Long-Term Medical Management of the Pediatric Patient After Liver Transplantation: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

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PREAMBLE

These recommendations provide a data-supported approach to establishing guidelines. They are based on the following: (1) a formal review and analysis of recently published world literature on the topic (via a PubMed/MEDLINE search from 1996 to July 2011 limited to the English language, human studies, and children 0-18 years old); (2) A Manual for Assessing Health Practices and Designing Practice Guidelines from the American College of Physicians1; (3) guideline policies, including the American Association for the Study of Liver Disease policy on the development and use of practice guidelines and the American Gastroenterological Association policy statement on the use of medical practice guidelines2; and (4) the experience of the authors in managing children undergoing liver transplantation (LT). Intended for use by pediatricians and 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 quality of the evidence supporting the recommendations, the Practice Guidelines Committee

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AR, acute rejection; AST, aspartate aminotransferase; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, chronic rejection; CT, computed tomography; EBV, Epstein-Barr virus; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HAT, hepatic artery thrombosis; LDH, lactate dehydrogenase; LT, liver transplantation; MR, magnetic resonance; mTOR, mammalian target of rapamycin; OLT, orthotopic liver transplantation; OR, odds ratio; PSC, primary sclerosing cholangitis; PTLD, posttransplant lymphoproliferative disorder; PVT, portal vein thrombosis; SPLIT, Studies of Pediatric Liver Transplantation.

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

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of the American Association for the Study of Liver Diseases requires a class (reflecting the benefit versus the risk) and level of evidence (assessing the strength or certainty) to be assigned to and reported with each recommendation. To more fully characterize the available evidence supporting the recommendations, the Practice Guidelines Committee has adopted the classification used by the Grading of Recommendations, Assessment, Development, and Evaluation workgroup with minor modifications\(^3,4\) (Table 1). In the Grading of Recommendations, Assessment, Development, and Evaluation system, the strength of recommendations is classified as (1) strong or (2) weak. The quality of evidence supporting strong or weak recommendations is designated by 1 of 3 levels: (A) high, (B) moderate, or (C) low.

### INTRODUCTION

Pediatric LT has dramatically changed the prognosis for many infants and children with liver failure and metabolic disease. As survival increases, long-term maintenance resources exceed perioperative care requirements. The commonest indication for LT is biliary atresia, which accounts for 50% of children requiring transplantation in the United States\(^5\) and for 74% in Europe.\(^6\) Most early deaths occur within 3 months after transplantation. The main causes of graft loss in the first week include primary nonfunction, hepatic artery thrombosis (HAT) or portal vein thrombosis (PVT), systemic sepsis, and multiorgan failure (<10%). Other significant complications are acute rejection (AR; 50%), chronic rejection (CR; 10%), biliary leaks and strictures (5%-25%), viral infections [especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV)], acute kidney injury, and fluid imbalance.\(^7-11\) The 1-year patient survival rate is 90%, and the survival rate is 75% at 15 to 20 years with good quality of life.\(^7-14\) Survival after transplantation for acute liver failure has improved from 70% at 1 year to 87%, with 5-year survival rates of 67% to 80%.\(^15-17\) The documented 5-year survival rates for transplantation are >90% for chronic liver disease and 89% for metabolic liver disease.\(^18,19\) Vital to survival are improved selection (prioritization and management of candidates with the Pediatric End-Stage Liver Disease score), better preoperative management of hepatic complications and nutritional support, innovative surgical techniques for expanding the donor pool, and improved postoperative immunosuppression and management.\(^7,20,21\)

As the emphasis moves from immediate survival and the prevention and management of early postoperative complications, attention has become focused on long-term outcomes and quality of life. Most studies have demonstrated improved nutrition, bone metabolism, endocrine function, and psychosocial development after successful transplantation, with recent studies documenting cognitive function, educational achievement, and patient and family perceptions of quality of life. Long-term issues include recurrent disease, adverse effects of immunosuppression (especially chronic kidney disease), hypertension, hyperlipidemia, the development of malignancies (e.g., posttransplant lymphoproliferative disease), and the management of adolescents’ transition to adult care. Although they undergo transplantation at specialized centers, recipients receive care from local providers, who must recognize potential long-term care challenges. This document provides an expert consensus on managing children from 3 months after LT. It focuses on preventing and diagnosing complications, preventing chronic infections, reducing the adverse effects of immunosuppression, ensuring a good quality of life, and managing the transition from childhood to adolescence and adulthood.

### ROUTINE MONITORING AND MANAGEMENT

#### Growth and Nutritional Rehabilitation

Physical measurements include height, weight, and lean muscle mass. Few pediatric LT studies have measured muscle mass, but weight gain appears to recover fully in patients with adequate graft function despite previous malnutrition. Linear growth failure is common in children with cirrhosis because of malnutrition secondary to fat malabsorption, abnormal

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**TABLE 1. Grading of Recommendations, Assessment, Development, and Evaluation**

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1. Strong</td>
<td>Factors influencing the strength of the recommendation include the quality of the evidence, the presumed patient-important outcomes, and the cost.</td>
</tr>
<tr>
<td>2. Weak</td>
<td>There is variability in the preferences and values or more uncertainty. The recommendation is made with less certainty, or the cost or resource consumption is higher.</td>
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<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Criteria</th>
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<tr>
<td>A. High</td>
<td>Further research is unlikely to change confidence in the estimate of the clinical effect.</td>
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<tr>
<td>B. Moderate</td>
<td>Further research may change confidence in the estimate of the clinical effect.</td>
</tr>
<tr>
<td>C. Low</td>
<td>Further research is very likely to affect confidence in the estimate of the clinical effect.</td>
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nitrogen metabolism, and increased energy expenditure and possibly growth hormone resistance. After successful LT and nutritional restitution, growth hormone and insulin-like growth factor 1 levels return to normal, and linear growth improves. Catch-up growth is dependent on steroid usage and may not occur until the second year; this plateau after 2 to 3 years, and up to 25% of patients have heights less than 5% for their age over the long term. The Studies of Pediatric Liver Transplantation (SPLIT) registry reveals that linear growth impairment (<10th percentile) is likelier in patients with metabolic diseases, including alpha-1-antitrypsin deficiency and urea cycle defects [odds ratio (OR) = 4.4], and with greater than 18 months of steroid exposure (OR = 3.02). Higher percentiles for weight (OR = 0.80) and height (OR = 0.62) at LT were protective. Prolonged steroid exposure was also associated with less catch-up growth. Weight and height z scores at transplant best predicted catch-up growth. Patients with lower weight percentiles exhibited less growth acceleration, whereas patients with lower height percentiles at transplant exhibited more linear growth acceleration. Previous reports examining pretransplant growth versus posttransplant growth have been inconclusive. Children with more severe growth arrest before transplantation require the most catch-up growth; without other limitations, the acceleration of their posttransplant linear growth may be more pronounced than in patients with closer-to-normal growth before transplantation. Growth improves with steroid withdrawal or discontinuation and with supplemental recombinant human growth hormone therapy, which improves height without advancing bone age beyond the chronological age or hindering adult height potential. However, up to 50% of recipients have a final adult height 1.3 standard deviations lower than their genetic potential, and patients with Alagille syndrome may not have improved growth despite these measures.

**Obesity**

The proportion of obese adult LT recipients approaches 30%, many exhibit diabetes (30%), hyperlipidemia (60%), and hypertension (60%). These comorbidities place adult and pediatric LT recipients at higher risk for serious cardiovascular disease. The impact of metabolic syndrome on pediatric LT recipients is just being appreciated. The observation and management of adult recipients suggest that as pediatric recipients age, these comorbidities could threaten their long-term survival and require therapy.

**Recommendations**

1. Optimize the nutritional status before and after LT (1B).
2. To encourage growth, routine immunosuppression protocols should minimize steroid exposure during the first 6 to 12 months after transplantation (1A).

3. Measure the height and weight to identify patients with growth impairment who may benefit from reduced steroid exposure (1B).
4. Monitor the body mass index and consider obesity management (2C).

**Endocrine and Bone Metabolism**

End-stage liver disease may cause endocrine complications (growth failure, pubertal delay, and hepatic osteodystrophy). After transplantation, high-dose immunosuppression (particularly potent glucocorticoids) and immobilization may prevent recovery. Reduced production of sex hormones due to severe liver disease before transplantation, particularly in adolescents, may affect growth and delay puberty. Steroid withdrawal syndrome may occur when the corticosteroid dose is decreased below physiological production. It is most common in patients treated with supraphysiological doses of corticosteroids for more than 3 months. Patients may experience fatigue, decreased appetite, weight loss, and nausea and respond to reinitiation of corticosteroids.

