

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

Deirdre A. Kelly,¹ John C. Bucuvalas,² Estella M. Alonso,³ Saul J. Karpen,⁴ Upton Allen,⁵ Michael Green,⁶ Douglas Farmer,⁷ Eyal Shemesh,⁸ and Ruth A. McDonald⁹

¹Liver Unit, Birmingham Children's Hospital, National Health Service Trust, Birmingham, United Kingdom;

²Integrated Solid Organ Transplant Program, Cincinnati Children's Hospital, Cincinnati, OH; ³Division of Gastroenterology, Hepatology and Nutrition, Ann and Robert H. Lurie Children's Hospital, Chicago, IL;

⁴Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Emory Children's Center, Atlanta, GA;

⁵Department of Pediatrics, Hospital for Sick Children, Toronto, Canada; ⁶Division of Infectious Diseases, Children's Hospital of Pittsburgh, Pittsburgh, PA; ⁷Dumont-UCLA Transplant Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; ⁸Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY; and ⁹Division of Pediatric Nephrology, Seattle Children's Hospital, Seattle, WA

Received March 12, 2013; accepted June 15, 2013.

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 Diseases 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; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; OLT, orthotopic liver transplantation; OR, odds ratio; PSC, primary sclerosing cholangitis; PTLN, 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.

Financial support for the development of this guideline was provided by the American Association for the Study of Liver Diseases.

Address reprint requests to Deirdre A. Kelly, M.D., Liver Unit, Birmingham Children's Hospital, National Health Service Trust, Birmingham, United Kingdom B4 6NH. Telephone: 44-121-333-8253; E-mail: deirdre.kelly@bch.nhs.uk

DOI 10.1002/lt.23697

View this article online at wileyonlinelibrary.com.

LIVER TRANSPLANTATION.DOI 10.1002/lt. Published on behalf of the American Association for the Study of Liver Diseases

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

Strength of Recommendation	Criteria
1. Strong	Factors influencing the strength of the recommendation include the quality of the evidence, the presumed patient-important outcomes, and the cost. 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.
2. Weak	
Quality of Evidence	Criteria
A. High	Further research is unlikely to change confidence in the estimate of the clinical effect.
B. Moderate	Further research may change confidence in the estimate of the clinical effect.
C. Low	Further research is very likely to affect confidence in the estimate of the clinical effect.

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 States⁵ 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 (eg, 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

nitrogen metabolism, and increased energy expenditure and possibly growth hormone resistance.²² After successful LT and nutritional restitution, growth hormone and insulin-like growth factor 1 levels return to normal, and linear growth improves.²³ Catch-up growth is dependent on steroid usage and may not occur until the second year^{24,25}; this plateaus 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.²⁴ 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.^{25,26} 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 that in patients with closer-to-normal growth before transplantation. Growth improves with steroid withdrawal or discontinuation and with supplemental recombinant human growth hormone therapy,^{27,28} which improves height without advancing bone age beyond the chronological age or hindering adult height potential.²⁹ However, up to 50% of recipients have a final adult height 1.3 standard deviations lower than their genetic potential,³⁰ and patients with Alagille syndrome may not have improved growth despite these measures.^{31,32}

Obesity

The proportion of obese adult LT recipients approaches 30%³³; many exhibit diabetes (30%), hyperlipidemia (60%), and hypertension (60%).³⁴ 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.³⁵ The observation and management of adult recipients suggest that as pediatric recipients age, these comorbidities could threaten their long-term survival and require therapy.³⁶

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).³⁷ After transplantation, high-dose immunosuppression (particularly potent glucocorticoids) and immobilization may prevent recovery.³⁸⁻⁴⁰ Reduced production of sex hormones due to severe liver disease before transplantation, particularly in adolescents, may affect growth and delay puberty.^{41,42} This is resolved after transplantation; most recipients undergo normal puberty.^{43,44} 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 reinstitution 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.⁴⁵⁻⁴⁸ More prolonged recovery with low bone mass (bone mineral density z score < -2) in 7% to 15% has been reported over the long term.^{48,49} Fractures are common in children before and after LT. Before transplantation, the fracture prevalence ranges from 10% to 28%⁴⁹⁻⁵³; after transplantation, it rises to 12% to 38%^{49,51,53} (50% in 1 case series⁴⁵). Vertebral and nonvertebral fractures have been reported.⁵³ Vertebral fractures may be asymptomatic. Risk factors include an older age at transplantation, male sex, fractures before transplantation,⁵¹ a low body weight, and the cumulative steroid dose.⁴⁸ The least bone mineral density improvement after orthotopic liver transplantation (OLT) occurs in pubertal and postpubertal subjects.^{45,49} 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.⁵⁴ All affected patients were adolescents; 3 underwent LT.⁵⁴ In a large retrospective series of solid organ transplant recipients,⁵⁵ 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 wedged vertebra, 20% had a history of vertebral fractures, 28% reported back pain

at rest, and 38% had scoliosis > 10 degrees. Males were predominantly affected.⁵⁶ 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.⁴⁹ Hepatic protein synthesis, including insulin-like growth factor 1 production, improves after LT⁴⁸ and spurs moderate catch-up growth. Vitamin D (25-hydroxyvitamin D) levels in children are low before and immediately after OLT^{45,46,48} but improve during the first year.⁴⁸ Routine vitamin D (3-10 times the recommended daily allowance³⁷) 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).⁵⁷ An appropriate intake of calcium and phosphate should be ensured, especially in children on immunosuppressants such as tacrolimus, which can cause phosphate loss.⁵⁸ 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 correction⁵⁹⁻⁶² 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.⁶³

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.⁶⁴⁻⁶⁸ 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.⁶⁹ 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.⁷⁰ Parents also reported symptoms of posttraumatic stress disorder and significant stress and anxiety related to the child's medical condition.^{71,72}

Medication concerns and treatment anxiety were significant among pediatric recipients.⁷³ 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.⁷⁴

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.^{69,75-83} 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.⁸⁴ 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.⁸⁵ 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.^{64,69,79,80,86,87} 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 skills⁸⁰; nearly 15% lose some hearing, and this is especially true for children who receive ototoxic medications before transplantation (eg, children with hepatoblastoma).⁸⁸ Approximately 30% require special education after transplantation.⁶⁴ 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.⁸⁷ 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.⁸⁹

Recommendations

9. Screen neurocognitive function before transplantation for LT candidates older than 5 years and at key junctures afterward to determine special education needs (1B).
10. Assess recipients for hearing loss in the first post-operative year and periodically thereafter as indicated (1B).
11. 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 rejection⁹⁰⁻⁹³ and death.⁹⁴ Measurement of adherence is difficult because different assessments yield different results.^{95,96} 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.⁹¹ One direct measure is the calculation of the standard deviation of consecutive immunosuppressant (tacrolimus) blood levels.⁹⁶ A higher standard deviation denotes more variability (less consistent ingestion). A fluctuation exceeding 2 or 2.5 standard deviations predicts clinically significant nonadherence.⁹⁶ Many reviews discuss the psychosocial factors that predict nonadherence,⁹⁷⁻⁹⁹ 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 messaging¹⁰⁰), and following up patients more intensively.¹⁰¹

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 life¹² and normal liver function. Survival rates are 70% to 90%.^{7,13,14,21} Two reviews summarize operative techniques.^{102,103} 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%.⁸ 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,¹⁰⁴ 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 angiographies¹⁰⁵]. 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%.^{8,11,106}; most cases are symptomatic. 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.¹⁰⁷ 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.¹⁰⁸ 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 ($\times 10^9/L$) 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 non-transplant 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,¹⁰⁹ 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.¹¹⁰

Late Biliary Strictures

The rates for biliary strictures after pediatric LT range from 5% to 25%.^{9,111} 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 choledochojejunostomy.¹¹² 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.¹¹² 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.^{9,113,114} 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.¹¹⁵

Incisional Hernia

An incisional hernia occurs in 5% to 18% of transplants.¹¹⁶ 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.^{117,118} Complications are relatively rare, but 2% to 5% of children may have a significant complication (usually postbiopsy bleeding).^{119,120} Noninvasive assessments of fibrosis with FibroScan, serum biomarkers of fibrosis, or MRI are being validated in children with cystic fibrosis or nonalcoholic liver disease.¹²¹⁻¹²³ 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.¹²⁴⁻¹²⁶ 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.^{127,128}

However, histological examinations of 5- and 10-year protocol biopsy samples from children have detected increased graft hepatitis and fibrosis.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 ($P < 0.001$). Fibrosis also increased: 52%, 81%, and 91% at 1, 5, and 10 years, respectively ($P < 0.001$). By 10 years, 15% had progressed to cirrhosis. No clear etiology was identified in particular; there was no evidence of a viral infection.^{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 ($P < 0.001$). Four children fulfilled the diagnostic criteria for de novo autoimmune hepatitis (AIH); 2 were hepatitis C-positive.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 immunosuppression.^{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% ($n = 66$) from 1 year after LT to 5 years. There was no increased incidence of fibrosis at 10 years (69%, $n = 55$), 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.^{132,133} De novo autoimmune or otherwise unexplained hepatitis occurs in 5% to 10% of children after transplantation.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 non-specific 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.^{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.¹³⁷ Recent studies have identified graft hepatitis in adults positive for hepatitis E or Torque teno virus; data are not available for children.^{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 immunosurveillance, DNA damage from antimetabolite medications, or a response to chronic inflammation. Skin cancer is rare during the first 10 to 15 years after transplantation.¹⁴⁰ An analysis of the Israel Penn Tumor Registry found that skin malignancies accounted for 12% of pediatric posttransplant cancers.¹⁴¹ In a Swedish study that linked all solid organ transplant patients younger than 18 years between 1970 and 2007 ($n = 536$) to the National Cancer Registry, 2 cases of nonmelanoma skin cancers were identified.¹⁴²

Recommendation

16. Encourage protective clothing, regular screening for skin lesions, and sunscreen (1B).

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 guidelines¹⁴³ and the American Academy of Pediatrics (*Red Book*).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 infections¹⁴⁵ (Table 2). Live attenuated vaccines are generally contraindicated after transplantation. Varicella vaccination is not recommended in children receiving long-term immunosuppression.¹⁴³⁻¹⁴⁵ One report found the measles-mumps-rubella vaccine to be safe.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.^{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.¹⁴⁷

Tattoos and Piercings

These are acceptable if the child has received the hepatitis B vaccine.^{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

