Biliary Atresia: A Transplant Perspective

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Biliary atresia is the most common single pediatric liver disease leading to liver transplantation (LT) during childhood.1 Between 1995 and 2002, 42% of children undergoing their first liver transplant while enrolled in the Studies of Pediatric Liver Transplantation (SPLIT) did so for a primary diagnosis of biliary atresia. There have been a number of recent reviews and advances related to the detection, diagnosis, and pathogenesis of biliary atresia.2-6 The purpose of this review is to focus on aspects of biliary atresia that are directly relevant to LT as a modality for its treatment. In particular, this review will concentrate on (1) specific indications for LT in the setting of biliary atresia, (2) management issues in children awaiting LT, (3) special surgical approaches in transplantation for biliary atresia, and (4) outcomes after LT.

Biliary atresia is a unique disease with a relatively well-characterized clinical course. Careful analysis of the clinical course permits identification of indications for and timing of LT (Table 1). Transplantation decisions should take into consideration therapeutic approaches to the specific indications and complications that have developed. Thus, the following sections will examine both indications for transplantation and the management of those clinical problems.

POOR EARLY RESPONSE TO HEPATOPORTOENTEROSTOMY (HPE): THE FAILED KASAI

The HPE (Kasai procedure) is an excellent surgical treatment for biliary atresia. In most cases, it is not a cure for this condition but provides a means of permitting bile flow and preventing rapid progression of disease from chronic high-grade cholestasis. The natural history of unrepaired biliary atresia is reasonably well documented; in the absence of LT, survival beyond 24 or 36 months of age is very unusual.7-10 Similarly, the natural history of children with biliary atresia who do not demonstrate bile flow after HPE (a “failed” Kasai) is very similar to the history of children with unrepaired biliary atresia.11-13 As such, the failed Kasai is a strong indication for early consideration of LT. Very few pediatric liver diseases have such a predictable prognosis. In general, these children have a brief period of relative well-being followed by progressive failure to thrive, development of ascites and/or spontaneous bacterial peritonitis, and variceal hemorrhage. Survival beyond 24 to 36 months of age without LT occurs in only a small minority of children. Quality of life is poor in the setting of a failed HPE as a result of repeated hospitalizations, failure to thrive, developmental delay, and intractable pruritus. Thus, an aggressive, preemptive approach to LT in this setting is justified in centers with technical expertise in the transplantation of infants.

One of the caveats with this important indication for pediatric LT is operationally defining a lack of bile flow. This operational definition must include both a marker of bile flow and a time period beyond which it is unlikely that bile flow will develop. In prior surgical eras, when externalization ostomies were utilized early after the Kasai, bile flow could be directly observed. This surgical approach has largely been abandoned, and thus indirect markers of bile flow must be utilized. Persistently acholic stools are a reasonable indication of poor bile flow, although caution must be exercised in the visual assessment of stool color. Comparisons to standardized color samples may improve this method, although it...
more common in children with biliary atresia. To date, there are no clearly described interventions to improve bile flow after the Kasai procedure. Controversy exists as to whether perioperative corticosteroid administration improves surgical outcome in biliary atresia. Reoperation is unlikely to be helpful in most cases of biliary atresia.

In the United States, utilization of the failed Kasai as the sole indication for LT typically necessitates a live donor approach. These infants have a reduced priority for transplantation because they typically have low pediatric end-stage liver disease (PELD) scores. In the setting of adequate nutrition, they almost always have normal or near-normal prothrombin times and albumin levels. Thus, they accumulate PELD points only on the basis of their total bilirubin levels, which are routinely less than 12 mg/dL. On occasion in some regions in the United States, a split liver may become available for an infant with a failed Kasai. Otherwise, pre-emptive transplantation in this setting before the development of classical complications of liver disease can occur only if a live donor is available. Most children with a failed HPE will undergo transplantation after the development of complications including most commonly failure to thrive, ascites, and/or variceal hemorrhage, which are subsequently described.

**FAILURE TO THRIVE**

Failure to thrive, typically defined as poor somatic growth, is very common in biliary atresia and is one of the most prevalent indications present in children who undergo LT. Growth failure was reported in 40% of patients who underwent LT in the SPLIT registry, and the mean height (−1.3) and weight (−1.4) z scores were below average for this large cohort of children with biliary atresia. A comprehensive retrospective multicenter analysis of children with biliary atresia confirmed the prevalence of this problem and correlated failure to thrive with poor outcome. The importance of growth failure is acknowledged in the current allocation system in the United States as children receive higher wait-list priority when this complication is present. The pathogenesis of growth failure and malnutrition in biliary atresia is multifactorial, with major contributions from increased energy expenditure and malabsorption related to cholestasis. Coupled with potential fat malabsorption, which correlates with the degree of cholestasis, biliary atresia puts children at tremendous risk for caloric deficits leading to failure to thrive.

