Present and Future of Liver Transplantation

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This is to acknowledge that Jorge Marrero, M.D. has disclosed that he does not have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Marrero will not be discussing off-label uses in his presentation.

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Dr. Marrero is a Professor in the division of Digestive and Liver. He is the medical director of liver transplantation. His clinical practice is on liver transplantation- pre- and post-transplant management. He has an active research program in early detection of hepatocellular carcinoma in patients with chronic liver disease. He has mentored several investigators that have gone on to secure federal funding.

Purpose and Overview:

- Purpose and Overview. The purpose is to provide the audience with the current state of liver transplantation pertaining to the conditions the lead to transplant and the outcomes. In addition, to provide the audience a view of the future of liver transplantation

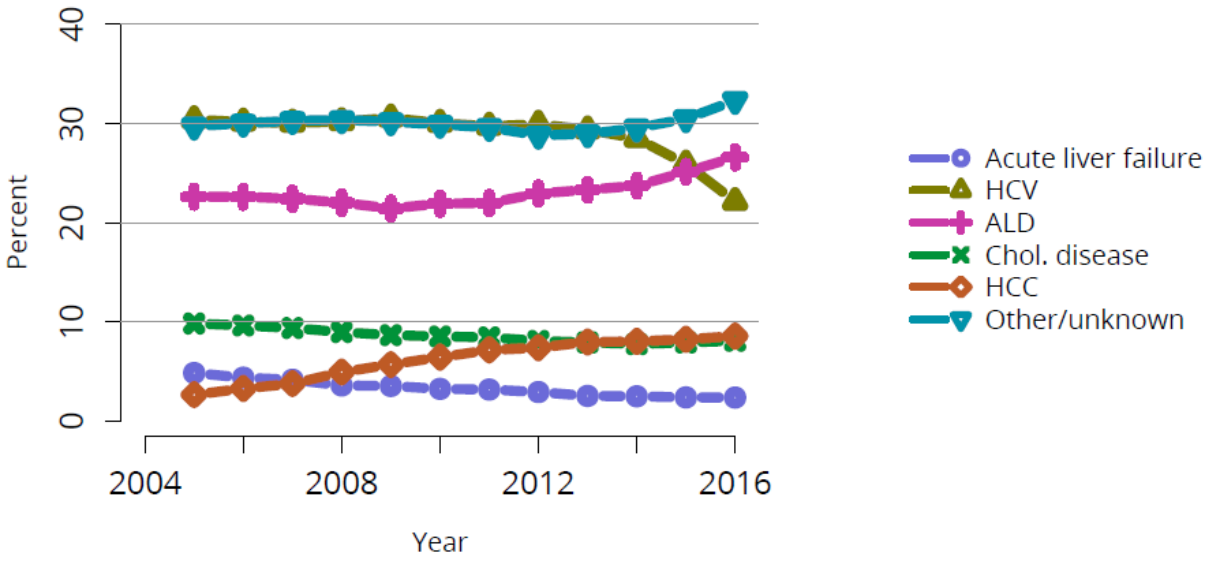
Educational Objectives. At the conclusion of this lecture, the listener should be able to:

- understand of the causes of liver disease that lead to liver transplantation
- understand of how transplant centers determine priority for liver transplantation
- understand of the outcomes from liver transplantation

End Stage Liver Disease in the United States:

Cirrhosis of the liver is a histologic definition of hepatic scarring that represents the most advanced histologic stage of liver injury. The prevalence in the US has been estimated at 0.27% [1]. The two most common causes for cirrhosis in the United States are alcohol abuse and chronic hepatitis C which also represent the two most common indications for liver transplantation (Figure 1) [2].

Figure 1. Indications for Liver Transplant in the US (2004-2016)