TABLE 2. Recommended Vaccines for Transplant Recipients

Vaccine	Inactivated or Live Attenuated	Recommended Before Transplantation	Recommended After Transplantation
Routine for all transplant recipients			
Diphtheria	Inactivated	Yes	Yes
Pertussis	Inactivated	Yes	Yes
Tetanus	Inactivated	Yes	Yes
Inactivated polio	Inactivated	Yes	Yes
<i>Haemophilus influenzae</i>	Inactivated	Yes	Yes
B (regardless of age)			
<i>Streptococcus pneumoniae</i> (13-valent pneumococcal conjugate/23-valent polysaccharide)*	Inactivated/inactivated	Yes	Yes
<i>Neisseria meningitidis</i> (conjugate C and conjugate quadrivalent)†	Inactivated	Yes	Yes
Influenza			
	Inactivated	Yes	Yes
	Live attenuated	No‡	No
Hepatitis B	Inactivated	Yes	Yes
Hepatitis A	Inactivated	Yes	Yes
Measles	Live attenuated	Yes	No
Mumps	Live attenuated	Yes	No
Rubella	Live attenuated	Yes	No
Varicella	Live attenuated	Yes	No
Rotavirus (if age-appropriate)	Live attenuated	Yes	No
Human papillomavirus	Inactivated	Yes	Yes
Special circumstances			
Bacillus Calmette–Guérin	Live attenuated	Yes	No
Rabies	Inactivated	Yes	Yes
Smallpox	Live attenuated	No	No
Anthrax	Inactivated	No	No

NOTE: This table was adapted with permission from *Pediatric Clinics of North America*.¹⁴⁵ Copyright 2010, Elsevier.
 *All required doses of the conjugate vaccine should be given before the polysaccharide vaccine. Children less than 24 months of age are unlikely to respond to the polysaccharide vaccine.
 †The conjugate quadrivalent vaccine is currently not licensed for children less than 24 months of age.
 ‡The live attenuated vaccine is approved for healthy patients. It may be given to healthy patients before transplantation. The vaccine should be administered 2 or more weeks before transplantation.

not available (eg, yellow fever). Recipients should carry information about their condition, medications, and contact numbers for their transplant center.

Recommendations

- Minimize infection risks related to hygiene, food, water, animals/pets, and travel (2C).
- Recipients can travel abroad 6 months after transplantation with normal precautions and the advice of their transplant center (2C).
- Combat childhood infections with recombinant or killed vaccines (1A).
- 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 tacrolimus¹⁴⁸ because it avoids the gingival hyperplasia and hirsutism associated with cyclosporine.¹⁴⁹ Augmentation with mycophenolate or mammalian target of rapamycin (mTOR) inhibitors may reduce reliance on steroids and high-dose CNIs.^{149,150} 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^{151,152} and/or interleukin-2 receptor-blocking antibodies.¹⁵³ AR is best prevented by regular blood test monitoring and immunosuppressant medications (see the Disease-Specific Issues and Recurrent

TABLE 3. Post-LT Immunosuppression

Time After LT (Months)	Standard				Nonimmune Complications of CNIs				High Immunological Risk	
	Tacrolimus Level (ng/mL)	Steroid Dose (mg)	Mycophenolate Mofetil Dose (mg/m ²)	Tacrolimus Level (ng/mL)	Tacrolimus Level (ng/mL)	Mycophenolate Mofetil Dose (mg/m ²)*	Tacrolimus Level (ng/mL)	Tacrolimus Level (ng/mL)	Steroid Dose (mg) [†]	Mycophenolate Mofetil Dose (mg/m ²)*
6-12	5-10	0	0-600	4-8	600	5-10	5-10	5-10	5-10	600
13-24	3-8	0	0	2-6	600	5-10	5-10	5	5	600
25-60	2-4	0	0	2-4	600	5-8	5-8	2-5	2-5	600

*Twice daily.

†Daily.

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 endotheliitis 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 obliterative 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.^{151,152}

Treatment

The protocols are similar to those for AR^{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.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.^{14,160} Immunosuppression medications are associated with an increased risk for diabetes, hyperlipidemia, hypertension, obesity, and metabolic syndrome.^{164,165} Long-term immunosuppression treatment incurs substantial complications.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 18%.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%.¹⁶⁸

Prevalence and Risk

Single-center studies suggest that renal function is stable for most pediatric LT recipients 1 to 5 years after transplantation¹⁶⁹⁻¹⁸⁶ 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 m².¹⁴⁴ According to the National Kidney Foundation classification of chronic kidney disease, 14.6% of the patients had stage 2 chronic kidney dis-

ease (GFR = 60-89 mL/minute/1.73 m²), 2.5% were at stage 3 (GFR = 30-59 mL/minute/1.73 m²), and 0.4% were at stage 4 or 5 (GFR < 30 mL/minute/1.73 m²). In a multivariate analysis of 289 patients, a calculated GFR < 90 mL/minute/1.73 m² 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.¹⁷⁰ Preexisting kidney disease can imperil renal function after transplantation. Patients with inborn metabolism errors, Alagille syndrome, and hepatic fibrosis appear at increased risk.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.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.¹⁷² Patients with decreased estimated or measured GFRs (< 90 mL/minute/1.73 m²) at transplant or during the first month have an increased risk for chronic kidney disease.^{170,171} Hepatorenal syndrome before LT is an associated risk factor for renal insufficiency after transplantation.¹⁷¹ CNIs are felt to be the principal cause of de novo posttransplant renal dysfunction and factor in the progression of renal disease.^{173,174} Acquired renal cystic disease may occur after transplantation.^{175,176} Renal lesions have been associated with moderate renal dysfunction, biopsy-proven chronic liver graft rejection, and thrombosis of the retrohepatic vena cava.¹⁷⁵ Cyclosporine A and renal dysfunction are associated with acquired cystic kidney disease.¹⁸⁷

Screening and Prevention

Anti-interleukin-2 receptor monoclonal antibody induction with lower doses of CNIs immediately after transplantation may be beneficial.¹⁷⁷ Renal dysfunction is best detected via the monitoring of serum creatinine or emerging urinary biomarkers,^{178,179} the maintenance of intravascular volume, and the avoidance of nephrotoxic medications.¹⁸⁰ Although measuring the GFR remains the preferred method, estimating the GFR with the updated Schwartz formula [height (cm) × 0.4/serum creatinine (mg/dL)] is acceptable,¹⁸¹ with the GFR ensured to be > 70 mL/minute/1.73 m² 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.^{182,183} 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.¹⁸³ Studies in adults and children more than 1 year after transplantation have demonstrated preserved and improved renal function with the lowering of CNI doses to 25% to 50% of the baseline dose and the addition of (or replacement with) mycophenolate.^{185,186} 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.^{188,189} 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.^{190,191} 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.¹⁹² The incidence was twice that observed in renal transplant recipients.¹⁹³ 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,¹⁸⁷ 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.^{190,191,194,195} Values for transplant patients should be compared with values for the normal population, and the patients should be treated accordingly.^{196,197}

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%.¹⁵⁸ Among 97 10-year survivors, 19% and 23% had increased cholesterol and triglycerides, respectively. No 10-year survivors reported statin use.¹⁹⁸ 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.¹⁹⁹ 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 parameters²⁰⁰⁻²⁰⁴ (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.¹³ Many recipients more than 2 years after LT maintain

normal graft function (as determined by liver blood tests) on monotherapy with tacrolimus (levels < 6 ng/mL) or cyclosporine (levels < 100 ng/mL).^{189,205} Many centers have reported that corticosteroids may be withdrawn within 6 months of transplantation²⁰⁶; data on corticosteroid avoidance are less robust.²⁰⁷ Immunosuppression minimization (specifically a once daily treatment with CNIs) may succeed in patients more than 5 years after transplantation.^{128,131,208} 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.²⁰⁹⁻²¹⁶ A team from Kyoto University reported that 15% of the members of a cohort of 581 pediatric recipients were withdrawn from immunosuppression.^{217,218} 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 allograft fibrosis,²¹⁹ which improves with the reinstitution of immunosuppression.^{217,218} Patients successfully withdrawn from immunosuppression have been reported to have monocytoid dendritic cell subsets with an increased proportion of plasmacytoids (type 2 dendritic cells) with respect to monocytoids (type 1 dendritic cells).^{215,220} Recipients with operational tolerance had an increased proportion of $\gamma\delta$ T cells.²²¹

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.¹⁵⁸ 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.^{222,223} 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%).²²³ 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.²⁰⁶ 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 adults²⁰⁶) remains to be determined. Distinguishing recurrent PSC from rejection or biliary tract complications requires biliary tract imaging and pathological assessment.²²⁴ 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.^{224,225} The largest published series of children undergoing transplantation for AIH reported outcomes for 113 children enrolled in SPLIT.²²⁶ 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.²²⁷ The diagnosis of recurrent AIH can be problematic because of the histological overlap with rejection²²⁵ 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 extrahepatic disease can be eradicated before LT.^{228,229} Because chemotherapy alone is

not considered curative for hepatoblastoma, surgical approaches (with and without chemotherapy) and transplantation are critical components of a therapeutic protocol.²³⁰ Patients who are able to undergo the complete surgical excision of a hepatoblastoma have overall survival rates > 80% at 5 years.^{231,232} A review of the United Network for Organ Sharing database reported on 135 children who underwent transplantation for hepatoblastoma between 1987 and 2004.²³³ 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.²²⁸ Optimal treatment and standardization of resectability are the goals of a multicenter consortium (Pediatric Liver Unresectable Tumor Observatory).²³² However, an increased risk for late mortality among patients who have undergone LT for hepatoblastoma has been observed in large multicenter^{14,160} and single-center cohorts.²³⁴ 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.^{235,236} After transplantation, the International Society of Paediatric Oncology suggests annual radiological or serum alpha-fetoprotein monitoring to detect recurring hepatoblastoma.²³⁵ 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.^{229,230,233,236,238,239} Other long-term issues include the optimization of exposure to pretransplant and posttransplant chemotherapy and concomitant marrow, cardiac, and ototoxicities.^{228,240} Finally, posttransplant immunosuppression regimens in these children may be minimized in comparison with regimens in children undergoing transplantation for non-oncological reasons.²³⁶ Postoperative monitoring should mirror coordinated care for children who survive these cancers without transplantation.²⁴⁰

Hepatocellular Carcinoma

Few children require transplantation for hepatocellular carcinoma, but in those with vascular invasion, results are improving, although recurrence rates are high.²⁴¹ 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).^{242,243} 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.^{244,245} The outcomes are not dissimilar from those for other indications for pediatric LT with a 5-year survival rate of approximately 85%,²⁴⁶ although there are more late deaths related to pulmonary failure.²⁴⁵ 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.^{245,247} 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 multi-specialist 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).^{248,249} 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 jirovecii*) as well as potentially severe disease from community-acquired pathogens (respiratory syncytial virus and influenza viruses). Children with uncorrected surgical complications (bile duct stenosis 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 asymptotically. 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 valganciclovir 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.^{252,253,256} 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,^{258,259} with symptomatic EBV infections and post-transplant 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.²⁵⁹ PTLD tends to affect organs of the reticuloendothelial system and/or the transplanted liver.²⁶⁰ A complete physical examination should be conducted with a meticulous assessment for lymphadenopathy and adenotonsillar 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.^{261,262} 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,^{263,264} 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.²⁶⁵ Immunohistopathology and immunochemistry may confirm EBV in affected tissue.

