

## AASLD PRACTICE GUIDELINE

# Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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This practice guideline has been approved by the American Association for the Study of Liver Diseases, the American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

*Abbreviations: ALF, acute liver failure; GRADE, Grading of Recommendation Assessment, Development, and Evaluation; HB, hepatoblastoma; HCC, hepatocellular carcinoma; HPE, hepatoportoenterostomy; LT, liver transplantation; OTPN, Organ Procurement and Transplantation Network; PFIC, progressive familial intrahepatic cholestasis; TIPS, transjugular intrahepatic portosystemic shunt.*

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## Preamble

Current American Association for the Study of Liver Diseases (AASLD) liver transplant evaluation guidelines include both adult and pediatric patients.<sup>1</sup> While pediatric liver transplants account for ~7.8% of all liver transplants in the United States, sufficient differences between pediatric and adult patients seeking liver transplantation (LT) now require independent, yet complementary documents. This document will focus on pediatric issues at each level of the evaluation process. Disease categories suitable for referral to a pediatric LT program are similar to adults: acute liver failure, autoimmune, cholestasis, metabolic or genetic, oncologic, vascular, and infectious. However, specific etiologies and outcomes differ widely from adult patients, justifying independent pediatric guidelines. Data supporting our recommendations are based on a Medline search of the English language literature from 1997 to the present.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD Practice Guidelines Committee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the

**Table 1. Grading of Recommendations, Assessment, Development and Evaluation (GRADE)**

Criteria	
<b>Strength of Recommendation</b>	
Strong [1]	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak [2]	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption
<b>Quality of Evidence</b>	
High [A]	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate [B]	Further research may change confidence in the estimate of the clinical effect
Low [C]	Further research is very likely to impact confidence on the estimate of clinical effect

quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong or weak.

## Literature Review Methods and Analysis

Each Association appointed at least one author to serve on the writing group. The Chair of the writing group was appointed by the AASLD. Members of the writing group were not compensated for their work and served as volunteers throughout the process from concept design through final publication. Writing group members had no financial conflict of interest or financial relationship with commercial entities relevant to the article. Topics relevant to liver transplant evaluation in the pediatric patients were identified through a conference call with all members of the writing group on July 11, 2012 and assignments were distributed among the members based on their particular expertise and interest.

The literature databases and the search strategies are outlined below. The resulting literature database was available to all members of the writing group. They selected references within their field of expertise and experience and graded the references according to the GRADE system. Data supporting our recommendations are based on a MEDLINE search of the English language literature from 1973 to the present. Primary search terms included: liver transplant evaluation, liver transplant, child, pediatric, and liver transplant outcome. In addition, each assessment (e.g., anesthesia, hepatology, renal, etc.); diagnosis (e.g., biliary atresia, organic acidemia, maple syrup urine disease, ductal plate malformation, etc.) and complication (e.g., hepa-

topulmonary syndrome, malignancy, etc.) was searched in the context of the primary search terms as well as individually when relevant clinical background information was needed.

The selection of references for the guideline was based on a validation of the appropriateness of the study design for the stated purpose, a relevant number of patients under study, and confidence in the participating centers and authors. References on original data were preferred and those that were found unsatisfactory in any of these respects were excluded from further evaluation. There may be limitations in this approach when recommendations are needed on rare problems or problems on which scant original data are available. In such cases it may be necessary to rely on less qualified references with a low grading.

## Pediatric Liver Transplant Evaluation Team

Children have distinct diseases, clinical susceptibilities, physiological responses, as well as neurocognitive and neurodevelopmental features that distinguish them from adults. In fact, even within the pediatric age group differences can be found between newborns, infants, children, and adolescents. Given the intra-abdominal anatomical variations associated with biliary atresia, the most common indication for pediatric LT, as well as the restricted abdominal cavity and small size of blood vessels in infants and young children, surgical teams with exhaustive pediatric experience will benefit the pediatric recipient of an LT. Members of the pediatric LT team (Table 2) use their expertise to tailor the LT evaluation plan (Table 3) to the unique needs of the child. The end product of the evaluation will ensure the elements for an informed decision to proceed to LT are met.<sup>2</sup>

### **Recommendation:**

***1. A multidisciplinary pediatric LT evaluation team should be skilled in pediatric conditions and properly communicate with the family and the child, when appropriate, the processes, risks, and benefits associated with LT. (2-B)***

## Timing of Referral for Pediatric Liver Transplant Evaluation

Based on the United States Organ Procurement and Transplantation Network (OTPN) from January 1, 2011, through May 31, 2013, indications for LT include biliary atresia (32%), metabolic/genetic conditions (22%), acute liver failure (11%), cirrhosis (9%), liver tumor (9%), immune-mediated liver and biliary

**Table 2. Potential Members of the Pediatric Liver Transplant Team**

General	
• Transplant surgeon	
• Hepatologist/gastroenterologist with expertise in pediatric liver disease	
• Infectious disease specialist	
• Critical care specialist	
• Social worker	
• Psychologist/neuropsychologist/child development specialist	
• Dietician	
• Physical/occupational therapist	
• Pharmacist	
• Psychiatrist	
• Transplant coordinator	
• Anesthesiologist	
• Patient educator	
Selected patients	
• Cardiologist	
• Nephrologist	
• Neurologist	
• Genetic/metabolic specialist	
• Pulmonologist	
• Radiologist, diagnostic	
• Radiologist, interventional	
• Ethics specialist	
• Child life specialist	
• Pastoral care	

injury (4%), and other miscellaneous conditions (13%) (Fig. 1). Within these broad categories rest many rare conditions with myriad presentations.

As timing for referral varies depending on the child's clinical circumstances, referral for LT may be emergent, urgent, or anticipatory. Acute liver failure (ALF) or an acute decompensation of an established liver disease may have a rapid and unpredictable course progressing to death or irreversible neurological damage.<sup>3</sup> Children

**Table 3. Components of the Pediatric Liver Transplantation Evaluation**

Secure all prior records to identify relevant diagnostic, management and clinical information
Establish appropriate indications for referral
Construct a patient and disease specific appointment itinerary
Confirm or affirm the diagnosis, associated systemic manifestations, and management plan
Assess disease severity and urgency for liver transplantation
Identify opportunities to maximize current medical therapy
Determine if non-transplant surgical options are available
Identify contraindications for liver transplantation
Consider appropriateness of a live donor option
Confirm immunization status; if incomplete, establish a strategy to complete immunizations
Establish a trusting relationship among the child, family and transplant team
Ensure finances are available
Anticipate potential complications following transplant
Develop a management and communication plan with the local managing physician
Clarify logistics when a potential donor liver is available

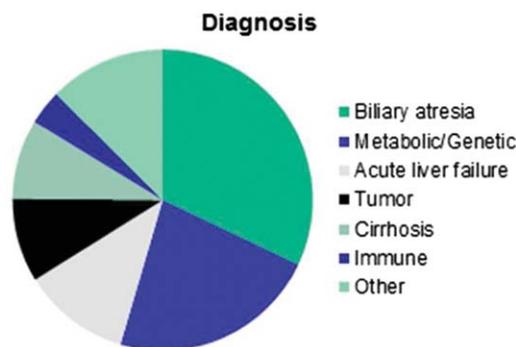


Fig. 1. Indications for pediatric liver transplant.

with metabolic liver disease, such as urea cycle defects or maple syrup urine disease, can suffer significant neurological sequelae as a consequence of metabolic crises.<sup>4</sup> Primary and secondary liver tumors are rare in children, with hepatoblastoma (HB) and hepatocellular carcinoma (HCC) being the most common. Survival for children with HB is dependent on response to initial chemotherapy and complete surgical resection.<sup>5</sup> Screening for HCC is imperfect, but an elevated or rising alpha-fetoprotein identifies a heightened risk for HCC.<sup>6</sup> Only 16% of children with biliary atresia survive to 2 years with their native liver if the total serum bilirubin measured 3 months following hepatoporoenterostomy (Kasai Procedure) is over 6 mg/dL, compared to 84% for those with a total bilirubin less than 2 mg/dL.<sup>7</sup> For some children with Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) types 1, 2, and 3, pruritus and/or deforming xanthomas can severely impact the child's quality of life despite relatively preserved liver function.<sup>8</sup> Sequelae associated with endstage liver disease place children at risk for life-threatening events.

#### Recommendations:

**2. Immediate contact with a pediatric LT center should be initiated for children with acute liver failure or acute decompensation of an established liver disease; emergent referral for LT evaluation may be required. (1-A)**

**3. Children with liver-based metabolic crises refractory to medical and/or surgical therapy (1-B), unresectable hepatoblastoma (1-B), or evidence of hepatocellular unresectable carcinoma (1-B) should be referred urgently for LT evaluation.**

**4. Biliary atresia (BA) patients who are post-hepatoporoenterostomy (HPE) should be promptly referred for LT evaluation if the total bilirubin is greater than 6 mg/dL beyond 3 months from HPE**

*(1-B); liver transplant evaluation should be considered in BA patients whose total bilirubin remains between 2-6 mg/dL. (1-B)*

**5. Referral for LT evaluation should be anticipated for children with chronic liver disease and evidence of deteriorating liver function characterized by poor weight gain, growth failure, variceal hemorrhage, intractable ascites, recurrent cholangitis, or episodes of spontaneous bacterial peritonitis, pruritus, advancing encephalopathy, and/or uncorrectable coagulopathy. (1-B)**

## Liver Transplant Evaluation

### *Affirm Diagnosis and Management*

The child's diagnostic evaluation as it relates to their primary disease, associated comorbidities, subspecialty consultations, and management strategies should be documented and provided by the primary pediatric specialist responsible for management of the child's liver disease. These documents should include clinical assessments, results of laboratory and diagnostic studies, medical and nutritional management, surgical procedures, pathology reports and slides, as well as radiographic reports and copies of the radiographs. Personal communication between a member of the LT evaluation team and the child's physician will identify clinical, social, and psychological factors that may not be apparent in the medical record. New or worsening comorbidities may be identified during the LT evaluation.<sup>9</sup>

### *Recommendations:*

**6. A review of the local records by the LT team prior to the LT evaluation will inform the evaluation schedule and enable affirmation of the primary diagnosis, assessment of comorbidities, and identify technical challenges related to LT. (2-B)**

**7. In collaboration with the local primary pediatric specialist, management of the primary disease and comorbidities should be reviewed and optimized. (2-B)**

### *Hepatology Assessment*

Complications associated with endstage liver disease include ascites, pruritus, portal hypertension, malnutrition, vitamin deficiencies, and delayed growth and development.<sup>10</sup> In cirrhosis patients, accumulation of ascites is a result of portal hypertension, vasodilatation, and hyperaldosteronism.<sup>11</sup> Hypoalbuminemia is an additional risk factor for ascites. Ultrasonography is sensitive enough to detect as little as an ounce of intra-abdominal fluid, while significantly more is required

for it to be detected on physical examination. Decisions to initiate diuretic therapy to manage ascites are ill-defined. Abdominal distension alone does not reliably predict ascites, as organomegaly and vascular congestion of the bowel may also contribute to distension. Fluid that is easily palpated between the abdominal wall and the surface of the liver ("ballotable fluid") would suggest sufficient ascites to warrant therapy; its presence can be used to judge response to therapy. Initial treatment includes spironolactone and a "no-added" salt diet. Loop-diuretics should be used with caution as overaggressive diuresis can precipitate hepatorenal syndrome. For hospitalized patients with significant ascites, intravenous albumin, with or without an accompanying diuretic, can improve diuresis and response to diuretics.<sup>12</sup> Tense ascites can compromise respiratory function and renal perfusion, heighten the risk for infection, and contribute to a poor quality of life.<sup>13</sup> Large-volume paracentesis<sup>14</sup> and transjugular intrahepatic portosystemic shunt (TIPS)<sup>15</sup> are effective if ascites is compromising the child's respiratory effort and is not responsive to medical therapy. Rapid accumulation of ascites should raise concern for obstruction of the portal or hepatic vein or bacterial peritonitis.

