Chapter 19

Liver Transplantation

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Introduction

Liver transplantation (LT) is used successfully both in children and adults with acute liver failure or in patients with complications of decompensated chronic liver disease in the hopes to extend survival with excellent quality of life [1, 2]. In the past decade, liver transplant has also been reported in a small number of patients with dyskeratosis congenita (DC)- and Telomere Biology Disorder (TBD)-associated severe liver disease. Although these reports are few, they do highlight the potential benefit of liver transplant in selected patients with DC/TBD and related hepatic complications [3-9].

Liver Transplant History

The first liver transplant was performed in a child in the 1960s by Dr. Thomas Starzl at the University of Colorado [10, 11]. Since then, substantial scientific progress in liver transplantation involving surgical techniques, postoperative management and immunosuppression treatments have significantly improved transplant patient and graft survival. Over 8000 liver transplants are performed yearly in the United States alone with survival rates at 5 years post-transplant ranging from 70-90% in children and adults [1, 2, 10-12].

Indications for Liver Transplant

There are several reasons that a patient may be referred for liver transplant consideration [1, 2, 10, 11]. In some patients, LT may be indicated due to primary, non-metastatic liver tumors or liver-centered metabolic diseases which are ineligible or refractory to medical or surgical intervention. In others, LT is considered when there is acute decompensation or chronic liver failure with significant liver dysfunction evidenced by abnormal serum albumin, bilirubin and INR/PT, or hyperammonemia, leading to hepatic encephalopathy. LT may also be indicated secondary to complications of chronic liver disease such as intractable ascites, variceal bleeding, and other liver-associated complications of portal hypertension like hepatopulmonary or portopulmonary hypertension. Additionally, pediatric patients may also be referred for LT if chronic liver disease causes poor weight gain/ growth failure. Timing for LT referral depends significantly on the clinical situation. Referral for may be emergent, urgent, or anticipatory.

DC/TBD and Liver Transplant

LT has been thus far reported in a small number of pediatric and adult patients with DC/TBD (Table) [3-9]. Progressive dyspnea and hypoxia suggestive of hepatopulmonary

syndrome were present in all patients and represented one of the main indications to LT. Decompensated cirrhosis with ascites and varices was also present in 3 of the 5 described patients. In these reports, the length of longitudinal follow-up periods varied from a few months to up to 10 years in one case. At the time the cases were published, all patients were reportedly alive with resolution of the complications of their DC/TBD-associated liver disease.

Liver Transplant Evaluation

In general, a formal liver transplant evaluation at an experienced transplant center aims to determine if a liver transplant will be useful at that time, exclude potential contraindications to transplant, and educate the patient and caregivers about the transplantation process, benefits, and risks [1, 2]. In order to accomplish these goals, a LT evaluation involves the following:

- Confirmation of diagnosis and extent/severity of the liver disease and its complications.
- Determination of the relative urgency of the liver transplantation.
- Identification and assessment of systemic comorbidities and suggestion/coordination of management plans to optimize patient's status prior to potential liver transplantation.

A liver transplant evaluation consists of a large multidisciplinary team who uses their expertise to tailor the liver transplant evaluation/investigation to the specific needs of the patient. This team typically involves many specialists including a transplant surgeon, transplant hepatologist, transplant coordinator, infectious disease specialist, social worker, dietician, transplant pharmacist, transplant anesthesiologist, psychologist/psychiatrist, and transplant financial coordinator. Depending on the patient's clinical situation, the LT evaluation may also require consultation with additional specialists such as a cardiologist, pulmonologist, nephrologist, hematologist, genetic/metabolic specialist, dentist, etc.

To confirm the current extent and severity of the primary disease and the patient's multiple organ systems, the LT evaluation will involve laboratory and diagnostic studies and review of medical, surgical and pathology reports. If additional assessment is required through additional testing or new subspecialty consultation, this will be ordered as part of the transplant evaluation. This extensive evaluation will allow the liver transplant team to have a clear assessment of the patient's liver, cardiopulmonary, renal, immunological, and nutritional status.