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.^{266,267} 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^{266,268} with preemptive reduction of immunosuppression.²⁶⁹ 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.²⁶⁶ Most centers reduce immunosuppression and escalate treatment on the basis of the clinical response and histopathological characteristics of PTLD.^{144,250-253,269-292} Second-line therapies include the anti-CD20 monoclonal antibody (rituximab) and low-dose chemotherapy with cyclophosphamide and prednisone.^{291,292} 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.^{144,272-274} Recipients may have prolonged viral shedding.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 prophylaxis²⁵⁰; 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.²⁵²

Recommendation

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

ADOLESCENT ISSUES

Adolescent Health

Adolescent nonadherence to medical recommendations is noteworthy,^{251,253} and risky behaviors include drug abuse²⁷⁶ and promiscuity with the risk of sexually transmitted diseases and/or pregnancy.^{277,278} Adolescents may lose insurance coverage as adults, and this may end or restrict care.^{279,293} Most adolescents work with parents toward a positive outcome.²⁸⁰

Sexuality and Sexually Transmitted Diseases

Physical disabilities/disfigurement 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.^{281,282} Although there are data on the normal development of puberty in girls after transplantation⁴³, 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 population²⁶⁹). 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.^{283,284} Appropriate advice about contraception, the timing of pregnancy, and immunosuppression during pregnancy should be provided.^{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.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.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.²⁸⁷ Mycophenolate has been associated with structural malformations and is not recommended.²⁸⁸ There are no good data on mTOR inhibitors.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 begin^{292,294} 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.²⁹³ 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 interventions^{308,309} 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.^{310,311} A lack of personal responsibility for health has been a barrier.³¹² 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 study³¹³ 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.³¹³ Another retrospective study examined whether adherence and medical outcomes deteriorated in transferred recipients.³¹⁴ 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.³¹⁵

Transfer Readiness

Measurement tools are available but have not yet been validated.^{316,317}

Transfer-of-Care Models

Viner³¹⁸ 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.^{319,320} Soanes and Timmons³²¹ 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).

ACKNOWLEDGMENT

This practice guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, which provided extensive peer review of the manuscript. The members of the committee include Jayant A. Talwalkar, M.D., M.P.H. (chair); Keith D. Lindor, M.D. (governing board liaison for the American Association for the Study of Liver Diseases); Sumeet Asrani, M.D.; Hari S. Conjeevaram, M.D., M.S.; David A. Gerber, M.D.; Marlyn J. Mayo, M.D.; Raphael B. Merriman, M.D., M.R.C.P.; Gerald Y. Minuk, M.D.; Alexander Monto, M.D.; Michael K. Porayko, M.D.; Benjamin L. Shneider, M.D.; Tram T. Tran, M.D.; and Helen S. Yee, Pharm.D. An external review was provided by Miriam B. Vos, M.D., M.S.P.H., and editorial assistance was provided by Geoffrey M. Giordano.

REFERENCES

1. Eddy D. A Manual for Assessing Health Practices and Designing Practice Guidelines. Philadelphia, PA: American College of Physicians; 1996.
2. American Gastroenterological Association policy statement on the use of medical practice guidelines by managed care organizations and insurance carriers. *Gastroenterology* 1995;108:925-926.
3. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med* 2003;139:493-498.
4. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; for GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
5. United Network for Organ Sharing. Data. <http://www.unos.org/donation/index.php?topic=data>. Accessed June 2013.
6. European Liver Transplant Registry. <http://www.eltr.org/>. Accessed June 2013.
7. Kamath BM, Olthoff KM. Liver transplantation in children: update 2010. *Pediatr Clin North Am* 2010;57:401-414.
8. Duffy JP, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, Busuttill RW. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg* 2009;208:896-903.

9. Anderson CD, Turmelle YP, Darcy M, Shepherd RW, Weymann A, Nadler M, et al. Biliary strictures in pediatric liver transplant recipients—early diagnosis and treatment results in excellent graft outcomes. *Pediatr Transplant* 2010;14:358-363.
10. Martin SR, Atkison P, Anand R, Lindblad AS; for SPLIT Research Group. Studies of Pediatric Liver Transplantation 2002: patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. *Pediatr Transplant* 2004;8:273-283.
11. Heffron TG, Pillen T, Smallwood G, Henry S, Sekar S, Casper K, et al. Incidence, impact, and treatment of portal and hepatic venous complications following pediatric liver transplantation: a single-center 12 year experience. *Pediatr Transplant* 2010;14:722-729.
12. Duffy JP, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg* 2010;252:652-661.
13. Bucuvalas J. Long-term outcomes in pediatric liver transplantation. *Liver Transpl* 2009;15(suppl 2):S6-S11.
14. Soltys KA, Mazariegos GV, Squires RH, Sindhi RK, Anand R; for SPLIT Research Group. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. *Am J Transplant* 2007;7:2165-2171.
15. Miloh T, Kerkar N, Parkar S, Emre S, Annunziato R, Mendez C, et al. Improved outcomes in pediatric liver transplantation for acute liver failure. *Pediatr Transplant* 2010;14:863-869.
16. Mohamed El Moghazy W, Ogura Y, Mutsuko M, Harada K, Koizumi A, Uemoto S. Pediatric living-donor liver transplantation for acute liver failure: analysis of 57 cases. *Transpl Int* 2010;23:823-830.
17. Farmer DG, Venick RS, McDiarmid SV, Duffy JP, Kattan O, Hong JC, et al. Fulminant hepatic failure in children: superior and durable outcomes with liver transplantation over 25 years at a single center. *Ann Surg* 2009;250:484-493.
18. Utterson EC, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R; for SPLIT Research Group. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005;147:180-185.
19. Arnon R, Annunziato R, Miloh T, Suchy F, Sakworawich A, Sogawa H, et al. Orthotopic liver transplantation for children with Alagille syndrome. *Pediatr Transplant* 2010;14:622-628.
20. McDiarmid SV, Anand R, Lindblad AS; for Principal Investigators and Institutions of the Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002;74:173-181.
21. Farmer DG, Venick RS, McDiarmid SV, Ghobrial RM, Gordon SA, Yersiz H, et al. Predictors of outcomes after pediatric liver transplantation: an analysis of more than 800 cases performed at a single institution. *J Am Coll Surg* 2007;204:904-914.
22. Maes M, Sokal E, Otte JB. Growth factors in children with end-stage liver disease before and after liver transplantation: a review. *Pediatr Transplant* 1997;1:171-175.
23. Sarna S, Laine J, Sipila I, Koistinen R, Holmberg C. Differences in linear growth and cortisol production between liver and renal transplant recipients on similar immunosuppression. *Transplantation* 1995;60:656-661.
24. Alonso EM, Shepherd R, Martz KL, Yin W, Anand R; for SPLIT Research Group. Linear growth patterns in prepubertal children following liver transplantation. *Am J Transplant* 2009;9:1389-1397.
25. McDiarmid SV, Gornbein JA, DeSilva PJ, Goss JA, Vargas JH, Martín MG, et al. Factors affecting growth after pediatric liver transplantation. *Transplantation* 1999;67:404-411.
26. Bartosh SM, Thomas SE, Sutton MM, Brady LM, Whittington PF. Linear growth after pediatric liver transplantation. *J Pediatr* 1999;135:624-631.
27. Sarna S, Sipilä I, Rönnholm K, Koistinen R, Holmberg C. Recombinant human growth hormone improves growth in children receiving glucocorticoid treatment after liver transplantation. *J Clin Endocrinol Metab* 1996;81:1476-1482.
28. Reding R. Steroid withdrawal in liver transplantation: benefits, risks, and unanswered questions. *Transplantation* 2000;70:405-410.
29. Puustinen L, Jalanko H, Holmberg C, Merenmies J. Recombinant human growth hormone treatment after liver transplantation in childhood: the 5-year outcome. *Transplantation* 2005;79:1241-1246.
30. Scheenstra R, Gerver WJ, Odink RJ, van Soest H, Peeters PM, Verkade HJ, Sauer PJ. Growth and final height after liver transplantation during childhood. *J Pediatr Gastroenterol Nutr* 2008;47:165-171.
31. Quiros-Tejeira RE, Ament ME, Heyman MB, Martín MG, Rosenthal P, Gornbein JA, et al. Does liver transplantation affect growth pattern in Alagille syndrome? *Liver Transpl* 2000;6:582-587.
32. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut* 2001;49:431-435.
33. Wawrzynowicz-Syczewska M, Karpińska E, Jurczyk K, Laurans L, Boroń-Kaczmarek A. Risk factors and dynamics of weight gain in patients after liver transplantation. *Ann Transplant* 2009;14:45-50.
34. Watt KD, Charlton MR. Metabolic syndrome and liver transplantation: a review and guide to management. *J Hepatol* 2010;53:199-206.
35. Perito ER, Glidden D, Roberts JP, Rosenthal P. Overweight and obesity in pediatric liver transplant recipients: prevalence and predictors before and after transplant, United Network for Organ Sharing Data, 1987-2010. *Pediatr Transplant* 2012;16:41-49.
36. Barlow SE; for Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;120(suppl 4):S164-S192.
37. Alonso EM. Growth and developmental considerations in pediatric liver transplantation. *Liver Transpl* 2008;14:585-591.
38. Ebeling PR. Approach to the patient with transplantation-related bone loss. *J Clin Endocrinol Metab* 2009;94:1483-1490.
39. Cohen A, Sambrook P, Shane E. Management of bone loss after organ transplantation. *J Bone Miner Res* 2004;19:1919-1932.
40. Cohen A, Shane E. Osteoporosis after solid organ and bone marrow transplantation. *Osteoporos Int* 2003;14:617-630.
41. Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, et al. Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. *Osteoporos Int* 2001;12:749-754.
42. Le Gars L. Bone involvement in patients with chronic cholestasis. *Joint Bone Spine* 2002;69:373-378.
43. Viner RM, Forton JT, Cole TJ, Clark IH, Noble-Jamieson G, Barnes ND. Growth of long-term survivors of liver transplantation. *Arch Dis Child* 1999;80:235-240.
44. Codoner-Franch P, Bernard O, Alvarez F. Long-term follow-up of growth in height after successful liver transplantation. *J Pediatr* 1994;124:368-373.

