



Medical management of children after liver transplantation

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Purpose of review

Successful outcomes in patient, graft survival, and quality of life depend on the prevention, early detection, and treatment of possible complications. The aim of the study was to highlight the common outcomes focusing on the unique features in children. Medical follow-up of children after liver transplantation includes monitoring of surgical complications: biliary and vascular, rejection, infections, posttransplant lymphoproliferative disease, other malignancies, recurrent disease, graft function, hypertension, diabetes, renal failure, among other conditions. The goal is to maintain normal graft function on minimal immunosuppression to avoid medication-induced side-effects.

Recent findings

Recent findings include the importance of meticulous follow-up of Epstein-Barr virus and Cytomegalic virus viral load, leading to early diagnosis and improved prognosis, increased prevalence of renal toxicity, cognitive dysfunction, autoimmune, atopic and eosinophilic disease, oral hygiene and chronic hepatitis, and fibrosis of allografts.

Summary

Caring for children after liver transplantation is extremely rewarding; however, careful attention must be paid to a variety of systems with understanding of the distinctiveness of pediatrics to assure optimal outcomes.

Keywords

children, liver transplantation, medical management, pediatric

INTRODUCTION

Liver transplantation is the standard treatment for children with end-stage liver disease, whether acute or chronic. Patient and graft survival have improved over time and exceed 90% (1 year) and 85% (5 year) patient survival, because of improved surgical techniques, immunosuppressive therapy, infectious monitoring, and close follow-up. Children have expected greater lifetime exposure to immunosuppression than adults with cumulative toxicity, and some liver transplantation recipients have survived longer than 20 years.

Medical management of children after liver transplantation changes over time. In the early post-operative time, both surgical and infection complications are more common. Long-term complications include immunosuppression toxicity, recurrent disease, and malignancy among late surgical and infection problems. Children are followed by a multi-disciplinary team including transplant surgery, hepatology, intensive care physicians, and a spectrum of other subspecialists and after discharge involving the primary care physician. Follow-up

visits decrease in frequency over time; however, patients require lifelong surveillance with medical history, review of systems and medications, physical exam including weight, height, and blood pressure, routine blood tests, and ongoing education. In cases of suspected graft dysfunction, other tests should be done including special biochemical tests and assuring adherence, infectious screening, autoantibodies, imaging, endoscopy, and biopsies, as clinically indicated. There is a fine balance of tailoring immunosuppression to each patient. The goal is to minimize immunosuppression-related risk of infections, malignancy, and side-effects, while maintaining optimal graft function. Some of the conditions may present decades after liver transplantation, like the high risk

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KEY POINTS

- The medical management of children after liver transplantation is complex and involves multiple systems. Successful outcomes in patient, graft survival, and quality of life depend on the prevention, early detection, and treatment of possible complications.
- Children have expected greater lifetime exposure to immunosuppression than adults with cumulative toxicity.
- Some complications are more common in children than adults: vascular, infectious, PTLD, and nonadherence. Some complications such as cardiovascular and recurrent disease are less frequent in children.

of cardiovascular disease, and prevention of these complications remains the cornerstone.

In this review, we will summarize the key points in the long-term medical management of children after liver transplantation. Growth, nutrition, quality of life, and transition of care will be discussed in a different chapter.

INFECTIONS

Infections are the most common implicated cause of mortality after liver transplantation and have been categorized into early (first 30 days), intermediate (1–6 months), and late (>6 months). Approximately, a third of children develop bacterial and 8% fungal infection within the first month after liver transplantation [1]. Young age and technical variant graft increase the risk. Long-term bacterial infections are mostly community acquired. There is a higher risk of invasive pneumococcal disease and immunizations should be confirmed [2]. Enteric bacteria from blood culture should raise the suspicion of a biliary obstruction. Patients on high-dose immunosuppression should receive prophylactic antibiotics before invasive interventional radiology or dental procedures. Recurrent episodes of cholangitis may require prophylactic antibiotics.

