Pediatric Liver Transplantation: Long-Term Follow-Up Issues

Maria Irene Bellini,[1] Augusto Lauro,[1] Vito D'Andrea,[1] Ignazio R. Marino[2]

Abstract

Pediatric liver transplant is an established life-saving procedure for children with end-stage liver diseases, achieving excellent graft and patient survival but with effects on quality of life and psychological welfare in the long-term. With the natural increase in the number of pediatric transplant patients becoming adults, it is essential to successfully plan and manage issues affecting late outcomes in the vulnerable pediatric transplant population. This study offers an overview of the long-term surgical complications, the consequences of immunosuppression (such as posttransplant diabetes, hypertension, cardiovascular disease, and renal dysfunction), and the infection and malignancy risks. Finally, because quality of life is now an inclusive measurement of patient satisfaction, guidance on how to facilitate the transition to adulthood, empowering transplant recipients, is also provided.

Key words: *Children, Long-term outcome, Quality of life, Surgical complications*

Introduction

Pediatric liver transplant (LT) has become an established life-saving procedure for children affected by end-stage liver disease, including metabolic disorders, liver cancer, and acute liver failure.[1]

From the [1]Department of Surgical Sciences, Sapienza University, Rome, Italy; and the [2]Department of Surgery, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Acknowledgements: *The authors have not received any funding or grants in support of the presented research or for the preparation of this work and have no declarations of potential conflicts of interest.*

Corresponding author: *Augusto Lauro, Department of Surgical Sciences, Sapienza University, Viale Regina Elena 324, 00161 Rome, Italy*
E-mail: *augustola@yahoo.com*

Experimental and Clinical Transplantation (2022) Suppl 3: 27-35

A recent meta-analysis[2] demonstrated that, although rates of short- and medium-term graft and patient survival (ie, from 3 months up to 1-year posttransplant) can rely on the success of modern surgery, achieving 85% and 72%, respectively, long-term transplant outcomes remain hindered by high complication rates. These complications are mainly vascular and infective issues, as well as difficulties encountered during the rehabilitation process and the overall quality of life, psychological welfare, and social insertion of the pediatric transplant recipients. As such, some aspects require a comprehensive approach that integrates diagnostic, therapeutic, and preventive care, to allow optimization of long-term outcomes.

In this review, we have provided guidance for clinical and psychosocial management of the long-term follow-up issues of pediatric LT recipients (Table 1). These issues include disease-specific issues and recurrence, bone development and growth, comorbidities (diabetes mellitus, hypertension, and cardiovascular disease), renal impairment, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections, posttransplant lymphoproliferative disease (PTLD) and incidences of other malignancies, the feasibility of immunosuppression withdrawal, community-acquired respiratory viruses and vaccination policies, adolescent issues and transition to adult care, life-saving and psychological aspects (such as noncompliance), and cognitive function and quality of life.

Surgical Aspects: Screening and Detection of Late Surgical Complications

The main challenge in the selection of an appropriate pediatric donor is graft size. Among pediatric transplant recipients, most patients reach end-stage liver disease within the first 2 years of life. Most available organs are far

10.6002/ect.PediatricSymp2022.L16

Table 1. Liver Transplantation in Children and Long-Term Follow-Up Issues

1. Screening and detection of late surgical complications
2. Disease-specific issues and recurrence
3. Growth and bone development
4. Immunosuppression complications: diabetes mellitus, hypertension and cardiovascular disease, renal impairment, CMV and EBV infections, malignancies
5. Immunosuppression withdrawal
6. Community-acquired respiratory viruses
7. Vaccinations
8. Adolescent and transition to adult care issues
9. Safe living and quality of life
10. Psychological issues: noncompliance and cognitive function

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus

too large,[3] and their transplant would imply a significant donor-recipient mismatch. To overcome this impediment, in the late 1980s and early 1990s, living donor LT from relatives[4] and split LT[5] were introduced, both aimed at reducing pediatric wait list mortality and expanding the organ donor pool.[6]

Because of the complexity of the surgery, major technical complications, including hepatic artery thrombosis (HAT), portal vein thrombosis (PVT), biliary strictures, and/or leaks, can occur with a frequency that has been calculated as being between 10%, in the case of vascular complications,[7,8] and up to 20% to 25% for biliary complications.[9,10] Generally, surgical complications are optimally investigated and treated at the transplant center.

Late hepatic artery thrombosis

In contrast to early HAT (which has a higher incidence in lower volume centers), late HAT is uncommon and could in fact represent a late detection of a progressive early HAT; it is eventually detected with ultrasonographic monitoring or by the deterioration of the patient's general health status.[11] At this stage, liver function remains mostly stable, given the presence of extensive collateralization, although occasionally transaminases could unexpectedly raise. Concomitant biliary complications, especially in the presence of the "parvus tardus" sign, could be diagnostic for late HAT.[12] In terms of treatment, thrombolysis and anticoagulation are not effective, but there is no indication for surgical intervention, if not of a possible re-LT, where medium- to long-term survival does not exceed 65% to 75%.[13] Interventional radiology remains the first-line treatment for late HAT.