The psychosocial assessment is another fundamental aspect of the transplant evaluation, as lifelong care is a prerogative of successful liver transplant. In this sense, both psychological and logistical barriers to medical adherence need to be identified and addressed prior to transplant to avoid a negative impact on outcomes. In adult patients, a continued destructive behavior resulting from drug and alcohol addiction may represent a contraindication to transplantation. For these reasons, psychologists, social workers, and psychiatrists are part of the liver transplant team, ensuring that social and psychological supports systems need to be in place for patients and their family.

In the LT evaluation process, it is also critically important to identify any contraindications for transplant, conditions such as extrahepatic malignancy or systemic infection, which make the patient high risk for transplant at that time, likely to develop potential complications after LT, or where a patient's overall condition is thought unlikely to benefit from a LT.

At the end of the liver transplant evaluation, each transplant center's multidisciplinary team comes to a consensus decision regarding the indication, severity and urgency for liver transplant. Each transplant center makes a team determination if the patient is likely to benefit from LT at that time, and, if so, will list the patient for transplant if the patient/family agrees. This determination of transplant listing eligibility is center-dependent and may differ between transplant centers. Patients and their families

may repeat the entire transplant evaluation process at different transplant centers, with different determinations of eligibility.

For patients with DC/TBD and pulmonary symptoms, cardiopulmonary assessment through cardiology and pulmonary consultation and specific imaging (e.g., computer tomography, bubble contrast echocardiography and/or albumin lung perfusion scan) is particularly important to evaluate the degree of pulmonary complications like pulmonary fibrosis, arteriovenous malformations, and hepatopulmonary syndrome (HPS). The distinction between these entities is fundamental as HPS may be reversible with liver transplant while pulmonary fibrosis is not and can impact a patients' eligibility for liver transplant as well as complicate the post-transplant course. LT is appropriate for the treatment of HPS in children with cirrhotic liver disease. For patients with noncirrhotic liver diseases, as in some patients with DC/TBD, consideration of alternate non-transplant therapies, such as occlusion of portosystemic shunt by surgical or interventional radiology approaches, should be explored. LT may be indicated in those patients who are not eligible for these interventions.

Types of Liver Transplant

Transplant livers may come from a deceased donor (whole liver or partial segment of a liver), or, a living donor who donates a segment of their liver (Figure) [1, 2, 10-12]. Given that organ scarcity remains the major limiting factor in liver transplantation, the advent of technical innovations have made it possible to safely transplant only segments of liver from deceased and living donors. This has further expanded the pool of available organs, significantly reducing the wait list mortality in children.

- **Whole liver:** A full liver is transplanted from a size matched deceased donor. Donor-to-recipient size mismatch is a limitation to this type of transplant.

- **Reduced size graft:** A whole liver is reduced in its size to match the recipient.

- **Split liver graft:** A whole liver is naturally divided into two sections. Depending on the size of the recipient, a section of the liver can be obtained from an adult deceased or living donor. In infant/toddler pediatric patients, a portion of the left lobe (the left lateral segment) of a deceased or living donor may be considered for transplantation.

- **Living-donor liver transplant (LDLT):** Either the left/ left lateral segment or right lobe of the liver can be used for transplantation, depending upon anatomic considerations and the size of both the donor and recipient liver. Both donor and recipient livers grow and regenerate within weeks to months.

Studies comparing these different types of LT have found a higher rate of perioperative complications with this last technique [1]. Long-term patient survival, however, seems comparable with that of deceased whole liver transplantation [1, 10]. If a patient is considered appropriate for listing for LT, the appropriateness of whether they can receive a living donor depends on the existing anatomy of the recipient patient, the organ size/associated tissues the patient requires, and the surgical risk of a living donor transplant to the recipient and donor. For LDLT to be appropriate, three things must be strongly considered:

1. The likelihood of the recipient's long-term survival must be high.
2. The risk of mortality to the donor must be low.
3. The donor must be well informed of all the potential risks of undergoing the donation and still agree to undergo the surgery of their own free will.