Clinical assessment of nutritional status in children with biliary atresia is less straightforward than it seems. Often the first visual impression of these patients is one of significant malnutrition, which is then not supported by routine height and weight measurements. Assessment of body weight is often quite misleading because of the effects of organomegaly and ascites. Diminishment of height and head circumference growth velocity is a late manifestation of poor nutritional status. Thus, a more accurate assessment of nutritional status in children with biliary atresia is dependent on more sensitive markers such as anthropometrics, including midarm muscle area and skinfold thickness. Therefore, transplant assessment of a child with biliary atresia should include a comprehensive analysis of growth, permitting a more accurate appreciation of the child’s clinical status. It is unusual for failure to thrive to be the sole indication for transplantation in biliary atresia, as it is typically accompanied by manifestations of poor bile flow. Accurate identification of failure to thrive may have implications for prioritization for transplant and permit important medical interventions.

The need for nutritional supplementation (such as nasogastric tube feeding or intravenous administration) for failure to thrive in children with biliary atresia is a risk factor for both wait-list and posttransplant

**TABLE 1. Primary Indications for Liver Transplantation in Biliary Atresia**

<table>
<thead>
<tr>
<th>More common (in approximate order of frequency)</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor early response to hepatopancreatoenterostomy</td>
<td>Hepatopulmonary syndrome</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Portopulmonary hypertension</td>
</tr>
<tr>
<td>Late-onset (adolescence) cholestasis</td>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>Primary approach (late initial presentation)</td>
<td>Intractable pruritus</td>
</tr>
<tr>
<td>Recurrent cholangitis</td>
<td>Intractable ascites</td>
</tr>
<tr>
<td>Portal hypertensive bleeding</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Osteoarthropathy</td>
</tr>
<tr>
<td>Poor quality of life</td>
<td>Encephalopathy</td>
</tr>
</tbody>
</table>

**Liver failure** must be acknowledged that these systems were developed as screening methods for biliary atresia and not for clinical follow-up. The finding of “pigmented” stools does not necessarily indicate adequate bile flow. Alternative techniques, such as hepatobiliary scintigraphy, to assess bile flow after HPE are not well described as a measure of outcome.

The most commonly utilized marker of bile flow after HPE is measurement of serum bilirubin levels. Total bilirubin levels, as opposed to direct or conjugated bilirubin levels, are most commonly utilized because of the variability of methods for the measurement of the latter. Coexisting Gilbert’s syndrome could complicate the use of total bilirubin levels in this setting, and thus clinicians should confirm that direct or conjugated bilirubin levels are significantly elevated in an infant who is suspected to have a poorly draining HPE. A total bilirubin in excess of 6 mg/dL (100 μM) at a time greater than 3 months after HPE has been associated with poor short-term outcome in biliary atresia and may be a reasonable marker of a failed Kasai. To date, there are no clearly described interventions to improve bile flow after the Kasai procedure. Controversy exists as to whether perioperative corticosteroid administration improves surgical outcome in biliary atresia. Reoperation is unlikely to be helpful in most cases of biliary atresia.

In the United States, utilization of the failed Kasai as the sole indication for LT typically necessitates a live donor approach. These infants have a reduced priority for transplantation because they typically have low pediatric end-stage liver disease (PELD) scores. In the setting of adequate nutrition, they almost always have normal or near-normal prothrombin times and albumin levels. Thus, they accumulate PELD points only on the basis of their total bilirubin levels, which are routinely less than 12 mg/dL. On occasion in some regions in the United States, a split liver may become available for an infant with a failed Kasai. Otherwise, pre-emptive transplantation in this setting before the development of classical complications of liver disease can occur only if a live donor is available. Most children with a failed HPE will undergo transplantation after the development of complications including most commonly failure to thrive, ascites, and/or variceal hemorrhage, which are subsequently described.
mortality. Similar findings have been found for failure to thrive in the more general population of children awaiting LT. At present, it is not clear whether one can reverse this mortality risk with aggressive nutritional support. Pretransplant growth retardation increases posttransplant length of stay and hospital costs. Long-term developmental outcome is likely to be adversely affected by malnutrition, especially if there is poor head growth. Therefore, nutritional support is a key part of the care of children with biliary atresia who await LT. A comprehensive description of this aspect of the care of these children is beyond the scope of this article, and interested readers are directed to recent reviews. Monitoring, including anthropometrics, fat-soluble vitamin levels, and prothrombin time, should be more frequent in children with evidence of more significant cholestasis. Fat-soluble vitamin supplementation should take advantage of the ability of tocopherol polyethylene glycol succinate to be absorbed independently of bile salts. Medium chain triglycerides are a superior form of enteral fat administration in cholestasis as they are also absorbed independently of bile salts.