Late portal vein thrombosis

The reported rate of late PVT is around 8%,[14] and it is often detected because of related symptoms of impaired graft function in addition to varices secondary to portal hypertension, ascites, and/or hepatopulmonary syndrome.[15] For patients with early PVT, re-LT is the only option; however, in late PVT, the development of collateral flow with natural shunts, generally more common in the venous circulation, can avoid graft failure and allow compensation. Portal vein anastomotic stenosis has been also described in split or reduced grafts and could be successfully treated with angioplasty.[16] Late thrombosis is usually treated with a meso-Rex shunt; if this approach is not feasible, it can be treated with a portosystemic shunt or, eventually, re-LT.[17] Thus, the treatment of portal vein complications varies and can include interventional radiology, surgery, and anticoagulation therapy, as well as an observation approach of "wait and see," which is recommended in mild to moderate cases.[18]

Inferior vena cava/hepatic vein obstruction

Vascular obstruction and stenosis of the hepatic veins/inferior vena cava are uncommon (<1%).[19] Therefore, for patients with protein-losing enteropathy, symptoms such as diarrhea, tissue swelling, ascites, and edema could appear, as shown with Budd-Chiari syndrome. Interventional radiology allows effective and safe treatment[20] of this type of complication, mostly by stenting.[21]

Late biliary strictures

Biliary leaks usually present early posttransplant, in contrast to biliary strictures, which develop later; the reported incidence is up to 25%,[22] despite notable improvements and innovations in surgical and preservation techniques. If not treated in a timely fashion, biliary strictures could become life-threatening to the vulnerable pediatric transplant recipients.[23]

Biliary strictures are often considered the Achille's heel of prolonged graft ischemia.[24,25] However, the way the biliary tract is reconstructed also plays an important role. In fact, choledochocholedochostomy rather than choledochojejunostomy is more often associated with anastomotic strictures. Symptoms like jaundice and pruritus should be considered suspicious for this late complication, particularly when biochemical alterations of cholangitis are present (ie, elevated alkaline phosphatase and gamma-glutamyltransferase values).

During magnetic resonance imaging of the liver graft, cholangiopancreatography can be helpful in diagnosing dilated ducts in challenging cases. Endoscopic[26] or percu-

taneous cholangiography often follows as a confirmation test and represents the treatment of choice.[27,28]

Incisional hernia

As previously mentioned, in view of the shortage of size-matched donors, the recipient size discrepancy is one of the most complex and challenging problems in pediatric LT.[3] Abdominal wall closure might be associated with high morbidity, thus increasing the risk of graft loss. The use of a primary mesh is per se associated with a higher incidence of incisional hernias in the long-term follow-up; although these are often reducible, a second surgical intervention via prosthetic or biological mesh is feasible and safe when direct closure cannot be achieved.[29]

Disease-Specific Issues and Recurrence

Indications for pediatric LT differ from those for adults. In children, they mostly consist of congenital or inherited defects[30] (namely, biliary atresia, familial intrahepatic cholestasis syndrome, hepatic manifestation of cystic fibrosis, citrullinemia type I, Alagille syndrome, autosomal recessive polycystic kidney disease, and Caroli-syndrome). As such, only a minority of recipients, that is, those with systemic diseases, including immunological conditions (primary sclerosing cholangitis, autoimmune hepatitis [AIH], cystic fibrosis) and oncological conditions (hepatoblastoma and hepatocarcinoma), are deemed for continuous monitoring of their underlying pathology for recurrence of the original indication and re-LT.

Primary sclerosing cholangitis

Primary sclerosing cholangitis is a rare cholestatic liver disease in children. It constitutes 2% to 3% of LTs according to the pediatric registry,[31] recurring in approximately 10% after 4 years of follow-up. In general, recipients with this condition are older at the time of transplant but present with significant growth retardation. Of note, there is a significant increase in the incidence of biliary complications.[32] The possible concomitance of inflammatory bowel disease is a worse prognostic factor, as for other organ transplants. Unfortunately, no consensus on effective therapeutic management exists.

Autoimmune hepatitis

Autoimmune hepatitis occurs in 2% to 5% of pediatric LTs,[33] who are typically female adolescents. The recurrence of AIH is affected by antirejection medication type; thus, patients are recommended to be maintained with a steroid-based regimen at a higher dose than for patients without AIH.[34] Reported graft and patient survival rates are comparable to those of the non-AIH pediatric population. The recurrence rate is variable, as well as the time from LT, with a mean recurrence at 5 years follow-up, although this may also occur as early as 1 month after LT.[35]

Cystic fibrosis

Children affected by cystic fibrosis could undergo LT alone or could have combined lung transplant and LT typically because of focal biliary cirrhosis.[36] The median age of patients on the wait list is 13.8 years,[37] and the long-term survival of this subgroup of patients is inferior compared with recipients who undergo LT for other indications.[38] A possible explanation is the poor nutritional status, with a higher incidence of pancreatitis, diabetes mellitus, and pulmonary insufficiency.[39] Therefore, death with a functioning graft might often be observed. Because cystic fibrosis is a chronic and multidisciplinary disease, a comprehensive approach is required to manage the long-term systemic complications.