Thus, LDLT is typically considered when deceased donor LT is not an option or a deceased donor LT organ has not become available. The determination if living donor LT is appropriate for a patient is transplant center-dependent and can differ between centers. In addition, living-donor transplantation is not performed at every LT center, and its availability should be discussed at the time of initial evaluation.
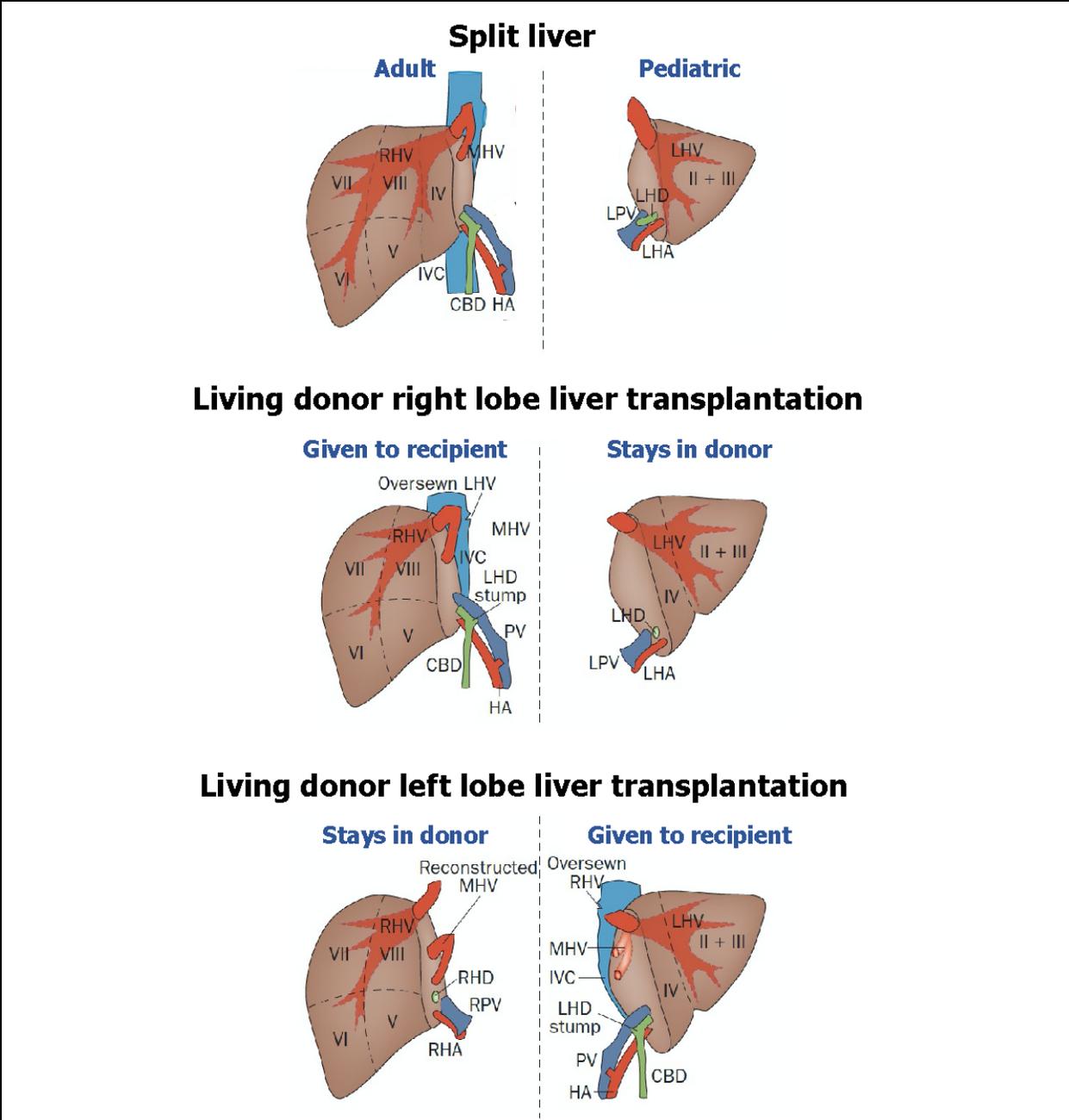
Split liver

Adult

Pediatric

Living donor right lobe liver transplantation

Given to recipient

Stays in donor

Living donor left lobe liver transplantation

Stays in donor

Given to recipient

Figure 1. Types of Liver Graft.
IVC: inferior vena cava; HA: hepatic artery; PV: portal vein; CBD: common bile duct; LHA: left hepatic artery; LPV: left portal vein; LHD: left hepatic duct; LHV: left hepatic vein; RHA: right hepatic artery; RPV: right portal vein; RHD: right hepatic duct; RHV: right hepatic vein; MHV: middle hepatic vein.