Nasogastric tube feeding in biliary atresia is often utilized and may in fact be underutilized. The exact indications for commencing nasoenteric tube feeding are not completely clear. Nasogastric tube feedings can enhance the nutritional status of children with biliary atresia. It is obvious that nutritional supplementation is indicated and perhaps late in the patient with inadequate intake and significant failure to thrive (for example, height or weight z score < -2). Interestingly, at initial presentation, the average child with biliary atresia has subnormal growth parameters. It is unknown whether nasogastric tube feedings at disease presentation can have an impact on overall long-term outcome. Between these two ends of the clinical spectrum of intervention, there are many questions as to the most advantageous approach to the use of nasogastric tube feeding.

Late Onset Cholestasis

Approximately 40% to 60% of infants with biliary atresia will achieve good bile drainage after HPE. The subsequent course in patients with good bile drainage is highly variable and often involves the development of biliary cirrhosis and complications of portal hypertension (discussed later). Some long-term survivors will redevelop significant cholestasis later in life. This cholestasis is likely the result of ongoing intrahepatic biliary injury and is potentially related to recurrent episodes of cholangitis. In our experience, late-onset cholestasis, if not an acute manifestation of cholangitis, is a harbinger of a worsening in near-term outcome. Nearly all of the patients in a recent review of adult-to-adult living donor transplantation for biliary atresia were cholestatic. Thus, in the older child or young adult, reoccurrence of jaundice/cholestasis should trigger reassessment of the transplant candidacy of that patient.

LT as the Primary Approach to the Management of Biliary Atresia

HPE is an excellent but imperfect surgical treatment for biliary atresia. There are numerous reports of long-term survival with native liver after HPE. Thus, in most circumstances, the concept of LT as the primary surgical approach to biliary atresia has been abandoned. Extensive evidence has been presented that indicates that age at HPE influences the response to surgery; in general, responses are better when surgery occurs at a younger age (Table 2). Despite this well-described phenomenon, there are some children who have a relatively successful postoperative outcome after HPE even when this procedure occurs after 100 or even 120 days of life. As such, a very reasonable question regarding HPE is when is it too late. Obviously, there is no simple answer to this question, and by corollary, there is no simple age at which LT is clearly preferred over HPE as the primary surgical therapy for biliary atresia. We have favored LT as the primary therapy for children who are greater than 120 days of age. Alternatively, if an infant has significant ascites or has had variceal hemorrhage as a complication of portal hypertension resulting from biliary atresia, it may be unwise to attempt HPE, but instead one might consider transplantation as the primary approach.

Recurrent Cholangitis

Cholangitis is a common complication after HPE for biliary atresia, occurring in at least 30% to 60% of children, typically in the first 1 to 2 years after surgery. Infection is presumed to be ascending and typically does not occur in children who have poor or no bile flow after HPE. Infection rates may approach 100% in children with evidence of good bile flow. Cholangitis is a clinical syndrome, typically consisting of fever, leukocytosis, and evidence of worsening cholestasis, although there are no universally accepted criteria for the diagnosis. A positive blood culture with an appropriate organism can often clarify the diagnosis, although positive cultures are seen in fewer than 50% of cases of cholangitis. As fevers are not uncommon in children less than 2 years of age, it can be difficult to be certain of this diagnosis and/or its true prevalence. Typical means of trying to prevent cholangitis include prophylactic antibiotics (for example, trimethoprim sulfamethoxazole) and/or special surgical techniques (intussuscepted antirefluxing valve), although the efficacy of these interventions is unproven. Cholangitis can be recurrent and/or refractory to medical management, which typically includes a prolonged course of intravenous antibiotics. Two to four distinct episodes of cholangitis in the first 2 years after HPE are not unusual. In cases in which the episodes are more frequent and/or refractory to appropriate and prolonged courses of antibiotics, additional surgical intervention may be indicated. In selected cases, revision of the HPE may be useful in relieving partial and/or complete obstruction that may predispose to the refractory disease.
Hepatobiliary scintigraphy may identify circumstances under which revision may be successful.\textsuperscript{48} LT may be indicated as a means of treating highly recurrent and/or refractory disease. The clinician should be extremely careful about being relatively certain about the diagnosis of cholangitis, especially if this is the primary reason to consider LT. In many cases, recurrent or refractory disease is followed by the development of high-grade cholestasis, which evolves into another indication to consider LT. In the era of multiresistant bacterial organisms, the pattern of antibiotic resistance of positive blood cultures may also influence transplant decision-making.