Cytomegalic virus (CMV) infection incidence has been as high as 40% and could present primary infection, reactivation of a latent infection, or superinfection with a different stain [1]. Preventive strategies and antiviral medications reduce the incidence and severity of CMV disease. Many patients may have viremia and remain asymptomatic; however, some may have nonspecific viral symptoms, fever, leukopenia, atypical lymphocytosis, and thrombocytopenia. Tissue invasive CMV disease is manifested by visceral organ involvement (diarrhea, elevated transaminases, and pneumonia). Mortality rates are as high as 19% and are higher with primary

infection, whereas reactivation and superinfection usually present with a milder disease. Patients treated with high doses of immunosuppression (especially antilymphocyte products) are at increased risk of severe disease. CMV infection increases the risk of rejection, fungal infection, and is associated with poorer patient and graft survival.

Prevention of CMV disease could either be by universal prophylaxis with gancyclovir or valgancyclovir, serial monitoring of CMV viral load, or by a hybrid approach. The risk of CMV infection is highest in young patients, donor positive or recipient negative, cadaveric donors [3] and is lowest in donor positive and recipient negative recipients. There are no consensus recommendations for CMV prophylaxis, but most centers start with intravenous gancyclovir and transition to oral valgancyclovir for 90–180 days after liver transplantation. Oral valgancyclovir is well tolerated with minimal side-effects (nephrotoxicity and myelosuppression) [4]. There are different algorithms to calculate the oral dose in pediatrics [5[¶]]. CMV viral load is monitored more frequently in the first year.

The diagnosis of CMV disease is confirmed by measuring the viral load in peripheral blood, CMV pp65 antigenemia assay, histology, and cultures (some patients may shed CMV asymptomatically). The threshold at which to start therapy varies among the centers. Early preemptive treatment with intravenous gancyclovir may prevent multisystem injury. Oral valgancyclovir is recommended in adult liver transplantation recipients with mild-to-moderate CMV disease; however, there is not enough data in children to recommend oral valgancyclovir as the initial therapy, but it can be used to complete CMV therapy in patients who responded to gancyclovir. Some centers add CMV immunoglobulin for severe cases. Therapy should be continued until CMV viral load is undetectable in two subsequent blood draws at least 1 week apart to decrease the risk of recurrence. Resistance to gancyclovir may develop in patients with persistent viremia despite at least 14 days of therapy. Resistance mutations will be sought and empiric therapy with foscarnet, cidofovir, and CMV immunoglobulin may be considered with reduced or discontinued immunosuppression.

Epstein-Barr virus (EBV) infection commonly occurs in the first year after liver transplantation and could reflect primary disease or reactivation, and is an important cause of morbidity and mortality especially in pediatric liver transplantation recipients. Most young children are EBV seronegative at the time of transplant and during primary exposure to EBV; significant immunosuppression (especially antilymphocyte antibody) increased the risk of symptomatic disease and posttransplant increases

lymphoproliferative disease (PTLD). In posttransplant pediatric patients, primary EBV infection occurs in up to 67%, whereas reactivation of latently infected lymphocytes may occur in up to 48% [6]. EBV infection may be asymptomatic. Clinical symptoms present in 22% [3]: nonspecific viral illness, infectious mononucleosis (fever, hepatosplenomegaly, lymphadenopathy, pharyngitis, and atypical lymphocytosis), organ involvement (hepatitis, pneumonitis, and gastroenteritis), hematological manifestations (leukopenia, thrombocytopenia, hemolytic anemia, and hemophagocytosis), and PTLD. Serial monitoring of EBV viral load has reduced the risk of PTLD to less than 3% and leads to earlier diagnosis of milder PTLD phenotype and improved clinical outcomes [7,8[■]]. EBV monitoring is recommended more frequently in the early postliver transplantation phase and annually thereafter.