45. D'Antiga L, Moniz C, Buxton-Thomas M, Cheeseman P, Gray B, Abraha H, et al. Bone mineral density and height gain in children with chronic cholestatic liver disease undergoing transplantation. *Transplantation* 2002; 73:1788-1793.
46. Argao EA, Balistreri WF, Hollis BW, Ryckman FC, Heubi JE. Effect of orthotopic liver transplantation on bone mineral content and serum vitamin D metabolites in infants and children with chronic cholestasis. *Hepatology* 1994;20:598-603.
47. Ulivieri FM, Lisciandrano D, Gridelli B, Lucianetti A, Roggero P, Nebbia G, et al. Bone mass and body composition in children with chronic cholestasis before and after liver transplantation. *Transplant Proc* 1999;31: 2131-2134.
48. Guthery SL, Pohl JF, Bucuvalas JC, Alonso MH, Ryckman FC, Balistreri WF, Heubi JE. Bone mineral density in long-term survivors following pediatric liver transplantation. *Liver Transpl* 2003;9:365-370.
49. Valta H, Jalanko H, Holmberg C, Helenius I, Mäkitie O. Impaired bone health in adolescents after liver transplantation. *Am J Transplant* 2008;8:150-157.
50. Okajima H, Shigeno C, Inomata Y, Egawa H, Uemoto S, Asonuma K, et al. Long-term effects of liver transplantation on bone mineral density in children with end-stage liver disease: a 2-year prospective study. *Liver Transpl* 2003;9:360-364.
51. Helenius I, Remes V, Salminen S, Valta H, Mäkitie O, Holmberg C, et al. Incidence and predictors of fractures in children after solid organ transplantation: a 5-year prospective, population-based study. *J Bone Miner Res* 2006;21:380-387.
52. D'Antiga L, Ballan D, Luisetto G, Cillo U, Guariso G, Zancan L. Long-term outcome of bone mineral density in children who underwent a successful liver transplantation. *Transplantation* 2004;78:899-903.
53. Hill SA, Kelly DA, John PR. Bone fractures in children undergoing orthotopic liver transplantation. *Pediatr Radiol* 1995;25(suppl 1):S112-S117.
54. Helenius I, Jalanko H, Remes V, Tervahartiala P, Salminen S, Sairanen H, et al. Avascular bone necrosis of the hip joint after solid organ transplantation in childhood: a clinical and MRI analysis. *Transplantation* 2006;81:1621-1627.
55. Helenius I, Jalanko H, Remes V, Sairanen H, Salminen S, Holmberg C, et al. Scoliosis after solid organ transplantation in children and adolescents. *Am J Transplant* 2006;6:324-330.
56. Helenius I, Remes V, Tervahartiala P, Salminen S, Sairanen H, Holmberg C, et al. Spine after solid organ transplantation in childhood: a clinical, radiographic, and magnetic resonance imaging analysis of 40 patients. *Spine (Phila Pa 1976)* 2006;31:2130-2136.
57. Höglér W, Baumann U, Kelly D. Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children. *J Pediatr Gastroenterol Nutr* 2012;54:313-321.
58. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. *J Bone Miner Metab* 2009;27:392-401.
59. Peltonen J, Remes V, Holmberg C, Jalanko H, Helenius I. Surgical correction of spinal deformities after solid organ transplantation in childhood. *Eur Spine J* 2006; 15:1230-1238.
60. Höglér W, Briody J, Woodhead HJ, Chan A, Cowell CT. Importance of lean mass in the interpretation of total body densitometry in children and adolescents. *J Pediatr* 2003;143:81-88.
61. Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD pediatric official positions. *J Clin Densitom* 2008;11:43-58.
62. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. *J Clin Densitom* 2008;11:75-91.
63. Bachrach LK, Ward LM. Clinical review 1: bisphosphonate use in childhood osteoporosis. *J Clin Endocrinol Metab* 2009;94:400-409.
64. Gilmour SM, Sorensen LG, Anand R, Yin W, Alonso EM; for SPLIT Research Consortium. School outcomes in children registered in the Studies for Pediatric Liver Transplant (SPLIT) consortium. *Liver Transpl* 2010;16: 1041-1048.
65. Bucuvalas JC, Britto M. Health-related quality of life after liver transplantation: it's not all about the liver. *J Pediatr Gastroenterol Nutr* 2003;37:106-108.
66. Cole CR, Bucuvalas JC, Hornung RW, Ryckman FC, Atherton H, et al. Impact of liver transplantation on HRQOL in children less than 5 years old. *Pediatr Transplant* 2004;8:222-227.
67. Sundaram SS, Landgraf JM, Neighbors K, Cohn RA, Alonso EM. Adolescent health-related quality of life following liver and kidney transplantation. *Am J Transplant* 2007;7:982-989.
68. Taylor RM, Franck LS, Gibson F, Donaldson N, Dhawan A. Study of the factors affecting health-related quality of life in adolescents after liver transplantation. *Am J Transplant* 2009;9:1179-1188.
69. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. *Am J Transplant* 2009;9:294-300.
70. Mintzer LL, Stuber ML, Seacord D, Castaneda M, Mesrkhani V, Glover D. Traumatic stress symptoms in adolescent organ transplant recipients. *Pediatrics* 2005; 115:1640-1644.
71. Walker AM, Harris G, Baker A, Kelly D, Houghton J. Post-traumatic stress responses following liver transplantation in older children. *J Child Psychol Psychiatry* 1999;40:363-374.
72. Alonso EM, Neighbors K, Barton FB, McDiarmid SV, Dunn SP, Mazariegos GV, et al.; for Studies of Pediatric Liver Transplant Research Group. Health-related quality of life and family function following pediatric liver transplantation. *Liver Transpl* 2008;14:460-468.
73. Weissberg-Benchell J, Zielinski TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, et al. Pediatric health-related quality of life: feasibility, reliability and validity of the PedsQL transplant module. *Am J Transplant* 2010;10:1677-1685.
74. Fredericks EM, Lopez MJ, Magee JC, Shieck V, Opiari-Arrigan L. Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. *Am J Transplant* 2007;7:1974-1983.
75. Stewart SM, Uauy R, Kennard BD, Waller DA, Benser M, Andrews WS. Mental development and growth in children with chronic liver disease of early and late onset. *Pediatrics* 1988;82:167-172.
76. Stewart SM, Uauy R, Waller DA, Kennard BD, Andrews WS. Mental and motor development correlates in patients with end-stage biliary atresia awaiting liver transplantation. *Pediatrics* 1987;79:882-888.
77. Stewart SM, Uauy R, Waller DA, Kennard BD, Benser M, Andrews WS. Mental and motor development, social competence, and growth one year after successful pediatric liver transplantation. *J Pediatr* 1989;114(pt 1): 574-581.

78. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. *Pediatr Transplant* 2003;7:385-389.
79. Kaller T, Schulz KH, Sander K, Boeck A, Rogiers X, Burdelski M. Cognitive abilities in children after liver transplantation. *Transplantation* 2005;79:1252-1256.
80. Krull K, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. *Pediatr Transplant* 2003;7:111-118.
81. Stewart SM, Campbell RA, McCallon D, Waller DA, Andrews WS. Cognitive patterns in school-age children with end-stage liver disease. *J Dev Behav Pediatr* 1992;13:331-338.
82. Stewart SM, Kennard BD, Waller DA, Fixler D. Cognitive function in children who receive organ transplantation. *Health Psychol* 1994;13:3-13.
83. Kennard BD, Stewart SM, Phelan-McAuliffe D, Waller DA, Bannister M, Fioravani V, Andrews WS. Academic outcome in long-term survivors of pediatric liver transplantation. *J Dev Behav Pediatr* 1999;20:17-23.
84. Campeau PM, Pivalizza PJ, Miller G, McBride K, Karpen S, Goss J, Lee BH. Early orthotopic liver transplantation in urea cycle defects: follow up of a developmental outcome study. *Mol Genet Metab* 2010;100(suppl 1):S84-S87.
85. Wayman KI, Cox KL, Esquivel CO. Neurodevelopmental outcome of young children with extrahepatic biliary atresia 1 year after liver transplantation. *J Pediatr* 1997;131:894-898.
86. Gritti A, Di Sarno AM, Comito M, De Vincenzo A, De Paola P, Vajro P. Psychological impact of liver transplantation on children's inner worlds. *Pediatr Transplant* 2001;5:37-43.
87. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM; for Studies of Pediatric Liver Transplantation (SPLIT) and Functional Outcomes Group (FOG). Cognitive and academic outcomes after pediatric liver transplantation: Functional Outcomes Group (FOG) results. *Am J Transplant* 2011;11:303-311.
88. Bucuvalas JC, O'Connor A, Buschle K, Krug S, Ryckman FC, Atherton H, et al. Risk of hearing impairment in pediatric liver transplant recipients: a single center study. *Pediatr Transplant* 2003;7:265-269.
89. Varni JW, Limbers CA, Sorensen LG, Neighbors K, Martz K, Bucuvalas JC, Alonso EM; for Studies of Pediatric Liver Transplantation Functional Outcomes Group. PedsQL™ Cognitive Functioning Scale in pediatric liver transplant recipients: feasibility, reliability, and validity. *Qual Life Res* 2011;20:913-921.
90. Molmenti E, Mazariegos G, Bueno J, Cacciarelli T, Alasio T, Khanna A, et al. Noncompliance after pediatric liver transplantation. *Transplant Proc* 1999;31:408.
91. Shemesh E, Shneider BL, Savitzky JK, Arnott L, Gondolesi GE, Krieger NR, et al. Medication adherence in pediatric and adolescent liver transplant recipients. *Pediatrics* 2004;113:825-832.
92. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatr Transplant* 2008;12:67-72.
93. Stuber ML, Shemesh E, Seacord D, Washington J III, Hellemann G, McDiarmid S. Evaluating non-adherence to immunosuppressant medications in pediatric liver transplant recipients. *Pediatr Transplant* 2008;12:284-288.
94. Lurie S, Shemesh E, Sheiner PA, Emre S, Tindle HL, Melchionna L, Shneider BL. Non-adherence in pediatric liver transplant recipients—an assessment of risk factors and natural history. *Pediatr Transplant* 2000;4:200-206.
95. De Bleser L, Dobbels F, Berben L, Vanhaecke J, Verleden G, Nevens F, De Geest S. The spectrum of non-adherence with medication in heart, liver, and lung transplant patients assessed in various ways. *Transpl Int* 2011;24:882-891.
96. 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.
97. Shemesh E. Adherence to medical regimens. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR, eds. *Pediatric Gastrointestinal Disease*. 4th ed. Ontario, Canada: BC Decker; 2004:2102-2110.
98. Shemesh E. Psychosocial adaptation and adherence. In: Fine RN, Webber SA, Olthoff KM, Kelly DA, Harmon WE, eds. *Pediatric Solid Organ Transplantation*. 2nd ed. Malden, MA: Blackwell; 2007:418-424.
99. Bender B, Milgrom H, Apter A. Adherence intervention research: what have we learned and what do we do next? *J Allergy Clin Immunol* 2003;112:489-494.
100. Miloh T, Annunziato R, Arnon R, Warshaw J, Parkar S, Suchy FJ, et al. Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. *Pediatrics* 2009;124:e844-e850.
101. Shemesh E, Annunziato RA, Shneider BL, Dugan CA, Warshaw J, Kerkar N, Emre S. Improving adherence to medications in pediatric liver transplant recipients. *Pediatr Transplant* 2008;12:316-323.
102. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. *World J Gastroenterol* 2009;15:648-674.
103. Busutil RW, Goss JA. Split liver transplantation. *Ann Surg* 1999;229:313-321.
104. Babyn PS. Imaging of the transplant liver. *Pediatr Radiol* 2010;40:442-446.
105. Marshalleck F. Pediatric arterial interventions. *Tech Vasc Interv Radiol* 2010;13:238-243.
106. Ueda M, Oike F, Kasahara M, Ogura Y, Ogawa K, Haga H, et al. Portal vein complications in pediatric living donor liver transplantation using left-side grafts. *Am J Transplant* 2008;8:2097-2105.
107. Wei BJ, Zhai RY, Wang JF, Dai DK, Yu P. Percutaneous portal venoplasty and stenting for anastomotic stenosis after liver transplantation. *World J Gastroenterol* 2009;15:1880-1885.
108. Shirouzu Y, Kasahara M, Takada Y, Taira K, Sakamoto S, Uryuhara K, et al. Development of pulmonary hypertension in 5 patients after pediatric living-donor liver transplantation: de novo or secondary? *Liver Transpl* 2006;12:870-875.
109. de Ville de Goyet J, Gibbs P, Clapuyt P, Reding R, Sokal EM, Otte JB. Original extrahilar approach for hepatic portal revascularization and relief of extrahepatic portal hypertension related to later portal vein thrombosis after pediatric liver transplantation. Long term results. *Transplantation* 1996;62:71-75.
110. Lee WS, John P, McKiernan P, de Ville De Goyet J, Kelly DA. Inferior vena cava occlusion and protein-losing enteropathy after liver transplantation in children. *J Pediatr Gastroenterol Nutr* 2002;34:413-416.
111. Tanaka H, Fukuda A, Shigeta T, Kuroda T, Kimura T, Sakamoto S, Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. *J Pediatr Surg* 2010;45:1668-1675.
112. Racadio JM, Kukreja K. Pediatric biliary interventions. *Tech Vasc Interv Radiol* 2010;13:244-249.
113. Moreira AM, Carnevale FC, Tannuri U, Suzuki L, Gibelli N, Maksoud JG, Cerri GG. Long-term results of percutaneous bilioenteric anastomotic stricture treatment in