**Hepatic Osteodystrophy**

In growing children, hepatic osteodystrophy affects bone material and growth plates. Children may develop low bone mass, fractures, rickets, spine abnormalities, and growth failure. Bone mineral density and bone mass are often low or low-normal in children with chronic liver disease. In the first 3 months after LT, bone mineral density remains low or may decrease before normalization after 1 year. More prolonged recovery with low bone mass (bone mineral density z score < −2) in 7% to 15% has been reported over the long term. Fractures are common in children before and after LT. Before transplantation, the fracture prevalence ranges from 10% to 28%, after transplantation, it rises to 12% to 38% (50% in 1 case series). Vertebral and nonvertebral fractures have been reported. Vertebral fractures may be asymptomatic. Risk factors include an older age at transplantation, male sex, fractures before transplantation, a low body weight, and the cumulative steroid dose. The least bone mineral density improvement after orthotopic liver transplantation (OLT) occurs in pubertal and postpubertal subjects. Avascular necrosis is a complication of high-dose steroid treatments and has been reported in 7 of 196 solid organ transplant recipients (3.6%) 9.2 years after transplantation. All affected patients were adolescents; 3 underwent LT. In a large retrospective series of solid organ transplant recipients, 13.5% suffered scoliosis, and some required surgery. Another study of 40 young adults undergoing transplantation during childhood reported that 35% had at least 1 compressed or wedge vertebra, 20% had a history of vertebral fractures, 28% reported back pain...
at rest, and 38% had scoliosis > 10 degrees. Males were predominantly affected. Low muscle mass, found in many children with liver disease, leads to low bone mass. The only relevant study showed a moderately reduced ratio of the bone mineral content to the lean tissue mass. Hepatic protein synthesis, including insulin-like growth factor 1 production, improves after LT and spurs moderate catch-up growth. Vitamin D (25-hydroxyvitamin D) levels in children are low before and immediately after OLT but improve during the first year. Routine vitamin D (3-10 times the recommended daily allowance) is recommended for cholestatic liver disease but is not yet routine after OLT.

Monitoring includes measurements of calcium, phosphate, vitamin D, and parathyroid hormone levels at least twice a year. Vitamin D should be given as cholecalciferol (vitamin D₃) or ergocalciferol (vitamin D₂). An appropriate intake of calcium and phosphate should be ensured, especially in children on immunosuppressants such as tacrolimus, which can cause phosphate loss. Children with pretransplant osteopenia should be monitored for scoliosis, and children older than 5 years should be monitored for fractures. Dual-energy X-ray absorptiometry scanning at LT and 12 and 24 months afterward may help with appropriate size correction and lateral thoracic spine X-rays. Bisphosphonates should be considered for low bone mass with a vertebral fracture, a lower extremity fracture, or 2 upper limb fractures.

Recommendations
5. Monitor patients for persistent hepatic osteodystrophy, risk factors for fractures, and scoliosis (1B).
6. Continue mineral and fat-soluble vitamin supplementation (especially D₂, or D₃) until vitamin D levels are normal (1B).

Psychosocial Development
Studies suggest that pediatric LT patients have lower physical and psychosocial function. A multicenter study of more than 800 recipients found psychosocial function more compromised than physical function, and psychosocial health was affected by school function, particularly if there was cognitive impairment or significant school absence. A large survey of children included in the SPLIT registry revealed that one-third missed more than 10 days of school in the previous year, and 18% missed more than 20 days. Absence was likelier for older participants and children with shorter intervals from LT. Programs caring for pediatric LT recipients might consider routine follow-up clinics for older children at times not interfering with school attendance. Up to 16% of adolescents reported symptoms consistent with posttraumatic stress disorder. Parents also reported symptoms of posttraumatic stress disorder and significant stress and anxiety related to the child’s medical condition.

Medication concerns and treatment anxiety were significant among pediatric recipients. Children reported that medications changed their physical appearance and that parents nagged them about adherence. Nonadherence has been associated with lower physical quality of life, limitations in social and school activities, increased parental emotional distress, and decreased family cohesion.

Recommendations
7. The follow-up of school-aged LT recipients should include an assessment of school functioning and school absence (1A).
8. Be aware of posttraumatic stress disorder or other mental health issues and refer a patient for a formal psychiatric evaluation if significant symptoms are present (1B).

Neurocognitive Function
The onset of liver disease in infancy impairs neurodevelopment. Infants with metabolic diseases (eg, urea cycle defects and tyrosinemia) may suffer significant neurological damage that may be alleviated by early therapy, which can include LT. Liver disease in infancy is commonly caused by biliary atresia or other biliary cirrhosis. These infants typically experience advanced malnutrition, growth arrest, and profound muscle weakness. Although many maintain low-average mental and motor development before transplantation, their function drops significantly during the transplant process. Recovery and delayed developmental catch-up in these infants have been associated with prolonged hospitalization, an older age at transplant, and malnutrition before transplantation. Studies comparing neurocognitive function before and after LT have noted that many patients’ delays persist after physical rehabilitation. Various groups have demonstrated severely impaired intellectual ability in 10% to 15% of recipients; newer studies have reported slightly better outcomes. Several studies have suggested differential impairment of language and verbal skills; nearly 15% lose some hearing, and this is especially true for children who receive ototoxic medications before transplantation (eg, children with hepatoblastoma). Approximately 30% require special education after transplantation. Early results of a longitudinal, multicenter study measuring intelligence, academic achievement, and executive function in recipients who received a transplant at less than 5 years of age indicated that a cognitive delay could be identified at 5 to 7 years. A mild to moderate delay was demonstrated in 28% of the members of this cohort, with little improvement 2 years later. Executive functions (organizational skills, multitasking, and behavior regulation) were also delayed in this group. The results of the 6-question Pediatric Quality of Life Inventory Cognitive Function Scale correlated well with formal testing of intelligence and executive function.
Assess recipients for hearing loss in the first post-operative year and periodically thereafter as indicated (1B).

Provide rehabilitation immediately after transplantation: physical therapy for infants with delayed motor development and speech and occupational therapy for older children with deficits (1B).

Adherence

Immunosuppression is essential for graft survival, and adherence to the prescribed regimen is essential to ensure adequate immunosuppression. Nonadherence could cause allograft rejection and death. Measurement of adherence is difficult because different assessments yield different results. Methods are subjective (self-reports and interviews) or objective (patient observation, medication blood levels, electronic monitoring, pill counts, and refill rates). Objective methods (especially direct measurements of ingestion) are preferred. One direct measure is the calculation of the standard deviation of consecutive ingestions. A fluctuation exceeding 2 or 2.5 standard deviations predicts clinically significant nonadherence. Many reviews discuss the psychosocial factors that predict nonadherence, such as psychological symptoms of the patient or the caretaker, family interactions, barriers to adherent behavior, health beliefs (including responsibility shifts between the caretaker and the child), the disease process (eg, the time since transplantation), care factors (prescription pattern and clinic makeup), and socioeconomic status. Strategies for improving adherence include simplifying treatment regimens, addressing risk factors, using interventions such as reminders (eg, text messaging), and following up patients more intensively.

Recommendations

12. The transplant team assesses and treats nonadherence with a multidisciplinary approach (2B).

13. Screen for nonadherence with objective methods such as the monitoring of immunosuppressant levels (1B).

Screening and Detection of Late Surgical Complications

Successful pediatric LT is associated with improved quality of life and normal liver function. Survival rates are 70% to 90%. Two reviews summarize operative techniques. The transplant center should summarize surgical details such as the type of allograft implanted (whole versus partial and living donor versus split), the type of biliary reconstruction employed (duct-to-duct reconstruction versus Roux-en Y choledochojejunostomy), and the type of abdominal wall closure used (primary fascial versus prosthetic reconstruction). Major complications (HAT, PVT, biliary strictures, and biliary leaks) should be communicated. A thorough physical examination, standard laboratory parameters, and ultrasound examinations of the liver, spleen, and kidneys generally define vascular patency and biliary complications.

Late Hepatic Artery Thrombosis

Most series have reported HAT rates between 3% and 10%. Early HAT commonly leads to early graft failure, retransplantation, or death. Collateralized arterial flow into the transplanted liver may minimize late HAT. Mild abnormalities (1.5-2 times normal levels) in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) are common but may indicate vascular problems. Because the blood supply to transplanted bile ducts is derived solely from the hepatic artery, HAT is frequently associated with biliary pathology. Serum total bilirubin, alkaline phosphatase, and gamma-glutamyltransferase (GGT) levels are sensitive indicators of late HAT. The first-line imaging test is usually a Doppler ultrasound examination of the liver. Although it is >90% sensitive for detecting early HAT, its utility for late HAT is poor. A definitive diagnosis of late HAT requires more advanced imaging (computed tomography (CT), magnetic resonance (MR), or standard angiographies). Treatment may not be required if the patient is stable and the liver receives adequate blood flow through arterial collaterals or the portal vein. If treatment is required, thrombolysis and anticoagulation are rarely effective, and surgical reconstruction is contraindicated. Radiological treatment of biliary strictures is indicated if necessary, and drainage of intrahepatic abscesses/bilomas is required. For symptomatic late HAT with cholangitis, hepatic abscesses, or diffuse biliary stricturing, retransplantation is frequently required.