Risk factors for PTLD include young age at transplant (less than 2), primary EBV infection, and at least one episode of 2 years rejection. Once patients seroconvert, or have increased EBV viral load, immunosuppression reduction is recommended. Initial work up includes an EBV viral load; imaging of head to pelvis and biopsy of potential disease sites (graft, intestines, bone marrow, and lymph node) remain the gold standard of diagnosis and staging. Adenotonsillar PTLD is often underestimated and can present with obstructive sleep apnea. PET-CT may be useful for occult disease. Histologically, PTLD is classified as early lesions, polymorphic PTLD, monomorphic PTLD, and other rare forms such as Hodgkin disease-like lesions. Treatment of PTLD is driven by the histologic stage and presence of B cells. Immunosuppression is withheld and therapeutic options include the use of anti CD20 monoclonal antibodies (rituximab) and low-dose chemotherapy with cyclophosphamide and prednisone. Chemotherapy may be escalated once frank lymphoma is diagnosed; EBV-negative PTLD has worse prognosis.

Pneumocystis jirovecii and other opportunistic infections are rare and more common in significant immunosuppression. Trimethoprim and sulfamethoxazole prophylaxis is recommended 6 months after liver transplantation and during and after treatment of rejection.

Most common respiratory tract infection after liver transplantation is caused by rhinovirus [9[■]]. Certain viral infections in children after liver transplantation may have a more severe and prolonged course [influenza, parainfluenza, and respiratory syncytial virus (RSV)] mostly early postliver transplantation and should be treated with caution, including medication prophylaxis for influenza (neuraminidase inhibitor) and RSV (aerosolized ribavirin). Recipients may have prolonged viral shedding. However,

most children with low immunosuppressant can experience common viral infection without complications. Children with direct contact with varicella should receive immunoprophylaxis with antibodies and acyclovir with the first symptom of infection.

Ideally, patients should be immunized before transplantation. Live-attenuated vaccines should be avoided in immunosuppressed children. However, there are centers that immunize children who have normal graft function on a low immunosuppressant dose for Varicella and are on mumps, measles and rubella (MMR). Annual influenza vaccination should be recommended for patients and household members. Patients below age 2 should be considered for RSV vaccine. Human papilloma virus (HPV) vaccine is encouraged to reduce the risk of cervical carcinoma and has been shown to be effective in liver transplantation recipients [10]. Immunizations are well tolerated and effective after transplant [11].

NEPHROTOXICITY

Renal injury is commonly associated with calcineurin inhibitor (CNI) toxicity. Serum creatinine cannot be used independently to estimate glomerular filtration rate (GFR) and the revised Schwartz formula can be used to estimate clearance [12[■]]. Close to 30% of children are hypertensive 10 years after liver transplantation [13] and approximately 15% have GFR less than 90 ml/min at 5 years after liver transplantation [14]. A third of patients after liver transplantation progress to stage 3 chronic kidney disease by 15 years [15]. Risk factors for chronic renal disease include a calculated GFR less than 90 ml/min/m² at transplant or during the first month after liver transplantation, preliver transplantation hepatorenal syndrome, older age at transplant, cyclosporine-based immunosuppression, primary indication for transplant (Alagille and metabolic disease), use of other hepatotoxic drugs (chemotherapy and cystic fibrosis), proteinuria, and height z score greater than 2 SD 12 months after liver transplantation. Gene polymorphisms related to CNI pharmacodynamics may play an important role in patient's susceptibility to renal injury. Membranous and membranoproliferative glomerulonephritis associated with chronic hepatitis B and C is rare. GFR may progressively decline with limited reversibility, even after discontinuation of CNI. Acquired cystic kidney disease may develop after liver transplantation.

Strategies to reduce the incidence of renal dysfunction include the use of postoperative antiinterleukin 2, mycophenolate mofetil, starting CNI late (POD 4) and keeping CNI levels low, maintaining adequate intravascular volume, and avoiding nephrotoxic drugs. Diagnosing hypertension may be

challenging in young children, and repeat measurement and home 24-h monitoring may be required. Treating hypertension is extremely important to decrease further progression of renal disease and the risk of cardiovascular disease, which is high after liver transplantation. The drug of choice to treat hypertension is an angiotensin-converting enzyme inhibitor and angiotensin 2 receptor blockers, as they slow GFR decline, improve blood pressure, and decrease proteinuria. In some patients, conversion of CNI to an mammalian target of rapamycin immunosuppressant may reverse the renal damage [16].