- liver-transplanted children. *Cardiovasc Intervent Radiol* 2010;33:90-96.
114. Lorenz JM, Denison G, Funaki B, Leef JA, Van Ha T, Rosenblum JD. Balloon dilatation of biliary-enteric strictures in children. *AJR Am J Roentgenol* 2005;184:151-155.
 115. Sunku B, Salvalaggio PR, Donaldson JS, Rigsby CK, Neighbors K, Superina RA, Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. *Liver Transpl* 2006;12:821-826.
 116. Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. *Liver Transpl* 2009;15(suppl 2):S12-S18.
 117. Lucey MR. Serial liver biopsies: a gateway into understanding the long-term health of the liver allograft. *J Hepatol* 2001;34:762-763.
 118. Yoshitomi M, Koshihara T, Haga H, Li Y, Zhao X, Cheng D, et al. Requirement of protocol biopsy before and after complete cessation of immunosuppression after liver transplantation. *Transplantation* 2009;87:606-614.
 119. Gonzalez-Vallina R, Alonso EM, Rand E, Black DD, Whittington PF. Outpatient percutaneous liver biopsy in children. *J Pediatr Gastroenterol Nutr* 1993;17:370-375.
 120. Azzam RK, Alonso EM, Emerick KM, Whittington PF. Safety of percutaneous liver biopsy in infants less than three months old. *J Pediatr Gastroenterol Nutr* 2005;41:639-643.
 121. Nobili V, Monti L, Alisi A, Lo Zupone C, Pietrobattista A, Tomà P. Transient elastography for assessment of fibrosis in paediatric liver disease. *Pediatr Radiol* 2011;41:1232-1238.
 122. Nobili V, Parkes J, Bottazzo G, Marcellini M, Cross R, Newman D, et al. Performance of ELF serum markers in predicting fibrosis stage in pediatric non-alcoholic fatty liver disease. *Gastroenterology* 2009;136:160-167.
 123. Boraschi P, Donati F, Gigoni R, Salemi S, Urbani L, Filipponi F, et al. Complications after liver transplantation: evaluation with magnetic resonance imaging, magnetic resonance cholangiography, and 3 dimensional contrast-enhanced magnetic resonance angiography in a single session. *Can Assoc Radiol J* 2008;59:259-263.
 124. Berenguer M, Rayón JM, Prieto M, Aguilera V, Nicolás D, Ortíz V, et al. Are posttransplantation protocol liver biopsies useful in the long term? *Liver Transpl* 2001;7:790-796.
 125. Targhetta S, Villamil F, Inturri P, Pontisso P, Fagioli S, Cillo U, et al. Protocol liver biopsies in long-term management of patients transplanted for hepatitis B-related liver disease. *World J Gastroenterol* 2006;12:1706-1712.
 126. Sebah M, Rifai K, Féray C, Yilmaz F, Falissard B, Roche B, et al. All liver recipients benefit from the protocol 10-year liver biopsies. *Hepatology* 2003;37:1293-1301.
 127. Rosenthal P, Emond JC, Heyman MB, Snyder J, Roberts J, Ascher N, Ferrell L. Pathological changes in yearly protocol liver biopsy specimens from healthy pediatric liver recipients. *Liver Transpl Surg* 1997;3:559-562.
 128. Evans HM, Kelly DA, McKiernan PJ, Hübscher S. Progressive histological damage in liver allografts following pediatric liver transplantation. *Hepatology* 2006;43:1109-1117.
 129. Davison SM, Skidmore SJ, Collingham KE, Irving WL, Hübscher SG, Kelly DA. Chronic hepatitis in children after liver transplantation: role of hepatitis C virus and hepatitis G virus infections. *J Hepatol* 1998;28:764-770.
 130. Peeters PM, Sieders E, vd Heuvel M, Bijleveld CM, de Jong KP, TenVergert EM, et al. Predictive factors for portal fibrosis in pediatric liver transplant recipients. *Transplantation* 2000;70:1581-1587.
 131. Scheenstra R, Peeters PM, Verkade HJ, Gouw AS. Graft fibrosis after pediatric liver transplant recipients: ten years of follow up. *Hepatology* 2009;49:880-886.
 132. Hübscher S. What does the long-term liver allograft look like for the pediatric recipient? *Liver Transpl* 2009;15(suppl 2):S19-S24.
 133. Kerker N, Hadzić N, Davies ET, Portmann B, Donaldson PT, Rela M, et al. De-novo autoimmune hepatitis after liver transplantation. *Lancet* 1998;351:409-413.
 134. Gupta P, Hart J, Millis JM, Cronin D, Brady L. De novo hepatitis with autoimmune antibodies and atypical histology: a rare cause of late graft dysfunction after pediatric liver transplantation. *Transplantation* 2001;71:664-668.
 135. Czaja AJ. Autoimmune hepatitis after liver transplantation and other lessons of self-intolerance. *Liver Transpl* 2002;8:505-513.
 136. Vergani D, Mieli-Vergani G. Autoimmunity after liver transplantation. *Hepatology* 2002;36:271-276.
 137. Andries S, Casamayou L, Sempoux C, Burlet M, Reding R, Bernard Otte J, et al. Posttransplant immune hepatitis in pediatric liver transplant recipients: incidence and maintenance therapy with azathioprine. *Transplantation* 2001;72:267-272.
 138. Burra P, Masier A, Boldrin C, Calistri A, Andreoli E, Senzolo M, et al. Torque teno virus: any pathological role in liver transplanted patients? *Transpl Int* 2008;21:972-979.
 139. Kamar N, Garrouste C, Haagsma EB, Garrigue V, Pischke S, Chauvet C, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 2011;140:1481-1489.
 140. Thomson MA, Suggett NR, Nightingale PG, Milford DV, Baumann U, Kelly DA, et al. Skin surveillance of a U.K. paediatric transplant population. *Br J Dermatol* 2007;156:45-50.
 141. Penn I. Post-transplant malignancy: the role of immunosuppression. *Drug Saf* 2000;23:101-113.
 142. Simard JF, Baecklund E, Kinch A, Brattström C, Ingvar A, Molin D, et al. Pediatric organ transplantation and risk of premalignant and malignant tumors in Sweden. *Am J Transplant* 2011;11:146-151.
 143. Danzinger-Isakov L, Kumar D; for AST Infectious Diseases Community of Practice. Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant* 2009;9(suppl 4):S258-S262.
 144. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:560-569.
 145. Allen U, Green M. Prevention and treatment of infectious complications after solid organ transplantation in children. *Pediatr Clin North Am* 2010;57:459-479.
 146. Rand EB, McCarthy CA, Whittington PF. Measles vaccination after orthotopic liver transplantation. *J Pediatr* 1993;123:87-89.
 147. Krasnoff JB, Mathias R, Rosenthal P, Painter PL. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. *Transplantation* 2006;82:211-217.
 148. McDiarmid SV, Anand R, Martz K, Millis MJ, Mazariegos G. A multivariate analysis of pre-, peri-, and