* Figure modified from Zarrinpar A and Busuttil RW, *Nat Rev Gastroenterol Hepatol*. 2013 [12].

Deceased and Living Donor Selection

When an organ from a deceased donor becomes available, the transplant team carefully reviews the donor's clinical and biochemical characteristics to assess the suitability of the transplant with regards to the specific potential recipient [1, 2, 10, 11, 14]. The donor's blood type, age, infectious status, intensive care hospitalization time, hemodynamic stability, and estimate of liver fatty infiltration are some of the many important factors which are considered, as they have been found to significantly impact transplant outcomes. In addition, particular attention is also paid to the size of the donor liver given that an adequate parenchymal volume is fundamental for the success of the transplant.

When a living donor is considered, the primary focus of the donor evaluation is the donor's safety. For this reason, the team evaluating the donor should be different from the recipient's team in order to avoid bias and conflicts of interest. Living-donor LT programs may require donors to be healthy adults, typically between 18 to 60 years of age with compatible blood type, normal liver tests, and appropriate medical and surgical past medical histories. Exact donor acceptance criteria may vary slightly between centers. If these criteria are met, then the potential donor may meet with the transplant surgeon and transplant hepatologist to discuss the surgical and medical details of LDLT. If the potential donor voluntarily expresses continued interest in being considered for live-donor transplantation, the donor candidate will then be referred for a complete medical and psychosocial assessment. This will entail several clinic visits, additional blood work, and abdominal imaging, which allows better characterization of the donor liver anatomy, and procedures like a liver biopsy. Additional testing to assess the potential donor's multiple organ systems may also be required to assess the donor's safety to undergo the operation. The typical evaluation process usually takes between 2 and 4 weeks. Once all the information has been gathered, the donor's evaluation team determines the donor's safety and suitability to undergo a LDLT from a medical, surgical, and psychological standpoint.

Although parents and siblings of patients can volunteer to be candidates for a LDLT, if they are carriers of a genetic variant for the recipient's liver condition, such as potentially in families of patients with DC/TBD, other donor options may be necessary due to the concern for disease recurrence.

Deceased Donor Organ Allocation in the USA

Since 2002, deceased donor liver allocation in the US requires centers to calculate scores which measure the patient's illness severity and the risk of death within three months on the liver waiting list [1, 2]. The Model for End-Stage Liver Disease (MELD) is used to prioritize patients 12 years of age and older for organ allocation in the United States. This formula includes the total serum bilirubin, creatinine, INR, and serum sodium. For patients younger than 12 years, the Pediatric End Stage Liver Disease (PELD) score is used instead, which utilizes lab values (total serum bilirubin, INR, and albumin) and presence of growth failure (height and weight) and an indicator of whether the patient is less than one year of age. A higher score indicates a worse severity of illness and higher risk of death.

Exception points can be requested when the MELD and PELD score are thought to not accurately reflect the patient's condition. Request for exceptions points is submitted to the national review board with supporting clinical documentation. The anonymous board reviews the documentation and decides if the request for exception points will be granted. If granted, the patient is listed using the exception point score. For patients with DC/TBD and indications for transplant like hepatocellular carcinoma and HPS in which the patient's liver function is not significantly impaired, exception points can be particularly useful.

Liver Transplantation Timeline

The preoperative management while awaiting LT is crucial to optimize the patient's clinical condition [1, 2]. Patients can require admission in the hospital during this time or can be managed at home however with close multidisciplinary follow up. While listed, the patient will continue to have outpatient follow-up appointments with the primary hepatology team and the transplant team and continue to get required lab testing and physical exams to renew transplant listing information.

If a suitable deceased-donor organ becomes available or the patient has been scheduled for living-donor liver transplant, the patient is admitted to the hospital prior to the operation. Depending on the recipient's needs during the transplant, the LT operation can take up to 12 hours, after which the patients will be transferred to the intensive care unit (ICU) for close post-operative surveillance and management. Generally, after a few days, most patients can be transferred to a general hospital unit. The duration of the transplant hospitalization may vary considerably depending on the degree of systemic medical conditions of the recipient.