Evaluation and management of esophageal varices in children varies widely among practitioners.<sup>16,17</sup> In the absence of data supporting primary prophylactic therapy for esophageal varices in children, screening endoscopy for esophageal varices has not been recommended.<sup>18</sup> Inflammatory bowel disease (IBD), particularly ulcerative colitis, is a notable comorbidity of children with primary sclerosing cholangitis (PSC). Following LT, some patients with autoimmune hepatitis and bile salt excretory pump disease are at risk for recurrence of their primary liver disease<sup>19,20</sup>; those with PSC may also be at increased risk for colon cancer.<sup>21,22</sup>

### *Recommendations:*

**8. Clinically detectable ascites can be managed initially with an aldosterone antagonist (2-B); more aggressive removal of ascitic fluid using paracentesis or transjugular intrahepatic portosystemic shunt or surgical shunt should be reserved for ascites that compromises respiratory effort or severely affects quality of life. (2-B)**

**9. Patients with conditions such as autoimmune hepatitis, PSC, and bile salt excretory pump disease should be informed that liver disease can recur post-LT. (2-B)**

**10. Patients at risk for extrahepatic complications such as IBD should be informed of the need for**

***scheduled monitoring for evidence of IBD, including colonoscopy, for colon cancer surveillance. (2-B)***

### ***Nutrition Assessment***

Children with chronic liver disease are at risk for malnutrition as they require 20%-80% more calories than normal children to achieve adequate growth.<sup>23-25</sup> Increased caloric requirements result from a hypermetabolic state coupled with malabsorption. Aggressive nutritional support prior to LT improves patient and graft survival as well as neurodevelopmental outcome.<sup>26,27</sup> Serial triceps skin fold and mid-arm circumference are the most reliable anthropometric assessments to judge nutritional status, as reliance on weight alone may overestimate nutritional adequacy in children with chronic liver disease.<sup>24,25,28</sup> Fat soluble vitamin (FSV) deficiency is common and dosing and monitoring recommendations to prevent FSV deficiency are available.<sup>24,25,29,30</sup> Enteral formulas that contain medium chain triglycerides (MCT) are preferred in cholestatic patients, but excessive administration of MCT can lead to essential fatty acid deficiency.<sup>31</sup> Protein intake should not be restricted in the absence of hyperammonemia.<sup>32</sup> When oral intake is not sufficient, initiation of nasogastric (NG) tube feeding improves body composition in children with chronic liver disease.<sup>33</sup> Parenteral nutrition may help reverse poor weight gain and growth in malnourished children with BA.<sup>34</sup>

Less than 15% of children receiving a liver transplant are obese.<sup>35</sup> Patients with body mass index (BMI) z-scores  $\geq 3$  have similar short-term survival as normal-weight counterparts, but had increased late (>12 years) mortality and are more likely to experience posttransplant obesity.<sup>36</sup> Metabolic syndrome occurs frequently in obese adult liver transplant recipients, but the rate in obese pediatric recipients is not known.<sup>37,38</sup>

### ***Recommendations:***

***11. Complete nutritional assessment should include serial triceps skin fold thickness and mid-arm circumference measurements (2-B); identification of nutritional goals to maximize health; fat soluble vitamin supplementation and monitoring (2-B); and in cholestatic infants, use of medium-chain triglyceride-containing formulas with normal protein administration (2-4 g/kg/day). (2-B)***

***12. Aggressive nutritional support for children awaiting LT should be initiated to optimize outcomes (1-B); NG tube feedings and parenteral nutrition may be needed in some circumstances. (2-B)***

### ***Cardiopulmonary Assessment***

Structural cardiac disease can be seen in children with BA and Alagille syndrome.<sup>39</sup> Cirrhotic cardiomyopathy (CC), characterized by increased cardiac output, impaired diastolic relaxation, myocardial hypertrophy, and repolarization abnormalities, carries a high risk of post-LT mortality in adults. Evidence of cardiomyopathy, as determined by two-dimensional echocardiography (2-DE), can also be found in children with cirrhosis as well as those with cardiomyopathy associated with glycogen storage disease or systemic mitochondrial disease. In one study, 70% of children with BA had evidence of CC.<sup>40</sup> While those with CC experienced a longer ICU and hospital stay, there were no differences in the 2-DE between those who died awaiting LT versus those who survived to LT.

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHN), both described in more detail below, are potentially life-threatening conditions that develop as a consequence of portosystemic shunting regardless of the severity of the liver disease.<sup>41,42</sup> Nonspecific clinical findings include digital clubbing, facial telangiectasia, dyspnea, wheezing, and syncope. Screening for HPS is performed by pulse oximetry detection of oxygen desaturation when in the sitting or standing position; pulse oximetry less than 97% on room air should be considered for further evaluation.<sup>43</sup> HPS is confirmed with 2-DE during infusion of agitated saline with the appearance of saline bubbles in the left atrium within 3-6 cardiac cycles. A <sup>99m</sup>Techneium-macroaggregated albumin (MAA) perfusion lung scan can be used to quantify and follow the degree of intrapulmonary shunting; an MAA shunt fraction of 27.8% was highly specific for intrapulmonary shunting associated with hypoxia.<sup>44,45</sup> Unlike HPS, screening procedures for PPHN are imperfect. While the chest radiograph and electrocardiogram may reveal a prominent pulmonary artery and right ventricular hypertrophy, but both may be normal.<sup>46</sup> In addition, 2-DE with Doppler may show elevations in right ventricular systolic pressures which should be confirmed by cardiac catheterization to exclude other causes of pulmonary hypertension such as increased central volume and high cardiac output due to a hyperdynamic cardiac physiology.<sup>47</sup>

Patients with cystic fibrosis (CF) referred for LT present a unique challenge. In addition to being at risk for development of HPS and PPHN, the severity of CF-related lung disease can impact outcome. The forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) have been used in a model

to predict survival.<sup>48</sup> FEV1 was found to be lower in CF patients with liver disease who subsequently receive LT than those who do not undergo LT and is used to monitor improvement following LT.<sup>49</sup>

**Recommendations:**

**13. Screening transcutaneous oxygen saturation with the patient in the upright position should be performed in all patients with possible portosystemic shunting. (2-B)**

**14. Two-dimensional echocardiography (2-DE) with Doppler should be performed in all patients at the time of liver transplant evaluation (2-B); if the right ventricular systolic pressure is over 50 mmHg by 2-DE, a right-heart cardiac catheterization is necessary to establish the diagnosis of portopulmonary hypertension. (2-B)**

**15. Pulmonary function tests, including forced expiratory volume in one second and forced vital capacity should be performed in patients with cystic fibrosis evaluated for liver transplant. (2-B)**

**Renal Assessment**

Glomerular filtration rate (GFR) is the most practical measure of kidney function.<sup>50</sup> Direct measurement of GFR using an exogenous filtration marker, such as iohexol plasma clearance, is impractical in the routine clinical setting.<sup>51</sup> Endogenous filtration markers, such as creatinine clearance, are hampered by the imperfections of timed urinary collections. Static measurements of naturally filtered molecules, such as creatinine, are affected by muscle mass, age, and gender as well as renal tubular absorption and secretion. At best, only an estimate of the GFR can be achieved.

Serum creatinine, while imperfect, is most often used to screen individuals for evidence of renal insufficiency, but cannot be used to estimate GFR independently. The recently revised Schwartz Formula utilizes the serum creatinine (sCr), patient height, and a “constant” to derive an estimated creatinine clearance (eCCL) and is easily used at the bedside.<sup>51</sup> The formula is  $0.413 \times [\text{sCr (mg/dL)} / \text{height (cm)}] = \text{GFR (mL/min/1.73 m}^2\text{)}$ . Cystatin C is a low molecular weight protein that is almost completely filtered by the glomerulus, is not excreted or absorbed by the renal tubules, and is not affected by muscle mass, age, or gender.<sup>52</sup> Normal values for cystatin C are high in infants but approach normal adult levels (0.51-0.98 mg/L) by 1 year of age.<sup>53</sup> A cystatin C level of 1.06 mg/L predicted a GFR <80 mL/min/1.73 m<sup>2</sup> with a sensitivity and specificity of 91% and 81%, respectively, in a pediatric cohort of 62 children with a

median age of 3.1 years (range 0.6-18.7 years) that included both pre- and post-LT patients.<sup>52</sup> For children with acute renal injury, the pediatric modified RIFLE (Risk for renal dysfunction, Injury to the kidney, Failure of the kidney, Loss of kidney function, and Endstage renal disease) criteria utilizes a combination of the eCCL by the Schwartz method and urine output to inform the severity of renal injury.<sup>54</sup>

Renal insufficiency that would necessitate combined liver and kidney transplant (CLKT) is less common in children than adults.<sup>55</sup> Renal dysfunction among children with chronic liver disease can be quite variable. For example, children with biliary atresia tend to have good renal function prior to and following liver transplant,<sup>56,57</sup> while those with tyrosinemia may have a glomerular filtration rate of less than 55 mL/min/1.73 m<sup>2</sup>.<sup>58</sup> Significant renal disease can be associated with primary hyperoxaluria, congenital hepatic fibrosis, and methylmalonic acidemia. Renal dysfunction prior to LT can be exacerbated following LT, particularly in children with inborn errors of metabolism, alpha-1-antitrypsin deficiency (A1ATD), and Alagille syndrome (AGS).<sup>59-62</sup> Increased susceptibility to renal toxicity caused by calcineurin inhibitors may be attributed to associated genetic polymorphisms in the ABCB1 gene.<sup>63</sup>

**Recommendations:**

**16. Renal function should be assessed in all patients, with special emphasis on those with metabolic liver diseases associated with renal dysfunction (1-B) and those at increased risk for calcineurin inhibitor toxicity. (2-B)**

**17. Serum creatinine alone should not be used to assess renal function (1-B); either cystatin C (2-B) or the revised Schwartz Formula (2-C) should be used to estimate the glomerular filtration rate in children with chronic liver disease.**

**18. The modified Risk for Renal Dysfunction, Injury, Failure, Loss, and Endstage renal disease could be used to assess the degree of acute renal injury. (2-B)**

**Dental Assessment**

Dental caries due to frequent and prolonged bottle-feeding occur in children with endstage liver disease.<sup>64,65</sup> A survey of transplant centers in the United States noted that a dental infection prior to transplantation resulted in cancellation or postponement of LT (38% of responding sites) and post-LT sepsis from a suspected dental source (27% of sites).<sup>66</sup> Preventive oral health care strategies are important in this patient population.<sup>66,67</sup>

**Recommendation:**

**19. Children with endstage liver disease should receive a careful oral examination looking for evidence of dental caries, gingival disease, or dental abscess; referral to a pediatric dentist should occur if abnormalities are identified. (2-B)**

**Anesthesiology Assessment**

General anesthesiology assessment should include determination of venous access, review of cardiovascular, respiratory, gastrointestinal, renal, central nervous system, hepatic, and hematological systems.<sup>68</sup> Pathophysiological changes associated with these systems will impact method of induction, intraoperative fluid management, drug dosing, and ventilatory requirements.<sup>68,69</sup> Risk factors that require careful assessment include patient age and weight, nutritional status, hypoalbuminemia, hepatopulmonary syndrome, and cardiomyopathy associated with cirrhosis.<sup>69,70</sup> Pediatric conditions and their associated comorbidities that may heighten anesthetic risk include Alagille syndrome (cardiac disease, vascular and renal abnormalities, and moyamoya), biliary atresia with splenic malformation (complex heart disease, interrupted inferior vena cava), and primary hyperoxaluria (renal and cardiac dysfunction).<sup>69</sup> A specialized LT anesthesia team has been associated with more favorable patient outcomes in adults, although pediatric centers were excluded from this study.<sup>71</sup> The United Network for Organ Sharing (UNOS) has recently modified policy to require liver transplant programs to designate a Director of Liver Transplant Anesthesia who has expertise in the area of perioperative care of liver transplant patients and can serve as an advisor to other members of the team.

**Recommendation:**

**20. An anesthesiologist familiar with pediatric indications for LT and associated comorbidities should ensure the LT evaluation includes appropriate disease-specific assessments to minimize intraoperative and postoperative anesthetic risk. (2-B)**

**Immunization Status and Assessment of Viral Susceptibilities**

Children with chronic liver disease are often not fully immunized prior to LT.<sup>72,73</sup> Development of a vaccine preventable disease (VPD) either before or after LT will increase morbidity and mortality and heightened the risk of graft injury or loss.<sup>74,75</sup> Timing of immunization administration in the LT candidate is important, as vaccines are more immunogenic before the development of endstage liver disease and more

immunogenic before than after LT. Humoral immunity to rubella, measles, and varicella vaccines is significantly decreased in children with biliary atresia compared to healthy controls.<sup>76</sup> VPD can develop in immunized children with chronic liver disease when antibody titers are low.<sup>77</sup> There is a paucity of data related to influenza vaccine in patients with chronic liver disease.<sup>78</sup> Hepatic decompensation has been reported with influenza,<sup>79</sup> and influenza vaccination in adults with cirrhosis significantly reduced the frequency of hepatic decompensation compared to those who did not receive the vaccine.<sup>80</sup> Guidelines for vaccination of liver transplant candidates and recipients are published periodically by the American Society of Transplantation.<sup>81</sup> Clinical practice guidelines for vaccination of the immunocompromised host were recently published by the Infectious Diseases Society of America.<sup>82</sup>

Vaccination of household contacts provides additional protection to the child.<sup>83</sup> Paralytic polio has been described in household contacts of oral polio vaccine recipients.<sup>84</sup> Data suggest that administration of live virus vaccines to household contacts, other than oral polio, poses minimal risk to the child.<sup>83</sup>

Both Epstein-Barr virus (EBV)-associated lymphoproliferative disease and disseminated cytomegalovirus (CMV) are associated with significant morbidity and mortality in children receiving LT. Children are at highest risk for these conditions if they are immunologically naive to EBV and CMV and receive a liver from a serologically positive donor.<sup>85,86</sup> LT candidates serologically positive for CMV remain at risk for developing post-LT CMV.<sup>87</sup> Preventive strategies to reduce EBV and CMV disease post-LT include assessment of EBV and CMV status in the recipient and have significantly improved LT outcomes.<sup>86,87</sup>

**Recommendations:**

**21. Completion of all age-appropriate vaccinations, for the child and family members, should occur prior to transplantation and ideally before the development of endstage liver disease (1-B); children who have not completed the necessary vaccine schedule can receive vaccinations on an accelerated schedule. (1-B)**

**22. Seasonal inactivated influenza vaccination should be given for listed patients older than 6 months and their family members, and to family members of infants less than 6 months. (1-A)**

**23. Family members of children evaluated for LT should be fully immunized using both live and attenuated virus vaccines (1-B); the oral polio vaccine should never be used. (1-A)**

**24. Evidence of a prior Epstein-Barr virus and cytomegalovirus infection, as determined by virus-specific serological measurements, should be performed on all individuals evaluated for liver transplant, recognizing that for children less than 12-18 months of age, antibodies may have been passively transmitted to the child from the mother. (1-A)**

#### **Psychosocial Assessment**

Successful LT requires lifelong care and presents unique challenges to families dealing with a child with a serious illness.<sup>88</sup> Feelings of guilt, inadequacy, stress, lack of control, uncertainty, anger, and fear by the primary caregiver can have a negative impact on disease management and family structure unless they are identified and addressed. Lack of parental understanding of the child's condition, of housing, and transportation are deleterious to the management of chronic conditions. Engagement of child protective services may be necessary if the principal impediment to successful disease management is the child's social situation.<sup>89,90</sup>