- post-transplant factors affecting outcome after pediatric liver transplantation. *Ann Surg* 2011;254:145-154.
149. Post DJ, Douglas DD, Mulligan DC. Immunosuppression in liver transplantation. *Liver Transpl* 2005;11:1307-1314.
 150. Jiménez-Rivera C, Avitzur Y, Fecteau AH, Jones N, Grant D, Ng VL. Sirolimus for pediatric liver transplant recipients with post-transplant lymphoproliferative disease and hepatoblastoma. *Pediatr Transplant* 2004;8:243-248.
 151. Kelly D, Jara P, Rodeck B, Lykavieris P, Burdelski M, Becker M, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004;364:1054-1061.
 152. Kelly D. Safety and efficacy of tacrolimus in pediatric liver recipients. *Pediatr Transplant* 2011;15:19-24.
 153. Spada M, Petz W, Bertani A, Riva S, Sonzogni A, Giovannelli M, et al. Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant* 2006;6:1913-1921.
 154. Sánchez-Fueyo A, Strom TB. Immunologic basis of graft rejection and tolerance following transplantation of liver or other solid organs. *Gastroenterology* 2011;140:51-64.
 155. Banff schema for grading liver allograft rejection: an international consensus document. *Hepatology* 1997;25:658-663.
 156. Höroldt BS, Burattin M, Gunson BK, Bramhall SR, Nightingale P, Hübscher SG, Neuberger JM. Does the Banff rejection activity index predict outcome in patients with early acute cellular rejection following liver transplantation? *Liver Transpl* 2006;12:1144-1151.
 157. Neil DA, Hübscher SG. Current views on rejection pathology in liver transplantation. *Transpl Int* 2010;23:971-983.
 158. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. *Pediatrics* 2008;122:e1128-e1135.
 159. Kelly DA. Current issues in pediatric transplantation. *Pediatr Transplant* 2006;10:712-720.
 160. Wallot MA, Mathot M, Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience. *Liver Transpl* 2002;8:615-622.
 161. Aw MM, Taylor RM, Verma A, Parke A, Baker AJ, Hadzic D, et al. Basiliximab (Simulect) for the treatment of steroid-resistant rejection in pediatric liver transplant recipients: a preliminary experience. *Transplantation* 2003;75:796-799.
 162. Jain A, Mazariegos G, Pokharna R, Parizhskaya M, Smith A, Kashyap R, et al. Almost total absence of chronic rejection in primary pediatric liver transplantation under tacrolimus. *Transplant Proc* 2002;34:1968-1969.
 163. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann Surg* 2000;232:490-500.
 164. Campbell K, Ng V, Martin S, Magee J, Goebel J, Anand R, et al.; for SPLIT Renal Function Working Group. Glomerular filtration rate following pediatric liver transplantation—the SPLIT experience. *Am J Transplant* 2010;10:2673-2682.
 165. Bucuvalas JC, Alonso E, Magee JC, Talwalkar J, Hanto D, Doo E. Improving long-term outcomes after liver transplantation in children. *Am J Transplant* 2008;8:2506-2513.
 166. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;349:931-940.
 167. Arora-Gupta N, Davies P, McKiernan P, Kelly DA. The effect of long-term calcineurin inhibitor therapy on renal function in children after liver transplantation. *Pediatr Transplant* 2004;8:145-150.
 168. Bartosh SM, Alonso EM, Whittington PF. Renal outcomes in pediatric liver transplantation. *Clin Transplant* 1997;11(pt 1):354-360.
 169. Herlenius G, Hansson S, Krantz M, Olausson M, Kullberg-Lindh C, Friman S. Stable long-term renal function after pediatric liver transplantation. *Pediatr Transplant* 2010;14:409-416.
 170. Goldstein SL, Devarajan P. Pediatrics: acute kidney injury leads to pediatric patient mortality. *Nat Rev Nephrol* 2010;6:393-394.
 171. Everson GT, Trotter JF, Kugelmas M, Forman L. Immunosuppression in liver transplantation. *Minerva Chir* 2003;58:725-740.
 172. Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTx) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001;72:1934-1939.
 173. Gonwa TA. Hypertension and renal dysfunction in long-term liver transplant recipients. *Liver Transpl* 2001;7(suppl 1):S22-S26.
 174. McCulloch MI, Burger H, Spearman CW, Cooke L, Goddard E, Gajjar P, et al. Nephrotoxic effects of immunosuppressant therapy in pediatric liver transplant recipients. *Transplant Proc* 2005;37:1220-1223.
 175. Franchi-Abella S, Mourier O, Pariente D, Frank-Soltysiak M, Bernard O, Debray D. Acquired renal cystic disease after liver transplantation in children. *Transplant Proc* 2007;39:2601-2602.
 176. Calvo-Garcia MA, Campbell KM, O'Hara SM, Khoury P, Mitsnefes MM, Strife CF. Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction. *Pediatr Transplant* 2008;12:666-671.
 177. Arora N, McKiernan PJ, Beath SV, deVillie de Goyet J, Kelly DA. Concomitant basiliximab with low-dose calcineurin inhibitors in children post-liver transplantation. *Pediatr Transplant* 2002;6:214-218.
 178. Du Y, Zappitelli M, Mian A, Bennett M, Ma Q, Devarajan P, et al. Urinary biomarkers to detect acute kidney injury in the pediatric emergency center. *Pediatr Nephrol* 2011;26:267-274.
 179. Goldstein SL. Urinary kidney injury biomarkers and urine creatinine normalization: a false premise or not? *Kidney Int* 2010;78:433-435.
 180. Goldstein SL, Devarajan P. Progression from acute kidney injury to chronic kidney disease: a pediatric perspective. *Adv Chronic Kidney Dis* 2008;15:278-283.
 181. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629-637.
 182. Tokunaga M, Kabashima N, Serino R, Shibata T, Matsumoto M, Miyamoto T, et al. Renoprotective effects of telmisartan in patients with advanced chronic kidney disease. *Clin Nephrol* 2010;73:139-146.

183. Laight DW. Therapeutic inhibition of the renin angiotensin aldosterone system. *Expert Opin Ther Pat* 2009;19:753-759.
184. Evans HM, McKiernan PJ, Kelly DA. Mycophenolate mofetil for renal dysfunction after pediatric liver transplantation. *Transplantation* 2005;79:1575-1580.
185. Ponton C, Vizcaíno L, Tomé S, Otero E, Molina E, Castroagudín JF, et al. Improvement of renal function after conversion to mycophenolate mofetil combined with low-level calcineurin inhibitor in liver transplant recipients with chronic renal dysfunction. *Transplant Proc* 2010;42:656-659.
186. Beckebaum S, Klein CG, Sotiropoulos GC, Saner FH, Gerken G, Paul A, Cicinnati VR. Combined mycophenolate mofetil and minimal dose calcineurin inhibitor therapy in liver transplant patients: clinical results of a prospective randomized study. *Transplant Proc* 2009;41:2567-2569.
187. Hathout E, Alonso E, Anand R, Martz K, Imseis E, Johnston J, et al.; for SPLIT Study Group. Post-transplant diabetes mellitus in pediatric liver transplantation. *Pediatr Transplant* 2009;13:599-605.
188. Casas-Melley AT, Falkenstein KP, Flynn LM, Ziegler VL, Dunn SP. Improvement in renal function and rejection control in pediatric liver transplant recipients with the introduction of sirolimus. *Pediatr Transplant* 2004;8:362-366.
189. Reding R, Gras J, Bourdeaux C, Wieers G, Truong QD, Latinne D, et al. Stepwise minimization of the immunosuppressive therapy in pediatric liver transplantation. A conceptual approach towards operational tolerance. *Acta Gastroenterol Belg* 2005;68:320-322.
190. Marchetti P. New-onset diabetes after liver transplantation: from pathogenesis to management. *Liver Transpl* 2005;11:612-620.
191. Pageaux GP, Faure S, Bouyabrine H, Bismuth M, Assenat E. Long-term outcomes of liver transplantation: diabetes mellitus. *Liver Transpl* 2009;15(suppl 2):S79-S82.
192. Kuo HT, Lau C, Sampaio MS, Bunnapradist S. Pre-transplant risk factors for new-onset diabetes mellitus after transplant in pediatric liver transplant recipients. *Liver Transpl* 2010;16:1249-1256.
193. Kuo HT, Sampaio MS, Ye X, Reddy P, Martin P, Bunnapradist S. Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. *Transplantation* 2010;89:1134-1140.
194. Charlton M. Obesity, hyperlipidemia, and metabolic syndrome. *Liver Transpl* 2009;15(suppl 2):S83-S89.
195. Laryea M, Watt KD, Molinari M, Walsh MJ, McAlister VC, Marotta PJ, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl* 2007;13:1109-1114.
196. Hayman LL, Williams CL, Daniels SR, Steinberger J, Paridon S, Dennison BA, McCrindle BW; for Committee on Atherosclerosis, Hypertension, and Obesity in Youth (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. Cardiovascular health promotion in the schools: a statement for health and education professionals and child health advocates from the Committee on Atherosclerosis, Hypertension, and Obesity in Youth (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;110:2266-2275.
197. Daniels SR, Greer FR; for Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198-208.
198. Ng VL, Alonso EM, Bucuvalas JC, Cohen G, Limbers CA, Varni JW, et al.; for Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the Studies of Pediatric Liver Transplantation experience. *J Pediatr* 2012;160:820-826.e3.
199. McLin VA, Anand R, Daniels SR, Yin W, Alonso EM; for SPLIT Research Group. Blood pressure elevation in long-term survivors of pediatric liver transplantation. *Am J Transplant* 2012;12:183-190.
200. Cambaceres CG, Rojas L, Fernandez MC, Licciardone N, Ferreira O, Diaz A, et al. Monitoring cyclosporine microemulsion at two hours post dosing in pediatric maintenance liver transplant recipients. *Transplant Proc* 2010;42:361-362.
201. Orlando G, Baiocchi L, Cardillo A, Iaria G, De Liguori Carino N, De Luca L, et al. Switch to 1.5 grams MMF monotherapy for CNi-related toxicity in liver transplantation is safe and improves renal function, dyslipidemia, and hypertension. *Liver Transpl* 2007;13:46-54.
202. Charlton MR, Wall WJ, Ojo AO, Ginès P, Textor S, Shihab FS, et al.; for International Liver Transplantation Society Expert Panel. Report of the first International Liver Transplantation Society expert panel consensus conference on renal insufficiency in liver transplantation. *Liver Transpl* 2009;15:S1-S34.
203. Karie-Guigues S, Janus N, Saliba F, Dumortier J, Duvoux C, Calmus Y, et al. Long-term renal function in liver transplant recipients and impact of immunosuppressive regimens (calcineurin inhibitors alone or in combination with mycophenolate mofetil): the TRY study. *Liver Transpl* 2009;15:1083-1091.
204. Pons JA, Ramírez P, Revilla-Nuin B, Pascual D, Baroja-Mazo A, Robles R, et al. Immunosuppression withdrawal improves long-term metabolic parameters, cardiovascular risk factors and renal function in liver transplant patients. *Clin Transplant* 2009;23:329-336.
205. Turmelle YP, Nadler ML, Anderson CD, Doyle MB, Lowell JA, Shepherd RW. Towards minimizing immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant* 2009;13:553-559.
206. Alabraba E, Nightingale P, Gunson B, Hubscher S, Olliff S, Mirza D, Neuberger J. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. *Liver Transpl* 2009;15:330-340.
207. Lerut J, Bonaccorsi-Riani E, Finet P, Gianello P. Minimization of steroids in liver transplantation. *Transpl Int* 2009;22:2-19.
208. Ekong UD, Melin-Aldana H, Seshadri R, Lokar J, Harris D, Whittington PF, Alonso EM. Graft histology characteristics in long-term survivors of pediatric liver transplantation. *Liver Transpl* 2008;14:1582-1587.
209. Girlanda R, Rela M, Williams R, O'Grady JG, Heaton ND. Long-term outcome of immunosuppression withdrawal after liver transplantation. *Transplant Proc* 2005;37:1708-1709.
210. Girlanda R, Vilca-Melendez H, Srinivasan P, Muiesan P, O'Grady JG, Rela M, Heaton ND. Immunosuppression withdrawal after auxiliary liver transplantation for acute liver failure. *Transplant Proc* 2005;37:1720-1721.
211. Hurwitz M, Desai DM, Cox KL, Berquist WE, Esquivel CO, Millan MT. Complete immunosuppressive withdrawal as a uniform approach to post-transplant lymphoproliferative disease in pediatric liver transplantation. *Pediatr Transplant* 2004;8:267-272.
212. Lee JH, Lee SK, Lee HJ, Seo JM, Joh JW, Kim SJ, et al. Withdrawal of immunosuppression in pediatric liver transplant recipients in Korea. *Yonsei Med J* 2009;50:784-788.
213. Mazariegos GV, Reyes J, Marino IR, Demetris AJ, Flynn B, Irish W, et al. Weaning of immunosuppression in