Late Portal Vein Thrombosis

PVT is generally reported at rates of 2% and 10%; most cases are asymptomatic. Early PVT frequently leads to graft failure, retransplantation, or death. Collateral flow around the transplanted liver with natural shunts is common and may compensate for PVT for years. Portal vein anastomotic strictures that develop in reduced or split grafts have also been reported. Children with PVT or portal vein anastomotic strictures will demonstrate a normal-size liver and an enlarged spleen. Superficial abdominal wall veins, caput medusae, or esophageal varices may be present. Ascites may develop with the severe portal hypertension associated with PVT. Clubbing of nail beds may also occur in advanced cases because PVT...
has been associated with hypoxia and hepatopulmonary syndrome and with portopulmonary hypertension. Laboratory testing provides further evidence of PVT. AST, ALT, and LDH levels typically may be normal to slightly abnormal (1.5-2 times normal levels). Serum bilirubin, alkaline phosphatase, and GGT levels are typically normal. The platelet count usually is very low (×10^9/L) because of hypersplenism. Anemia is common and is related to subclinical gastrointestinal bleeding or splenic sequestration and destruction. First-line imaging with Doppler hepatic ultrasound is usually diagnostic. The liver texture is typically coarsened or nodular because PVT is associated with nodular regenerative hyperplasia. The extrahepatic portal vein is more readily imaged, and thrombosis can commonly be detected. Splenomegaly and ascites can easily be detected with this modality. Contrast radiography with CT, MR, or standard angiography will clearly define the location of the thrombus within the portal vein as well as its extension into feeding vessels such as the splenic or superior mesenteric vein. Endoscopy for detecting esophageal and gastric varices may confirm late PVT. The treatment is similar to that for portal hypertension in the nontransplant setting. Endoscopic treatment of varices can also prevent or limit gastrointestinal bleeding. Transjugular intrahepatic portosystemic shunts have almost no role because of thrombosis of the portal vein. Surgical shunts (selective distal splenorenal, systemic mesocaval, and meso-Rex) are useful, but retransplantation may be indicated.

**Inferior Vena Cava/Hepatic Vein Obstruction**

Inferior vena cava/hepatic vein obstruction or stenosis with ascites and protein-losing enteropathy is rare and presents with diarrhea, hypoalbuminemia, and ascites. The diagnosis is made with Doppler ultrasound and hepatic venography. The radiological insertion of a stent may be successful.

**Late Biliary Strictures**

The rates for biliary strictures after pediatric LT range from 5% to 25%.

In contrast to biliary leaks, which are an early biliary complication, biliary strictures present late after LT. The main cause of late biliary strictures is graft ischemia; HAT can be ruled out with definitive imaging. Ischemic biliary strictures are frequently multiple and affect all aspects of the biliary tree. In contrast, solitary biliary strictures are usually associated with the surgical anastomosis. These strictures are more common with choledochocholedochostomy than choledochojunostomy. The physical examination may be normal. Biliary strictures present with jaundice and pruritus. Laboratory testing is helpful in diagnosis; classically, AST, ALT, and LDH levels are normal or mildly elevated. The earliest findings are elevated alkaline phosphatase and GGT values 5 to 10 times normal levels. This can be confirmed with hepatic duplex ultrasonography: CT or magnetic resonance imaging (MRI). A definitive diagnosis is obtained with contrast radiography or MR cholangiopancreatography combined with MR angiography to assess the hepatic artery. The most usual invasive test is transhepatic cholangiography. Invasive cholangiography and the placement of a biliary stent will decompress the biliary tree. Endoscopic retrograde cholangiopancreatography is performed only in those patients who have received a duct-to-duct anastomosis. Treatment of late biliary strictures is highly successful if the hepatic artery is patent and if there is an anastomotic or solitary stricture. Surgery is usually reserved for patients for whom transhepatic therapy has failed. Retransplantation is usually required for diffuse and multiple biliary strictures and particularly for those associated with late HAT; retransplantation should be considered.

**Incisional Hernia**

An incisional hernia occurs in 5% to 18% of transplants. The lowest incidence is after primary fascial closure, and this is followed by the incidence in patients closed with a prosthetic mesh/material. This can be diagnosed with a physical examination. An assessment of hernia contents and their reducibility is crucial. A tender, nonreducible hernia requires an urgent surgical consult; most only require conservative treatment. The preoperative preparation should include an assessment of the liver allograft. CR, HAT, or PVT may contraindicate a repair.

**Recommendation**

14. Surgical complications are optimally investigated and treated at a transplant center (2B).

**Protocol Liver Biopsy**

The rationale for surveillance liver biopsy in patients with normal biochemical liver function tests is to document the natural history of the graft, diagnose rejection or CMV/EBV, identify graft hepatitis or fibrosis, guide the withdrawal of immunosuppression, and detect occult biliary disease or other recurrent disease. Complications are relatively rare, but 2% to 5% of children may have a significant complication (usually postbiopsy bleeding). Noninvasive assessments of fibrosis with FibroScan, serum biomarkers of fibrosis, or MRI are being validated in children with cystic fibrosis or nonalcoholic liver disease. Protocol biopsy has been performed in adults at 7 to 21 days, at 1, 2, 5, and 10 years, or annually to detect hepatitis B or C or recurrent disease. A few pediatric centers have evaluated serial protocol liver biopsy samples after transplantation to assess histological changes. Most found that 1-year protocol biopsy samples from children with normal biochemical liver function were mostly normal (68% in one series), and they did not provide sufficient additional information on graft histology.
However, histological examinations of 5- and 10-year protocol biopsy samples from children have detected increased graft hepatitis and fibrosis.\textsuperscript{128-131} In one study, 158 asymptomatic children underwent protocol liver biopsy. Chronic hepatitis was common: 22\%, 43\%, and 64\% at 1, 5, and 10 years, respectively (\textit{P} < 0.001). Fibrosis also increased: 52\%, 81\%, and 91\% at 1, 5, and 10 years, respectively (\textit{P} < 0.001). By 10 years, 15\% had progressed to cirrhosis. No clear etiology was identified in particular; there was no evidence of a viral infection.\textsuperscript{128,129} Autoantibody positivity was a predictor for 13\% and 10\% of children with normal biopsy results at 5 and 10 years, respectively, and for 72\% and 80\% of those with chronic hepatitis at 5 and 10 years, respectively (\textit{P} < 0.001). Four children fulfilled the diagnostic criteria for de novo autoimmune hepatitis (AIH); 2 were hepatitis C–positive.\textsuperscript{128} It is not clear whether these histological changes represent a form of CR due to the immunosuppression regimes or de novo AIH because the graft hepatitis improved with increased immunosuppres-\textsuperscript{sion.130,131} An increase in graft fibrosis, but not graft hepatitis, was also reported after transplantation by another group that noted fibrosis increasing from 31\% to 65\% (\textit{n} = 66) from 1 year after LT to 5 years. There was no increased incidence of fibrosis at 10 years (69\%, \textit{n} = 55), but the proportion of patients with severe fibrosis increased from 10\% at 5 years to 29\%. The fibrosis was not related to rejection, chronic hepatitis, or immunosuppressive therapy but may have reflected underimmunosuppression.\textsuperscript{132,133} De novo autoimmune or otherwise unexplained hepatitis occurs in 5\% to 10\% of children after transplantation.\textsuperscript{132-134} This syndrome is characterized by biochemical, serological, and histological features indistinguishable from AIH in patients undergoing transplantation for conditions other than autoimmune disorders. It is characterized by histological evidence of chronic hepatitis associated with circulating nonspecific autoantibody formation (anti-nuclear antibodies and smooth muscle antibodies), an elevation of immunoglobulins (particularly immunoglobulin G), and allograft dysfunction. The cause may be a form of low-grade CR and may be related to molecular mimicry or oversuppression of T cells.\textsuperscript{135,136} The increased incidence in children may be related to a disruption of normal T cell maturation. Most cases respond to increased steroids or azathioprine.\textsuperscript{137} Recent studies have identified graft hepatitis in adults positive for hepatitis E or Torque teno virus; data are not available for children.\textsuperscript{138,139} Screening for immunoglobulins and nonspecific autoantibodies every year for 5 years and testing for CMV, EBV, and hepatitis B, C, and E may detect de novo AIH or occult viral infections and guide the need for biopsy.