Psychosocial factors impact posttransplant outcomes, specifically factors related to treatment adherence.<sup>91-93</sup> Risk factors for nonadherence include a history of resistance to taking medications, substance abuse, physical or sexual abuse, school absenteeism, single parent home, and having received public assistance. Psychiatric assessment tools designed for pediatric LT candidates can identify risk factors such as parental psychopathology, substance abuse by the parent/guardian or patient, chaotic family environment, family perceptions, and lack of financial resources suggesting high-risk candidates who would benefit from targeted early intervention, including barriers to adherence.<sup>93-96</sup>

#### **Recommendations:**

**25. Families should be assessed to ensure social services and psychosocial support systems are adequate for LT-candidates in order to optimize posttransplantation outcomes. (1-B)**

**26. Patients and families at potential risk for nonadherence should be identified and receive focused psychosocial interventions prior to and following transplantation. (1-B)**

**27. Members of the transplant team, in conjunction with the child's primary care provider, may need to serve as the child's advocate in situations where support systems are inadequate to the degree that the child's transplant candidacy in impaired or a high risk of noncompliance is identified. (1-B)**

#### **Neurocognitive and Neurodevelopmental Assessment**

Cognitive measures have revealed reduced global cognitive functioning in children following LT,<sup>97-99</sup> and specific weaknesses in motor skills and receptive language development following LT.<sup>100,101</sup> Poorer nutritional status early in life, reduced head circumference, poor weight gain and growth, and low vitamin E levels correlate with poor cognitive functioning before and after transplantation.<sup>98,102,103</sup> The association of serum bilirubin at transplantation was reported to correlate with adverse neurocognitive outcomes after LT remains controversial.<sup>100,103</sup>

Children with biliary atresia demonstrate weaknesses in gross motor and expressive language development, with females being more vulnerable. Fine motor, visual problem solving, and receptive language development fell within the average range for age.<sup>104</sup> Age at Kasai correlated inversely with receptive language performance.<sup>105</sup>

The presence of a severe intellectual or developmental disability has raised concerns of candidacy for LT. Those concerns center upon compliance with a rigorous and lifelong posttransplant management schedule, potential for increased risk for malignant or infectious complications related to genetic or physical disabilities, and assessment of quality of life. Unfortunately, data to address these concerns are very limited. Results of a survey received from 50 of 88 pediatric solid organ transplant programs suggests a wide variation among centers regarding the importance of neurodevelopmental delay in the decision to list for organ transplantation.<sup>106</sup> Successful renal transplantation with good graft function over a mean observation period of 41 months was possible in a highly selected cohort of 25 multiply handicapped pediatric renal transplant candidates.<sup>107</sup>

#### **Recommendations:**

**28. Neurocognitive testing should be performed in children awaiting LT to identify areas warranting early intervention to minimize later cognitive difficulties (2-B).**

**29. Aggressive nutritional management and early intervention should be initiated to minimize neurocognitive and developmental deficits (2-B).**

#### **Consideration for Living-Related and Living-Donor LT**

The numbers of pediatric deaths awaiting LT were dramatically reduced with the introduction of living-related liver transplantation (LRLT).<sup>108</sup> As surgical

techniques for both the donor and recipient improved, the potential donor pool was extended to nonrelatives for living-donor liver transplantation (LDLT) including, in rare instances, anonymous living liver donation.<sup>109-111</sup> An example of the potential advantage of LDLT over LRLT would be in recipients with genetic hepatopathies (e.g., Alagille syndrome) when the donor may be an asymptomatic relative and not a good candidate if they share common alleles.

To consider LDLT, LT must 1) be the only therapeutic option, or 2) deceased donor LT is not an option, or 3) a deceased donor organ has not become available. Furthermore, for the LDLT to be ethically appropriate, the likelihood the recipient will survive following LDLT should be high, the mortality risk to the donor low, and the donor is well informed of the risks to his/her short- and long-term health.<sup>108</sup> Considerable pressure is placed on the potential donor from both internal and external sources to save the life of a child or relative. These pressures should be addressed throughout the donor evaluation process to ensure the donor's "free will" to proceed with liver donation and have the ability to confidentially remove him or herself from consideration at any time.

Consideration of LDLT for a child with acute liver failure has raised concerns that the emergent clinical environment might be coercive to a potential donor and impede honest informed consent. While coercion is difficult to assess, postoperative evaluation of donors have found positive emotional and psychological outcomes regardless of the outcome for the patient.<sup>112</sup> Pediatric patients with acute liver failure who received LDLT had decreased wait times to LT, decreased cold ischemia time, and improved survival compared to a group who received a cadaveric donation.<sup>113</sup>

In addition to the standard evaluation requirements to assess general health status, surgical risks, volume of the segments to be removed, and evidence of a transmissible virus, the potential donor will require additional assessments that include psychological assessment and social support systems. If the potential recipient has an inherited metabolic disease, the feasibility of a parent wishing to serve as an LRLT donor should be determined in the context of the child's genetic condition.<sup>114</sup> LRLT has been successfully performed using heterozygote donors for conditions such as Crigler-Najjar syndrome type 1,<sup>115</sup> Wilson's disease,<sup>116</sup> carbamoyl-phosphate synthase 1 deficiency,<sup>117</sup> propionic acidemia,<sup>118</sup> arginosuccinic aciduria,<sup>119</sup> progressive familial intrahepatic cholestasis,<sup>120</sup> alpha-1 antitrypsin deficiency,<sup>121</sup> tyrosinemia,<sup>121</sup> Alagille syndrome,<sup>122</sup> and others. In patients with Alagille syn-

drome receiving LRLT, poor recipient outcomes or technical failure due to bile ducts being too small to utilize are reported if the donor has bile duct hypoplasia.<sup>122</sup> Children receiving an LRLT for arginosuccinic aciduria may still require arginine supplementation during periods of physiological stress or fasting due to persistent deficiency in extrahepatic tissues.<sup>119</sup>

#### **Recommendations:**

**30. Living-related liver transplantation (LRLT) can be performed in many inherited genetic conditions (2-B); long-term follow-up is necessary to determine the full impact of LRLT for these rare conditions and to assess potential risk to the donor. (2-B)**

**31. A first-degree family member may be considered for living donation in Alagille syndrome, but donor evaluation must include careful assessment to rule out bile duct hypoplasia that may include liver biopsy and/or cholangiography (2-B); if the potential donor and recipient share the same mutant Jagged 1 or Notch 2 allele the donor should be carefully evaluated for bile duct hypoplasia and vascular anomalies, but LRLT is not advisable in most circumstances. (2-B)**

## **Indications for Liver Transplantation**

### **Biliary Atresia**

Biliary atresia (BA) is universally fatal if untreated and is the single most common cause of liver disease leading to LT in children.<sup>123,124</sup> Diagnosis of BA and performance of a hepatopertoenterostomy (HPE; Kasai Procedure) by 8 to 10 weeks of age is optimal for transplant-free survival beyond early childhood. Infants with BA with vitamin K nonresponsive coagulopathy, hypoalbuminemia, histologically advanced cirrhosis, ascites, portal hypertension, and poor nutritional status prior to HPE have poor outcomes.<sup>125</sup> Following HPE, up to 70% of BA patients may have prolonged transplant-free survival if the total serum bilirubin falls below 2 mg/dL within 3 months following the HPE.<sup>7,124,126</sup> Children with biliary atresia splenic malformation (BASM) may have less favorable rates of transplant-free survival as reported in some studies,<sup>7,125,127-131</sup> but not others.<sup>132,133</sup>

Post-HPE complications include ongoing cholestasis, cholangitis, portal hypertension with or without variceal hemorrhage, poor weight gain, fat soluble vitamin deficiencies, hepatopulmonary syndrome, portopulmonary hypertension, and rarely hepatocellular carcinoma. Post-HPE regimens to promote bile flow (i.e.,

ursodeoxycholic acid) in BA patients are not standardized.<sup>124,126,134-136</sup> Prophylactic antibiotic regimens with either trimethoprim/sufamethaxazole or neomycin reduce recurrent rates of cholangitis and improve survival.<sup>137,138</sup> High-dose corticosteroid therapy initiated within 72 hours of HPE was not shown to improve bile drainage at 6 months, nor did it enhance transplant-free survival up to 2 years of age.<sup>139</sup> Aggressive nutritional support to ensure adequate growth and prevention of fat soluble vitamin deficiency can improve neurodevelopmental and transplant outcome.<sup>27,103,140,141</sup> Management of portal hypertension remains poorly studied in children and use of beta-blocker therapy for primary prophylaxis of variceal hemorrhage is controversial in childhood.<sup>18</sup> Variceal hemorrhage may be the sentinel event that prompts LT evaluation. Anecdotal cases of hepatocellular carcinoma (HCC) in BA patients have been reported, including patients less than 1 year of age, but the risk of HCC in BA is low.<sup>142-144</sup>

LT is recommended for BA patients' post-HPE with complications of chronic liver disease.<sup>7</sup> Recurrent cholangitis with or without associated decompensation of liver function can be an indication for LT in BA.<sup>145</sup> At least 80% of patients with BA are transplanted by 20 years of age, with the majority transplanted under 4 years of age.<sup>7,126</sup> Technical variant grafts (i.e., living related, split) are frequently utilized in smaller children with comparable results.<sup>140</sup> In the U.S., the overall 10-year actuarial graft and patient survival for liver transplant in BA is 73% and 86%, respectively.<sup>146</sup>

#### **Recommendations:**

**32. Hepatopertoenterostomy (HPE) is the preferred initial management for biliary atresia (1-B), but liver transplant evaluation should be considered in infants with evidence of decompensated liver disease prior to HPE. (2-B)**

**33. Aggressive nutritional support prior to LT is needed to improve outcomes in cholestatic children with BA. (1-B)**

**34. BA patients post-HPE should be promptly referred for LT evaluation if the total bilirubin is greater than 6 mg/dL beyond 3 months from HPE (1-B); liver transplant evaluation should be considered in BA patients whose total bilirubin remains between 2-6 mg/dL (1-B), and for those with lesser bilirubin values who have unmanageable consequences of biliary cirrhosis or portal hypertension. (2-B)**

**35. High-dose corticosteroid therapy initiated within 72 hours of HPE is not recommended. (1-B)**

#### **Alagille Syndrome**

Alagille syndrome (AGS) is an autosomal dominant, multisystem disorder which may affect the liver, heart, eyes, and skeleton, kidneys, and cerebro-vascular or peripheral vascular systems with recognizable facial features including triangular facies, hypertelorism, prominent forehead, and pointed chin.<sup>147-150</sup> Liver involvement ranges from minimal liver test abnormalities to biliary cirrhosis. Infants and children with AGS and significant cholestasis may experience well-compensated liver disease with absent or minimal evidence of clinical liver disease later in life.<sup>151</sup>

An estimated 20% to 30% of patients with AGS will require LT.<sup>152-155</sup> Impaired synthetic function, uncontrolled portal hypertension, and chronic encephalopathy are uncommon in AGS. Complications of profound cholestasis, intractable pruritus, failure to thrive, severe hypercholesterolemia, and osteodystrophy have prompted consideration for LT.<sup>62,122,153,155-157</sup> However, partial internal biliary diversion,<sup>158</sup> partial external biliary diversion,<sup>159</sup> and ileal exclusion<sup>160</sup> have improved pruritus, xanthoma burden, and quality of life in some patients. Hypercholesterolemia associated with AGS is predominantly due to elevations in lipoprotein X which may, in fact, protect against atherosclerosis.<sup>161</sup> Reduced somatic growth parameters are recognized components of AGS. While cholestasis is resolved by LT, growth parameters may not be completely reversed by LT.

The potential for multisystem involvement seen in AGS adds to the complexity of LT decisions, including vascular anomalies, cerebral aneurysms, narrowing of the internal carotid artery, abdominal coarctation, and renal artery stenosis. There is no consensus on imaging the head and neck for vascular anomalies in the absence of symptoms, as surgical intervention is unlikely under those circumstances. However, repair of a coarctation of the abdominal aorta or renal artery stenosis should be considered prior to LT.<sup>161</sup> Comorbidities resulting from multiorgan involvement have a significant impact on the outcome of LT, with structural cardiac disease being the most important contributor to mortality.<sup>152,162</sup>

Increased intraoperative fluid requirements place a significant burden on cardiac function and pulmonary blood flow. Patients with AGS often have established right ventricular hypertrophy which, coupled with increased pulmonary vascular resistance associated with pulmonary artery stenosis, may increase the risk of diminished cardiac output and poor graft perfusion. Echocardiogram alone may be insufficient to assess the descending aorta and peripheral pulmonary artery

branches.<sup>151</sup> Utilization of a dynamic stress test with dobutamine during cardiac catheterization can identify those patients who can successfully increase their cardiac output by over 40%, the necessary cardiac response for successful LT.<sup>163</sup>

Posttransplant survival rates vary between 82.9% and 87% at 1 year, 78.4% and 86% at 5 years,<sup>164</sup> and 80.9% at 10 years.<sup>165</sup> Long-term survival rates between AGS and all other pediatric liver transplant recipients were reported to be similar in a single-center experience.<sup>165</sup> However, a review of the UNOS database revealed 5-year graft and patient survival was worse for AGS compared BA patients, 61.5% versus 70% ( $P=0.02$ ) and 78.4% versus 84% ( $P=0.01$ ), respectively.<sup>164</sup> Risk factors for poor outcome among AGS patients included neurological and cardiac complications. Renal disease associated with AGS will require a renal-sparing immunosuppressive regimen to minimize the risk of renal dysfunction following LT.<sup>166</sup>

#### **Recommendations:**

**36. Patients with AGS should be carefully assessed for evidence of extrabepatic manifestations of this multisystem disorder; decisions regarding liver transplant should be individualized to include potential nontransplant treatment options for nonlife-threatening complications such as intractable pruritus and deforming xanthoma with biliary diversion or ileal exclusion. (1-B).**

**37. Realistic expectations related to growth potential following LT should be made clear to the family. (1-B)**

**38. Careful assessment of cardiac and renal function should occur during LT evaluation in all liver transplant candidates. (2-B)**

**39. Pretransplant vascular imaging of the intra-abdominal vasculature should be performed (2-B); vascular imaging of the head and neck may be considered. (2-C)**

#### **Wilson's Disease**

Wilson's disease (WD) is a chronic liver condition with a myriad of presentations. WD may be clinically indistinguishable from autoimmune hepatitis, nonalcoholic fatty liver disease, or cryptogenic cirrhosis.<sup>167</sup> The most dramatic presentation is fulminant WD, particularly when encephalopathy is present. A child over 5 years of age with ALF accompanied by a Coombs-negative hemolytic anemia and low or normal serum alkaline phosphatase should heighten the suspicion for WD. WD presenting with an acute hemolytic crisis carries a poor prognosis; short-term clinical and

biochemical improvement following plasma exchange coupled with chelation therapy is noted, but outcomes are variable.<sup>168</sup> The AASLD produced joint adult and pediatric guidelines that include recommendations for liver transplant evaluation.<sup>167</sup>

#### **Acute Liver Failure**

Pediatric acute liver failure (PALF) is a rapidly evolving condition that differs from adults with ALF in areas of etiology, management, and outcomes.<sup>169,170</sup> Efforts to define PALF remain challenging, but entry criteria established for the PALF longitudinal research study serve to identify children who require focused diagnostic and management strategies. Those entry criteria include: 1) absence of a known, chronic liver disease; 2) liver-based coagulopathy that is not responsive to parenteral vitamin K; 3) International Normalized Ratio (INR) between 1.5 and 1.9 with clinical evidence of encephalopathy or 2.0 and higher regardless of the presence of clinical encephalopathy.