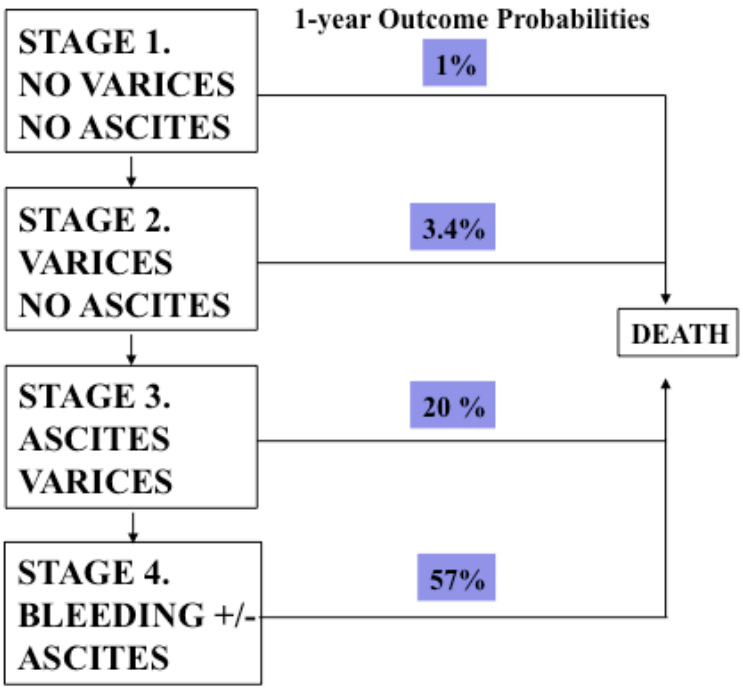
Hepatitis C, until recently the most common indication for liver transplantation, affects 3-5 million individuals in the United States. Approximately 20-30% of individuals with chronic hepatitis C will develop cirrhosis over a 20-30 year timeframe. Recent advances in medical therapy for HCV can result in virologic cures in well over 95% of individuals. It is anticipated that in the coming 5-10 years, hepatic decompensation and the need for transplantation for HCV will decline.

In contrast, non-alcoholic fatty liver disease is a rapidly growing cause of chronic liver disease affecting approximately 30% of individuals in the DFW area [3] and 20-25% of individuals in the United States. Approximately 20% of individuals with NAFLD have non-alcoholic steatohepatitis (NASH) [4], a variant of non-alcoholic fatty liver disease diagnosed histologically and characterized by inflammation and progressive fibrosis. NAFLD is a rising indication for liver transplantation and is expected to become the most common indication in the next 10-20 years [5]. The estimated 60-80 million people in the United States with NAFLD is >10-fold higher than the number of individuals with HCV. NASH is expected to eclipse HCV as a cause for cirrhosis and decompensated liver disease.

As cirrhosis is a histological definition, patients with cirrhosis may remain clinically stable for years and even decades. Once cirrhosis develops, decompensation (formation of ascites, varices, or hepatic encephalopathy) occurs at a rate of approximately 10% per year (Figure 2

[6]) heralding a more ominous phase in the disease process. Transplant-free survival after development of ascites is approximately 50% at 5 years, despite the best medical therapies [7]. Bleeding esophageal varices carry a mortality rate of 20-30% per episode, though this risk can be decreased with medical and endoscopic therapy.

Figure 2. 1 Year Survival after Cirrhotic Decompensation

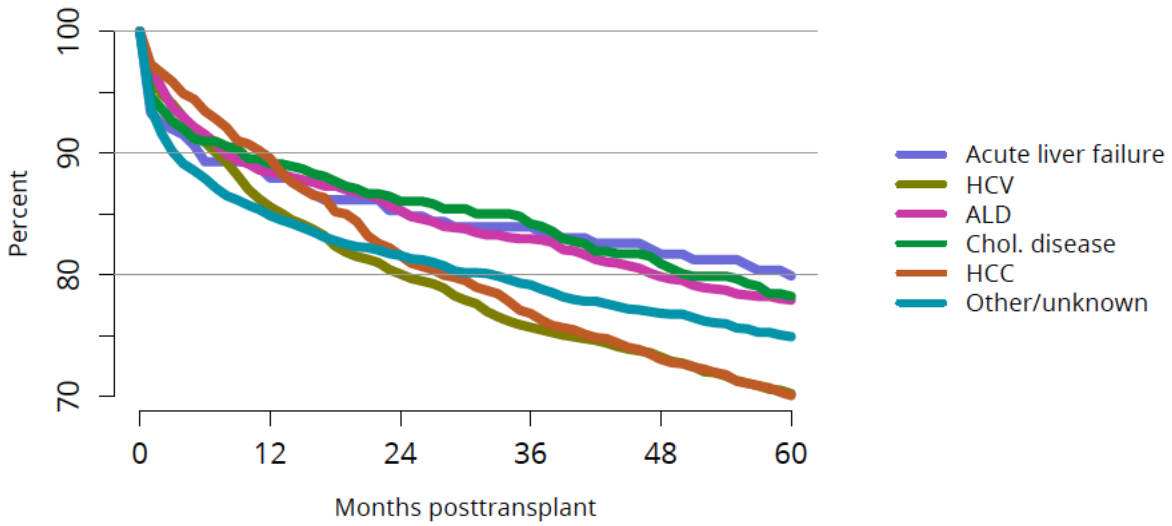


Liver Transplantation:

Overview

For many patients with cirrhosis, liver transplantation remains the only solution for long-term survival. Liver transplantation was first performed in 1963 by Thomas Starzl, though the patient did not survive the operation [8]. The first patient to survive to one year post transplant was transplanted in 1967, though outcomes remained poor through the 1970's. Advances in immunosuppression and surgical techniques in the ensuing decades resulted in dramatically improved outcomes such that current 5-year post transplant survival is now ~75%, and long-term survival increasingly common (Figure 3) [2].