PORTAL HYPERTENSIVE GASTROINTESTINAL BLEEDING

Variceal hemorrhage is a prominent and potentially fatal complication that develops in a significant number of children with biliary atresia.\textsuperscript{49-53} Significant portal hypertension develops very early and can be present at the time of HPE.\textsuperscript{54} Hepatic synthetic function can be relatively intact at the time of variceal hemorrhage, so clinical decision-making and management approaches must take into consideration the near-term prognosis for an individual patient. Approaches to the management of variceal hemorrhage in children are largely anecdotal and derived from studies in adults.\textsuperscript{55} Primary prophylaxis of variceal hemorrhage in children is not the typical standard of care but is employed by some experienced clinicians.\textsuperscript{56} The approach to secondary prophylaxis is largely dependent on the presence or absence of bile flow, which has a significant impact on near-term mortality.\textsuperscript{57} Children with evidence of poor bile flow, as manifest by a total bilirubin greater than or equal to 10 mg/dL, have a high risk of near-term mortality, and thus LT is the approach of choice for these patients. In contrast, children with evidence of good bile flow, that is, total bilirubin less than 4 mg/dL, have a much lower risk of near-term mortality. As such, endoscopic band ligation may be the initial treatment of choice in these patients.\textsuperscript{58} Beta blockade has been utilized in children, although the physiologic parameters guiding its use are not well described in pediatrics.\textsuperscript{59} Children with refractory hemorrhage or varices that are not amenable to endoscopic approaches may be candidates for portosystemic shunting, especially distal splenorenal shunts.\textsuperscript{60-62} Portosystemic shunting in small children requires reasonable expertise in pediatric hepatobiliary and vascular surgery.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis occurs in children with biliary atresia, although there is a surprising lack of comprehensive literature on this important complication in children with chronic liver disease.\textsuperscript{63-65} A high index of suspicion needs to be maintained for this entity in order to permit timely diagnosis and successful intervention. Prophylactic antibiotics are sometimes used in adults with chronic low albumin ascites, although there are no clear guidelines for this approach in children.\textsuperscript{66} In children with advanced liver disease and pharmacologically refractory ascites, LT is indicated, and prophylactic antibiotics with trimethoprim sulfamethoxazole while they await LT are reasonable. In adults, development of spontaneous bacterial peritonitis is associated with increased near-term mortality.\textsuperscript{67-69} By corollary, the occurrence of an episode of spontaneous bacterial peritonitis in a child with biliary

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### TABLE 2. Outcome After Hepatoportoenterostomy (HPE) with Respect to Age at Surgery

<table>
<thead>
<tr>
<th>Center</th>
<th>Age at HPE (Days)</th>
<th>Bile Flow (% Yes)</th>
<th>Survival with Native Liver (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Years</td>
<td>5 Years</td>
</tr>
<tr>
<td>Sendai, Japan</td>
<td>46–60</td>
<td>61</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;90</td>
<td>48</td>
<td>90</td>
<td>48</td>
</tr>
<tr>
<td>Taipei, Taiwan</td>
<td>&lt;60</td>
<td>63</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>91–120</td>
<td>44</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td>32</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Denver, CO</td>
<td>&lt;61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Registry</td>
<td>31–60</td>
<td>69</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>91–120</td>
<td>53</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td>35</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Kremlin-Bicetre, France</td>
<td>30–60</td>
<td></td>
<td>41</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td></td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>London, England</td>
<td>41–60</td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td></td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor, MI</td>
<td>&lt;60</td>
<td></td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>&gt;90</td>
<td></td>
<td>70</td>
<td>28</td>
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<tr>
<td>US Biliary Atresia Research Consortium</td>
<td>60</td>
<td></td>
<td>57</td>
<td>15</td>
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<tr>
<td></td>
<td>90–120</td>
<td></td>
<td>67</td>
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<td></td>
<td>&gt;120</td>
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<td>0</td>
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LIVER TRANSPLANTATION.DOI 10.1002/lt. Published on behalf of the American Association for the Study of Liver Diseases
Hepatorenal syndrome is an uncommon but severe complication of end-stage liver disease in children. It is thought to be a manifestation of a profound reduction in renal perfusion and associated renal insufficiency. There is little if any specific literature dedicated to pediatric experiences with this condition, so extrapolations must be made from adult experiences. The diagnosis is suggested when there is an acute worsening of renal function in the setting of portal hypertension. Oliguria and azotemia are present in the setting of no specific exacerbating conditions, and there is no evidence of intrinsic renal damage. Newer medical approaches, including vasoconstrictors and albumin infusions, have not been extensively examined in children but are worth considering as empiric interventions. Hepatorenal syndrome typically reverses after LT, so children with biliary atresia and this complication should be prioritized for transplant.