Children with PALF may experience rapid clinical progression to irreversible brain injury or death.<sup>3,171</sup> Diagnoses differ between infants, children, and adolescents with some that are potentially treatable, such as herpes simplex,<sup>172</sup> gestational alloimmune liver disease,<sup>173</sup> autoimmune hepatitis,<sup>174</sup> acute acetaminophen toxicity,<sup>175</sup> and Wilson's disease.<sup>168,176</sup> As clinical deterioration can occur rapidly and unexpectedly, coordinated management at a pediatric liver transplant center involving a pediatric gastroenterologist with expertise in liver disease, intensive care specialist, and liver transplant surgeon, along with other supportive personnel will optimize patient outcome. Outcomes vary among and between etiologies, patient age groups, and disease severity.<sup>169</sup> However, children with an indeterminate diagnosis are more likely to receive a liver transplant.<sup>177</sup>

Decisions to proceed to liver transplant in PALF are complicated by difficulties in predicting outcome. Unfortunately, disease severity scores fall short in predicting the likelihood of death for an individual patient, raising the possibility that some children may have survived without a liver transplant.<sup>178,179</sup> Equally problematic is the absence of tools or clinical paradigms to predict irreversible brain injury. Contraindications to LT in PALF include severe multisystem mitochondrial disease, particularly those associated with valproic acid toxicity,<sup>180</sup> uncontrolled sepsis, and irreversible cerebral edema with uncal herniation. Children presenting with ALF due to hemophagocytic lymphohistiocytosis are candidates for nonliver transplant therapies which include immunosuppressive therapy or bone marrow transplantation.<sup>181</sup>

**Recommendations:**

**40. Pediatric acute liver failure (PALF) patients should receive early contact with and/or referral to a pediatric liver transplant center for multidisciplinary care. (1-B)**

**41. Establish an etiology of PALF in order to identify conditions that are treatable without LT or contraindicated for LT. (1-B)**

**Hepatic Tumors**

**Hepatoblastoma.** Gold standard treatment of hepatoblastoma (HB) is perioperative chemotherapy followed by complete resection of all viable tumor.<sup>182,183</sup> The Children's Oncology Group protocol for hepatoblastoma (COG-AHEP0731) suggests that tumors with potential for complete resection can be identified after 2-4 rounds of cisplatin-based chemotherapy. Those who undergo primary LT for unresectable HB have an 82% 10-year survival, while those who receive an LT for recurrence of HB following chemotherapy and resection ("rescue" LT) have a 30% 10-year survival.<sup>184</sup> The PRETEXT (Pretreatment Extent of disease)<sup>185</sup> is used to gauge extent of disease at the time of diagnosis and triage patients for early referral to a program with experience in both pediatric hepatobiliary surgery and liver transplantation. Patients with PRETEXT IV disease (disease involving all four sections of liver), complex PRETEXT III disease (multifocal or presence of venous thrombosis), or centrally located tumors whose location makes a tumor-free excision plane unlikely have poor outcomes with chemotherapy and surgical resection alone.<sup>186</sup> A recent report from a single institution reported 93% survival with aggressive resection in POST-TEXT III and IV patients with hepatoblastoma.<sup>187</sup>

Patients with pulmonary metastases (PM) at the time of diagnosis have recurrence-free survival following LT that is similar to those without PM at the time of diagnosis if either of the following occurs following chemotherapy: 1) PM are no longer seen by computerized tomography (CT) or 2) residual PM are completely resected and tumor-free margins are identified.<sup>184</sup> In the absence of significant response to chemotherapy that would allow surgical resection of the liver tumor with clear margins and sufficient functional residual hepatic mass, total hepatectomy with LT has been demonstrated to have satisfactory long-term outcomes.<sup>188-191</sup>

**Recommendations:**

**42. Children with nonmetastatic and otherwise unresectable hepatoblastoma should be referred for**

**LT evaluation at the time of diagnosis or no later than after 2 rounds of chemotherapy. (1-B)**

**43. Patients with HB and pulmonary metastases can be considered for LT if, following chemotherapy, a chest CT is clear of metastases or, if a tumor is identified, the pulmonary wedge resection reveal the margins are free of the tumor. (1-B)**

**Hepatocellular Carcinoma.** Hepatocellular carcinoma (HCC) is associated with chronic viral hepatitis (hepatitis B and hepatitis C), metabolic disease (tyrosinemia, progressive familial intrahepatic cholestasis, alpha-1 antitrypsin deficiency, Wilson's disease, glycogen storage disease, cholesterol ester storage disease), biliary atresia, Alagille syndrome, and parenteral nutrition associated liver disease. The incidence of HCC may be higher for children with vertically transmitted hepatitis B who seroconverted from hepatitis B e-antigen to hepatitis B e-antibody before the age of 3 years.<sup>192</sup> For the majority of adults, HCC is identified in cirrhotic livers; the opposite is true for children, as 60-70% of HCC cases are found in a noncirrhotic liver.<sup>193</sup> HCC is rare and often advanced and inoperable at the time of diagnosis.<sup>194</sup> Screening procedures for HCC are not uniform, but alpha-fetoprotein is typically elevated over 400 ng/dL, often reaching over 1,000 ng/dL.<sup>195,196</sup> Cure is accomplished only with complete surgical resection, although chemotherapy may be more effective in children than adults.<sup>193</sup> High recurrence rates in adults fell when LT was restricted to individuals who met the Milan criteria: a single tumor diameter less than 5 cm, no more than 3 foci with each one not exceeding 3 cm, and absence of vascular invasion, or extrahepatic involvement.<sup>197</sup> However, Milan criteria may not be applicable in children and recommendations must be individualized.<sup>190,193,195,198</sup> Successful LT outcomes have been achieved even for those children who did not meet the more liberal University of California San Francisco Criteria (single tumor <6.5 cm or maximum of three tumors with none >4.5 cm and cumulative tumor size <8 cm) or the "up-to-seven" criteria (absence of angioinvasion, number of nodules plus the maximum size of the largest nodule equal or lower than 7).<sup>144</sup> Satisfactory LT outcomes have been achieved in some children with large, multifocal tumors, with some having microscopic blood vessel invasion or limited local extrahepatic extension.<sup>186,190,193</sup>

**Recommendations:**

**44. Prompt referral to a liver transplant center should occur for children with or suspected to have hepatocellular carcinoma. (2-B)**

**45. As the Milan criteria may not be applicable to children, transplantation for hepatocellular carcinoma must be individualized and should be considered in the absence of radiological evidence of extrahepatic disease or gross vascular invasion, irrespective of size of the lesion or number of lesions. (2-B)**

**46. Absolute contraindications to transplant include radiological evidence of extrahepatic disease (1-B); relative contraindications to transplant include major venous invasion, or rapid disease progression despite chemotherapy. (2-B)**

**47. Hepatocellular carcinoma (HCC) is uncommon among children and there are no current data to support general screening for HCC in children; children with bile salt excretory pump disease and tyrosinemia are at higher risk for developing HCC and should undergo periodic screening. (2-B)**

**Hemangioendothelioma.** Infantile hemangioma (IH), the most common pediatric tumor, has three categories: 1) focal lesions, 2) multifocal lesions, and 3) diffuse lesions.<sup>199</sup> All focal and most multifocal lesions are asymptomatic and involute spontaneously. However, some multifocal lesions present with high output cardiac failure and can lead to a fatal outcome in the first year of life. Multifocal and diffuse lesions express GLUT-1, which may biologically distinguish them from focal lesions.<sup>200</sup> With diffuse lesions, the liver is almost completely occupied by hemangiomas and symptoms include respiratory insufficiency due to an abdominal mass effect, abdominal compartment syndrome, coagulopathy (Kasabach-Merritt syndrome), multiorgan system failure, and hypothyroidism due to overproduction of type 3 iodothyronine deiodinase which converts thyroid hormone to its inactive form.<sup>201</sup> Diffuse hemangiomas often do not respond to steroid therapy<sup>202</sup> and most require surgical resection or beta-blocker therapy to improve hematologic parameters. Hepatic artery ligation and embolization have limited effect. Other treatment options for diffuse lesions include vincristine,<sup>203</sup> actinomycin, and cyclophosphamide and propranolol.<sup>204</sup>

**Recommendations:**

**48. Liver transplant evaluation for IH is indicated if the hemangioendothelioma is not responding to treatment or is associated with life-threatening complications. (1-B)**

**49. Candidates being considered for LT for a hemangioendothelioma should be screened for hypothyroidism. (2-B)**

**Cystic Fibrosis-Associated Liver Disease**

Liver disease is present in up to 35% of cystic fibrosis (CF) patients, but only 5-10% of patients have cirrhosis.<sup>205,206</sup> Ursodeoxycholic acid therapy is recommended, although its impact on the progression of CFLD is not known.<sup>207-209</sup> Endstage liver disease is characterized by coagulopathy and hypoalbuminemia and is not attributable to malabsorption. Portal hypertensive-related hemorrhage alone, in the absence of other signs of decompensated liver disease, may not be a sufficient indication for LT in CF patients, as alternative therapies may be equally acceptable.<sup>210-212</sup> Optimal timing for isolated LT involves careful assessment of cardiopulmonary function, infections, and nutritional status in CF patients. Currently, Model for Endstage Liver Disease (MELD) / Pediatric Endstage Liver Disease (PELD) exception points are permitted for those patients with CF whose pulmonary function tests (PFTs) are <40% of predicted FEV1.<sup>213,214</sup>

Five-year posttransplant survival rates for CFLD are lower than for those who underwent transplantation for other etiologies. Compared to those patients remaining on the waiting list, pediatric and adult transplant recipients with CF gained a significant survival benefit.<sup>215</sup> A different analysis of the UNOS database and various single center reports convey similar patient and graft survival data among patients with CF.<sup>212,216,217</sup> While LT may improve pulmonary function and nutritional status,<sup>218,219</sup> CF patients may be at higher relative risk for the development of posttransplant diabetes mellitus and renal impairment.<sup>220-223</sup>

**Recommendation:**

**50. The indications for liver transplantation in CF are guided by the degree of hepatic synthetic failure and the presence of otherwise unmanageable complications of portal hypertension. Optimal timing for isolated liver transplantation involves careful assessment of pulmonary and cardiac function and nutritional status in CF patients. (2-B)**

**Urea Cycle Defects**

Urea cycle disorders (UCDs) are inborn errors of nitrogen detoxification/arginine synthesis caused by defects in the urea cycle enzymes [carbamoylphosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase 1 (ARG1)], leading to respective deficiencies.<sup>224</sup> The prevalence of UCDs is likely underestimated, as their clinical presentation can be similar to sepsis and death can occur before a diagnosis of UCDs is considered.<sup>225,226</sup>

OTC deficiency is inherited in an X-linked manner, while the other UCDs are inherited in an autosomal recessive manner. Clinical manifestations occur at any age, but most commonly affect neonates. Typically, infants present within hours to days after birth with a catastrophic illness, starting with poor feeding, lethargy, vomiting, and tachypnea and then progressing rapidly to coma and death.<sup>227</sup> Hyperammonemic crises, which account for the devastating neurological outcomes associated with UCDs, are frequently triggered by catabolic events, protein overload, or certain drugs.