Hepatoblastoma and hepatocellular carcinoma

Hepatoblastoma is the most common liver cancer in children.[40] Liver transplant is an option reserved for unresectable tumors or recurrent malignancy with or without extrahepatic disease. So far, no consensus exists on its optimal management, particularly in the presence of lung metastases.[41] Reported disease-free survival is >80% at 3 years.[42]

Hepatocellular carcinoma is mainly associated with inherited liver diseases. Although the recurrence rate is high, with a reported disease-free survival rate at 3 years post-LT of 62%,[42] LT still provides a long-term survival advantage,[43] even in the pediatric population. For long-term management of these malignancies, a multidisciplinary approach[44,45] that includes oncologists, hepatologists, and radiologists is recommended.

Growth and Bone Development

Chronic liver disease severely hinders growth plates (ie, bone length and bone strength), which can lead to short stature and osteodystrophy. Several contributors are thought to play an important role in the pathophysiology

of this multifactorial condition, both before and after LT.[46] Contributors before LT include malnutrition and malabsorption linked to deficient hepatic protein synthesis, poor mobility, and hypogonadism. Posttransplant contributors include high-dose immunosuppression, especially steroids,[47] which could delay or hinder recovery. Although the challenges in this vulnerable population remain unique, steroid withdrawal[48] and supplemental recombinant human growth hormone therapy[49] have been linked to positive outcomes in pediatric LT recipients, with a so-called "catch-up growth" phenomenon. Vitamin D supplementation is also recommended to correct the important insufficiency in children undergoing LT until levels are normal,[50] as fractures secondary to reduced bone mass and disorder of the bone architecture, particularly at the wrist, hip, and spine, can affect 20% to 40% of this population.[51]

Immunosuppression

Better patient and graft survival rates have led to an increase in years of survival in pediatric patients affected by end-stage liver failure. With longer life, patients can present with comorbid conditions linked to immunosuppression exposure, including diabetes, kidney function impairment, increased cancer, and infection risks. It is important to prevent these conditions, as they remain the main causes of death in the later period after transplant.[52,53]

Diabetes mellitus

The incidence of diabetes mellitus is approximately 10%,[54] although this condition can be reversible with modifications of immunosuppression regimens, especially by reducing tacrolimus and steroid doses. Patients may present with other glucose abnormalities; in fact, incidence of impaired glucose tolerance that can reach up to 30%.[55] Management and treatment of this condition should be tailored to the patient (patients >5 years of age and Hispanic patients are generally at higher risk), concomitant medical conditions (immune disease risk of recurrence), and overall liver function. Yearly screening with fasting glucose test is recommended.[56]

Hypertension and cardiovascular disease

Hypertension and cardiovascular disease are main causes of death in the long term after transplant. Similar to adult transplant recipients, pediatric patients can have cardiovascular diseases[57] (namely, cerebral hemorrhage, heart attack, and arterial thrombosis) that are directly related to onset of hypertension.[8] Systemic hypertension has been reported to occur in about 80% of children undergoing LT and is often severe.[59] The use of antihypertensive agents, as well as reduction/withdrawal of calcineurin inhibitors, is associated with benefits.

Renal impairment

Renal dysfunction is a frequent complication among pediatric LT recipients, particularly as a consequence of hypertension. The related parenchymal damage is represented by proteinuria onset, especially as a direct calcineurin inhibitor nephrotoxicity.[60] Perioperative factors can also affect long-term renal function, for example, as acute kidney injury predicts mortality in all LT recipients.[61]

Cytomegalovirus and Epstein-Barr virus infections

These infections are common complications in pediatric LT recipients. The CMV serology of the donor-recipient pair is the main risk factor; therefore, antiviral prophylaxis according to risk stratification or instead preemptive therapy is recommended (Table 2).[62] Furthermore, graft rejection is often a consequence of CMV infection; EBV coinfection or reactivation can have detrimental consequences, potentially leading to PTLD.[63] Assessment of the CMV infection viral load should be routinely performed when there is clinical suspicion. Oral/venous valganciclovir administration and modulation of the treatment duration are generally effective.[64]

Posttransplant lymphoproliferative disease and other malignancies

There is a well-known association between primary EBV infection and subsequent development of PTLD.[63] The pathogenesis is multifactorial: impaired immune surveillance of tumor cells due to immunosuppression decreases antiviral immune activity, oncogenic effect of EBV, and derangement of molecular signaling/DNA repair mechanisms by direct effects of immunosuppressive agents.[65]

Table 2. Antiviral Prophylaxis Recommendations for Cytomegalovirus

1. Diagnosis: CMV pp65 antigenemia
2. Prophylaxis is not recommended for CMV donor-negative/recipient-negative children
3. Prophylaxis is recommended (intravenous ganciclovir) for all CMV donor-positive/recipient-negative children
4. If ganciclovir-resistant: second-line treatment (foscarnet and cidofovir)

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus

Patients with EBV-associated PTLD present with fever, exudative tonsillitis, and organomegaly. Atypical lymphocytosis is shown in laboratory exams, and the diagnosis is confirmed by histopathology.