Intractable pruritus

Pruritus is a common and very problematic clinical issue in children with chronic cholestasis. In its severe form, it can have a significant impact on quality of life and/or family dynamics. The exact pathophysiology of the pruritus is not completely clear, although its severity loosely correlates with serum concentrations of bile salts. It is a major feature in the clinical course of children with progressive familial intrahepatic cholestasis and Alagille syndrome. In biliary atresia, it can be a major issue but is not typically as severe as that observed in these other causes of intrahepatic cholestasis. In rare circumstances, intractable pruritus is the predominant problem in a child with biliary atresia,
and it becomes the leading indication for LT. In that circumstance, certain provisos are worth considering. First, one should exclude other causes of chronic pruritus in children, such as atopy, pediculosis, and urticaria. Second, one should be certain that the initial diagnosis of biliary atresia was correct and/or was the only cause of cholestasis. Alagille syndrome and biliary atresia can be very similar in their early presentation. There are interesting findings of Jagged 1 defects in children with well-characterized biliary atresia. The finding of Alagille syndrome has implications for the evaluation of parents as potential living donors. An affected parent, in this autosomal dominant disease with variable penetrance, could have unsuspected bile duct hypoplasia that could make donation untenable. Third, one should be certain that appropriate avenues have been pursued in the treatment of the pruritus. Antihistamines are utilized for allergic causes of pruritus. They are fairly ineffective in cholestasis, with the exception of aiding in sleep because of their sedating side effects. Ursodeoxycholic acid or cholestyramine therapy can be effective in some children, presumably by modifying the circulating bile salt pool. Rifampin has also been effective in some children with severe pruritus. This agent is potentially hepatotoxic, so monitoring is warranted. Other agents for pruritus, such as opiate antagonists, sertraline, gabapentin, and ultraviolet light therapy, are not well characterized for use in children and should be employed with caution.

INTRACTABLE ASCITES

Ascites develops in a significant number of children with biliary atresia. It can develop transiently in the perioperative period and can also be a manifestation of advancing cirrhosis and portal hypertension. In the setting of poor bile flow or other major complications of end-stage liver disease, it adds to the indications to proceed with LT. It is most easily documented by the recognition of an inappropriate increase in body weight. Abdominal girth is quite unreliable as a means of documenting ascites. Ascites with normal serum sodium levels is typically managed with salt restriction and diuretic administration to maintain a total daily negative sodium balance. In our experience with younger children, sodium restriction is not the major issue, and ascites responds relatively quickly to a combination of furosemide (1-2 mg/kg/day) and spironolactone (3-5 mg/kg/day). With more advanced disease, the ascites is coupled with hyponatremia and reflects total body water overload. This is a worrisome finding and carries a poor near-term prognosis.

On rare occasion, intractable ascites is the primary indication to consider LT in children. In this setting, it is important to make sure that there is well-documented ascites. Children with organomegaly can give the appearance of having significant ascites when in fact there is minimal free fluid in the abdominal cavity. It is equally important to make sure that the patient is receiving the prescribed diuretic regimen and that there is not a history of excessive sodium intake. Portal vein thrombosis can predispose to more refractory ascites, so Doppler sonography is an appropriate part of the evaluation of these children. Finally, we have observed children with massive and intractable ascites that developed on the basis of a bile leak. These children have relatively normal bilirubin levels as bile flow is good, although it flows into the wrong place. Measurement of ascites bilirubin levels and/or hepatobiliary scintigraphy can document a bile leak, which may be amenable to surgical revision of the HPE. In this circumstance, LT can be deferred for long periods of time.