### Recommendation

15. Protocol liver biopsy 1 year after transplantation is not required (1B).

### Screening for Skin Cancer

De novo cancer may reflect decreased tumor immuno-surveillance, DNA damage from antimetabolite medications, or a response to chronic inflammation. Skin cancer is rare during the first 10 to 15 years after transplantation.\textsuperscript{140} An analysis of the Israel Penn Tumor Registry found that skin malignancies accounted for 12\% of pediatric posttransplant cancers.\textsuperscript{141} In a Swedish study that linked all solid organ transplant patients younger than 18 years between 1970 and 2007 (\textit{n} = 536) to the National Cancer Registry, 2 cases of nonmelanoma skin cancers were identified.\textsuperscript{142}

### Safe Living

Transplant recipients should be advised on minimizing post-LT risks (food, water, animals, and travel). The following is adapted from the AST Infectious Diseases Community of Practice guidelines\textsuperscript{143} and the American Academy of Pediatrics (\textit{Red Book}).\textsuperscript{144} The following is adapted from the AST Infectious Diseases Community of Practice guidelines\textsuperscript{143} and the American Academy of Pediatrics (\textit{Red Book}).\textsuperscript{144}

### Immunizations

Routine vaccinations should be given before transplantation; these include immunoprophylaxis against varicella, measles, pneumococcal diseases, influenza viruses, hepatitis A and B, and travel-related infections\textsuperscript{145} (Table 2). Live attenuated vaccines are generally contraindicated after transplantation. Varicella vaccination is not recommended in children receiving long-term immunosuppression.\textsuperscript{143-145} One report found the measles-mumps-rubella vaccine to be safe.\textsuperscript{146} Live vaccines, with the exception of polio, may be given to family members. Synthetic vaccines are safe, with optimum immune responses observed with lower levels of immunosuppression. Household contacts’ immunizations, particularly for influenza, should be up to date.\textsuperscript{143,144}

### Sports and Recreation

Full physical activity, including sports, can be expected 8 to 12 weeks after LT upon agreement by the transplant center.\textsuperscript{147}

### Tattoos and Piercings

These are acceptable if the child has received the hepatitis B vaccine.\textsuperscript{148,149}

### Travel Advice

Patients should be assessed at least 2 months before travel. Visits should be discouraged to high-risk areas experiencing acute outbreaks or with endemic life-threatening infections for which effective prevention is
not available (eg, yellow fever). Recipients should carry information about their condition, medications, and contact numbers for their transplant center.

**Recommendations**

17. Minimize infection risks related to hygiene, food, water, animals/pets, and travel (2C).
18. Recipients can travel abroad 6 months after transplantation with normal precautions and the advice of their transplant center (2C).
19. Combat childhood infections with recombinant or killed vaccines (1A).
20. Immunize household contacts. Recipients and relatives should receive the annual influenza immunization (1B).

**IMMUNOSUPPRESSION**

Adequate immunosuppression is needed to support graft function but must be balanced against the risks of side effects and potential overimmunosuppression (Table 3). There is no standard-of-care designation for immunosuppression choice and dose. Current practice includes calcineurin inhibitor (CNI)–based regimens: they are mainly based on tacrolimus because it avoids the gingival hyperplasia and hirsutism associated with cyclosporine. Augmentation with mycophenolate or mammalian target of rapamycin (mTOR) inhibitors may reduce reliance on steroids and high-dose CNIs. Steroids can often be withdrawn within 3 to 6 months. Monitoring for graft dysfunction and adequate immunosuppression levels includes immunosuppression trough levels and liver indices (ALT, AST, and GGT).

**Acute Rejection**

AR occurs within the first 7 to 10 days after transplantation. The incidence has been reduced with tacrolimus and/or interleukin-2 receptor-blocking antibodies. AR is best prevented by regular blood test monitoring and immunosuppressant medications (see the Disease-Specific Issues and Recurrent
Disease section). AR is typically indicated by elevated bilirubin, transaminase, or GGT levels and/or low immunosuppressant levels. Patients who are stable more than a year after transplantation may be adequately monitored 2 to 4 times a year. The balance between T helper 1 and T helper 17 CD4\(^+\) T cells may play a role in AR.\(^{154}\) There is no serum or clinical marker that correlates with AR or clinically measured levels of immunosuppressants; histological proof is needed to diagnose AR because elevated serum bilirubin, transaminase, or GGT levels can occur during infections. An international working group definition of liver allograft rejection (the Banff criteria) using a tripartite pathological focus on lymphocyte-predominant portal infiltrates, cholangiolar damage, and endothelitis has been validated.\(^{155-157}\)

**Late Onset**

In recent SPLIT findings among 461 children up to 5 years after LT, approximately 50% experienced AR in the first year, and 60% experienced AR by year 5.\(^{158}\) Approximately 1 in 5 patients who avoided early AR developed late-onset AR between 1 and 5 years.

**Treatment**

Most children respond to bolus doses of steroids, increased CNI levels, and/or immunosuppressants such as mycophenolate and mTOR inhibitors.\(^{102,159}\)

**Recommendations**

21. Serial measurements of bilirubin, ALT, AST, GGT, and immunosuppressant blood levels are the main means of detecting graft dysfunction and AR (1B).

22. A histological assessment of a liver biopsy sample remains the best means of diagnosing AR (1A).

**Chronic Rejection**

CR may cause long-term graft dysfunction and fibrosis. Its presentation usually is associated with jaundice, pruritus, or biliary obstruction with elevated bilirubin, AST, ALT, alkaline phosphatase, and GGT levels. The Banff group defined the minimal histological features of CR as biliary epithelial changes affecting a majority of bile ducts with or without duct loss, foam cell obliterator arteriopathy, or bile duct loss affecting >50% of portal tracts.\(^{158-161}\) SPLIT focused on late graft loss in 35 of 872 children followed for more than 1 year after transplantation.\(^{14}\) Thirteen (37%) lost grafts because of CR, and 4 (11%) lost grafts because of AR. Steroid-resistant AR was strongly associated with late graft loss with a hazard ratio of 3.46 (95% confidence interval = 1.81-6.44). Having more than 1 AR episode was also associated with a 2-fold increased risk of late graft loss. A Belgian study found similar results.\(^{160}\) Other reports have suggested that tacrolimus may markedly reduce CR in comparison with cyclosporine regimens.\(^{162,163}\) A longer term trial comparing cyclosporine...
to tacrolimus indicated reduced rates of AR and CR with tacrolimus.\textsuperscript{151,152}

**Treatment**

The protocols are similar to those for AR\textsuperscript{153,161} with retransplantation for those who do not respond. SPLIT reported CR in 21 patients within 5 years of transplantation: 8 (38\%) underwent retransplantation.\textsuperscript{158} Future randomized controlled trials are required for definitive management.

**Recommendations**

23. CR is a major cause of late graft loss and should be considered in the setting of poorly responsive AR with biopsy findings supportive of CR (1A).

24. Treat CR with one of a variety of choices: use a higher serum level of the immunosuppressive (eg, tacrolimus), switch to different immunosuppressives (eg, from tacrolimus to mTOR inhibitors), and/or add other immunosuppressives (eg, mycophenolate; 1B).

**Adverse Effects of Immunosuppression**

Two-thirds of late deaths can be attributed to complications of immunosuppression, infections, and malignancies.\textsuperscript{14,160} Immunosuppression medications are associated with an increased risk for diabetes, hyperlipidemia, hypertension, obesity, and metabolic syndrome.\textsuperscript{164,165} Long-term immunosuppression treatment incurs substantial complications.\textsuperscript{166} The minimization or withdrawal of immunosuppression should be managed cautiously to prevent allograft damage.

**Renal Function**

CNIs, the principal immunosuppressive medications used to prevent graft rejection, contribute to de novo acute and chronic posttransplant renal dysfunction. The cumulative 5-year incidence of chronic renal failure among adult LT recipients has been estimated to exceed 15\%.\textsuperscript{167} In children, the prevalence is not as well defined because serum creatinine is not a reliable measure of renal function and only a few studies have directly measured the glomerular filtration rate (GFR). Estimates of renal dysfunction in LT recipients range from 24\% to greater than 70\%.\textsuperscript{168}

**Prevalence and Risk**

Single-center studies suggest that renal function is stable for most pediatric LT recipients 1 to 5 years after transplantation\textsuperscript{169-186} and that only a small subgroup develops progressive deterioration. In a recent multicenter, cross-sectional study of the measured GFR in 397 pediatric patients 1 or more years (mean = 5.2 years) after LT, 17.6\% had a measured GFR < 90 mL/minute/1.73 m\textsuperscript{2}.\textsuperscript{144} According to the National Kidney Foundation classification of chronic kidney disease, 14.6\% of the patients had stage 2 chronic kidney disease (GFR = 60-89 mL/minute/1.73 m\textsuperscript{2}), 2.5\% were at stage 3 (GFR = 30-59 mL/minute/1.73 m\textsuperscript{2}), and 0.4\% were at stage 4 or 5 (GFR < 30 mL/minute/1.73 m\textsuperscript{2}). In a multivariate analysis of 289 patients, a calculated GFR < 90 mL/minute/1.73 m\textsuperscript{2} at transplant, an older age at transplant, cyclosporine as the primary immunosuppression, and a height z score < -2 standard deviations 12 months after transplantation predicted a reduced GFR. Another study measured the GFR with technetium-99m/diethylenetriamine pentaacetic acid before transplantation and annually thereafter in 60 pediatric LT recipients who received 69 transplants on a tacrolimus regimen. In children older than 2 years, the measured GFR declined significantly in the first year with no significant decline afterward. In children less than 2 years old, the picture was confounded by renal maturation, but the GFR did not fall significantly up to 5 years after transplantation. Although 22\% of the patients developed renal dysfunction, none required renal replacement.\textsuperscript{170} Preexisting kidney disease can imperil renal function after transplantation. Patients with inborn metabolism errors, Alagille syndrome, and hepatic fibrosis appear at increased risk.\textsuperscript{171} In addition, those whose treatment involves significant nephrotoxic agents (primary liver tumors and cystic fibrosis) have an increased risk of chronic renal dysfunction after transplantation.\textsuperscript{164} Membranous and membranoproliferative glomerulonephritis associated with hepatitis B and C is rare. Perioperative factors can affect long-term renal function. Acute kidney injury predicts mortality in critical care patients.\textsuperscript{172} Patients with decreased estimated or measured GFRs (<90 mL/minute/1.73 m\textsuperscript{2}) at transplant or during the first month have an increased risk for chronic kidney disease.\textsuperscript{170,171} Hepatorenal syndrome before LT is an associated risk factor for renal insufficiency after transplantation.\textsuperscript{171} CNIs are felt to be the principal cause of de novo posttransplant renal dysfunction and factor in the progression of renal disease.\textsuperscript{173,174} Acquired renal cystic disease may occur after transplantation.\textsuperscript{175,176} Renal lesions have been associated with moderate renal dysfunction, biopsy-proven chronic liver graft rejection, and thrombosis of the retrohepatic vena cava.\textsuperscript{175} Cyclosporine A and renal dysfunction are associated with acquired cystic kidney disease.\textsuperscript{187}