DIABETES MELLITUS

Postliver transplantation diabetes mellitus has been associated with tacrolimus and steroids, and its incidence in children is lower than adults, however, higher than in renal transplant recipients [17[■]]. Glucose intolerance and diabetes mellitus are most common in the first month after liver transplantation at a mean duration of 75 months. Most patients will require a transient course of insulin. The cumulative incidence of newly diagnosed diabetes mellitus after liver transplantation is 5.9, 8.3, and 11.2% at 1, 3, and 5 years, respectively, after liver transplantation [18]. Risk factors include older age at liver transplantation, African-American and Hispanic race, early use of corticosteroids and tacrolimus, primary diagnosis of cystic fibrosis, primary sclerosing cholangitis (PSC) and fulminant hepatitis [17[■]], and underlying kidney dysfunction. Occasionally, diabetes mellitus presents at times of stress and steroid exposure (treating rejection) [19[■]]. Patients should be routinely screened with fasting glucose and diabetes should be treated. Untreated diabetes will exacerbate posttransplant metabolic syndrome, and may affect graft function and lead to multiorgan failure.

Elevated triglycerides were found in 16–50% of children after liver transplantation, and its relationship with BMI was variable. Dyslipidemia is more common in cyclosporine and steroid-based immunosuppression [20]. Metabolic syndrome was found in 14% of pediatric liver transplant recipients and was associated with moderate liver steatosis in protocol liver biopsies [21[■]]. Patients and families should be educated to prevent and treat metabolic syndrome with healthy diet and regular physical activity.

NEUROLOGIC COMPLICATIONS

Up to 10% of children will have a seizure after liver transplantation, mostly associated with posterior

reversible encephalopathy syndrome (PRES) and are more common in the first few weeks of CNI exposure. Seizures are associated with high CNI levels and low magnesium. Short-term antiepileptic medication may be required; however, chronic seizure disorder is very rare. Migraine and tremors are mostly CNI dose related [22]. Liver transplantation improves hepatic encephalopathy but is frequently followed by new-onset cognitive and academic dysfunction [23[■]]. Pretransplant nutritional status and operative complications predicted intellectual outcome [24[■]].

HEMATOLOGIC DISEASE

Close to a quarter of children after liver transplantation are found to have chronic anemia. Risk factors included gastrointestinal bleeding, leukopenia, cyclosporine and steroid-based immunosuppression, calculated glomerular filtration rate less than 90 ml/min/1.73 m², and use of antihypertensive medications [25]. Thrombocytopenia may develop as a consequence of portal hypertension, bone marrow suppression from medication, and infection. Autoimmune hemolytic disease, immune thrombocytopenic purpura, and Evan's syndrome have a higher incidence after transplant [26].

EOSINOPHILIC GASTROINTESTINAL DISEASE AND ATOPY

Atopy occurs in approximately 14% of pediatric liver transplantation recipients, with manifestations including food allergy, eczema, allergic rhinitis, and asthma [27]. In children with gastrointestinal symptoms who underwent endoscopy, more than 70% were found to have eosinophilic infiltrate [28], which may be related to the use of CNI. Overall, food allergies are more common in liver transplantation recipient than renal transplant recipients with increased risk in young age at transplant, young donor age, and use of tacrolimus [29[■]]. Most children outgrow these allergies.

ORAL HEALTH

In an Italian study, the prevalence of caries, poor periodontal status, bleeding on probing, and dental enamel defects was higher in children after liver transplantation than healthy controls [30[■]]. Polypoid lesions over the dorsum of the tongue, lip swelling, angular cheilitis, fissures of the lips, mucosal tags, cobblestone appearance, and fissures of the tongue were described in young liver transplantation recipients on tacrolimus [31[■]]. Routine dental follow-up should be recommended with consideration of

prophylactic antibiotics for invasive procedures in significant immunosuppressed children.