The treatment of PTLD is not yet standardized, but it is generally accepted to reduce immunosuppression and commence chemotherapy. Surgical intervention consistent with debulking or resection of the involved part of intestine is also recommended.

Most cancer-related deaths in the pediatric LT population are due to PTLD. However, because cancer risk is significantly higher among immunosuppressed young adults with a previous transplant, general screening, in particular for skin cancer, is highly recommended.[66]

Immunosuppression withdrawal

Immunosuppression weaning or withdrawal in stable pediatric and adult LT recipients has been reported to be successful,[67] and several protocols are underway to expand the use of regulatory T cells and identify biomarkers for immunotolerance.[68] Liver transplant recipients with long-term survival are systematically over-immunosuppressed; consequently, drug weaning, whether incomplete or complete, is an important management strategy, providing it is done slowly and under careful physician surveillance.[67]

For patients being withdrawn from immunosuppression therapy, follow-up liver biopsies are recommended to identify early chronic rejection. In fact, liver graft fibrosis after pediatric LT has been reported to occur in >90% of cases,[55] including in cases of mild fibrosis, although in the latter, the clinical significance remains to be ascertained.

Community-Acquired Respiratory Viruses

Community-acquired lower respiratory infections are the most common cause of intensive care unit admission. Therefore, medical providers must consider these events as risks in immunosuppressed transplant recipients.[69] Importantly, viruses once thought to be rare and clinically unimportant, notably rhinovirus and coronaviruses, are now being recognized as significant and common; thus, prevention measures, such as vaccination, are warranted.[70]

Vaccinations

Children should receive a full complement of routine vaccines before transplant,[71] including those against varicella, measles, pneumococcal diseases, influenza viruses, hepatitis A and B, and travel-related infections. Live attenuated vaccines are still under debate after LT.[72] However, these vaccinations, as in the case of the varicella virus, have been shown to be possibly safe and effective also after transplant.[73]

Adolescent Issues and Transition to Adult Care

Transition to adolescence, and later to adulthood, could be challenging in terms of monitoring long-term liver function and possible complications, especially as patients reach for independent education, occupation, and general life opportunities.[74]

Proper education of patients is recommended, particularly to make the population aware of any risk behaviors. Immunosuppressed patients are more at risk of infections, particularly sexually transmitted infections or those linked to drug abuse. In this context, the role of physicians is essential, both to monitor that patients continue to use their posttransplant medications and to monitor that patients adhere to their routine control visits.[75] Screening to identify nonadherence risk is of upmost importance. In fact, disagreements are frequent among parents and children about freedoms or responsibilities, particularly on the patient health status during teenage years.

For girls, menstrual problems are frequent in patients affected by chronic liver disease. Although fertility may be reduced, pregnancy is possible by adjustment of the immunosuppressive therapy.[76]

Safe Living and Quality of Life

Transplant recipients should be advised to minimize post-LT risks (including those involving food, water, animals, and travel) as they aim to conduct a "normal" life. Quality of life generally improves significantly in LT recipients during the first year. Later on, the improvement reaches a plateau, with the possibility to decline if other events occur, such as those linked to the physical condition or alternative psychological parameters (depression, anxiety, sexual function) or sociodemographic elements (professional state, sex, marital state).[77] For this reason, a comprehensive approach is needed for these patients that considers psychological, neurological, and familiar conditions to prevent noncompliance.

Psychological Issues

Children affected by end-stage liver disease face imminent risk of death; thus, LT represents a life-saving operation, as does a lifelong treatment, heavily relying on daily medications and ongoing monitoring of graft function to prevent and treat possible complications, arising not only from the surgical procedure but also from the immunosuppression itself.[75]

The psychological toll from the entire transplant experience can leave emotional scars that persist in the long term, particularly in grown children who feel "different" from their peers. The concept of survivorship,[78] which originally was applied to patients with cancer, acknowledges the ongoing spectrum of care and support that transplant patients require for issues related to noncompliance and cognitive function.

Noncompliance

Young adult LT recipients have the highest nonadherence rates of all age groups regarding immunosuppressive medication and posttransplant care.[79] Psychosocial predictors of adherence are not evidence-based; given the lack of universal protocols, a joint pediatric and adult care team approach, in addition to routine check of immunosuppressant blood levels, is strongly recommended, with the aim of reducing any conflict in these patients' lives.