The full complement of the “proximal” urea cycle enzymes (e.g., CPS1, OTC, and ASS) are almost exclusively expressed in the liver, while “distal” enzymes (e.g., ASL, ARG1) also have cerebral expression of uncertain clinical significance. LT essentially serves as an “enzyme replacement” therapy and appears to be curative, allowing for resumption of a normal diet and elimination of hyperammonemic crises.<sup>228-230</sup> LT should be considered early in patients with severe UCDs, as irreversible neurological damage can occur.<sup>114,231</sup> For patients with severe neurological disease or sequelae, LT may stabilize, but will not improve neurological outcome. Living related donation, after confirmation of the donor phenotype, has the advantage of allowing optimal timing of the procedure.<sup>114,232,233</sup>

**Recommendation:**

**51. Urgent referral for LT should be considered when patients present in the first year of life with severe UCDs in order to prevent or minimize irreversible neurological damage (1A); living related liver transplantation may be an option for some patients. (1-B)**

**Crigler-Najjar Type I**

Crigler-Najjar syndrome type I (CNI) results from complete deficiency of the hepatocyte enzyme uridine diphosphate glucuronosyl transferase (UGT).<sup>234</sup> CNI becomes apparent during the neonatal period by marked unconjugated hyperbilirubinemia. Treatment consists of initial exchange transfusions and long-term utilization of phototherapy, to prevent kernicterus.<sup>235</sup> While phototherapy can effectively manage hyperbilirubinemia and prevent kernicterus,<sup>236</sup> it is difficult to maintain. Successful phototherapy requires maximal body irradiance for 20-24 hours per day during hyperbilirubinemic crises and a minimum of 8-12 hours every day to maintain an acceptable bilirubin level. LT is the only effective treatment.<sup>237,238</sup>

**Recommendation:**

**52. Referral for LT evaluation should be considered for CNI patients before the development of brain damage, ideally at the time of diagnosis when the option of LT can be discussed. (1A)**

**Immune-Mediated Liver Disease**

**Autoimmune Hepatitis.** Autoimmune hepatitis (AIH) is a progressive inflammatory liver disorder characterized by increased aminotransferases, high serum levels of immunoglobulin G (IgG), and the presence of autoantibodies: antinuclear antibody (ANA), antismooth muscle antibody (ASMA), antiliver-kidney microsomal antibody (anti-LKM), with a potentially more aggressive course in children.<sup>239</sup> Type 1, characterized by positive ANA and/or ASMA, is more common,<sup>240</sup> although Type 2, characterized by a positive anti-LKM, is more frequently associated with fulminant liver failure.<sup>240</sup> In a study of 55 consecutive children with clinical and biochemical evidence of AIH, 27/55 (50%) had cholangiographic findings consistent with autoimmune sclerosing cholangitis (ASC).<sup>240</sup> ASC subsequently developed in a patient with AIH and ulcerative colitis. Conventional treatment includes prednisone with or without azathioprine for both AIH and AIH/ASC; ursodeoxycholic acid may be helpful for those with AIH/ASC.<sup>241</sup> LT is required in 10%-20% of children with AIH.<sup>239</sup> Despite a greater degree of immunosuppression required in the posttransplant period, outcomes are similar to the overall transplanted population in terms of infectious or metabolic complications. The risk of late rejection is higher for those who receive LT for AIH, but this does not result in increased chronic rejection, steroid resistant rejection, or the need for retransplantation,<sup>242</sup> which differs from adults.<sup>243</sup> Pediatric patients transplanted for AIH may be at greater risk of developing ulcerative colitis after LT than adult patients.<sup>244</sup> The risk of relapse of AIH posttransplant is estimated to be 10%-35%<sup>19,245,246</sup>; however, criteria for recurrent AIH remain controversial.

**Recommendations:**

**53. LT is considered in patients with autoimmune hepatitis (AIH) who present with acute liver failure associated with encephalopathy and those who develop complications of endstage liver disease not salvageable with medical therapy (2-B).**

**54. Children with AIH and families being evaluated for LT should be informed they may require more immunosuppression than children transplanted**

*for other indications and remain at risk for recurrence of AIH. (2-B)*

**Primary Sclerosing Cholangitis.** Primary sclerosing cholangitis (PSC) is characterized by chronic inflammation and obliterative fibrosis of the intra- and/or extrahepatic biliary tree, leading to bile stasis and cirrhosis.<sup>240,241,247</sup> Children with biliary features consistent with PSC can have isolated biliary tract disease or have histologic characteristics may present prior to, coincident with, or subsequent to histological and biochemical features of autoimmune hepatitis (AIH) type 1.<sup>248</sup> Autoimmune sclerosing cholangitis (ASC) is the term used to describe the biliary features present in children with a primary diagnosis of AIH and it is more common in children than adults.<sup>240</sup> There is uncertainty whether ASC in children and PSC in adults have similar biological underpinnings or outcomes. In lieu of the phrase “overlap” syndrome, which suggests two separate conditions occurring in the same patient, the International Autoimmune Hepatitis Group posits that patients should be categorized by the predominant condition (e.g., AIH, PSC) and those with “overlapping” features should not be considered to be unique diagnosis.<sup>249</sup> Langerhans cell histiocytosis, primary and secondary immunodeficiencies, and cystic fibrosis have histological findings similar to PSC. LT is the only therapeutic option for endstage liver disease resulting from PSC.<sup>250</sup>

Immunoglobulin G4-associated cholangitis (IAC) is a newly recognized multisystem condition with intra- and extrahepatic biliary strictures that is often, but not always, associated with autoimmune pancreatitis.<sup>251,252</sup> Strictures disappear with corticosteroid therapy. Evidence of IAC in children is currently limited to case reports with a similar clinical and biochemical presentation and response to corticosteroids that is seen in adults.<sup>253</sup>

Patients with PSC are at higher risk of developing inflammatory bowel disease (IBD) than the general population, with ulcerative colitis and Crohn's disease diagnosed before LT in 46% and 3.3% of children, respectively, and IBD diagnosed after LT in another 9.8%.<sup>254</sup> Cholangiocarcinoma in children is rare and not all cases are associated with PSC.<sup>255</sup> Risks associated with cholangiocarcinoma in PSC are not well defined in children,<sup>250</sup> but HCC may be more prevalent among children with Crohn's disease and PSC.<sup>255</sup>

PSC accounts for 3.5% of pediatric patients listed for LT,<sup>256</sup> and 2.6% pediatric transplants.<sup>254</sup> LT is effective therapy for endstage liver disease due from PSC.<sup>257</sup> Patient and graft survival rates are comparable to those of age-matched children who undergo trans-

plantation for other indications.<sup>254</sup> Post-LT complications include intrahepatic biliary strictures, cholangitis, and disease recurrence in the graft.<sup>254</sup> Patients with IBD and PSC have a higher recurrence rate post-LT compared to those with PSC alone. Five-year survival following LT for PSC is >80%.<sup>258,259</sup>

#### **Recommendations:**

**55. Surveillance for inflammatory bowel disease with a full colonoscopy with biopsy both before and after LT in patients with features of primary sclerosing cholangitis is recommended. (2-B)**

**56. LT evaluation should be considered for patients with decompensated liver disease, recurrent cholangitis, unmanageable bile duct strictures, and/or concerns for the risk of cholangiocarcinoma. (2-B)**

#### **Other Metabolic or Genetic Disorders**

**Progressive Familial Intrahepatic Cholestasis.** Progressive familial intrahepatic cholestasis (PFIC) refers to a group of autosomal recessive cholestatic conditions. The nomenclature for these conditions is evolving as the underlying genetic defects and affected proteins are identified. Diagnosis is based on clinical manifestations, liver histology and genetic testing, as well as on specific tests excluding other causes of childhood cholestasis.<sup>260-262</sup>

Familial intrahepatic cholestasis 1 (FIC1) disease, formerly PFIC-1, results from a mutation in the *ATP8B1* gene and is a systemic disorder which may affect structural and functional integrity of microvilli.<sup>263</sup> FIC1 disease typically presents in the first year of life with severe cholestasis and a normal serum gamma-glutamyl transferase (GGT). Vitamin D-deficient rickets and intracerebral bleeding as a consequence of vitamin K deficiency may be presenting features of FIC1 disease. Other symptoms include chronic diarrhea, asthma-like symptoms, and sensorineural hearing loss, likely as a result of abnormal microvilli in affected cells in the intestine, lungs, and cochlear hair cells. Ursodeoxycholic acid may improve cholestasis to the degree that other interventions can be delayed or avoided in about 30% of cases.<sup>264</sup> Partial external biliary diversion (PEBD) or ileal exclusion (IE), if performed prior to the development of cirrhosis, can significantly slow disease progression with improvements in cholestasis, pruritus, growth, as well as contribute to clinical, biochemical, and histological improvement in FIC1 patients.<sup>265</sup> Longer follow-up is needed to determine whether PEBD can obviate the need for LT in FIC1 disease.<sup>265</sup> LT for FIC1 disease is an option for patients with advanced liver disease that

would not be amenable to PEBD or IE. Due to ATP8B1 expression in extrahepatic organs, including the small intestine and pancreas, short stature and diarrhea may develop or worsen following LT, which may affect quality of life.<sup>264</sup> Progressive steatohepatitis that can lead to cirrhosis in the allograft liver have been described following LT.

Bile salt excretory pump (BSEP) disease, formerly PFIC-2, results from a mutation in the *ABCB11* gene that encodes the adenosine triphosphate (ATP)-dependent BSEP that is the principal bile acid transport protein located on the hepatocyte canalicular membrane. Similar to FIC1 disease, BSEP presents with a normal GGT cholestasis associated with profound fat soluble vitamin deficiency. However, BSEP disease is a more rapidly progressive liver disease associated with a greater degree of liver injury manifested by higher levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), giant cell hepatitis, early development of cirrhosis and liver failure, cholelithiasis, and a high risk of developing HCC.<sup>264</sup> A favorable clinical response to ursodeoxycholic acid and biliary diversion may be more likely for children with mild mutations, such as missense mutations.<sup>264</sup> Unlike FIC1 disease, a successful LT in BSEP disease is curative for most children and is not associated with extrahepatic manifestations. However, there are reports of recurrent low GGT cholestasis following LT for BSEP disease that is associated with significant morbidity and mortality.<sup>20</sup>

Multidrug resistance protein-3 (MDR-3) disease, formerly PFIC-3, results from a mutation in the *ABCB4* gene that codes for the MDR3 glycoprotein which serves as a phosphatidylcholine flippase, transferring the lipid from the inner to the outer leaflet of the canalicular membrane.<sup>261</sup> The resultant low levels of phosphatidylcholine likely allow bile acids with a high detergent quality to injure bile ducts resulting in progressive biliary disease. MDR-3 disease is associated with cholelithiasis, intrahepatic cholestasis of pregnancy, transient neonatal cholestasis, drug-induced cholestasis, and an autosomal recessive cholestatic liver disease associated with a high GGT.<sup>266</sup> The age at presentation can range from infancy to adulthood. Initial symptoms include jaundice, pruritus, and biochemical evidence of hepatic dysfunction. Treatment with ursodeoxycholic acid can result in complete or partial clinical and biochemical improvement, but the disease can be unresponsive and rapidly progressive in about 15% of cases.<sup>266</sup> Among 28 children with MDR3 disease followed by an Italian consortium, one died and five underwent successful LT.<sup>266</sup> Those who died or

received an LT had either no response to ursodeoxycholic acid or a partial response that was associated with flares of liver injury and decompensated cirrhosis. In a Japanese cohort of 717 LRLT recipients, only 14 had PFIC: 11 FIC1, 3 BSEP, and 0 MDR3.<sup>267</sup>

#### **Recommendations:**

**57. Ursodeoxycholic acid therapy followed by partial external biliary diversion (PEBD) or ileal exclusion (IE) should be an early consideration to improve cholestasis and pruritus for children with FIC1 and BSEP disease. (1-B)**

**58. Patients with BSEP disease should be monitored regularly for the development of HCC. (2-B)**

**59. LT in FIC1 disease can be associated with worsening extrahepatic manifestations and should be considered only if PEBD or IE failed or could not be performed. (2-B)**

**60. Families of children with BSEP disease who require LT should be cautioned that the disease may recur following LT. (2-B)**

**61. LT evaluation is indicated for patients with MDR3 disease whose disease fails to respond to ursodeoxycholic acid. (2-B)**

**62. The use of PFIC heterozygote live donor organs from family members remains a viable and feasible option for FIC1 and BSEP patients requiring LT but ongoing follow-up is needed. (2-B)**

**Alpha-1 Antitrypsin Deficiency.** Liver disease associated with alpha-1 antitrypsin deficiency (A-1ATD) in children has protean manifestations.<sup>268</sup> Only about 7% of children with the PI\*ZZ-associated A-1ATD will have any prolonged obstructive jaundice in the first few months of life, and up to 80% of those children will not have evidence of chronic liver disease by 18 years of age.<sup>269,270</sup> A-1ATD will rarely present with a rapidly progressive, life-threatening liver disease in infancy necessitating LT in the first few months of life.<sup>271</sup> Case studies reveal a portion of children will have a slowly progressive course which may either stabilize or continue toward decompensated liver disease.<sup>272</sup> Hepatocellular carcinoma can develop in children with cirrhosis and A-1ATD.<sup>273</sup> New medical therapies for A-1ATD are being investigated.<sup>274</sup>

**Bile Acid Synthesis Disorders.** Inborn errors resulting in bile acid synthesis disorders (BASD) most commonly present as neonatal cholestasis or neonatal hepatitis, but can present as chronic liver disease in older children.<sup>275-277</sup> These diseases are characterized by a failure to produce normal bile acids and an accumulation of unusual bile acids and bile acid

intermediaries.<sup>278</sup> Unlike most cholestatic diseases, patients with inborn errors of bile acid synthesis generally present with the hallmark features of normal or low serum levels of primary bile acids, normal GGT concentrations, and the absence of pruritus.<sup>279</sup> For a definitive diagnosis, fast atom bombardment-mass spectrometry (FAB-MS) and gas chromatography-mass spectrometry (GC-MS) analyses of serum and urine is recommended, but is only available in a few specialized referral laboratories.<sup>280</sup> Early diagnosis of some defects of bile acid synthesis can be treated effectively with cholic acid and/or chenodeoxycholic acid, which down-regulate endogenous bile acid synthesis resulting in clinical, biochemical, and histologic improvement if therapy is initiated before significant liver disease is established.<sup>281,282</sup> LT is indicated for progression to endstage liver disease.<sup>283</sup>

**Recommendation:**

**63. Bile acid replacement therapy should be initiated as early as possible in children with a confirmed bile acid synthetic disorder; LT should be considered only in patients with progressive endstage liver disease due to inborn errors of bile acid synthesis or those known to be refractory to medical therapy. (1-B)**

**Hereditary Tyrosinemia Type 1.** Hereditary tyrosinemia type 1 (HT) is a multisystem disorder often presenting in infancy with a profound coagulopathy despite minimally elevated or normal serum aminotransferase levels.<sup>284</sup> Older children and even adults can present with features of chronic liver disease. Treatment with NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione) results in rapid clinical and biochemical improvement, manifested by undetectable levels of succinylacetone in the urine within 24 hours, and has reduced early complications as well as the need for LT. There has been an increase in mean age at transplantation from  $1.82 \pm 2.86$  years between 1988-1998 to  $3.70 \pm 4.42$  years between 1999-2008.<sup>285</sup> Failure to respond to NTBC within a week may be due to noncompliance or subtherapeutic NTBC, manifested by persistence of succinylacetone in the urine, or a fulminant course despite therapy.