HEPATOCELLULAR CARCINOMA (HCC)

Between 1987 and 2004, there were 41 children who underwent LT for HCC in the United States, although it is not clear how many of those children had an underlying diagnosis of biliary atresia. HCC is an uncommon but reported complication in children with biliary atresia. It has often been an incidental finding and has been reported in an 8-month-old infant. In almost all of the reported cases of biliary atresia, serum alpha-fetoprotein levels have been elevated. The results of treatment of metastatic HCC are relatively unfavorable, and thus the goal is to identify this lesion early to permit complete surgical resection. Nodular lesions may be seen in children with biliary atresia; in the setting of cirrhosis, the nodules are primarily related to the development of regenerative foci. Magnetic resonance imaging with contrast administration can be especially useful in differentiating lesions that may have a high likelihood of being malignant. A child with suspected HCC should undergo a metastatic evaluation and, if negative, should be prioritized for LT. Surveillance for HCC in adults with cirrhosis is becoming an accepted standard of care. Typical approaches in adults include sonography and measurement of serum alpha-fetoprotein levels every 6 months. A similar standard of care does not exist for children, although almost all of the authors of reported cases of HCC in biliary atresia have concluded that surveillance in biliary atresia is warranted. The diminished prevalence of HCC in children with respect to adults alters the potential effectiveness of surveillance in the pediatric age range. Thus, it is difficult to make definitive recommendations for HCC surveillance in the setting of biliary atresia. On the basis of published anecdotal experiences, it might be worth considering surveillance as a reasonable approach in those children with biliary atresia who survive with their native liver into adolescence. In addition, screening at the time of listing for LT might also be worthwhile as a means of wait-list prioritization.

HYPERTROPHIC OSTEOARTHROPATHY

Hypertrophic osteoarthropathy can be a painful syndrome of arthritis and joint deformities that has been observed in chronic liver disease, including biliary atre-
In some circumstances, it has been responsive to standard anti-inflammatory treatments. In cases in which pharmacologic intervention has been ineffective, symptoms have resolved relatively quickly after LT. As such, hypertrophic osteoarthropathy is an unusual but occasionally plausible indication to consider LT in biliary atresia.

**ENCEPHALOPATHY**

Chronic encephalopathy is not well described as a primary indication to consider LT in children with biliary atresia. It may complicate other features of end-stage liver disease that become transplant indications. Recent descriptions of subclinical encephalopathy in children with extrahepatic portal vein obstruction beg the question as to whether chronic encephalopathy may be an unrecognized cause of significant morbidity in biliary atresia.

**POOR QUALITY OF LIFE**

Some long-term survivors with biliary atresia can have a quality of life that is similar to that of the general population. This is not always the case, and in some, the combination of the clinical sequelae of biliary atresia can lead to a relatively poor quality of life. In particular, failure to thrive, intractable pruritus, and potential subclinical encephalopathy can combine to yield an unacceptable existence for children with biliary atresia. Neurodevelopmental performance can be adversely impacted by these issues. As such, LT is sometimes pursued as a means of improving quality of life. In the absence of other major complications, the decision to proceed with liver replacement needs to be individualized. Prioritization for available organs from deceased donors is typically low for these children, and live donor transplantation may be required.

**LIVER FAILURE**

True hepatic failure can develop in children with biliary atresia, although it is usually a late phenomenon preceded by other major complications that are typically indications in their own right for LT. In our experience, liver failure, as manifested by synthetic failure, does not develop until the second or third year of life in children with un repaired biliary atresia. Severe coagulopathy prior to that time may instead be a manifestation of vitamin K deficiency or infection.

**SURGICAL APPROACHES IN TRANSPLANTATION FOR BILIARY ATRESIA**

The first attempted liver transplant for biliary atresia in March 1963 by Dr. Thomas Starzl was in a young child with biliary atresia. The child succumbed in the operating room from intractable coagulopathy. Children with biliary atresia have frequently presented surgical challenges to the transplant surgeon; innovation driven by these technical challenges has led to improvements that have dramatically improved survival rates for all children undergoing LT. Furthermore, the increased demand brought on by successful transplantation has led to technical advances in pediatric LT such as split liver and living donor transplantation.

Surgical issues encountered in these patients are the general ones common to many patients with previous abdominal surgery, such as intra-abdominal adhesions related to previous HPE as well as those found uniquely in syndromic biliary atresia.