- liver transplant recipients. *Transplantation* 1997;63:243-249.
214. Mazariegos GV, Sindhi R, Thomson AW, Marcos A. Clinical tolerance following liver transplantation: long term results and future prospects. *Transpl Immunol* 2007;17:114-119.
 215. Mazariegos GV, Zahorchak AF, Reyes J, Chapman H, Zeevi A, Thomson AW. Dendritic cell subset ratio in tolerant, weaning and non-tolerant liver recipients is not affected by extent of immunosuppression. *Am J Transplant* 2005;5:314-322.
 216. Scheenstra R, Torringa ML, Waalkens HJ, Middelveld EH, Peeters PM, Slooff MJ, et al. Cyclosporine A withdrawal during follow-up after pediatric liver transplantation. *Liver Transpl* 2006;12:240-246.
 217. Koshiha T, Li Y, Takemura M, Wu Y, Sakaguchi S, Minato N, et al. Clinical, immunological, and pathological aspects of operational tolerance after pediatric living-donor liver transplantation. *Transpl Immunol* 2007;17:94-97.
 218. Takatsuki M, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Fujita S, et al. Weaning of immunosuppression in living donor liver transplant recipients. *Transplantation* 2001;72:449-454.
 219. Demetris AJ, Lunz JG III, Randhawa P, Wu T, Nalesnik M, Thomson AW. Monitoring of human liver and kidney allograft tolerance: a tissue/histopathology perspective. *Transpl Int* 2009;22:120-141.
 220. Mazariegos GV, Zahorchak AF, Reyes J, Ostrowski L, Flynn B, Zeevi A, Thomson AW. Dendritic cell subset ratio in peripheral blood correlates with successful withdrawal of immunosuppression in liver transplant patients. *Am J Transplant* 2003;3:689-696.
 221. Martínez-Llordella M, Puig-Pey I, Orlando G, Ramoni M, Tisone G, Rimola A, et al. Multiparameter immune profiling of operational tolerance in liver transplantation. *Am J Transplant* 2007;7:309-319.
 222. Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. *Clin Res Hepatol Gastroenterol* 2011;35:446-454.
 223. Miloh T, Anand R, Yin W, Vos M, Kerkar N, Alonso E; for Studies of Pediatric Liver Transplantation Research Group. Pediatric liver transplantation for primary sclerosing cholangitis. *Liver Transpl* 2011;17:925-933.
 224. Duclos-Vallee JC, Sebahg M. Recurrence of autoimmune disease, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis after liver transplantation. *Liver Transpl* 2009;15(suppl 2):S25-S34.
 225. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. *Liver Transpl* 2006;12:1813-1824.
 226. Martin SR, Alvarez F, Anand R, Song C, Yin W; for SPLIT Research Group. Outcomes in children who underwent transplantation for autoimmune hepatitis. *Liver Transpl* 2011;17:393-401.
 227. Chai PF, Lee WS, Brown RM, McPartland JL, Foster K, McKiernan PJ, Kelly DA. Childhood autoimmune liver disease: indications and outcome of liver transplantation. *J Pediatr Gastroenterol Nutr* 2010;50:295-302.
 228. Otte JB, Pritchard J, Aronson DC, Brown J, Czauderna P, Maibach R, et al.; for International Society of Pediatric Oncology (SIOP). Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatr Blood Cancer* 2004;42:74-83.
 229. Tiao GM, Bobey N, Allen S, Nieves N, Alonso M, Bucuvalas J, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. *J Pediatr* 2005;146:204-211.
 230. Finegold MJ, Egler RA, Goss JA, Guillerman RP, Karpen SJ, Krishnamurthy R, O'Mahony CA. Liver tumors: pediatric population. *Liver Transpl* 2008;14:1545-1556.
 231. Browne M, Sher D, Grant D, Deluca E, Alonso E, Whittington PF, Superina RA. Survival after liver transplantation for hepatoblastoma: a 2-center experience. *J Pediatr Surg* 2008;43:1973-1981.
 232. Otte JB, Meyers R. PLUTO first report. *Pediatr Transplant* 2010;14:830-835.
 233. Austin MT, Leys CM, Feurer ID, Lovvorn HN III, O'Neill JA Jr, Pinson CW, Pietsch JB. Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. *J Pediatr Surg* 2006;41:182-186.
 234. Evrard V, Otte JB, Sokal E, Rochet JS, Haccourt F, Gennari F, et al. Impact of surgical and immunological parameters in pediatric liver transplantation: a multivariate analysis in 500 consecutive recipients of primary grafts. *Ann Surg* 2004;239:272-280.
 235. Otte JB. Progress in the surgical treatment of malignant liver tumors in children. *Cancer Treat Rev* 2010;36:360-371.
 236. Suh MY, Wang K, Gutweiler JR, Misra MV, Krawczuk LE, Jenkins RL, et al. Safety of minimal immunosuppression in liver transplantation for hepatoblastoma. *J Pediatr Surg* 2008;43:1148-1152.
 237. Gupta AA, Gerstle JT, Ng V, Wong A, Fecteau A, Malogolowkin MH, et al. Critical review of controversial issues in the management of advanced pediatric liver tumors. *Pediatr Blood Cancer* 2011;56:1013-1018.
 238. Lautz TB, Ben-Ami T, Tantemsapya N, Gosiengfiao Y, Superina RA. Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. *Cancer* 2011;117:1976-1983.
 239. Otte JB, de Ville de Goyet J, Reding R. Liver transplantation for hepatoblastoma: indications and contraindications in the modern era. *Pediatr Transplant* 2005;9:557-565.
 240. Faraj W, Dar F, Marangoni G, Bartlett A, Melendez HV, Hadzic D, et al. Liver transplantation for hepatoblastoma. *Liver Transpl* 2008;14:1614-1619.
 241. Kosola S, Lauronen J, Sairanen H, Heikinheimo M, Jalanko H, Pakarinen M. High survival rates after liver transplantation for hepatoblastoma and hepatocellular carcinoma. *Pediatr Transplant* 2010;14:646-650.
 242. Jara P, Hierro L, Martínez-Fernández P, Alvarez-Doforno R, Yáñez F, Diaz MC, et al. Recurrence of bile salt export pump deficiency after liver transplantation. *N Engl J Med* 2009;361:1359-1367.
 243. Keitel V, Burdelski M, Vojnisek Z, Schmitt L, Häussinger D, Kubitz R. De novo bile salt transporter antibodies as a possible cause of recurrent graft failure after liver transplantation: a novel mechanism of cholestasis. *Hepatology* 2009;50:510-517.
 244. Fridell JA, Bond GJ, Mazariegos GV, Orenstein DM, Jain A, Sindhi R, et al. Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. *J Pediatr Surg* 2003;38:1152-1156.
 245. Dowman JK, Watson D, Loganathan S, Gunson BK, Hodson J, Mirza DF, et al. Long-term impact of liver transplantation on respiratory function and nutritional status in children and adults with cystic fibrosis. *Am J Transplant* 2012;12:954-964.
 246. Mendizabal M, Reddy KR, Cassuto J, Olthoff KM, Faust TW, Makar GA, et al. Liver transplantation in patients with cystic fibrosis: analysis of United Network for Organ Sharing data. *Liver Transpl* 2011;17:243-250.

247. Melzi ML, Kelly DA, Colombo C, Jara P, Manzanares J, Colledan M, et al.; for EGS/TCF, European Liver Transplant Association (ELTA), and European Cystic Fibrosis Society (ECFS). Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. *Transpl Int* 2006;19:726-731.
248. Bowman JS, Green M, Scantlebury VP, Todo S, Tzakis A, Iwatsuki S, et al. OKT3 and viral disease in pediatric liver transplant recipients. *Clin Transplant* 1991;5:294-300.
249. Humar A, Snyderman D; for AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. *Am J Transplant* 2009;9(suppl 4):S78-S86.
250. Michaels MG, Fonseca-Aten M, Green M, Charsha-May D, Friedman B, Seikaly M, Sánchez PJ. Respiratory syncytial virus prophylaxis: a survey of pediatric solid organ transplant centers. *Pediatr Transplant* 2009;13:451-456.
251. Penkower L, Dew MA, Ellis D, Sereika SM, Kitutu JM, Shapiro R. Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. *Am J Transplant* 2003;3:1418-1425.
252. Martin SI, Fishman JA; for AST Infectious Diseases Community of Practice. *Pneumocystis pneumonia* in solid organ transplant recipients. *Am J Transplant* 2009;9(suppl 4):S227-S233.
253. Smith BA, Shuchman M. Problem of nonadherence in chronically ill adolescents: strategies for assessment and intervention. *Curr Opin Pediatr* 2005;17:613-618.
254. Sia IG, Wilson JA, Groettum CM, Espy MJ, Smith TF, Paya CV. Cytomegalovirus (CMV) DNA load predicts relapsing CMV infection after solid organ transplantation. *J Infect Dis* 2000;181:717-720.
255. Pang XL, Fox JD, Fenton JM, Miller GG, Caliendo AM, Preiksaitis JK; for American Society of Transplantation Infectious Diseases Community of Practice and Canadian Society of Transplantation. Interlaboratory comparison of cytomegalovirus viral load assays. *Am J Transplant* 2009;9:258-268.
256. Madan RP, Campbell AL, Shust GF, Kahn AR, Wistinghausen B, Posada R, et al. A hybrid strategy for the prevention of cytomegalovirus-related complications in pediatric liver transplantation recipients. *Transplantation* 2009;87:1318-1324.
257. Boivin G, Goyette N, Rollag H, Jardine AG, Pescovitz MD, Asberg A, et al. Cytomegalovirus resistance in solid organ transplant recipients treated with intravenous ganciclovir or oral valganciclovir. *Antivir Ther* 2009;14:697-704.
258. Green M. Management of Epstein-Barr virus-induced post-transplant lymphoproliferative disease in recipients of solid organ transplantation. *Am J Transplant* 2001;1:103-108.
259. Preiksaitis JK. New developments in the diagnosis and management of posttransplantation lymphoproliferative disorders in solid organ transplant recipients. *Clin Infect Dis* 2004;39:1016-1023.
260. Allen U, Preiksaitis J; for AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. *Am J Transplant* 2009;9(suppl 4):S87-S96.
261. Allen U, Humar A, Limaye A, Michaels M, Miller R. Discipline of transplant infectious diseases (ID). Foreword. *Am J Transplant* 2009;9(suppl 4):S1-S2.
262. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al.; for Haemato-Oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients—BCSH and BTS guidelines. *Br J Haematol* 2010;149:675-692.
263. Bianchi E, Pascual M, Nicod M, Delaloye AB, Duchosal MA. Clinical usefulness of FDG-PET/CT scan imaging in the management of posttransplant lymphoproliferative disease. *Transplantation* 2008;85:707-712.
264. McCormack L, Hany TI, Hübner M, Petrowsky H, Mullhaupt B, Knuth A, et al. How useful is PET/CT imaging in the management of post-transplant lymphoproliferative disease after liver transplantation? *Am J Transplant* 2006;6:1731-1736.
265. Nalesnik MA. The diverse pathology of post-transplant lymphoproliferative disorders: the importance of a standardized approach. *Transpl Infect Dis* 2001;3:88-96.
266. Stevens SJ, Verschuuren EA, Verkuujlen SA, Van Den Brule AJ, Meijer CJ, Middeldorp JM. Role of Epstein-Barr virus DNA load monitoring in prevention and early detection of post-transplant lymphoproliferative disease. *Leuk Lymphoma* 2002;43:831-840.
267. Tsai DE, Douglas L, Andreadis C, Vogl DT, Arnoldi S, Kotloff R, et al. EBV PCR in the diagnosis and monitoring of posttransplant lymphoproliferative disorder: results of a two-arm prospective trial. *Am J Transplant* 2008;8:1016-1024.
268. Green M, Soltys K, Rowe DT, Webber SA, Mazareigos G. Chronic high Epstein-Barr viral load carriage in pediatric liver transplant recipients. *Pediatr Transplant* 2009;13:319-323.
269. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. II. Longitudinal study of menstrual patterns in the early postmenarcheal period, duration of bleeding episodes and menstrual cycles. World Health Organization Task Force on Adolescent Reproductive Health. *J Adolesc Health Care* 1986;7:236-244.
270. Reshef R, Vardhanabhuti S, Luskin MR, Heitjan DF, Hadjilias D, Goral S, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. *Am J Transplant* 2011;11:336-347.
271. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al.; for Haemato-Oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients—BCSH and BTS guidelines. *Br J Haematol* 2010;149:693-705.
272. Ison MG. Respiratory viral infections in transplant recipients. *Antivir Ther* 2007;12(pt B):627-638.
273. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med* 1997;102:2-9.
274. López-Medrano F, Aguado JM, Lizasoain M, Folgueira D, Juan RS, Díaz-Pedroche C, et al. Clinical implications of respiratory virus infections in solid organ transplant recipients: a prospective study. *Transplantation* 2007;84:851-856.
275. Weinstock DM, Gubareva LV, Zuccotti G. Prolonged shedding of multidrug-resistant influenza A virus in an immunocompromised patient. *N Engl J Med* 2003;348:867-868.
276. Thoma RJ, Monnig MA, Lysne PA, Ruhl DA, Pommy JA, Bogenschutz M, et al. Adolescent substance abuse: the effects of alcohol and marijuana on neuropsychological performance. *Alcohol Clin Exp Res* 2011;35:39-46.
277. Sucato GS, Murray PJ. Developmental and reproductive health issues in adolescent solid organ transplant recipients. *Semin Pediatr Surg* 2006;15:170-178.