The child that survives initial presentation without LT can experience an extended interval of good health. Hepatic nodules, if present initially, may persist, regress, or disappear on a combination of NTBC therapy and a low tyrosine / low phenylalanine diet. The AFP is elevated at presentation, but will normalize or

fall to levels less than 10 ng/L on NTBC therapy. Even if metabolic stability is achieved with NTBC therapy, compliance with dietary restrictions and NTBC administration can be challenging for some families. Despite best efforts with medical and dietary therapy, hepatocellular cancer may still occur and hence regular surveillance with AFP and liver imaging is recommended.<sup>286,287</sup>

**Recommendations:**

**64. Initial treatment of hereditary tyrosinemia type 1 is with NTBC when the diagnosis is established. (1-A)**

**65. Referral for LT evaluation should occur promptly if the child has progressive liver disease despite an adequate dose of and compliance with NTBC, rising AFP while on NTBC, a change in liver imaging with a single nodule exceeding 10 mm or an increase in the number or size of hepatic nodules, or if management with NTBC and diet cannot be adequately maintained. (1-B)**

**Glycogen Storage Disease.** There are now 11 glycogen storage diseases (GSD) described and most have many subtypes.<sup>288</sup> GSDs can have hepatic, muscular, cardiac, neurological, immunological, or mixed presentations that are increasingly identified within each class of GSD with the help of advancing metabolic and genetic techniques. The degree to which extrahepatic manifestations of GSD are evident will vary with each patient as enzymes necessary for glycogen metabolism are found in many tissues. Among the family of GSDs, LT has been performed predominantly in patients with GSD I, III, and IV.<sup>289</sup>

Glycogen storage disease type I (GSDI) is comprised of two major subtypes<sup>290</sup>: GSD type Ia (glucose-6-phosphatase deficiency) and GSD 1b (glucose-6-phosphate translocase deficiency) that affect the liver, kidney, and intestinal mucosa causing excessive accumulation of glycogen and fat in these organs. With good metabolic control, clinical manifestations such as growth retardation, hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia, and hyperlipidemia can be managed. Nephrocalcinosis, glomerular hyperfiltration, proteinuria, and endstage renal disease can occur. Hepatic adenomas (HA) are common and the prevalence of HCC increases with age reaching an estimated 50%-80% by the third decade of life.<sup>291</sup> Histology is the only sure way to differentiate HA from HCC, but may not be possible when numerous HAs are present. GSD type Ib has additional features that include neutropenia and impaired neutrophil

function, resulting in recurrent bacterial infections and oral and intestinal mucosa ulceration that resembles inflammatory bowel disease, particularly Crohn's disease.

The majority of patients with GSD III (debranching deficiency) have a disease that is generalized (type IIIa, 80% of cases) to involve liver, muscle, cardiac muscle, erythrocytes, and fibroblasts and a minority having disease that is restricted to the liver (Type IIIb).<sup>292</sup> The presence of fibrosis, ranging from minimal to cirrhosis, occurs in GSD III but not GSD I. Aminotransferase elevations can be marked in childhood,<sup>293</sup> but become less apparent with time. Despite the presence of fibrosis or cirrhosis, synthetic function is typically preserved. Life expectancy for patients with GSD III has improved, such that the development of endstage liver disease and risk for HCC may heighten the need for LT for GSD IIIb patients. LT should be carefully considered in patients with GSD type IIIa as muscle weakness and cardiomyopathy can be slowly progressive and will not be reversed by LT and may progress despite LT.<sup>294</sup>

GSD IV (glycogen brancher deficiency) is a systemic, yet heterogeneous disorder resulting in accumulation of insoluble amylopectin-like polyglucosan in the liver heart, muscle, nervous system, and skin.<sup>295</sup> The most common form in children appears to be predominantly hepatic with relatively rapid progression to cirrhosis and liver failure, with death by 5 years of age. Similar to GSD III, HCC can occur. The majority of reported cases of LT for GSD IV suggest a favorable outcome.<sup>294,296,297</sup> However, systemic progression of amylopectin-like deposits in the heart and muscle can occur post-LT resulting in cardiac and neuromuscular dysfunction and, in some cases, death. GSD type III and type IV may be associated with hepatocellular carcinoma or hepatic failure.<sup>6,298</sup>

LT for GSD serves to replace the enzyme deficiency in the liver and significantly improve metabolic control. Long-term survival following LT for GSD I, III, and IV appears to be better than a comparable control population who received an LT for conditions other than GSD.<sup>289</sup> However, this study was not able to assess the impact or development of extrahepatic morbidities such as cardiomyopathy, myopathy, infectious complications, or inflammatory bowel disease.

#### **Recommendations:**

**66. LT evaluation should be considered for patients with: GSD I with poor metabolic control, multiple hepatic adenomas, and/or concern for HCC**

**(1-B); GSD III and IV with poor metabolic control, complications of cirrhosis, progressive hepatic failure, and/or suspected liver malignancy. (1-B)**

**67. Disease-specific counseling for post-LT expectations should include, for: GSD Ia and Ib: heightened risk of renal complications; GSD Ib: development of inflammatory bowel disease; GSD IIIa and GSD IV: development of neuromuscular and cardiac complications; GSD I, III, IV: identification of HCC in explanted liver and risk of recurrence if it is present. (2-B)**

**Fatty Acid Oxidation Defects.** Fatty acid  $\beta$ -oxidation is a key metabolic pathway for the maintenance of energy homeostasis for high energy requiring organs such as the heart and skeletal muscle, and provides the main energy supply during prolonged fasting.<sup>299</sup> Fatty acid oxidation defects (FAOD) are inherited metabolic diseases with serious life-threatening symptoms such as hypoketotic hypoglycemia,<sup>300,301</sup> acute encephalopathy, cardiomyopathy,<sup>302</sup> rhabdomyolysis,<sup>303</sup> metabolic acidosis, and liver dysfunction.<sup>304</sup> Triggering events include febrile illnesses, vomiting, and fasting can lead to severe complications. Hepatic presentation with hypoketotic hypoglycemia and Reye-like syndrome is usually seen in infancy, but can extend into childhood and adolescence.<sup>304</sup> Infants born to mothers who develop acute fatty liver of pregnancy and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) are at risk for having a FAOD.<sup>305,306</sup> FAOD may present as recurrent episodes of PALF.<sup>307</sup>

Treatment for FAOD is mostly dietary and involves recommendations with regard to the fat and carbohydrate content of the diet and the maximal length of fasting periods; intravenous glucose infusion of at least 10 mg/kg/min to maintain serum glucose above 100 mg/dL during a crisis. Abnormalities in fatty acid oxidation may predispose to a worse outcome in acute liver failure.<sup>304</sup> Prompt dietary intervention may reverse symptoms, including those associated with PALF, and preclude the need for LT. LT is an acceptable therapeutic option for patients with FAOD who present with fulminant liver failure, but fail medical and dietary intervention.<sup>308</sup>

#### **Recommendations:**

**68. Management of FAOD with diet and intravenous glucose should be the first line of therapy. (2-B)**

**69. Patients with FAOD should be considered for LT evaluation if they experience recurrent episodes of PALF or have failed medical therapy. (2-B)**

**Primary Hyperoxaluria Type 1.** Primary hyperoxaluria Type 1 (PH1) is an autosomal recessive inborn error of glyoxylate metabolism, caused by a deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT). PH1 results in overproduction and excessive urinary excretion of oxalate, causing recurrent nephrolithiasis, nephrocalcinosis, or endstage kidney disease. Patients experience progressive decline in renal function and death from endstage renal disease. Calcium oxalate deposition extends to blood vessels, retina, heart, peripheral nerves, bone and bone marrow, subcutaneous tissue, and synovial fluid.<sup>309</sup>

As only the liver can detoxify glyoxylate, LT halts excess oxalate production and arrests further damage to the kidneys and/or other organs.<sup>310</sup> CLKT is recommended for patients with significant native renal injury.<sup>311,312</sup> A sequential procedure with isolated LT followed by dialysis and then subsequent kidney transplantation reduces the systemic oxalate load and may be proposed in individual patients with endstage renal disease. While separate deceased donor organs are often used, successful sequential liver and kidney transplantation from a single living donor has been reported.<sup>313</sup> An isolated preemptive LT may be considered in patients with reduced renal function not requiring dialysis.<sup>314</sup>

#### **Recommendation:**

**70. Referral for LT evaluation should be considered at the time of diagnosis to allow all transplant options to be considered (2-B); decisions to proceed with preemptive LT (2-B), or CLKT (2-B), or sequential LT then KT (2-B) will depend on current and anticipated renal function.**

**Organic Acidemia.** Organic acidemias, also known as organic acidurias, are a group of disorders characterized by increased excretion of (nonamino) organic acids in urine.<sup>315</sup> In aggregate, these diseases are categorized into five groups: branched chain organic acidemias, multiple carboxylase deficiencies, glutaric acidurias, fatty acid oxidation defects, and disorders of energy metabolism. Numerous types of organic acidemias exist, with methylmalonic acidemia (MMA), propionic acidemia, and isovaleric acidemia among the most prevalent forms. Other forms of organic acidemias include maple syrup urine disease (MSUD), homocystinuria, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, ketothiolase deficiency, and glutaricacidemia type I

(GA I). The typical clinical presentation is a toxic encephalopathy associated with vomiting, poor feeding, and neurologic symptoms such as seizures, abnormal tone, and lethargy that progresses to coma. In older children, variant forms of organic acidemias present with loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent ketoacidosis, or psychiatric symptoms.

Prolonged fasting, which can occur prior to anesthesia or diagnostic tests, can produce a catabolic state and precipitate a metabolic crisis. Therefore, elective hospitalizations or procedures that require the child with an organic acidemia to be fasted should be carefully planned with proper intravenous glucose support and metabolic monitoring. In particular, children admitted to hospital awaiting LT may experience an unexpectedly prolonged period of fasting while the donor organ is procured and its quality is assessed. Strategies to monitor and manage the metabolic disease during this period should be in place.<sup>316</sup>

LT may be indicated in patients with organic acidemia experiencing frequent episodes of metabolic decompensation, uncontrollable hyperammonemia, restricted growth, or severe impairment of health-related quality of life with conventional medical treatment.<sup>114,315</sup> A collaborative discussion with specialized metabolic teams is critical. LT may not completely correct the metabolic defect. For example, in the case of MMA, serum levels of MMA and protein tolerance improve following LT but do not normalize. Thus, MMA patients remain at risk for neurological deterioration and/or progressive renal insufficiency following LT.<sup>317</sup>

In classic variant maple syrup urine disease (MSUD), a severe mitochondrial deficiency of the branch chain keto acid dehydrogenase (BCKDH) complex associated with volatile metabolic derangements with impaired brain development or unpredictable risk of neurologic crisis, the level of current metabolic control imparted by strict dietary management does not necessarily indicate protection against further episodes of metabolic decompensation.<sup>318</sup> Patients with classic variant MSUD defined by clinical phenotype of severe leucine intolerance (<15-30 mg/kg/day) have undergone LT successfully with elimination of dietary protein restriction and stabilization but without reversal of underlying neurocognitive deficits.<sup>316,319</sup> Due to the ubiquitous presence of BCKDH complex in non-MSUD patients, explanted livers from patients receiving a transplant for MSUD may be transplanted to a non-MSUD patient ("domino" transplant),<sup>320</sup> thereby improving organ utilization.