CHRONIC HEPATITIS, FIBROSIS, AND DE NOVO AUTOIMMUNE HEPATITIS

Protocol liver biopsies in asymptomatic children with normal transaminases have found chronic hepatitis in 22, 43, and 65% and fibrosis in 52, 81, and 91% at 1, 5, and 10 years after liver transplantation, respectively. Cirrhosis was found in 15% by 10 years [32]. Deceased versus living donor grafts, prolonged ischemia time, lymphoproliferative disease, and biliary and vascular complications were found to be the risk factors for graft fibrosis [33[■]]. In fact, only 5% had normal histology, suggesting poor correlation between serum liver enzymes and histology. The cause of the chronic hepatitis and fibrosis remains unclear. The clinical significance and whether these histologic changes should lead to immunosuppressant modification are yet uncertain. Most centers do not perform surveillance biopsies and noninvasive measures are being investigated. Acoustic radiation force impulse (ARFI) [34[■]] or transient elastography [35[■]] was found to be effective in diagnosis of significant graft fibrosis.

De novo autoimmune hepatitis (AIH) is defined as characteristic allograft dysfunction, autoantibody (ANA, ant smooth muscle Ab, and hypergammaglobulinemia), and histological features of AIH in patients transplanted for nonautoimmune disease. It occurs in 5–10% of children after liver transplantation [36] and is thought to be due to overimmunosuppression and dysfunction of Tregs. De novo AIH responds to steroids or azathioprine therapy.

MALIGNANCY

Skin cancer is more prevalent after solid-organ transplant, though remains rare. Sunscreens, protective clothing, and screening of skin lesions should be encouraged. Other recommendations include gynecological screening for cancer and immunization for HPV.

RECURRENT DISEASE

The most common indication for liver transplantation in children is biliary atresia which does not recur in the graft. Hepatitis B and C are indications for liver transplantation in children are rare indications.

PSC may recur in 10% of children at a mean of 18 months after liver transplantation [37]. Distinguishing recurrent PSC from chronic rejection

and biliary tract complications may be challenging. Colonoscopy screening for colon cancer should be instituted.

Patients with AIH are treated with a higher degree of immunosuppression, and recurrent AIH was reported in 39% of children at a mean time of 33 months after liver transplantation [38]. AIH may recur as early as 1 month after liver transplantation and diagnosis is made by characteristic autoimmune antibodies with histologic confirmation. AIH before liver transplantation places children at higher risk for other autoimmune disease after liver transplantation.

Children transplanted for hepatoblastoma have a 66% 10-year survival rate with most deaths (54%) because of metastatic or recurrent disease. Radiologic surveillance and screening with alpha fetoprotein is recommended. Posttransplant immunosuppression regimen should be lowered.

Progressive familial intrahepatic cholestasis type 2 (PFIC 2) is a deficiency in bile salt export pump. Jaundice and pruritus may present up to 12 years after liver transplantation because of the development of antibilie salt export pump antibody as a result of development.

Nonalcoholic steatohepatitis (NASH) is a rare indication for liver transplantation in children and is expected to become the leading cause for liver transplantation in adults within the next decade because of the obesity epidemic. As more adolescents develop cirrhosis because of NASH, recurrence in graft is a major concern.

CONCLUSION

The medical management of children after liver transplantation involves multiple aspects aimed at achieving optimal patient and graft health. The follow-up includes the collaboration of the patient, caregiver, transplant physician, and primary care provider among numerous other specialists. It involves lifelong visits with meticulous history, physical exam and routine laboratory tests addressing well being, graft function and review of the systems mentioned above to prevent, diagnose, and treat the various complications associated with liver transplantation and some more particular in children.

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Conflicts of interest

There are no conflicts of interest.

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