Complications of Liver Transplantation

Complications can occur both early in the postoperative period as well as months and years after a transplant [15-19]. Important transplant complications are briefly reviewed below:

- **Graft primary non function:** This is the most common reason for early retransplantation (a second or subsequent LT). Graft primary non function is characterized by early graft failure which can occur intraoperatively or in the immediate postoperative hours. It is thought to be multifactorial with several factors playing a role such as donor advanced age, hemodynamic instability, sub-optimal donors, cold ischemia time, and reperfusion damage.

- **Vascular complications:** Hepatic artery thrombosis (HAT) is the most common vascular complication and affects pediatric LT recipients 3-4 times more frequently than the adult LT recipients. When HAT occurs early in the post-transplant period, it can lead to ischemic graft damage and may require re-transplantation. Later complications of HAT can lead to biliary ductal complications such as intrahepatic biliomas and biliary strictures. Less commonly, portal vein thrombosis can occur. This is an acute presentation in which patients may show signs of graft failure while later occurring portal vein thrombosis may manifest as signs of portal hypertension with decreased platelets count, splenomegaly, or gastrointestinal bleeding.

- **Biliary complications** remain a common source of morbidity for LT recipients with an estimated incidence of 10-15% in deceased donor transplants and as high as 15-30% in adults and pediatric LDLT or split-liver transplant recipients. Bile duct complications can also include bile leaks, which tend to occur in the early postoperative period, and biliary strictures, which are more common and occur in later stages of transplant. As mentioned above, HAT is one of the main risk factors for bile duct complications post-transplant.

- **Hemorrhage:** When present, it typically manifests within the first 48 hours post-transplantation. It is most commonly treated conservatively but in 10-15% of adult and pediatric recipients might require a return to the operating room for surgical exploration to determine the source of bleeding.

- **Rejection:** If immunosuppressive medications are not given, the recipient's native immune system inevitably recognizes the transplanted liver as a foreign body, triggering an immune response aimed at destroying the graft itself. The process of the recipient's native immune system causing inflammation and injury to the transplanted organ is called rejection. In order to minimize the likelihood of this process, immunosuppressive medications are given with the transplant operation and maintained in the post-transplant period. Determining a patient's adequate

immunosuppression is a continual balance between the risk of rejection and the risk of infection from over-immunosuppression.

Rejection can be:

- o **Hyperacute,** occurring within minutes to hours from the LT. It is usually antibody and complement mediated and generally irreversible.

- o **Acute**, occurring within weeks to months after transplant, but it can also happen at any time after transplant. It is T-cell lymphocyte mediated and generally responds to currently available immune suppressants. Patients present with elevated liver enzymes without symptoms, or it is sometimes associated with non-specific symptoms like general malaise or abdominal discomfort. A liver biopsy confirms the diagnosis of acute cellular rejection. The treatment involves measures to increase the patient's level of immunosuppression, which usually involves a short course of high dose IV steroids and increase in baseline immunosuppression level. Switching immune suppressive agent or adding a second drug may also be considered.

- o **Chronic**. It is also T-cell mediated but occurs over months to years after LT. This process involves long-term graft dysfunction and liver fibrosis and manifests as progressive cholestasis and most often does not respond to immunosuppressive medications, causing late graft loss.

- **Infections**: Because of the continuous immunosuppression, which weakens the immune system, LT recipients are at risk for opportunistic infections including viruses (especially cytomegalovirus, Epstein-Barr virus, and herpes zoster and simplex), bacteria (such as *mycobacteria*, *listeria*, and *Nocardia*), and fungi (including *Pneumocystis jirovecii*, *Aspergillus*, and *Cryptococcus*). Moreover, prolonged hospitalization and invasive procedures may lead to nosocomial (hospital acquired) bacterial infection, such as pneumonia, cholangitis,

bacteremia, or urinary tract infection. Strategies to limit the infectious risk of these patients include prophylactic use of antimicrobials in selected cases, optimization of immunization status when possible, and avoidance of high-risk exposures. Transplant teams constantly strive to find a careful balance between the risk of underimmunosuppression, and therefore rejection, with the risk of overimmunosuppression, and therefore infections and medications side effects.