278. Sucato GS, Murray PJ. Gynecologic health care for the adolescent solid organ transplant recipient. *Pediatr Transplant* 2005;9:346-356.
279. Dowshen N, D'Angelo L. Health care transition for youth living with HIV/AIDS. *Pediatrics* 2011;128:762-771.
280. Helgeson VS, Reynolds KA, Siminerio L, Escobar O, Becker D. Parent and adolescent distribution of responsibility for diabetes self-care: links to health outcomes. *J Pediatr Psychol* 2008;33:497-508.
281. Jabiry-Zieniewicz Z, Kaminski P, Bobrowska K, Pietrzak B, Wielgos M, Smoter P, et al. Menstrual function in female liver transplant recipients of reproductive age. *Transplant Proc* 2009;41:1735-1739.
282. Mass K, Quint EH, Punch MR, Merion RM. Gynecological and reproductive function after liver transplantation. *Transplantation* 1996;62:476-479.
283. Armenti VT, Daller JA, Constantinescu S, Silva P, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. *Clin Transpl* 2006:57-70.
284. Coscia LA, Constantinescu S, Moritz MJ, Radomski JS, Gaughan WJ, McGrory CH, Armenti VT; for National Transplantation Pregnancy Registry. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2007:29-42.
285. Fuchs KM, Coustan DR. Immunosuppressant therapy in pregnant organ transplant recipients. *Semin Perinatol* 2007;31:363-371.
286. Armenti VT, Moritz MJ, Cardonick EH, Davison JM. Immunosuppression in pregnancy: choices for infant and maternal health. *Drugs* 2002;62:2361-2375.
287. Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. *Teratology* 1995;51:45-46.
288. Klieger-Grossmann C, Chitayat D, Lavign S, Kao K, Garcia-Bournissen F, Quinn D, et al. Prenatal exposure to mycophenolate mofetil: an updated estimate. *J Obstet Gynaecol Can* 2010;32:794-797.
289. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation* 2006;82:1698-1702.
290. Surti B, Tan J, Saab S. Pregnancy and liver transplantation. *Liver Int* 2008;28:1200-1206.
291. Fredericks EM. Nonadherence and the transition to adulthood. *Liver Transpl* 2009;15(suppl 2):S63-S69.
292. Sussman S, Skara S, Ames SL. Substance abuse among adolescents. *Subst Use Misuse* 2008;43:1802-1828.
293. St Lawrence JS, Brasfield TL, Jefferson KW, Alleyne E, O'Bannon RE III, Shirley A. Cognitive-behavioral intervention to reduce African American adolescents' risk for HIV infection. *J Consult Clin Psychol* 1995;63:221-237.
294. Hassan A, Csemy L, Rappo MA, Knight JR. Adolescent substance abuse around the world: an international perspective. *Adolesc Med State Art Rev* 2009;20:915-929.
295. Millstein SG, Irwin CE Jr, Adler NE, Cohn LD, Kegeles SM, Dolcini MM. Health-risk behaviors and health concerns among young adolescents. *Pediatrics* 1992;89:422-428.
296. Patel PH, Sen B. Teen motherhood and long-term health consequences. *Matern Child Health J* 2012;16:1063-1071.
297. McDonagh JE, Kelly DA. Trans-plan-sition! Transplantation and transition. *Pediatr Transplant* 2007;11:578-581.
298. Sawyer SM, Aroni RA. Self-management in adolescents with chronic illness. What does it mean and how can it be achieved? *Med J Aust* 2005;183:405-409.
299. Peter NG, Forke CM, Ginsburg KR, Schwarz DF. Transition from pediatric to adult care: internists' perspectives. *Pediatrics* 2009;123:417-423.
300. Boyle MP, Farukhi Z, Nosky ML. Strategies for improving transition to adult cystic fibrosis care, based on patient and parent views. *Pediatr Pulmonol* 2001;32:428-436.
301. Reynolds JM, Morton MJ, Garralda ME, Postlethwaite RJ, Goh D. Psychosocial adjustment of adult survivors of a paediatric dialysis and transplant programme. *Arch Dis Child* 1993;68:104-110.
302. Gold LM, Kirkpatrick BS, Fricker FJ, Zitelli BJ. Psychosocial issues in pediatric organ transplantation: the parents' perspective. *Pediatrics* 1986;77:738-744.
303. Phillips S, Sandstrom KL. Parental attitudes toward youth work. *Youth Soc* 1990;22:160-183.
304. Annunziato RA, Parkar S, Dugan CA, Barsade S, Arnon R, Miloh T, et al. Brief report: deficits in health care management skills among adolescent and young adult liver transplant recipients transitioning to adult care settings. *J Pediatr Psychol* 2011;36:155-159.
305. Fredericks EM, Dore-Stites D, Lopez MJ, Well A, Shieck V, Freed GL, et al. Transition of pediatric liver transplant recipients to adult care: patient and parent perspectives. *Pediatr Transplant* 2011;15:414-424.
306. Creer TL, Backial M, Burns KL, Leung P, Marion RJ, Miklich DR, et al. Living with asthma. I. Genesis and development of a self-management program for childhood asthma. *J Asthma* 1988;25:335-362.
307. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. *J Pediatr Psychol* 2008;33:590-611.
308. Annunziato RA, Emre S, Shneider BL, Dugan CA, Aytaman Y, McKay MM, Shemesh E. Transitioning health care responsibility from caregivers to patient: a pilot study aiming to facilitate medication adherence during this process. *Pediatr Transplant* 2008;12:309-315.
309. Meade MA, Creer TL, Mahan JD. A self-management program for adolescents and children with renal transplantation. *J Clin Psychol Med Settings* 2003;10:165-171.
310. Cappelli M, MacDonald NE, McGrath PJ. Assessment of readiness to transfer to adult care for adolescents with cystic fibrosis. *Child Health Care* 1989;18:218-224.
311. Freyer DR, Kibrick-Lazear R. In sickness and in health: transition of cancer-related care for older adolescents and young adults. *Cancer* 2006;107(suppl):1702-1709.
312. Reid GJ, Irvine MJ, McCrindle BW, Sananes R, Ritvo PG, Siu SC, Webb GD. Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics* 2004;113(pt 1):e197-e205.
313. Watson AR. Problems and pitfalls of transition from paediatric to adult renal care. *Pediatr Nephrol* 2005;20:113-117.
314. Annunziato RA, Emre S, Shneider B, Barton C, Dugan CA, Shemesh E. Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult services. *Pediatr Transplant* 2007;11:608-614.
315. McPherson M, Weissman G, Strickland BB, van Dyck PC, Blumberg SJ, Newacheck PW. Implementing community-based systems of services for children and youths with special health care needs: how well are we doing? *Pediatrics* 2004;113(suppl):1538-1544.
316. Fredericks EM, Dore-Stites D, Well A, Magee JC, Freed GL, Shieck V, James Lopez M. Assessment of transition readiness skills and adherence in pediatric liver transplant recipients. *Pediatr Transplant* 2010;14:944-953.

-
317. Annunziato RA, Shemesh E. Tackling the spectrum of transition: what can be done in pediatric settings? *Pediatr Transplant* 2010;14:820-822.
318. Viner R. Transition from paediatric to adult care. Bridging the gaps or passing the buck? *Arch Dis Child* 1999; 81:271-275.
319. Betz CL. Facilitating the transition of adolescents with chronic conditions from pediatric to adult health care and community settings. *Issues Compr Pediatr Nurs* 1998;21:97-115.
320. Blum RW. Transition to adult health care: setting the stage. *J Adolesc Health* 1995;17:3-5.
321. Soanes C, Timmons S. Improving transition: a qualitative study examining the attitudes of young people with chronic illness transferring to adult care. *J Child Health Care* 2004;8:102-112.