Cognitive function and quality of life

Pediatric LT recipients often demonstrate deficits in intellectual, academic, and language capabilities, in particular showing delayed motor and speech development.[80] School performance tends to correlate with the level of maternal primary education degree.81 Borderline personality disorder and hearing loss are common; thus, long-term neurological follow-up is useful to support children so that they can succeed in their careers and improve their quality of life.

Conclusions

The excellent results shown in pediatric LT recipients has led to a growing attention toward quality of life, with screening for prevention and treatment of long-term complications. These are heavily dependent on a prompt referral of the child to the transplant center, where available, because a multidisciplinary management approach is often required.

In parallel to the growing-up process, it is also essential that the children are encouraged to develop self-management of their condition posttransplant, taking responsibility for medication and clinical appointments, to actively contribute to the improvement of their own health status.

References

1. Kelly DA, Bucuvalas JC, Alonso EM, et al. 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. *Liver Transpl.* 2013;19(8):798-825. doi:10.1002/lt.23697
2. Hou Y, Wang X, Yang H, Zhong S. Survival and complication of liver transplantation in infants: a systematic review and meta-analysis. *Front Pediatr.* 2021;9:628771. doi:10.3389/fped.2021.628771
3. Akdur A, Kirnap M, Ozcay F, et al. Large-for-size liver transplant: a single-center experience. *Exp Clin Transplant.* 2015;13 Suppl 1:108-110.
4. Raia S, Nery JR, Mies S. Liver transplantation from live donors. *Lancet*. 1989;2(8661):497. doi:10.1016/s0140-6736(89)92101-6
5. Bismuth H, Morino M, Castaing D, et al. Emergency orthotopic liver transplantation in two patients using one donor liver. *Br J Surg.* 1989;76(7):722-724. doi:10.1002/bjs.1800760723
6. Dalzell C, Vargas PA, Soltys K, et al. Living donor liver transplantation vs. split liver transplantation using left lateral segment grafts in pediatric recipients: an analysis of the UNOS database. *Transpl Int.* 2022;36:10437. doi:10.3389/ti.2022.10437
7. Arnon R, Annunziato R, Miloh T, et al. Liver transplantation in children weighing 5 kg or less: analysis of the UNOS database. *Pediatr Transplant.* 2011;15(6):650-658. doi:10.1111/j.1399-3046.2011.01549.x
8. D'Alessandro AM, Knechtle SJ, Chin LT, et al. Liver transplantation in pediatric patients: twenty years of experience at the University of Wisconsin. *Pediatr Transplant.* 2007;11(6):661-670. doi:10.1111/j.1399-3046.2007.00737.x
9. Sanada Y, Katano T, Hirata Y, et al. Biliary complications following pediatric living donor liver transplantation: risk factors, treatments, and prognosis. *Transplantation.* 2019;103(9):1863-1870. doi:10.1097/TP.0000000000002572
10. Luthold SC, Kaseje N, Jannot AS, et al. Risk factors for early and late biliary complications in pediatric liver transplantation. *Pediatr Transplant.* 2014;18(8):822-830. doi:10.1111/petr.12363
11. Bellini MI, Fresilli D, Lauro A, et al. Liver transplant imaging prior to and during the COVID-19 pandemic. *Biomed Res Int.* 2022;2022:7768383. doi:10.1155/2022/7768383
12. Yazigi NA. Long term outcomes after pediatric liver transplantation. *Pediatr Gastroenterol Hepatol Nutr.* 2013;16(4):207-218. doi:10.5223/pghn.2013.16.4.207
13. Herden U, Ganschow R, Grabhorn E, Briem-Richter A, Nashan B, Fischer L. Outcome of liver re-transplantation in children--impact and special analysis of early re-transplantation. *Pediatr Transplant.* 2014;18(4):377-384. doi:10.1111/petr.12264