**Recommendations:**

**71. LT may be indicated in patients with organic acidemia receiving conventional medical therapies who continue to experience frequent episodes of metabolic decompensation, uncontrollable hyperammonemia, restricted growth, or severe impairment of health-related quality of life with conventional medical treatment. (1-B)**

**72. Evaluation for LT should be considered in any patient with classic variant MSUD manifested by severe leucine intolerance. (2-B)**

**73. Meticulous management protocols should be in place for the preoperative period prior to LT surgery to prevent and, if necessary, treat metabolic decompensation while the child is fasting prior to LT. (2-B)**

**74. Domino LT should be considered an option in the setting of LT in MSUD. (2-B)**

**Familial Hypercholesterolemia.** Familial hypercholesterolemia is an autosomal dominant disorder resulting from a mutation in the gene that encodes the low-density lipoprotein receptor. Severe hypercholesterolemia, atherosclerosis, and ischemic cardiac disease in the pediatric age group have been described. Recurrent plasma apheresis and statin medications can lower cholesterol levels and prevent the development of cardiovascular complications.<sup>321</sup> Patients require a thorough cardiovascular evaluation prior to transplantation to assess the severity of residual atherosclerotic disease. Coronary artery bypass graft surgery may be indicated prior to transplantation if atherosclerotic disease is severe. Early LT may provide an opportunity to improve management and minimize cardiovascular disease.<sup>322</sup>

**Mitochondrial Hepatopathy and Systemic Mitochondrial Disease.** Disorders of mitochondrial energy metabolism occur due to dysfunction of the respiratory chain (RC) with resultant cellular ATP deficiency, increased production of reactive oxygen species and toxic metabolites, and cell death.<sup>323,324</sup> Mutations of nuclear or mitochondrial DNA result in disorders of mitochondrial energy metabolism, and can be inherited as autosomal dominant, autosomal recessive, or maternal inheritance. When a mutation of mtDNA occurs, both normal and mutant mtDNA can coexist in a single cell. However, the resultant phenotype is determined by the proportion of abnormal mtDNA. During cell division, mitochondria are randomly partitioned into daughter cells, resulting in heterogeneous levels of mutated mtDNA, and subsequent mitochondrial dysfunction in various organs and tissues. This likely explains why the disease phenotype may change

with age.<sup>325</sup> While RC defects can involve any organ, those with high-energy requirements such as brain, liver, and muscle are more commonly affected.<sup>326</sup> The three main RC defects associated with liver disease are deficiencies of RC enzymes, mtDNA depletion syndrome, and Alper's syndrome. The natural history of all three disorders is almost always fatal.<sup>325,327-329</sup>

Mitochondrial diseases can have disparate manifestations ranging from acute liver failure in infancy, to multiorgan disease with significant neuromuscular involvement, to isolated chronic liver disease in the absence of overt neurological findings.<sup>323,330-332</sup> Magnetic resonance imaging (MRI) of the brain, cerebral spinal fluid analysis, assessment of muscle enzymes, muscle biopsy for mitochondrial and respiratory chain analysis, echocardiogram, and assessment of renal tubular function are important to exclude systemic disease.<sup>333,334</sup> Next-generation sequencing panels are becoming available to aid in the identification of these disorders.

Outcomes following LT for RC defects are mixed and available reports have limited follow-up.<sup>330,334,335</sup> If the disease is confined to the liver a favorable outcome is possible, although exclusion of extrahepatic involvement is difficult, especially in the context of acute liver failure.<sup>334</sup> Posttransplant neurological deterioration is possible even if a comprehensive pretransplant assessment for extrahepatic disease was normal.<sup>324</sup> Progression of neurological disease in Alper's syndrome is inevitable after liver transplantation and leads to death.<sup>331,336</sup> Valproic acid-associated acute liver failure in children less than 8 years of age may represent an "unmasking" of an undiagnosed systemic mitochondrial disease, as 1-year survival following LT is 20% with no survivors beyond 10 years, compared to a 69% 1- and 10-year survival rate for pediatric ALF not due to valproate.<sup>180</sup>

A decision to exclude an individual with a mitochondrial hepatopathy from LT is difficult.<sup>337</sup> In general, children with multiorgan mitochondrial disease, usually as evidenced by neuromuscular involvement, are poor candidates for LT, as they have had uniformly poor posttransplant neurological outcomes.<sup>324,331,336,338</sup> Recently, a mitochondrial depletion syndrome caused by a mutation in the DGUOK gene was noted to present as neonatal hemochromatosis, which should prompt consideration of a systemic mitochondrial disease in patients presenting with ALF in the first weeks of life, hyperferritinemia, and hemosiderosis involving the liver and other organs.<sup>339</sup>

**Recommendations:**

**75. Alper's syndrome or valproate-associated liver failure are contraindications to LT. (1-B)**

**76. Children with severe, life-threatening extrahepatic multiorgan mitochondrial disease are contraindicated for LT evaluation, as they have had uniformly poor posttransplant neurological outcomes. (1-B)**

**77. Absence of evidence for extrahepatic mitochondrial disease prior to LT does not exclude its development after LT; the family of potential LT candidates should be well informed of this possibility. (1-B)**

#### **Other Fibrotic/Cirrhotic Conditions**

**Ductal Plate Malformations.** LT for biliary ductal plate malformations (DPM) associated with autosomal recessive polycystic kidney disease (ARPKD), Caroli's disease, and isolated congenital hepatic fibrosis is not often required in the pediatric age group.<sup>340</sup> Progression of kidney and liver diseases are independent, and variability in severity of either liver or kidney disease does not correlate with genotype.<sup>341</sup> Complications associated with DPM include recurrent cholangitis, biliary sepsis, and portal hypertension complicated by variceal hemorrhage or pulmonary conditions (e.g., hepatopulmonary syndrome, pulmonary hypertension). Non-LT options to control bleeding varices include banding, transjugular intrahepatic portosystemic shunt (TIPS), and surgical portosystemic shunt. Transplant options include isolated LT (iLT), combined liver-kidney transplant (CLKT), and isolated kidney transplant (iKT). Decisions to proceed with iLT can be complicated by the degree of renal dysfunction. A mortality rate of 21% was identified in patients with ARPKD who received an iKT and it was directly related to recurrent cholangitis associated with Caroli's disease.<sup>342</sup> When required, LT outcomes are excellent.<sup>343</sup>

#### **Recommendations:**

**78. Early referral of LT evaluation for ductal plate malformations should be considered for patients who develop recurrent cholangitis or complications associated with portal hypertension to further assess renal dysfunction in the context of the patients liver disease. (2-B)**

**79. General recommendations on when to proceed to iLT, CLKT, or iKT cannot be made, as decisions should be individualized based on morbidity associated with the liver and/or kidney disease and anticipated "tolerance" of the nontransplanted organ to surgical and medical therapies associated with transplantation. (2-B)**

**80. Patients with endstage renal disease associated with Caroli's disease should be strongly considered for combined liver and kidney transplantation. (1-C)**

**Parenteral Nutrition-Associated Liver Disease.** Patients with parenteral nutrition-associated liver disease (PNALD) are referred for LT in the context of three clinical scenarios: 1) in combination with intestinal or multi-visceral transplantation; 2) isolated LT (iLT) in children with intestinal failure approaching but not achieving enteral autonomy; and 3) isolated LT after enteral autonomy is achieved, but the consequences of endstage liver disease persist and impact longevity.<sup>344</sup> Early reports of iLT for selected patients with PNALD were encouraging.<sup>345</sup> However, a recent report from Birmingham, UK suggest that it is currently difficult to predict who will achieve enteral autonomy following iLT, with 8/14 surviving at a median of 107.5 months (range 89-153) and 5/8 surviving children able to be weaned from PN to enteral nutrition within a median of 10 months (range 3-32) following iLT.<sup>346</sup>

PNALD results from myriad factors including prematurity, sepsis, lack of enteral feeding, intestinal failure, abdominal surgery, as well as various component of PN including protein, glucose infusion rate, and in particular lipid administration. Prolonged administration of a soy-based lipid exceeding 1 gm/kg/d in the management of pediatric intestinal failure has been implicated as an important factor in the development of cholestasis.<sup>347,348</sup>

Strategies that have been used to manage children with PNALD include cycling PN, initiation and advancement of enteral feeds, and minimizing the risk of sepsis with good central line care coupled with appropriate use of antibiotic and/or ethanol lock therapy.<sup>349</sup> Alteration of PN management is also beneficial by keeping the glucose infusion rate below 15-16 mg/kg/minute as well as alternative lipid strategies. Reduction of daily infusion of a soy-based lipid to 1 gm/kg/d has resulted in reversal of PNALD.<sup>348</sup> Use of lipid that is not soy-based (e.g., fish oil-based) at an infusion rate of 1 gm/kg/d has also resulted in reversal of cholestasis, but it may not reverse progression of fibrosis.<sup>350,351</sup>

#### **Recommendations:**

**81. Prior to consideration of LT referral, strategies should be initiated to prevent and reverse PNALD that include lipid-minimization, intravenous lipids that are not soy-based, enteral feeding, PN management, and prevention of infections. (1-B)**

**82. Referral for isolated LT for PNALD should be considered for children who have achieved enteral autonomy but have developed complications of cirrhosis (2-B); for those who continue to require PN, LT evaluation should take place at a center with an**

*experienced multidisciplinary intestinal failure and intestinal transplant team (2-B).*

**Cryptogenic Cirrhosis.** Cryptogenic cirrhosis leading to endstage liver disease is relatively rare in children. “Burnt out” nonalcoholic fatty liver disease needs to be considered, particularly because of the associated risk of cardiovascular disease. In patients suspected of having “burnt out” nonalcoholic fatty liver disease, LT evaluation should include careful cardiovascular assessment, particularly impaired flow-mediated vasodilatation and increased carotid artery intimal medial thickness, both of which are markers of subclinical atherosclerosis.<sup>352</sup> Rare inborn errors of metabolism, such as bile acid synthetic defects, should be considered, as the diagnosis may inform subsequent pregnancies and an available treatment may alter outcome.

#### **Miscellaneous Conditions**

**Factor VII Deficiency.** Factor VII deficiency is managed with fresh-frozen plasma, plasma-derived factor concentrates, or recombinant factor VIIa.<sup>353,354</sup> Treatment is typically reserved for bleeding prevention prior to surgical procedures and spontaneous bleeding. Prophylaxis is reserved for newborns who are prone to early and severe gastrointestinal and central nervous system bleeding and others with a history of severe bleeding associated with surgery or menstruation. Affected patients can expect normal longevity if the condition is properly managed. LT is curative, but should be reserved for the most severely affected patients.<sup>355,356</sup> Children undergoing transplantation will require factor replacement during the surgery and first 1-3 days after transplant surgery.<sup>357</sup>

**Protein C Deficiency.** Purpura fulminans in the newborn period is the most dramatic and life-threatening presentation of protein C deficiency.<sup>358,359</sup> Beyond the newborn period, clinical manifestations are heterogeneous but are associated with an increased risk of vascular thrombosis. Current management of protein C deficiency includes oral anticoagulants, low molecular weight heparin, and intravenous or subcutaneous protein C concentrate.<sup>359,360</sup> LT is curative, and typically occurs in the setting of multivisceral transplantation following an abdominal catastrophe due to mesenteric vein thrombosis or renal vein thrombosis.<sup>361</sup>

#### **Recommendation:**

**83. Medical management of Factor VII and Protein C deficiency is preferred; LT should be considered only for those who experience complications or failure of management. (2-B)**

**Budd-Chiari Syndrome.** Budd-Chiari syndrome (BCS) is the result of hepatic venous outflow tract obstruction at any level from any mechanism, exclusive of cardiac disease. An underlying risk factor for thrombosis is identified in up to 87% of adult BCS cases.<sup>362,363</sup> Whether this prevalence is similar in children with BCS is not known, as evaluation for underlying prothrombotic conditions has not been routinely investigated in this age group. Prognostic scoring systems have not been systematically evaluated in children.<sup>363,364</sup> Transjugular intrahepatic portosystemic shunts (TIPS) should be considered in the majority of patients not responsive to medical therapy and have been successfully used in children.<sup>365,366</sup> Well-selected patients with acute liver failure or advanced chronic disease from BCS can benefit from LT with good long-term posttransplant survival. LT is generally thought to be contraindicated for BCS that occurs due to paroxysmal nocturnal hemoglobinuria, as recurrence of intravascular thrombosis in the graft can be expected; however, scheduled treatments with the anti-complement antibody eculizumab, before and after LT, resulted in stable graft function without radiographic recurrence of thrombosis 1.5 years following LT.<sup>367</sup> Most patients transplanted for BCS remain on some form of prolonged anticoagulation.<sup>368-371</sup>

#### **Recommendation:**

**84. Patients with progressive endstage liver disease from BCS benefit from LT, where others with less severe disease may benefit from alternative therapy. (2-B)**

**Noncirrhotic Portal Hypertension.** Noncirrhotic portal hypertension (NCPH) is often classified based on the level of the vascular obstruction into suprahepatic, intrahepatic, or prehepatic, and is the result of an obliterative vasculopathy resulting from a variety of insults such as infections, drugs or toxins, immune disorders, or thrombophilic states. Patients of all age groups will typically present with gastrointestinal hemorrhage and splenomegaly, and less commonly with hepatic synthetic failure.<sup>372</sup> Endoscopic control of variceal hemorrhage, TIPS, or surgical shunts are usually available as options in the management of patients with NCPH.<sup>373</sup> The meso-Rex bypass is an excellent option if the child has an accessible intrahepatic left portal vein.<sup>373</sup> Increasingly, hepatopulmonary syndrome (HPS) is recognized as a complication of NCPH.<sup>374,375</sup> If HPS is present prior to initiating a management strategy for portal hypertension associated with NCPH, the clinical features of HPS may worsen

HPS, or if not present, may develop.<sup>15,373,376</sup> Symptoms of HPS in patients with NCPH can resolve following LT.<sup>374,377-381</sup>

**Recommendation:**

**85. The role of LT in NCPH should be considered in those patients with cardiopulmonary complications of portal hypertension. (2-B)**

**Sickle Cell Anemia.** LT has been successfully performed in a small number of children and adults with advanced liver disease in the setting of sickle cell anemia, but morbidity from vascular thrombosis including graft thrombosis, stroke or pulmonary embolus, and infections is common.<sup>382-384</sup> Vaso-occlusive crises continue after LT.<sup>384</sup> Careful patient selection as well as management of the sickle cell disease, including exchange transfusion, is required in order to successfully perform LT in patients with this systemic disorder.