**Technical Considerations in All Children with Biliary Atresia Undergoing LT**

Surgical risks of transplantation common to these children include the risk of postoperative enteral leak, perforation, or fistula due to dissection, the technical challenges of hepatic arterial anastomoses in young infants, and the management of potentially large-for-size grafts.

Intestinal perforation is reported to occur in 4%-20% of children undergoing LT for biliary atresia and should be suspected in cases of unexplained sepsis or clinical deterioration. Treatment for presumed fungal infection should also be strongly considered in these cases. Reoperation for bleeding is also not uncommon after pediatric LT and occurs in 5%-10% of children. In children undergoing LT for biliary atresia, the frequency of prior operations, significant intra-abdominal adhesions, and post-LT coagulopathy may make bleeding more likely.

Hepatic arterial complications are reported to occur in 5%-15% of children undergoing LT for biliary atresia. Hepatic arterial thrombosis rates have improved to 1%-3%, however, with microsurgical arterial reconstruction or loupe magnification. Portal venous complications may be anticipated to be more frequent in LT for biliary atresia because of the hypoplastic nature of the portal vein in addition to the anatomical considerations seen in syndromic biliary atresia. Portal venous thrombosis has been reported in 6%-14% of cases. Technical considerations include the complete mobilization of the portal vein to the splenomesenteric vein junction (discussed later) and ensuring that “steal” phenomena from prominent collaterals such as the coronary vein are eliminated by the ligation of these vessels when encountered. Direct anastomoses are preferred as long as tension is avoided. If needed, fresh venous interposition segments from the live donor or an autologous segment of the recipient internal jugular vein may be preferable to preserved venous grafts and certainly to cryopreserved grafts. Portal venous thrombosis that occurs in the early postoperative period may be treated by thrombectomy or venous interposition grafts. Late portal venous thrombosis may be treated successfully by Rexshunt (mesenterico-left portal vein bypass).

Biliary complications have occurred frequently in the reported series of LT for biliary atresia (18%-20%) and in general pediatric transplant series including technical variant grafts (11%-27%). Current management of biliary strictures with surgical
approaches\textsuperscript{132} or interventional radiologic techniques in selected patients\textsuperscript{136} is successful in the majority of cases, and retransplantation can often be avoided.

Large-for-size grafts may be defined by a graft to recipient body weight ratio greater than 4\%. In these cases, proper surgical wound management is critical to avoid tension on the graft. Techniques such as skin closure without fascial closure or temporary closure with prosthetic material are used satisfactorily in these instances\textsuperscript{137} Alternatively, backtable reduction of the large graft or monosegmental transplantation has been used\textsuperscript{138}

Reoperation is common after transplantation for biliary atresia, occurring in up to 48\% of children in the large multicenter SPLIT report.\textsuperscript{16} Twenty-six percent required a single reoperation, and 12\% underwent one or more reoperations.

 Syndromic Biliary Atresia

Although syndromic biliary atresia has been previously associated with poor outcomes after transplantation, several technical modifications and greater experience have led to successful outcomes in these children. Raynor et al. in 1988\textsuperscript{139} and Farmer et al.\textsuperscript{140} initially reported on successful deceased donor LT for patients with situs inversus. The anomalies commonly associated with syndromic biliary atresia include polysplenia, aberrant hepatic arterial supply from the suprarenal artery, gut malrotation and situs inversus, preduodenal portal vein, and interrupted inferior vena cava withazygous continuation (Fig. 1). Because the retrohepatic cava is absent, the hepatic outflow is directly anastomosed to the atrial-hepatic cuff of the recipient. Other technical modifications may include dissection of the preduodenal vein down to the splenic and superior mesenteric vein junction, where the caliber may facilitate anastomosis or interposition grafting, and the use of arterial vascular grafts as necessary. Technical variant grafts and live donor segmental grafts have been successfully used.\textsuperscript{141} However, the absence of the retrohepatic cava may lead to a greater incidence of vascular torsion of the outflow anastomosis; the split segment graft should therefore be secured in a suitable anatomic position prior to closure with the falciform ligament or liver capsule.

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<tr>
<td>Study Reference</td>
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<tr>
<td>Diem et al.\textsuperscript{129}</td>
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<td>Fouquet et al.\textsuperscript{128}</td>
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<td>Utterson et al.\textsuperscript{16}</td>
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<td>Barshes et al.\textsuperscript{142}</td>
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<td>Chen et al.\textsuperscript{124}</td>
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<td>Shneider and Mazariegos, current report</td>
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Abbreviations: DDTV, deceased donor technical variant; N/A, not applicable; DD, deceased donor; N/A, not available.