14. Stevens JP, Xiang Y, Leong T, Naik K, Gupta N. Portal vein complications and outcomes following pediatric liver transplant: data from the society of pediatric liver transplantation. *Liver Transpl*. 2022. doi:10.1002/lt.26412
15. Gad EH, Abdelsamee MA, Kamel Y. Hepatic arterial and portal venous complications after adult and pediatric living donor liver transplantation, risk factors, management and outcome (A retrospective cohort study). *Ann Med Surg (Lond)*. 2016;8:28-39. doi:10.1016/j.amsu.2016.04.021
16. Naik KB, Hawkins CM, Gill AE, Gupta NA. Clinical efficacy of percutaneous transhepatic portal vein angioplasty for late-onset portal vein stenosis in pediatric liver transplant patients. *Transplantation*. 2018;102(6):e282-e287. doi:10.1097/TP.0000000000002138
17. Flynn E, Huang JY, Hardikar W, Herd L, Hodgson A, Monagle P. Antithrombotic management and thrombosis rates in children post-liver transplantation: A case series and literature review. *Pediatr Transplant*. 2019;23(4):e13420. doi:10.1111/petr.13420
18. Cheng YF, Ou HY, Yu CY, et al. Section 8. Management of portal venous complications in pediatric living donor liver transplantation. *Transplantation*. 2014;97 Suppl 8:S32-S34. doi:10.1097/01.tp.0000446272.05687.ce
19. Grimaldi C, Spada M, Maggiore G. Liver transplantation in children: an overview of organ allocation and surgical management. *Curr Pediatr Rev*. 2021;17(4):245-252. doi:10.2174/1573396317666210604111538
20. Zhang ZY, Jin L, Chen G, et al. Balloon dilatation for treatment of hepatic venous outflow obstruction following pediatric liver transplantation. *World J Gastroenterol*. 2017;23(46):8227-8234. doi:10.3748/wjg.v23.i46.8227
21. Uller W, Knoppke B, Schreyer AG, et al. Interventional radiological treatment of perihepatic vascular stenosis or occlusion in pediatric patients after liver transplantation. *Cardiovasc Intervent Radiol*. 2013;36(6):1562-1571. doi:10.1007/s00270-013-0595-1
22. Sanada Y, Katano T, Hirata I, et al. Interventional radiology treatment for vascular and biliary complications following pediatric living donor liver transplantation - a retrospective study. *Transpl Int*. 2018;31(11):1216-1222. doi:10.1111/tri.13285
23. Laurence JM, Sapisochin G, DeAngelis M, et al. Biliary complications in pediatric liver transplantation: Incidence and management over a decade. *Liver Transpl*. 2015;21(8):1082-1090. doi:10.1002/lt.24180
24. Bellini MI, Nozdrin M, Yiu J, Papalois V. Machine perfusion for abdominal organ preservation: a systematic review of kidney and liver human grafts. *J Clin Med*. 2019;8(8):1221. doi:10.3390/jcm8081221
25. Bellini MI, Yiu J, Nozdrin M, Papalois V. The effect of preservation temperature on liver, kidney, and pancreas tissue ATP in animal and preclinical human models. *J Clin Med*. 2019;8(9):1421. doi:10.3390/jcm8091421
26. Dechene A, Kodde C, Kathemann S, et al. Endoscopic treatment of pediatric post-transplant biliary complications is safe and effective. *Dig Endosc*. 2015;27(4):505-511. doi:10.1111/den.12420
27. Vaccari S, Minghetti M, Lauro A, et al. Destiny for rendezvous: is cholecysto/choledocholithiasis better treated with dual- or single-step procedures? *Dig Dis Sci*. 2022;67(4):1116-1127. doi:10.1007/s10620-022-07450-7
28. Sanada Y, Sakuma Y, Onishi Y, et al. Hepatolithiasis after living donor liver transplantation in pediatric patients: mechanism, diagnosis, treatment, and prognosis. *Transpl Int*. 2022;35:10220. doi:10.3389/ti.2022.10220
29. Gul-Klein S, Dziodzio T, Martin F, et al. Outcome after pediatric liver transplantation for staged abdominal wall closure with use of biological mesh-Study with long-term follow-up. *Pediatr Transplant*. 2020;24(3):e13683. doi:10.1111/petr.13683
30. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2014;59(1):112-131. doi:10.1097/MPG.0000000000000431
31. Miloh T, Anand R, Yin W, et al. Pediatric liver transplantation for primary sclerosing cholangitis. *Liver Transpl*. 2011;17(8):925-933. doi:10.1002/lt.22320
32. Heinemann M, Liwinski T, Adam R, et al. Long-term outcome after living donor liver transplantation compared to donation after brain death in autoimmune liver diseases: Experience from the European Liver Transplant Registry. *Am J Transplant*. 2022;22(2):626-633. doi:10.1111/ajt.16864
33. Martin SR, Alvarez F, Anand R, Song C, Yin W, Group SR. Outcomes in children who underwent transplantation for autoimmune hepatitis. *Liver Transpl*. 2011;17(4):393-401. doi:10.1002/lt.22244
34. Montano-Loza AJ, Ronca V, Ebadi M, et al. Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation. *J Hepatol*. 2022:S0168-8278(22)00067-8. doi:10.1016/j.jhep.2022.01.022
35. Chai PF, Lee WS, Brown RM, et al. Childhood autoimmune liver disease: indications and outcome of liver transplantation. *J Pediatr Gastroenterol Nutr*. 2010;50(3):295-302. doi:10.1097/MPG.0b013e3181bf0ef7
36. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. *Hepatology*. 1999;30(5):1151-1158. doi:10.1002/hep.510300527
37. Cheng K, Rosenthal P, Roberts JP, Perito ER. Liver transplant in children and adults with cystic fibrosis: Impact of growth failure and nutritional status. *Am J Transplant*. 2022;22(1):177-186. doi:10.1111/ajt.16791
38. Black SM, Woodley FW, Tumin D, et al. Cystic fibrosis associated with worse survival after liver transplantation. *Dig Dis Sci*. 2016;61(4):1178-1185. doi:10.1007/s10620-015-3968-2
39. Hayes D, Jr., Patel AV, Black SM, et al. Influence of diabetes on survival in patients with cystic fibrosis before and after lung transplantation. *J Thorac Cardiovasc Surg*. 2015;150(3):707-713.e2. doi:10.1016/j.jtcvs.2015.06.041
40. Czauderna P, Lopez-Terrada D, Hiyama E, Haberle B, Malogolowkin MH, Meyers RL. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. *Curr Opin Pediatr*. 2014;26(1):19-28. doi:10.1097/MOP.0000000000000046