**Screening and Prevention**

Anti-interleukin-2 receptor monoclonal antibody induction with lower doses of CNIs immediately after transplantation may be beneficial.\textsuperscript{177} Renal dysfunction is best detected via the monitoring of serum creatinine or emerging urinary biomarkers.\textsuperscript{178,179} The maintenance of intravascular volume, and the avoidance of nephrotoxic medications.\textsuperscript{180} Although measuring the GFR remains the preferred method, estimating the GFR with the updated Schwartz formula [height (cm) x 0.4/serum creatinine (mg/dL)] is acceptable.\textsuperscript{181} with the GFR ensured to be >70 mL/minute/1.73 m\textsuperscript{2} and with CNI immunosuppression reduced as required. Angiotensin-converting enzyme
inhibitors and angiotensin II receptor blockers should be used in patients with hypertension and/or proteinuria. Studies have shown that these agents have renoprotective effects and slow GFR declines in addition to improving blood pressure and decreasing proteinuria, even in patients with advanced chronic kidney disease. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be used in consultation with a pediatric nephrologist because the renal function and the potassium level must be closely monitored. Early conversion from a CNI to mTOR inhibitor immunosuppression has been used for patients with renal insufficiency at the time of transplantation, but long-term outcomes have not been defined. With stage 3 or greater chronic kidney disease, a reduction of CNI exposure may have limited utility. There are insufficient data to support the complete withdrawal of immunosuppressive medications.

**Recommendation**

25. Regularly screen renal function with the eGFR and practice calcineurin minimization. Consider renal-sparing drugs when the calculated GFR is <70 mL/minute/1.73 m² (1B).

**Diabetes Mellitus**

Our understanding of posttransplant diabetes mellitus has been complicated by the lack of a uniform definition. The reported prevalence is probably half that observed in adults. Outcomes reported to the United Network for Organ Sharing revealed that 10% of primary LT recipients developed new-onset diabetes after transplantation with cumulative incidences of 5.9%, 8.3%, and 11.2% at 1, 3, and 5 years, respectively. The incidence was twice that observed in renal transplant recipients. An older age at transplant, African American race, a primary diagnosis of cystic fibrosis, and, to a lesser degree, primary sclerosing cholangitis (PSC) and acute hepatic necrosis all increased the risk of developing diabetes. Effects of obesity and concomitant medications could not be assessed because the data were not consistently reported to the United Network for Organ Sharing. In a study of 1611 patients who underwent primary LT, glucose intolerance and posttransplant diabetes mellitus were identified in 13%; 78% developed glucose intolerance/diabetes within the first month at a mean duration of 75 days. Glucose intolerance and diabetes occurred less frequently more than 30 days after transplantation. An age >5 years, cholestatic liver disease other than biliary atresia, Hispanic race, early use of corticosteroids, and tacrolimus use were associated with an increased risk of early- and late-onset diabetes.

**Recommendation**

26. Screen LT recipients older than 5 years annually with fasting glucose in the early post-LT period and during long-term follow-up. Diagnose and treat posttransplant diabetes mellitus with the current standardized criteria (1A).

**Cardiovascular Disease**

It seems inevitable that premature cardiovascular events will affect pediatric LT patients because immunosuppressive medications increase the risk for diabetes, hyperlipidemia, hypertension, obesity, and metabolic syndrome. Values for transplant patients should be compared with values for the normal population, and the patients should be treated accordingly.

**Prevalence and Risk**

SPLIT data on 461 5-year survivors undergoing transplantation between 1991 and 2001 found obesity (a weight exceeding the 95th percentile) in 12% and hypercholesterolemia in 7%. Among 97 10-year survivors, 19% and 23% had increased cholesterol and triglycerides, respectively. No 10-year survivors reported statin use. A study of 815 recipients older than 5 years between 5 and 10 years after transplantation determined that approximately 20% had a blood pressure greater than the 95th percentile or were taking antihypertensive medications. A decreased GFR and the use of corticosteroids at the time of measurement predicted an elevated blood pressure.

**Treatment**

Multiple studies have demonstrated improved renal function, decreased blood pressure, and improved metabolic parameters (blood glucose, blood lipid, and uric acid levels) with the modification, withdrawal, or minimization of immunosuppression (specifically corticosteroids and CNIs).

**Recommendation**

27. Screen recipients annually for cardiovascular risks (body mass index, blood pressure, and fasting lipids) and treat them according to age-specific guidelines. Consider modifying immunosuppression regimens (1B).

**Withdrawal of Immunosuppression**

Most transplant recipients require chronic immunosuppression to ensure graft function, prevent rejection, and avoid graft loss, so minimization or withdrawal may be difficult. During the past 15 to 20 years, immunosuppression for pediatric LT recipients has been reduced. The use of anti-lymphocyte antibodies has decreased, and tacrolimus has replaced cyclosporine as the primary CNI at most centers.
normal graft function (as determined by liver blood tests) on monotherapy with tacrolimus (levels < 6 ng/mL) or cyclosporine (levels < 100 ng/mL). Many centers have reported that corticosteroids may be withdrawn within 6 months of transplantation. Data on corticosteroid avoidance are less robust. Immunosuppression minimization (specifically a once daily treatment with CNIs) may succeed in patients more than 5 years after transplantation. On the basis of single-center experiences in which recipients were weaned from immunosuppression, approximately 19% of adult LT recipients and up to 33% of pediatric LT recipients are functionally tolerant. A team from Kyoto University reported that 15% of the members of a cohort of 581 pediatric recipients were withdrawn from immunosuppression. Preliminary results from an Immune Tolerance Network pilot trial indicated that 12 of 20 subjects were successfully withdrawn; liver biopsy samples 1 year later did not show progressive inflammatory or fibrotic changes (Feng, S, MD, PhD, unpublished data, 2011). A long-term absence of immunosuppression may lead to allo-graft fibrosis, which improves with the reinstition of immunosuppression. Patients successfully withdrawn from immunosuppression have been reported to have monocytoid dendritic cell subsets with an increased proportion of plasmacytoid (type 2 dendritic cells) with respect to monocytoids (type 1 dendritic cells). Recipients with operational tolerance had an increased proportion of γδ T cells.

Recommendations

28. Corticosteroids may be withdrawn within 6 months of transplantation for patients who receive tacrolimus as their primary immunosuppression (1B).

29. For patients more than 1 year after transplantation with normal liver blood tests, maintain tacrolimus therapy with target immunosuppression levels < 6 ng/mL (1C).

30. More than 5 years after transplantation, immunosuppression minimization (defined as a CNI once daily) may be considered if there is no history of CR, liver tests are normal, and a biopsy sample shows minimal or no portal inflammation and less than stage 3 fibrosis (2C).

31. Complete immunosuppression withdrawal may be indicated if there are significant immune-related complications, but this should occur only within clinical trials (2C).

DISEASE-SPECIFIC ISSUES AND RECURRENT DISEASE

Indications for LT in children are distinct and more diverse than those for adults who undergo transplantation for diseases that may recur (chronic viral hepatitis, alcoholic liver disease, and hepatocellular carcinoma). The main indications for children are congenital or inherited defects. A minority require transplantation for diseases that may recur or for whole body systemic issues, including immunological disease (eg, PSC and AIH) and oncological (eg, hepatoblastoma) or multisystem disease (eg, cystic fibrosis).

