kasai operation, the level of experience at the treating center in management of BA has been shown to have impact on outcomes.[58,59] This association has led to centralization of care of BA patients in Europe with improved survival. Further research into this issue is indicated.

Longer follow up of survivors with their native liver is needed to further delineate long-term consequences after portoenterostomy, clarify optimal time of liver transplantation, and verify whether BA can be cured.[40,56] Quality of life remains a concern in patients with chronic liver disease. Further investigations into nutrition, neurocognitive development, and the psychosocial outcomes of patients with BA would be valuable, as well.[44,56]

Conclusions

Although transition of care programs continue to evolve for patients with surgically correctable congenital malformations and gastrointestinal diseases, none focus on the subset with CDCs or BA. Those who have undergone operative repair need continued follow up for life. Patients with CDCs are at increased risk for development of biliary malignancies, cholangitis, and anastomotic strictures after surgical resection. Patients with BA are likely to develop progressive liver failure over time, necessitating liver transplantation to avoid death. They also have a propensity to develop hepatobiliary malignancies in their native liver. At present, there are no consensus guidelines regarding the timing or frequency of follow up and surveillance postoperatively. Studies in pediatric cardiac surgery, pediatric neurosurgery, pediatric gastrointestinal diseases, and anorectal malformations have demonstrated that implementation of standardized transition of care programs that emphasize complete transmission of data and appropriate follow up are instrumental to best practice. Based on the best available evidence, we propose a schema for long-term surveillance that can be used in the transition of care process for patients with CDCs and BA (Tables 2 and 4).

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