- **Post-Transplant Lymphoproliferative Disorder (PTLD):** Typically involves uncontrolled B cell proliferation and includes a heterogeneous group of disorders ranging from benign lymphatic hyperplasia to lymphoma. Studies have shown that the degree of T-cell immunosuppression and recipient EBV serologic status represent the main risk factors of PTLD. Specifically, EBV-negative recipients of EBV-positive donor organs are at highest risk of developing PTLD. It is more common in pediatric patients likely because a higher percentage of children are EBV-seronegative prior to transplantation. PTLD treatment consists of reduction or complete withdrawal of immunosuppressive medications, administration of antiviral drugs, and in the most severe cases, administration of chemotherapy or irradiation, and monoclonal antibody therapy such as rituximab.

Long-Term Management of Liver Transplant Recipients

All LT recipients require lifelong monitoring and management by liver transplant teams in order to ensure (1) graft health, (2) adequate immunosuppressive treatment with minimization of its long-term toxicities and related complications, (3) surveillance of potential recurrence of primary liver disease and, in general, to (4) promote health after LT [15, 16]. Routine monitoring should be comprehensive with scheduled clinic visits and blood work which occurs as frequently as weekly in the immediate post-transplant period and later can be progressively spaced out in stable patients. Imaging and serial histological evaluations are also part of the graft surveillance.

Immunosuppression

Immunosuppression is one of the cardinal determinants of a successful liver transplantation with the goal to prevent rejection and therefore loss of the graft [15, 16]. The management of immunosuppression is tailored based on the patient and their comorbidities, the indication for liver transplant, and the time from transplant. Generally, the priority in the early pre-transplant period is avoiding rejection, while later on limiting long-term immunosuppression side effects and complications becomes more relevant.

In the immediate transplant period, patients usually receive a combination of high dose immune suppressive medications to minimize the body's reaction to the new, foreign liver. Although there is no universally accepted immune suppressive regimen for liver transplant recipients and combinations of different drugs are possible, calcineurin inhibitors are often the cornerstone of long-term immunosuppression maintenance. At the time of transplant, some patients might also receive a so-called induction therapy with basiliximab, a monoclonal antibody against interleukin-2 receptors, which inhibits T-lymphocyte proliferation in addition to steroids and calcineurin inhibitors. Systemic steroids can often be discontinued within weeks to month after transplant. Calcineurin inhibitors are a class of medication which works by inhibiting T-lymphocytes and includes cyclosporine and tacrolimus. Cyclosporine, first used in the 1980s, allowed for tremendous progress in transplant surgery when it was found to dramatically decrease graft rejection. Over the years cyclosporine has been largely replaced by tacrolimus which is more effective in preventing rejection, and in comparison to cyclosporine less likely to be associated with side effects such as gingival hypertrophy, hirsutism, nephrotoxicity, neurotoxicity, and hypertension. Both cyclosporine and tacrolimus are most commonly dosed twice a day and can be taken by mouth as liquid formulation or capsule. A patient's immunosuppression is monitored with serial blood draws to assess the drug trough level and subsequently adjust its dose to maintain the desired trough within a recommended target range. A patient's particular immunosuppression drug target range varies according to co-morbidities, risk of infection and timing from

transplant. In general, the level of desired of immune suppression is highest immediately after transplant and gradually decreases over time. Drug level monitoring occurs more frequently in the immediate post-transplant period and can then be spaced out farther apart when patients are more stable.

Mycophenolate mofetil, azathioprine and sirolimus are additional immunosuppressive drugs that can be used in selected patients and may depend on the following reasons: primary indication for liver transplant, rejection history, severe calcineurin inhibitor toxicity, and need of steroid withdrawal facilitation.

All of these immunosuppressive medications need monitoring for signs of side effects. Side effects are more commonly encountered when higher doses are required soon after transplant but must also be monitored long-term for signs of chronic toxicity. Immunosuppressive medications have been associated with increased risk of renal (kidney) dysfunction, hypertension (high blood pressure), hyperlipidemia (increased lipids), diabetes, obesity, and metabolic syndrome. Patients are regularly screened with physical exams, routine blood pressure measurements, and blood work, including creatinine, glucose, and lipid panel to assess renal function and to evaluate presence of diabetes and cardiovascular disease. Moreover, immunosuppressive medications predispose patients to infectious complications and malignancies, both of which require maintaining a high level of suspicion at all times in transplant recipients. Transplant teams work continually to find the best immunosuppression regimen for each patient's specific needs which carefully balances the risks and benefits of immunosuppression.