Primary Sclerosing Cholangitis

Approximately 2% to 3% of children and adults who undergo LT in the United States undergo transplantation for PSC. In a review of 113 such children in the SPLIT database over a 13-year period, the mean rate of survival up to 5 years after transplantation was similar to the rate for a non-PSC group (approximately 86%). Recurrent PSC was present in approximately 10% and presented at a mean of 18 months after transplantation; the rate of recurrence in adults was 23% at a mean of 4 years after transplantation. Thus, recurrence may be underestimated. Moreover, most patients have inflammatory bowel disease. Whether or not colectomy before transplantation in children with PSC and inflammatory bowel disease reduces recurrent PSC (as seen in adults) remains to be determined. Distinguishing recurrent PSC from rejection or biliary tract complications requires biliary tract imaging and pathological assessment. There are no guidelines regarding the optimal management of recurrent PSC, nor are there data to suggest that ursodeoxycholic acid affects recurrence or graft survival in children or adults.

Autoimmune Hepatitis

In adults, the recurrence of AIH is more prevalent (approximately 22%-41%) and more rapid (median interval ~ 2 years) than the recurrence of PSC. The largest published series of children undergoing transplantation for AIH reported outcomes for 113 children enrolled in SPLIT. There were no differences between AIH children and non-AIH children in patient or graft survival or in the incidence of first rejection up to 5 years after transplantation. Generally, AIH patients were treated with higher degrees of immunosuppression longer than children undergoing transplantation for non-AIH indications. The SPLIT database cannot track AIH recurrence. A series from Birmingham reported recurrence in 39% (7/18 patients) at a mean posttransplant duration of 33 months. The diagnosis of recurrent AIH can be problematic because of the histological overlap with rejection and difficulties in interpreting autoantibody levels after transplantation. AIH before transplantation may still place select children at increased risk for other autoimmune diseases after LT.

Hepatoblastoma

Hepatoblastoma is the most common childhood liver malignancy. LT is viable in patients with unresectable tumors, recurrent hepatoblastoma after initial attempts at resection, and pulmonary metastases at diagnosis if their extrabiliary disease can be eradicated before LT. Because chemotherapy alone is...
not considered curative for hepatoblastoma, surgical approaches (with and without chemotherapy) and transplantation are critical components of a therapeutic protocol. Patients who are able to undergo the complete surgical excision of a hepatoblastoma have overall survival rates > 80% at 5 years. A review of the United Network for Organ Sharing database reported on 135 children who underwent transplantation for hepatoblastoma between 1987 and 2004. The 10-year survival rate was 66%, with most deaths (54%) due to metastatic or recurrent disease. Children with unresectable hepatoblastoma who underwent primary transplantation (without an attempt at resection) fared better than those who underwent inadequate resection before transplantation. Optimal treatment and standardization of resectability are the goals of a multicenter consortium (Pediatric Liver Observatory). A review of the United Network for Organ Sharing database reported on 135 children who underwent transplantation for hepatoblastoma between 1987 and 2004. The 10-year survival rate was 66%, with most deaths (54%) due to metastatic or recurrent disease. Children with unresectable hepatoblastoma who underwent primary transplantation (without an attempt at resection) fared better than those who underwent inadequate resection before transplantation. Optimal treatment and standardization of resectability are the goals of a multicenter consortium (Pediatric Liver Observatory).

The International Society of Paediatric Oncology protocols recommend planning transplantation within the course of chemotherapy. This has implications for postoperative management, minimization of immunosuppression, and the use of a renal-sparing regimen such as induction with basiliximab. After transplantation, the International Society of Paediatric Oncology suggests annual radiological or serum alpha-fetoprotein monitoring to detect recurring hepatoblastoma. Although the recurrence risk for those children with vascular invasion, metastasis, multifocal disease, or distinct histological subtypes has not been clarified, several case reports have indicated long-term success. Other long-term issues include the optimization of exposure to pretransplant and posttransplant chemotherapy and concomitant narrow, cardiac, and otoxicities. Finally, posttransplant immunosuppression regimens in these children may be minimized in comparison with regimens in children undergoing transplantation for non-oncological reasons. Postoperative monitoring should mirror coordinated care for children who survive these cancers without transplantation.

Hepatocellular Carcinoma

Few children require transplantation for hepatocellular carcinoma, but in those with vascular invasion, results are improving, although recurrence rates are high. The postoperative management and monitoring are similar to those for hepatoblastoma.

Recurrent Progressive Familial Intrahepatic Cholestasis 2

The recurrence of this disease was recognized in several children who underwent transplantation for a deficiency of the canalicular bile salt export pump (adenosine triphosphate–binding cassette B11). Features of recurrent bile salt export pump deficiency (jaundice and pruritus) developed up to 12 years after transplantation. Histological and immunological evaluations showed that patients developed anti–bile salt export pump antibodies and liver cellular infiltrations against this epitope, which essentially acts as a neoantigen.

Cystic Fibrosis

A growing number of children with cystic fibrosis are undergoing transplantation either for liver disease alone or as a part of combined lung-liver transplantation. The outcomes are not dissimilar from those for other indications for pediatric LT with a 5-year survival rate of approximately 85%, although there are more late deaths related to pulmonary failure. Children with cystic fibrosis who undergo isolated LT will continue to have other extrahepatic manifestations of cystic fibrosis that require close multidisciplinary care. These daily concerns include nutrition (associated pancreatic insufficiency), increased energy requirements, enhanced susceptibility to infections (primarily in the lungs), and potential effects of cystic fibrosis medications on immunosuppression drug levels. Patients with cystic fibrosis have the highest risk for long-term diabetes mellitus: up to 30% of these children may have pretransplant diabetes, and the incidence increases to 55% to 68% over the long term. The early withdrawal or dose reduction of corticosteroids may improve glycemic control in children with diabetes before transplantation.

Among the more complex issues related to the post-transplant care of the cystic fibrosis patient with isolated LT is the best way to monitor and treat infections and optimize lung function; some infections may lead to concurrent mild elevations of ALT, AST, and GGT. Caregivers may prescribe standard antimicrobials (doxycycline and fluconazole).

Recommendations

32. Be aware of the risk of recurrence of PSC and AIH in children after transplantation and the need to continue steroids (1B).
33. Periodic screening for colon cancer after transplantation for PSC with colitis may be beneficial; the optimal intervals are unknown (2B).
34. A multidisciplinary approach to hepatoblastoma care involving oncology, radiology, hepatology, and surgery can improve posttransplant survival (2B).
35. Patients with cystic fibrosis require close multispecialist care after isolated LT, with particular attention paid to nutrition, lung function, and infectious risks (1A).

INFECTIONS

Late Viral Infections

Infections have been categorized into 3 periods: early (0-30 days), intermediate (1-6 months), and late (>6 months). Early infectious complications tend to
be related to surgical manipulations, technical complications of the surgery, and catheters and other foreign bodies. Intermediate infections are more attributable to immunosuppression, which risks infections with opportunistic pathogens (CMV and Pneumocystis jiroveci) as well as potentially severe disease from community-acquired pathogens (respiratory syncytial virus and influenza viruses). Children with uncorrected surgical complications (bile duct sepsis and obstructions) may suffer recurrent bacterial disease. In the late period, recipients are on lower levels of immunosuppression, tend to experience less serious infections, and can handle community-acquired infections similarly to age-matched immunocompetent children. With late rejection, augmented immunosuppression increases the infection risk.

**Cytomegalovirus**

CMV, one of the most common causes of viral infections, may be symptomatic or asymptomatic because of a primary infection, the reactivation of a latent infection, or a superinfection with a different strain in a previously seropositive individual. The reported incidence has been as high as 40%, with mortality rates as high as 19%250. Preventive strategies and ganciclovir markedly decrease the rates and severity. Without prophylaxis, CMV usually presents 1 to 3 months after transplantation, although late CMV has been recognized. Late CMV may be associated with longer periods of chemoprophylaxis, but some cases occur with late rejection. Primary CMV infections, typically from organ donors, are associated with the highest morbidity and mortality rates. The reactivation of a latent infection or a superinfection with a new CMV strain tends to result in milder illness.251 Patients treated with unusually high doses of immunosuppressive agents (especially anti-lymphocyte products) have increased rates of CMV.252,253 CMV disease may manifest as a nonspecific viral syndrome or tissue-invasive disease. Nonspecific viral syndrome is characterized by fever and hematological abnormalities (leukopenia, atypical lymphocytosis, and thrombocytopenia). Tissue-invasive CMV disease is manifested by visceral organ involvement (gastrointestinal tract, liver, and lungs). CMV has also been associated with rejection, fungal infection, and late patient and graft loss.