41. Meyers RL, Maibach R, Hiyama E, et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. *Lancet Oncol.* 2017;18(1):122-131. doi:10.1016/S1470-2045(16)30598-8
42. Boster JM, Superina R, Mazariegos GV, et al. Predictors of survival following liver transplantation for pediatric hepatoblastoma and hepatocellular carcinoma: experience from the Society of Pediatric Liver Transplantation (SPLIT). *Am J Transplant.* 2022;10.1111/ajt.16945. doi:10.1111/ajt.16945
43. Ozcay F, Balci Sezer O, Sarialioglu F, et al. Seventeen years of pediatric liver transplantation experience for cirrhosis and hepatocellular carcinoma. *Exp Clin Transplant.* 2022. doi:10.6002/ect.2021.0469
44. Balli HT, Aikimbaev K, Guney IB, et al. Trans-arterial radioembolization with yttrium-90 of unresectable and systemic chemotherapy resistant hepatoblastoma in three toddlers. *Cardiovasc Intervent Radiol.* 2022;45(3):344-348. doi:10.1007/s00270-021-03026-6
45. Manzia TM, Gravante G, Di Paolo D, et al. Liver transplantation for the treatment of nodular regenerative hyperplasia. *Dig Liver Dis.* 2011;43(12):929-934. doi:10.1016/j.dld.2011.04.004
46. Weber DR. Bone health in childhood chronic disease. *Endocrinol Metab Clin North Am.* 2020;49(4):637-650. doi:10.1016/j.ecl.2020.07.002
47. Ng VL, Alonso EM, Bucuvalas JC, et al. 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(5):820-826.e3. doi:10.1016/j.jpeds.2011.10.038
48. Miloh T, Barton A, Wheeler J, et al. Immunosuppression in pediatric liver transplant recipients: Unique aspects. *Liver Transpl.* 2017;23(2):244-256. doi:10.1002/lt.24677
49. Sotos JF, Tokar NJ. Growth hormone significantly increases the adult height of children with idiopathic short stature: comparison of subgroups and benefit. *Int J Pediatr Endocrinol.* 2014;2014(1):15. doi:10.1186/1687-9856-2014-15
50. Yuksel M, Demir B, Mizikoglu O, Akyildiz M, Baygul A, Arikan C. Course of vitamin D levels before and after liver transplantation in pediatric patients. *Pediatr Transplant.* 2021;25(7):e14049. doi:10.1111/petr.14049
51. Hogler 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(3):313-321. doi:10.1097/MPG.0b013e31823e9412
52. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. *World J Gastroenterol.* 2009;15(6):648-674. doi:10.3748/wjg.15.648
53. Cheng K, Feng S, Bucuvalas JC, Levitsky J, Perito ER. Not everything that counts can be counted: Tracking long-term outcomes in pediatric liver transplant recipients. *Am J Transplant.* 2022;22(4):1182-1190. doi:10.1111/ajt.16932
54. Regelmann MO, Goldis M, Arnon R. New-onset diabetes mellitus after pediatric liver transplantation. *Pediatr Transplant.* 2015;19(5):452-459. doi:10.1111/petr.12523
55. Perito ER, Lustig RH, Rosenthal P. Prediabetes in pediatric recipients of liver transplant: mechanism and risk factors. *J Pediatr.* 2017;182:223-231.e3. doi:10.1016/j.jpeds.2016.11.070
56. Grundman JB, Wolfsdorf JI, Marks BE. Post-transplantation diabetes mellitus in pediatric patients. *Horm Res Paediatr.* 2020;93(9-10):510-518. doi:10.1159/000514988
57. Bellini MI, Paoletti F, Herbert PE. Obesity and bariatric intervention in patients with chronic renal disease. *J Int Med Res.* 2019;47(6):2326-2341. doi:10.1177/0300060519843755
58. Arikanoglu E, Tabel Y, Selimoglu A. Evaluation of arterial hypertension by ambulatory blood pressure monitoring in pediatric liver transplant recipients. *Blood Press Monit.* 2022;27(1):39-42. doi:10.1097/MBP.0000000000000563
59. Lawless S, Ellis D, Thompson A, Cook DR, Esquivel C, Starzl T. Mechanisms of hypertension during and after orthotopic liver transplantation in children. *J Pediatr.* 1989;115(3):372-379. doi:10.1016/s0022-3476(89)80834-0
60. Bellini MI, Koutroutsos K, Nananpragasam H, Deurloo E, Galliford J, Herbert PE. Obesity affects graft function but not graft loss in kidney transplant recipients. *J Int Med Res.* 2020;48(1):300060519895139. doi:10.1177/0300060519895139
61. Teo VXY, Heng RRY, Tay PWL, et al. A meta-analysis on the prevalence of chronic kidney disease in liver transplant candidates and its associated risk factors and outcomes. *Transpl Int.* 2021;34(12):2515-2523. doi:10.1111/tri.14158
62. Onpoaree N, Sanpavat A, Sintusek P. Cytomegalovirus infection in liver-transplanted children. *World J Hepatol.* 2022;14(2):338-353. doi:10.4254/wjh.v14.i2.338
63. Ramos-Gonzalez G, Crum R, Allain A, et al. Presentation and outcomes of post-transplant lymphoproliferative disorder at a single institution pediatric transplant center. *Pediatr Transplant.* 2022;e14268. doi:10.1111/petr.14268
64. Bedel AN, Hemmelgarn TS, Kohli R. Retrospective review of the incidence of cytomegalovirus infection and disease after liver transplantation in pediatric patients: comparison of prophylactic oral ganciclovir and oral valganciclovir. *Liver Transpl.* 2012;18(3):347-354. doi:10.1002/lt.22471
65. Fararjeh FA, Mahmood S, Tachtatzis P, et al. A retrospective analysis of post-transplant lymphoproliferative disorder following liver transplantation. *Eur J Haematol.* 2018;100(1):98-103. doi:10.1111/ejh.12988
66. Aberg F, Isoniemi H, Pukkala E, et al. Cancer after liver transplantation in children and young adults: a population-based study from 4 Nordic countries. *Liver Transpl.* 2018;24(9):1252-1259. doi:10.1002/lt.25305
67. Mazariegos GV, Reyes J, Marino IR, et al. Weaning of immunosuppression in liver transplant recipients. *Transplantation.* 1997;63(2):243-249. doi:10.1097/00007890-199701270-00012
68. Du X, Chang S, Guo W, Zhang S, Chen ZK. Progress in liver transplant tolerance and tolerance-inducing cellular therapies. *Front Immunol.* 2020;11:1326. doi:10.3389/fimmu.2020.01326
69. Dominguez F, Blodget E. Community-acquired respiratory viruses. *Curr Opin Organ Transplant.* 2019;24(4):511-514. doi:10.1097/MOT.0000000000000667
70. Ison MG, Hirsch HH. Community-acquired respiratory viruses in transplant patients: diversity, impact, unmet clinical needs. *Clin Microbiol Rev.* 2019;32(4):e00042-19. doi:10.1128/CMR.00042-19