**Complications of Portal Hypertension**

**Hepatopulmonary Syndrome.** Hepatopulmonary syndrome (HPS) is a condition in which intrapulmonary vascular dilatations (IPVD) develop in the setting of portal systemic shunting.<sup>385</sup> The presence of HPS is associated with increased morbidity and mortality,<sup>386</sup> but is generally reversible after transplantation and is not a contraindication for transplantation.<sup>387</sup> HPS is present in 4 to 29% chronic liver disease patients of all ages.<sup>43,388,389</sup> Among patients with biliary atresia, HPS may occur more commonly in children with splenic malformation syndrome.<sup>125,381</sup> It is important to recognize that HPS can occur in patients without evidence of liver dysfunction (e.g., congenital hepatic fibrosis, portal vein thrombosis, cavernous transformation of the portal vein). The diagnosis of HPS in children is confirmed by the presence of hypoxia and one of the following demonstrating the presence of IPVD: 1) contrast-enhanced transthoracic echocardiography; 2) technetium-labeled macro-aggregated albumin lung perfusion scan demonstrating a shunt fraction of >6%; or 3) cardiac catheterization demonstrating IPVD.<sup>44</sup> Severe shunting of >20%, as determined by macro-aggregated albumin scan, is associated with increased posttransplantation morbidity and mortality in adults.<sup>44,386</sup> The median survival in the absence of LT in adults with severe HPS (paO<sub>2</sub> <50 mmHg) is less than 12 months, but is unknown in children.<sup>390-</sup>

<sup>392</sup> Patients with HPS may benefit from supplemental oxygen, particularly during periods of increased physical activity.<sup>12</sup> LT is appropriate for the treatment of HPS in children with cirrhotic liver disease and may

be appropriate in some noncirrhotic patients with HPS. Noncirrhotic liver disease or congenital/acquired portosystemic venous communications (e.g., Abernathy syndrome) resulting in HPS may present opportunities for alternative nontransplant approaches to management.<sup>387,393-396</sup> These approaches include ligation of the shunt or endovascular treatment using an occlusion device placed by an interventional radiologist.

**Recommendations:**

**86. Children with portosystemic shunting associated with cirrhotic or noncirrhotic portal hypertension or congenital/acquired portosystemic shunts should be regularly screened for the development of HPS with room air pulse oximetry in an upright position. (2-B)**

**87. Closure of a congenital portosystemic shunt should be considered as an alternative to LT. (2-B)**

**88. Transplantation is indicated in children with HPS and portosystemic shunting resulting from either a congenital or acquired vascular anomaly or liver disease (cirrhotic or noncirrhotic) and portal hypertension who are not candidates for closure of the shunt. (2-B)**

**Portopulmonary Hypertension.** Portopulmonary hypertension (PPH) is a rare, insidious, and devastating complication of portosystemic shunting of any cause.<sup>46</sup> Presenting symptoms include dyspnea, cough, or syncope, but these cardiopulmonary symptoms may be absent. Cardiomegaly may or may not be present on chest x-ray and an electrocardiogram (EKG) may reveal right ventricular hypertrophy, but is most often normal.<sup>46,397</sup> A transthoracic echocardiogram (ECHO) with evidence of right ventricular wall thickening, tricuspid valve regurgitation, and a calculated pulmonary artery systolic pressure  $\geq 40$  mmHg is the best noninvasive screening tool.<sup>398</sup> Flattening of the inter-ventricular septum, if present on ECHO, may suggest pulmonary artery pressures are near systemic pressure. Cardiac catheterization to exclude other causes of pulmonary hypertension and measure the mean pulmonary artery pressure (MPAP) is required to establish the diagnosis of PPH. A PPH severity scale is not established for children, but in adults PPH is considered mild, moderate, or severe if the MPAP is >25 to  $\leq 35$ , >35 to  $\leq 45$ , and >45 mmHg, respectively.<sup>399</sup> The presence of severe PPH with MPAP of >50 mmHg has a high risk of mortality, but long-term survival has been reported in a few patients.<sup>399</sup>

Experience with PPH in children is limited to case reports and single-site experiences.<sup>46</sup> Medical therapy

can stabilize and improve PPH in children and lead to successful LT and subsequent resolution of PPH.<sup>397,400</sup> Case reports suggest that treatment with endothelin receptor antagonists, prostanoids, and sildenafil can lower the pulmonary pressure and enable liver transplantation. Severe, uncorrected PPH with MPAP >45 mmHg remains a contraindication for LTx in adults. However, a child with PPH responsive to aggressive medical management but not achieving a MPAP of <45 mmHg did undergo a successful LT.<sup>397</sup> This raises the possibility that MPAP setpoints for adults may not apply to children. Listed patients with severe PPH who are responsive to medical therapy indicated by a reduction of the MPAP to <35mmHg now qualify for a model for endstage liver disease (MELD) score exception to receive a liver transplant. However, a similar algorithm has not been developed for children less than 12 years of age. Pulmonary hypertension not responsive to medical therapy is probably a contraindication for transplantation.<sup>401</sup>

**Recommendation:**

**89. Children with evidence of PPH should be promptly referred for LT evaluation. (2-B)**

## Contraindications to Liver Transplantation

Due to the scarcity of donor organs, transplant professionals must identify those in greatest need for LT as well as identify which patients are truly benefited by listing for and ultimately undergoing liver transplant.<sup>402,403</sup> Absolute contraindications to LT are those clinical circumstances that consistently lead to poor outcome for the patient and graft. Relative contraindications are those situations which may lead to poor patient and graft outcome, but are potentially correctable (Table 4).

### Extrahepatic Malignancy

Given that the need for posttransplant immunosuppression inherently increases the risk of *de novo* and recurrent malignancy, most centers require some period of recurrence-free survival and a low projected rate of recurrence of primary malignancy before listing for LT.<sup>404</sup> Active, uncontrolled extrahepatic malignancy should be considered an absolute contraindication to LT in children. Patients who have liver metastases from neuroendocrine tumors are a potential exception to this category, a situation rarely encountered in pediatrics.<sup>405</sup> Specific discussions regarding the evaluation of extrahepatic extension of liver-based tumors in childhood are located in other sections of this guideline.

**Table 4. Contraindications to Liver Transplantation**

Absolute	
Hepatocellular carcinoma with extrahepatic disease and rapid progression	
Generalized extrahepatic malignancy	
Exception: Hepatoblastoma with isolated pulmonary metastases	
Uncontrolled systemic infection	
Severe multisystem mitochondrial disease	
Valproate induced liver failure	
Niemann-Pick Disease Type C	
Severe portopulmonary hypertension not responsive to medical therapy	
Relative	
Hepatocellular carcinoma with	
Venous invasion	
Rapid progression despite chemotherapy	
High certainty of nonadherence despite multidisciplinary interventions and support	
Hemophagocytic lymphohistiocytosis	
Critical circumstances not amenable to psychosocial intervention.	

**Recommendation:**

**90. Active, uncontrolled extrahepatic malignancy is an absolute contraindication to LT in children. (1-A)**

### Systemic Infection

Active uncontrolled infection from bacteria, fungus, or virus can lead to high postsurgical mortality and therefore LT in this situation is to be avoided.<sup>402,403,406</sup> Blood cultures and peritoneal fluid cultures (if applicable) should be negative for at least 48 hours prior to listing for transplant. Isolated case reports of successful LT in PALF associated with herpes simplex despite positive blood cultures have been reported.<sup>407,408</sup>

**Recommendation:**

**91. Active uncontrolled systemic infection from bacteria, fungus, or virus can lead to high postsurgical mortality, and therefore LT in this situation is to be avoided. (1-B)**

### Niemann-Pick Disease Type C

Niemann-Pick disease type C (NP-C) is a rare autosomal recessive systemic neuro-visceral disease characterized by progressive disabling neurological symptoms and premature death in most patients.<sup>409</sup> Clinical presentations of NP-C are heterogeneous and include cholestasis, hepatosplenomegaly, and acute liver failure.<sup>409-412</sup> Diagnosis requires demonstration of impaired intracellular cholesterol transport by filipin staining in fibroblasts cultured from patient skin biopsies. DNA sequencing should ideally be performed in parallel with filipin staining where possible, but cannot replace filipin staining as the primary diagnostic method.<sup>409</sup> Bone marrow infiltration with foam cells is a measure of disease burden, but may be minimal

with early disease.<sup>409</sup> Histological features diagnostic of NP-C are found on liver biopsy in only 50% of cases.<sup>413</sup> LT has been shown to be ineffective in altering the progression of neurological deterioration.<sup>414</sup>

**Recommendation:**

**92. LT is contraindicated in NP-C as it does not alter neurological disease progression. (1-B)**

**Hemophagocytic Lymphohistiocytosis Presenting as Acute Liver Failure**

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder of cellular immunity characterized by reduced or absent cytotoxic T cell and NK cell activity, which results in loss of control of histiocyte/T-cell proliferation and activation in response to stimuli. Primary (familial) HLH is inherited as an autosomal recessive disorder, while secondary (acquired) HLH occurs following systemic infection or due to immunodeficiency.<sup>415,416</sup> Although the onset and clinical course of familial HLH is variable, most cases (80%) occur within the first year of age. Familial HLH has been reported in neonates as early as the first days, and even in preterm infants.<sup>417,418</sup> Symptoms result from the infiltration of various organs by hyperactivated macrophages and lymphocytes, and diffuse intravascular hemophagocytosis. Infantile acute liver failure remains a rare presentation of HLH, but is critically important to recognize, as chemotherapy and bone marrow transplantation (BMT) may reverse an otherwise unfavorable prognosis. At the present time, LT is considered contraindicated given the relapse risk in the transplanted organ.<sup>417,419</sup>

**Recommendation:**

**93. Recognition of HLH as a potential cause of acute liver failure is important, as more specific medical therapy, such as chemotherapy and bone marrow transplantation, is available (2-B).**

**Organ Allocation in the USA**

The Model for Endstage Liver Disease (MELD) utilizes a formula that includes total serum bilirubin, International Normalized Ratio of prothrombin time (INR), and serum creatinine and is used for adults and children  $\geq 12$  years of age.<sup>420</sup> The Pediatric Endstage Liver Disease (PELD) score was developed from children enrolled in the Studies of Pediatric LT (SPLIT) database. PELD is designed for children under 12 years of age and utilizes total serum bilirubin, INR, height, weight, and albumin.<sup>421</sup> The PELD system has benefited children in many ways.<sup>422</sup> How-

ever, just over 50% of children did not undergo LT with their calculated PELD score.<sup>423</sup> Rather, letters of exception were required to secure additional points or to request Status 1 listing for reasons other than liver failure in order to receive an LT. In addition, regional differences in PELD score utilization are noted.<sup>423</sup> A study using UNOS registry data reached a similar conclusion, indicating that PELD has not resulted in standardization of listing practices in pediatric LT.<sup>424</sup>

**PELD Exceptions**

When the PELD score is believed not to reflect the severity of liver disease or its consequences, an appeal letter can be written to the Regional Review Board (RRB). UNOS and the RRBs established conditions in which the PELD score can be adjusted higher; these conditions include failure to thrive, intractable ascites, pathologic bone fractures, refractory pruritus, and hemorrhage due to complications associated with portal hypertension.

A pediatric liver transplant candidate with a urea cycle disorder or organic acidemia shall be assigned a PELD (less than 12 years old) or MELD (12-17 years old) score of 30. If the candidate does not receive a transplant within 30 days of being listed with a MELD/PELD of 30, then the candidate may be listed as a Status 1B. Candidates meeting these criteria will be listed as a MELD/PELD of 30 and subsequent Status 1B without RRB reviews. A similar policy exists for hepatoblastoma, although the 30 days at PELD 30 is no longer required before status 1B. Hospitalization is not a requirement for listing in Status 1B for these candidates. Candidates with other metabolic diseases may apply to the RRB for an appropriate PELD (less than 12 years old) or MELD (12-17 years old) score. RRB will accept or reject the center's requested MELD/PELD score based on guidelines developed by each RRB. A study conducted using UNOS database revealed that widespread regional variations exist.<sup>425</sup>

International Experiences Liver organ allocation policies vary worldwide. Some individual and collaborating countries, such as the United Kingdom, Brazil, and Eurotransplant,<sup>426-428</sup> have a national organ registry, while others have regional/provincial or center-based waiting lists in place as seen in Australia, Canada, and others.<sup>429-431</sup>

**Technical Variants**

**Technical Variant Grafts**

LT in children is optimally performed in centers of excellence with broad experience in pediatric

hepatology and surgical expertise in pediatric hepatobiliary surgery and all applicable liver transplant techniques. The introduction of live donor LT, as well as other technical variant grafts such as deceased donor split grafts, has significantly reduced mortality on the pediatric liver list.<sup>432</sup> While comprehensive registry analyses suggest some detrimental impact on long-term graft survival with deceased donor split grafts,<sup>433-435</sup> these techniques have been successfully applied in carefully selected cases by experienced practitioners.

### **Domino Transplantation**

The first sequential or domino LT was performed using structurally normal liver from a familial amyloidotic neuropathy (FAP) patient in Portugal.<sup>436</sup> Livers removed from patients with maple syrup urine disease (MSUD) have also been utilized for domino transplantation with satisfactory outcome reported in a small number of MSUD-liver recipients.<sup>437</sup> Morphologically normal livers from patients with primary hyperoxaluria type 1 (PH1) were used for domino transplant in Europe, but all PH1-liver recipients developed kidney failure within the first 4 weeks after transplantation.<sup>438</sup> A PH1-liver was used in a neonate with acute liver failure as a bridge to survival; the patient was retransplanted within 4 months after domino transplant.<sup>439</sup> Besides technical challenges, domino transplant also carries ethical dilemma in terms of allocation of a liver allograft with known genetic defect. These issues should be thoroughly discussed with recipients of a domino organ.

### **Recommendation:**

**94. Domino LT using a donor liver with a known metabolic defect should be used in selected conditions and requires further analysis on long-term outcomes of recipient cases. (2-B); livers from patients with primary hyperoxaluria type 1 should not serve as domino organs. (2-B).**

### **Liver Cell/Hepatocyte Transplantation**

Hepatocyte transplantation (HcT) has been trialed in limited settings in both acute liver failure and metabolic disease.<sup>440</sup> Currently, results of HcT have been limited by insufficient donor cell engraftment as well as a limited ability to monitor function of the transplanted cells or identify rejection in a timely fashion to alter immunosuppression before the graft is lost.<sup>441,442</sup> Consideration for hepatocyte transplantation can be considered in the context of approved clinical research trials either as a bridge to solid organ transplantation or in selected cases as definitive therapy.

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