**Diagnosis.** The diagnosis is confirmed by measurements of the viral load in the peripheral blood, histopathology, or cultures.252,253 Cultures of urine and respiratory secretions (including bronchoalveolar lavage specimens) can be difficult to interpret because patients frequently shed CMV asymmetrically. A histological examination to confirm CMV remains the gold standard when invasive CMV disease is suspected. Measuring the CMV load in the peripheral blood is the standard strategy for detecting a subclinical infection (this allows for preemptive antiviral therapy to prevent clinical disease in infected recipients) and for supporting a diagnosis of symptomatic CMV disease in a patient with a compatible clinical syndrome.252,253 The CMV load is measured with quantitative nucleic acid amplification tests or a CMV pp65 antigenemia assay. The relative value of CMV loads as well as relevant threshold values at which the CMV load is felt to identify a risk for or the presence of CMV disease varies among centers, although data support the strong reproducibility of CMV load results within a given center.254

**Prevention.** Strategies include universal prophylaxis or serial monitoring of the CMV viral load to inform the use of preemptive ganciclovir. Chemoprophylaxis with ganciclovir or oral valganciclovir has been recommended for adult donor-positive/recipient-negative liver recipients, for whom the recommended duration of chemoprophylaxis is 90 to 180 days.252,253 Data confirming the efficacy of oral chemoprophylaxis and preemptive therapy in pediatric recipients are lacking; consensus recommendations are based on the use of intravenous ganciclovir, particularly in younger recipients.252,253 Although the duration of intravenous ganciclovir is influenced by the risk of catheter-related complications and varies among centers. A proposed alternative entails a short course of chemoprophylaxis with intravenous ganciclovir followed by serial monitoring of the CMV load to inform the use of secondary preemptive therapy.254,255 The low incidence of CMV disease in donor-negative/recipient-negative recipients limits the necessity for prophylaxis or monitoring in this population.

**Treatment.** Ganciclovir dramatically improves outcomes; intravenous ganciclovir is recommended as the initial therapy. Oral valganciclovir is recommended for adult recipients with mild to moderate CMV disease.252,253 But there are not enough data for pediatric recipients to recommend its use as the initial treatment; some centers use oral ganciclovir to complete CMV treatment in children who have demonstrated a clinical response. A detectable CMV load at the end of antiviral therapy is associated with increased recurrence; ganciclovir should be continued until the CMV load becomes undetectable.252,253 CMV immunoglobulin and ganciclovir are sometimes considered for CMV disease in infants and for more severe CMV disease. Resistance to ganciclovir occurs in patients with refractory clinical symptoms or persistent/rising CMV loads despite at least 14 days of antiviral therapy.252,253,257 Patients with suspected resistance should be referred to their transplant centers for definitive management, which should include genotypic testing for resistant mutations and the empiric use of foscarnet, cidofovir, or CMV intravenous immunoglobulin. Immunosuppression should be reduced or discontinued in patients with suspected ganciclovir resistance.

**Recommendations**

36. Diagnose with quantitative nucleic acid-based or CMV pp65 antigenemia viral load assays in patients with a compatible clinical syndrome (1A).
37. No specific prophylactic strategy is routinely indicated for CMV donor-negative/recipient-negative children, but the use of intravenous ganciclovir for all CMV donor-positive/recipient-negative recipients is recommended (1A).

38. The primary transplant center should coordinate the management of symptomatic or asymptomatic patients with detectable CMV polymerase chain reaction and/or rising titer CMV viral loads (1B).

39. Intravenous ganciclovir is recommended as the initial antiviral therapy; continue this until the CMV load becomes undetectable (2C).

40. Consider ganciclovir resistance in patients with refractory clinical symptoms or children with persistent/rising CMV loads despite at least 14 days of antiviral therapy. Consider genotypic testing for resistance mutations and second-line therapies (foscarnet and cidofovir; 1B).

**Epstein-Barr Virus and Posttransplant Lymphoproliferative Disorder**

EBV is an important cause of morbidity and mortality, with symptomatic EBV infections and posttransplant lymphoproliferative disorder (PTLD) more common after primary EBV infections (which disproportionately affect children, who are frequently EBV-seronegative before transplantation). Primary infections and high/repetitive doses of anti-lymphocyte globulin are recognized risk factors for early PTLD. Confusion may arise in children less than 18 months of age who have passive maternal antibodies but are seronegative. A wide spectrum of EBV disease is recognized, and this spectrum ranges from asymptomatic seroconversion to a nonspecific viral illness and/or PTLD, usually during the first year after transplantation. Most patients do not develop PTLD but have symptoms of infectious mononucleosis (fever, malaise, exudative pharyngitis, lymphadenopathy, hepatosplenomegaly, and atypical lymphocytosis). Organ diseases (hepatitis, pneumonitis, and gastrointestinal symptoms) and hematological manifestations (leukopenia, thrombocytopenia, hemolytic anemia, and hemophagocytosis) may also occur. PTLD tends to affect organs of the reticuloendothelial system and/or the transplanted liver. A complete physical examination should be conducted with a meticulous assessment for lymphadenopathy and adenonsillar hypertrophy. The EBV load in the peripheral blood should be measured, imaging studies should be used to identify and localize occult disease, and potential disease sites should be biopsied. The imaging choice depends largely on the location of the suspected lesions and the historical sequence of prior radiographic testing. A head CT or MRI scan is recommended in the initial workup because the presence of central nervous system lesions will significantly influence the treatment and outcome. Most centers employ a total body CT scan (head to pelvis) as part of the initial assessment of PTLD. CT scanning of the neck may help to define the extent of involvement or detect subtle early changes that necessitate biopsy to rule out PTLD. Depending on the location (eg, central nervous system lesions), MRI may be more suitable than CT scanning because of radiation concerns with CT scans and more precise lesion delineation with MRI. Positron emission tomography/CT is useful in evaluating PTLD, although additional data are needed across the heterogeneous spectrum of PTLD lesions. The diagnosis and management should be coordinated by the primary transplant center. A histopathological examination of affected tissue remains the gold standard for PTLD diagnosis.

Sequential EBV loads in peripheral blood have been evaluated as a diagnostic test (ie, levels above a specific quantitative threshold are diagnostic of PTLD), and they have good sensitivity for detecting EBV-positive PTLD but miss EBV-negative PTLD and some cases of localized and donor-derived PTLD. Because high viral load states variably antedate the clinical presentation of PTLD, there are data to support quantitative EBV viral load monitoring for PTLD prevention in high-risk populations with preemptive reduction of immunosuppression. There is no consensus on how to prevent PTLD: antivirals with or without immunoglobulin are sometimes employed for EBV donor-positive/recipient-negative patients. Community-based clinicians should be aware of treatment options for PTLD. Most centers reduce immunosuppression and escalate treatment on the basis of the clinical response and histopathological characteristics of PTLD. Second-line therapies include the anti-CD20 monoclonal antibody (rituximab) and low-dose chemotherapy with cyclophosphamide and prednisone. Patients with malignant disease (frank lymphomas) should be considered for chemotherapy and management by an oncologist familiar with EBV-associated PTLD in organ transplant recipients.

**Recommendations**

41. Determine the EBV serostatus of recipients and donors to identify patients at high risk for PTLD (1B).

42. Seronegative patients before transplantation should be screened with EBV viral loads annually afterward to determine their susceptibility to a primary infection. Screen recipients at increased risk for EBV disease (donor-positive/recipient-negative) and PTLD weekly or biweekly during the first year after transplantation (1B).

43. Patients presenting with typical symptoms such as persistent fever and lymphadenopathy should be clinically evaluated for PTLD with histopathology and EBV viral loads. Those with rising EBV viral loads should be discussed with their transplant center; management might include reduced immunosuppression and/or specific therapy (1B).
Community-Acquired Respiratory Viruses

Most children who undergo LT experience common respiratory viral infections without significant problems, although infections due to influenza, parainfluenza, or respiratory syncytial virus can lead to more severe disease.\textsuperscript{144,272,274} Recipients may have prolonged viral shedding.\textsuperscript{275} Preventive strategies are available against influenza A and influenza B (including the pandemic strain of H1N1). Live attenuated influenza vaccine is contraindicated. The need for respiratory syncytial virus immune globulin and its efficacy in the prevention of respiratory syncytial virus disease are unproven. One survey of 67 centers revealed that 40\% of respondents were given respiratory syncytial virus prophylaxis\textsuperscript{296}; palivizumab was used most in the first season after transplantation, generally in children less than 2 years old. Contact/droplet precautions should be enforced to minimize nosocomial infections. Specific antiviral agents may be required for select pathogens (eg, neuraminidase inhibitors for influenza viruses or aerosolized ribavirin for respiratory syncytial virus).

**Recommendation**

44. Immunize recipients against community-acquired viruses (influenza A, B) annually. No guidance exists for respiratory syncytial virus prophylaxis (1B).

**Pneumocystis jirovecii**

*P. jirovecii* is a cause of life-threatening pneumonia. Absent prophylaxis, it presents 1 to 6 months after transplantation, although late cases have been reported. Trimethoprim/sulfamethoxazole prophylaxis is used to prevent *P. jirovecii*. Most centers recommend trimethoprim/sulfamethoxazole for 6 months after transplantation; anecdotal evidence supports long-term use. The resumption of prophylaxis should be considered to cover periods of increased immunosuppression.\textsuperscript{292}

**Recommendation**

45. Give at least 6 months’ prophylaxis with trimethoprim/sulfamethoxazole (1B).

**ADOLESCENT ISSUES**

**Adolescent Health**

Adolescent nonadherence to medical recommendations is noteworthy.\textsuperscript{251,253} and risky behaviors include drug abuse\textsuperscript{276} and promiscuity with the risk of sexually transmitted diseases and/or pregnancy.\textsuperscript{277,278} Adolescents may lose insurance coverage as adults, and this may end or restrict care.\textsuperscript{279,283} Most adolescents work with parents toward a positive outcome.\textsuperscript{280}

**Sexuality and Sexually Transmitted Diseases**

Physical disabilities/disfiguration might hinder sexual encounters. In an immunosuppressed individual, any infection, including a sexually transmitted disease, may be more serious. Sexual health education, including advice about barrier contraception, should be emphasized.