71. Burroughs M, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. *Clin Infect Dis*. 2000;30(6):857-869. doi:10.1086/313823
72. Kemme S, Kohut TJ, Boster JM, Diamond T, Rand EB, Feldman AG. Live Vaccines in pediatric liver transplant recipients: "to give or not to give". *Clin Liver Dis (Hoboken)*. 2021;18(4):204-210. doi:10.1002/cld.1123
73. Laue T, Oms E, Ohlendorf J, Baumann U. Long-term varicella zoster virus immunity in paediatric liver transplant patients can be achieved by booster vaccinations-a single-centre, retrospective, observational analysis. *Children (Basel)*. 2022;9(2):130. doi:10.3390/children9020130
74. Burra P. The adolescent and liver transplantation. *J Hepatol*. 2012;56(3):714-722. doi:10.1016/j.jhep.2011.07.032
75. Duncan-Park S, Danziger-Isakov L, Armstrong B, et al. Posttraumatic stress and medication adherence in pediatric transplant recipients. *Am J Transplant*. 2022;22(3):937-946. doi:10.1111/ajt.16896
76. Westbrook RH, Yeoman AD, Agarwal K, et al. Outcomes of pregnancy following liver transplantation: The King's College Hospital experience. *Liver Transpl*. 2015;21(9):1153-1159. doi:10.1002/lt.24182
77. Onghena L, Develtere W, Poppe C, et al. Quality of life after liver transplantation: State of the art. *World J Hepatol*. 2016;8(18):749-756. doi:10.4254/wjh.v8.i18.749
78. Lai JC, Ufere NN, Bucuvalas JC. Liver transplant survivorship. *Liver Transpl*. 2020;26(8):1030-1033. doi:10.1002/lt.25792
79. Killian MO, Schuman DL, Mayersohn GS, Triplett KN. Psychosocial predictors of medication non-adherence in pediatric organ transplantation: A systematic review. *Pediatr Transplant*. 2018;22(4):e13188. doi:10.1111/petr.13188
80. Krull K, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. *Pediatr Transplant*. 2003;7(2):111-118. doi:10.1034/j.1399-3046.2003.00026.x
81. Goldschmidt I, van Dick R, Jacobi C, Pfister ED, Baumann U. Identification of impaired executive functioning after pediatric liver transplantation using two short and easily applicable tests: cognitive functioning module PedsQL and children's color trail test. *Children (Basel)*. 2021;8(7):571. doi:10.3390/children8070571