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WAIT-LIST MORTALITY

In the SPLIT study, 3% of children with biliary atresia died while awaiting LT. Most had PELD scores > 20 and had evidence of growth failure. Probability of transplant from time of listing was 40%, 60%, and nearly 80% at 3, 6, and 12 months, respectively. United Network for Organ Sharing (UNOS) data demonstrated a median wait time of 90 days and a median PELD score at the time of transplantation of 15 versus 12 at registration.

OUTCOMES AFTER LT

Recent large series of outcomes after LT for biliary atresia are summarized in Table 3. The previously published series to date indicate excellent patient and graft survival rates at 10 years of 81%-86% and 71%-73%, respectively. A recent series of living donor LT for biliary atresia demonstrated 90% 10-year patient survival. At Children's Hospital of Pittsburgh, 308 primary liver transplants were performed between 1995 and 2006. Of these, 103 (33%) were performed for biliary atresia. Overall patient survival and graft survival were 90% and 82%, respectively. Kaplan-Meier patient and graft survival at 1, 5, and 10 years was 95%/87%, 90%/82%, and 88%/81%, respectively (Fig. 2).

Multivariate analyses of risk factors for patient death and graft loss are summarized in Table 4. As might be expected, growth failure was reported to be predictive for patient death by the SPLIT study, and this suggested a significant role for nutritional support when needed and early consideration of LT before nutritional and growth failure occurs. Although one study reported the impact of polysplenia syndrome on death, previous HPE has not been associated with patient mortality in any of these studies. Appropriately timed HPE, as described earlier, is clearly important in the initial management of children with biliary atresia. Infants were at greater mortality risk than older children in both the US SPLIT and UNOS reports.

Factors linked to graft loss include immunologic factors such as type of calcineurin inhibition used and

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**Table 4. Multivariate Factors Predictive for Patient and Graft Survival After Liver Transplantation (LT) in Biliary Atresia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Factors Predictive for Patient Survival</th>
<th>Factors Predictive for Graft Survival</th>
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<tbody>
<tr>
<td>Diem et al.</td>
<td>Pretransplant recipient weight</td>
<td>Type of calcineurin inhibitor</td>
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<tr>
<td>Fouquet et al.</td>
<td>Indication for LT</td>
<td>Age at LT &gt; 6 years</td>
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<tr>
<td>Utterson et al.</td>
<td>Age at LT</td>
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<tr>
<td>Barshes et al.</td>
<td>Polysplenia syndrome</td>
<td>N/A</td>
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<td>UNOS status 1</td>
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<td></td>
<td>Donor age &gt; 25 years</td>
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<td></td>
<td>Perioperative complications</td>
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<td></td>
<td>Infant age</td>
<td>Height/weight &lt; 2 SD</td>
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<td>Height/weight &lt; 2 SD</td>
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<td>CSA versus TAC</td>
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<td>Retransplant</td>
<td>Rejection</td>
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<td></td>
<td>DD partial/reduced (not split)</td>
<td>Donor age &lt; 5 months</td>
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<td>Life support at LT</td>
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</table>

**Abbreviations:** DDTV, deceased donor technical variant; N/A, not applicable; SD, standard deviation; UNOS, United Network for Organ Sharing; CSA, cyclosporine; TAC, tacrolimus; DD, deceased donor.
impact of rejection. Technical variant grafts were associated with greater loss in the SPLIT study but were not associated with increased patient mortality. Deceased donor technical variant partial or reduced grafts were associated with increased patient mortality in the UNOS report. Living donor transplantation at experienced centers is associated with favorable outcomes.

Taken as a whole, these multicenter and large case series indicate that using a full complement of current surgical techniques (whole organ as well as deceased and live donor technical variants) in experienced centers can minimize mortality for children waiting for LT and lead to excellent long-term outcomes. Careful assessment and management of medical issues in children with biliary atresia is essential. Failure of HPE mandates appropriate urgent consideration of LT and focus on maintaining adequate nutritional status preoperatively. Meticulous posttransplant care is critical to successful management of these challenging patients.

In-depth analysis of post-LT morbidity and mortality is beyond the scope of this article. However, it is clear that immunologic concerns still affect long-term graft function and that infection and sepsis continue to contribute to patient mortality, especially late mortality. Further improvements in long-term outcomes will likely be made as more patient-specific immunosuppression is achieved, with immune monitoring being used to guide individual titration of immunosuppression.

ACKNOWLEDGMENT
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