**Menstrual Abnormalities**

Chronic liver disease is associated with menstrual abnormalities in adult women; these are resolved after successful LT.\textsuperscript{281,282} Although there are data on the normal development of puberty in girls after transplantation,\textsuperscript{43} there are no comprehensive studies showing whether chronic liver disease, subsequent LT, or both affect the onset of menstruation or are associated with additional menstrual problems at menarche in adolescent girls regardless of the age at transplantation.

A study of 471 girls (age = 10-20 years) with liver disease or after transplantation found that 74 were referred to a gynecologist for contraceptive advice or because of menstrual problems; 7.4\% had menstrual problems (a rate similar to the rate for the general population\textsuperscript{260}). Thirty-seven of the 74 cases occurred after transplantation; 47\% had a heavy or irregular period (a rate similar to the rate for girls with liver disease). No posttransplant girls had primary amenorrhea; the timing of menarche was normal. Reassurance, support, and simple treatment controlled symptoms in 60\% of the girls.

**Contraception**

In the aforementioned series, 12 of 37 girls sought contraceptive advice. Hormonal treatments were used by 10 (28.6\%) either for contraception or to regulate periods (the combined oral contraceptive pill in 22.9\%; a progesterone-only pill was used by 5.7\%). In 4 girls, cyclical progestogens were used to induce withdrawal bleed or postpone their period. No medications hindered liver or renal function.

**Pregnancy**

Many successful pregnancies follow LT.\textsuperscript{283,284} Appropriate advice about contraception, the timing of pregnancy, and immunosuppression during pregnancy should be provided.\textsuperscript{285,286} The timing of pregnancy is relevant only to postpubertal girls, but 1 year after transplantation has been considered the minimum time for conception after transplantation.\textsuperscript{284} Although prednisolone crosses the placental barrier, it is not teratogenic at therapeutic doses and is safe; however, mothers must be screened for gestational diabetes.\textsuperscript{287} Azathioprine also crosses the placenta and has been shown to be teratogenic in animals; the risk in humans appears small. Dose-related fetal myelosuppression has occurred but is unusual in maternal doses less than 2 mg/kg. Cyclosporine and tacrolimus maintain fertility without an increased risk of congenital abnormalities.\textsuperscript{287} Azathioprine has been associated with structural malformations and is not recommended.\textsuperscript{288} There are no good data on mTOR inhibitors.\textsuperscript{289}

Birth might be complicated by a history of major surgery; surgical guidance should be obtained.
Mothers are more likely to experience pregnancy-induced hypertension and preeclampsia, but overall mortality is no different from that for the general population. Rates of AR and graft loss are similar to those for nonpregnant liver recipients.290

Nonadherence
Common among adolescents,291 nonadherence is complicated by shifting care responsibilities. Disagreement about who is responsible for medication taking appears with children as young as 9 years91; many children will assume some responsibility at the age of 12 years.91 From then to young adulthood, parents and children might disagree about the freedom or responsibilities that the child should have.

Risk Behavior
Although these issues apply to all adolescents, they may be overlooked during transplant follow-up. Substance abuse may begin292,294 and is common among nonadherent youths.295 Substance abuse counseling and/or testing may be indicated.

Peer Pressure
Peer groups become increasingly important and potentially lead to nonadherence through patient efforts to “be like everyone else” (ie, stop taking the medications) or greater sensitivity to side effects such as hirsutism and obesity.

Partner Intimacy
This can be protective (increase adherence) or a risk: this depends on the partner and the relationship’s dynamics.

Pregnancy
Having dependents might make young mothers or fathers less able to care for themselves, take medications on time, or keep medical appointments. Although teen pregnancy is associated with poor physical illness,296 the putative relationship between nonadherence and teen pregnancy after transplantation has not been studied systematically.

Recommendations
46. All adolescent girls should receive advice about fertility, contraception, and safe immunosuppression during pregnancy and should avoid mycophenolate (2B).
47. All girls with menstrual problems should be reviewed by a gynecologist for advice and management (2C).
48. Transfer adolescents who become pregnant to adult care to manage their immunosuppression (2B).
49. Inquire about prospective health insurance at the age of 17 to 19 years (depending on the locale; 2B).
50. Discuss the avoidance of substance abuse and smoking, advise minimal alcohol intake, and review risky behaviors annually (2C).

Transition to Adult Care
LT success means that many children must adhere to a lifelong medical regimen with regular follow-up. The transition involves effective communication by the recipient and the care providers.297 Young people should be educated so that they develop self-management and advocacy skills, take responsibility for medication and appointments, engage with care providers, and seek care.298 A knowledge of signs and symptoms requiring urgent medical attention is essential.299,300 Having a full understanding of their illness and being involved in medical decisions was rated as important by 69% of young adult survivors and as the most helpful coping strategy by 36%.301 Recipients must understand adolescent development in the context of chronic illness and know their role in the process.301-303

Components of Self-Management
Self-management includes adhering to treatment regimens, taking responsibility for medications, undergoing required blood tests, and scheduling and attending appointments.251 Maintaining a healthy lifestyle and avoiding risk behaviors (a lack of exercise, poor diet, substance abuse, and unsafe sex) are crucial. In one study, fewer than half of young adult LT recipients reported consistently managing their liver disease independently, making appointments, and understanding insurance issues.304 Recipients often disagree with parents about the degree of responsibility that they have or wish they had,305 and this suggests that family conflict may hamper the transition.

Self-Management Interventions
There are no empirically supported treatments available for improving self-management in LT recipients. In young people with asthma, a randomized controlled trial demonstrated that psychoeducational programs improved care management.306 Education combined with cognitive behavioral strategies such as problem solving improved health behaviors among adolescents.251 A meta-analysis of 70 adherence-promoting interventions delivered to adolescents with chronic health needs found multicomponent interventions more effective than education alone.307 Uncontrolled multicomponent interventions308,309 addressing adherence only among recipients have promising results and good acceptance by families.

Self-Management in Transferring to Adult Care Centers
This is related to achieving self-management in the pediatric setting as demonstrated by studies of cystic
fibrosis patients and patients with congenital heart defects. A lack of personal responsibility for health has been a barrier. Factors related to a successful transfer center on an assumption of care responsibility, an adherence to treatment recommendations, and appropriate preparation. The consequences of an unsuccessful transfer to the adult health system may be significant: one study found that 8 of 10 young adult patients experienced graft rejection after their transfer. In 7 cases, this was unexpected and was likely related to nonadherence. Another retrospective study examined whether adherence and medical outcomes deteriorated in transferred recipients. The authors compared 14 recently transitioned patients to 2 cohorts of patients receiving care solely in a pediatric or adult-oriented clinic. Adherence significantly declined both after the transfer and with respect to the comparison groups. Furthermore, 4 patients in the transferred cohort died after they left pediatrics; there were no deaths at any point in the other cohorts. Among adolescents who were 14 to 17 years old in the 2001 National Survey of Children With Special Health Care Needs, 15% of the more than 5400 participants reported receiving guidance and support associated with their upcoming transfer to adult medicine.

**Transfer Readiness**

Measurement tools are available but have not yet been validated.

**Transfer-of-Care Models**

Viner described disease-based transfer programs versus generic transfer programs in either adolescent medicine or primary care. Disease-based services address a population’s specific needs and are economically efficient but may not always capture patients’ changing needs. Soanes and Timmons suggested that an adolescent specialist in subspecialty clinics reconcile these approaches.

**Adult Perspective**

An adult care group should be identified that is willing to work closely with the transferring pediatrician and a key worker trained in adolescent health and transitional care for 6 to 12 months through either joint clinics or scheduled appointments. This time should be devoted to familiarizing the patient with the new setting and expectations of adult care providers, to identifying gaps in the new provider’s knowledge or understanding of the case, and to allowing the patient time to seek clarification about care before the transfer. Upon transfer, the patient should be scheduled initially for more frequent visits, and adherence should be monitored closely in the first 2 to 3 years (according to local treatment protocols).

**Recommendations**

51. The transition process is multidisciplinary and should begin around the age of 10 to 11 years according to developmental maturity (2B).
52. Prepare a standard transition protocol involving pediatric and adult providers (2B).
53. Before the transfer, achieve readiness by building the patient’s understanding of the illness, self-management skills, and ability to assume responsibility over his or her care (2B).
54. Identify an adult care group to work closely with the transferring pediatrician and the patient for at least 1 year before the transfer (2C).

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**REFERENCES**


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95. Shemesh E, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating non-adherence to medications in transplant recipients? Pediatr Transplant 2010;14:940-943.


130. McDiarmid SV, Anand R, Martz K, Millis MJ, Mazariogos G. A multivariate analysis of pre-, peri-, and