In the majority of cases, immune suppression is required lifelong to ensure graft survival. In a select minority of liver transplant recipients, the immune system may develop tolerance to the graft, and immunosuppression may possibly be discontinued many years after transplant.

Conclusion

Liver transplant is an option for a variety of liver disorders and has been done successfully in both children and adults [1, 2, 10, 11]. The decision for undergoing liver transplantation requires an in-depth and comprehensive evaluation by a multidisciplinary liver transplant team. Consideration to the short- and long-term risks of the liver transplant surgery and immunosuppression must be made in relation to the patient's specific condition. Liver disease is reported in about 7% of DC/TBD individuals, and there is no specific curative treatment thus far [3-9]. There have only been a small number of case reports published of patients with DC/TBD and severe liver disease who underwent LT. All of these DC/TBD patients presented with progressive dyspnea and hypoxia concerning for hepatopulmonary syndrome alongside, in some cases, decompensated chronic liver disease. At this time, there is no consensus recommendation as to the role of LT in DC/TBD-associated severe liver disease, given the small number of patients described and the lack of long-term post-transplant data. It can, however, be cautiously noted that this small series of patients suggests acceptable early LT outcomes in selected patients.

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Table. Reported cases of liver transplant in patients with DC/TBD

Patient [reference number]	Gender	Genetic variant	Age at DC/TBD diagnosis	BM involvement	Age at liver disease diagnosis	Liver disease	Age at LT	Type of LT	Additional information	Post LT-follow up
1 [4]	M	TERT p.Lys1050Asn	35 y/o	Normal complete blood counts	N/A	HPS, Splenomegaly, NRH	40 y/o	N/A	Normal lung parenchyma at time of liver disease diagnosis	Hypoxia and dyspnea resolved within 3 months after LT. Developed IPF 12 years after LT.
2 [4]	M	RTEL1 p.Arg1010X	49 y/o	Normocellular BM	N/A	HPS, splenomegaly, intractable ascites, NRH	53 y/o	N/A	Mild lung fibrosis at time of liver disease diagnosis	Hypoxia and dyspnea resolved within 3 months post LT. Within 18 months pt again O2 dependent.
3 [5]	M	Not reported	27 y/o	BMF during teenage years, transfusion dependent, HCT not pursuable given severe liver disease	Approx. 20 y/o	Decompensated cirrhosis, HPS	29 y/o	Whole liver	At time of HPS diagnosis pt was also found to have evidence of fibrotic lung disease and was also considered for lung transplant	Pulmonary function improved significantly with minimal oxygen needs; pt removed from lung transplant list. No further transfusion requirements. Follow up duration N/A.

Patient [reference number]	Gender	Genetic variant	Age at DC/TBD diagnosis	BM involvement	Age at liver disease diagnosis	Liver disease	Age at LT	Type of LT	Additional information	Post LT-follow up
4 [7]	M	Unknown, clinical diagnosis	24 y/o	BMF requiring multiple transfusion. HCT at age 25 y/o	31 y/o	Decompensated cirrhosis, HPS	34 y/o	LDLT (left hemiliver)	Chest CT with ILD involving b/l lower lobes and apices	22 months post LT, no supplemental O2 requirements, normal PFTs. Chest CT with stable ILD.
5 [8]	M	TINF2 c.845G>A	5 y/o	BMF requiring HCT at 28 months of age	5 y/o	HPS, splenomegaly. No histologic finding of cirrhosis.	5 y/o	Combined lung and LT	Rapid worsening of hypoxemia requiring ECMO. No evidence of IPF. Chest CT suggestive of PAVM not suitable for embolization	11 months post LT normal liver function and no hypoxemia

Abbreviations: F:female; M: male; y/o: years old; BM: bone marrow; BMF: bone marrow failure; HCT: hematopoietic cell transplant; LT: liver transplant; HPS: hepatopulmonary syndrome; NRH: nodular regenerative hyperplasia; IPF: idiopathic pulmonary fibrosis; IS: immunosuppression.