Figure 3. Post Liver Transplant Patient Survival



Patients with conditions once felt to be contraindications to transplant now achieve excellent outcomes. Prior to the development of potent antiviral medicines, transplantation outcomes for HBV–related liver disease was poor. In recent years, allograft loss due to recurrent HBV infection is almost unheard of. Hepatocellular cancer, once a relative contraindication to transplant, is one of the most common indications for transplantation [9]. Excellent outcomes after liver transplantation in well-selected candidates with hepatocellular cancer mirror transplantation in patients with liver failure from other etiologies (Figure 2). In fact, low waitlist mortality and excellent outcomes after transplantation for hepatocellular cancer has led to periodic reassessment of the organ allocation policies in order to allocate organs in a fair manner. Until recently, transplantation for hepatitis C has resulted in below average post-transplant outcomes, particularly in HIV infected individuals. Furthermore, post-transplant HCV recurrence often led to rapid allograft fibrosis and cirrhosis at a rate approaching 20% by 5 years post liver transplant [10]. Liver transplant recipients who lost their allograft to recurrent HCV were generally not re-transplanted due to poor re-transplant outcomes. The availability of the current generation of direct acting antiviral has led to dramatic improvements in outcomes for these patients. In general, post-transplant treatment of HCV results in a virologic cure in > 95% of treated patients, a rate approximating cure rates in non-transplant patients [11-13] and we expect that allograft loss due to recurrent hepatitis C after transplantation to be rare in the future. Advances continue to be made in both management of post-transplant disease recurrence and immunosuppression such that allograft loss to either is increasingly rare. Because many more patients are living longer, long-term medical complication of post-transplant medications and conventional medical issues are increasingly the cause of long-term morbidity in liver transplant recipients and highlight the need for close partnership between primary care physicians and transplant providers.

The MELD-Na Priority Score

Though many patients may live for years with well-compensated cirrhosis, decompensation occurs at a rate of about 30% over 10 years [6] Though disabling symptoms of cirrhosis,

such as ascites and encephalopathy have not been reflected in predictive models, the onset of such symptoms is a good indication for liver transplant evaluation referrals. The MELD score, originally designed to predict morality after transjugular intrahepatic portosystemic shunt, has been adapted for use in prioritizing patients on the transplant list [14]. The MELD score provides excellent predictive value in three-month mortality, and thus fits the "sickest go first" organ allocation approach. Implementation of the MELD score in 2002, led to declines in wait list mortality[15, 16]. It originally included the bilirubin, INR, and creatinine. More recently, serum sodium has been added to the calculation of this score; now termed the MELD-Na score. This is the version currently used for liver transplant organ allocation in the US. In general, a patient with a MELD-Na score of 10-15 should be referred for liver transplant evaluation for two important reasons. Firstly, if mortality with and without liver transplantation in a patient with a given MELD are compared, the patient with a MELD score in the mid-teens is likely to live longer with a liver transplant than without. Secondly, early referral for liver transplant evaluation allows medical and non-medical issues to be addressed that may otherwise be a barrier to transplant.

Hepatocellular Cancer Screening recommendations:

Early detection is essential in our ability to achieve excellent post-transplant outcomes in patients with hepatocellular carcinoma (HCC). If HCC is detected after symptoms develop, the tumor has likely progressed beyond transplant criteria. The American Association for the Study for Liver disease has recommended that all patients with cirrhosis be screened for HCC by liver sonogram every 6 months [17]. If a new lesion is detected, magnetic resonance imaging (MRI) or computed tomography (CT) can often diagnose HCC if features are characteristic. Liver transplantation for HCC often does not require a tissue diagnosis.

Hepatocellular Cancer and Transplantation:

Hepatocellular cancer is the most common primary hepatic malignancy and represents one of the most rapidly growing cancer cause of death in the United States [18]. Small hepatocellular cancers discovered pre-transplant and those discovered incidentally in explants, typically do not impact post-transplant survival however tumors that are large and those with vascular invasion, represent a contraindication to transplant. Mazzaferro and colleagues evaluated liver transplant recipients who had up to three tumors, each < 3 cm, or one liver mass < 5 cm, and without vascular invasion and showed excellent post-transplant survival [9]. Conversely, patients who exceeded these criteria had decreased survival post liver transplant. These are called the Milan Criteria, and have been used to define patients who are eligible for MELD priority exception points for transplant. In region 4, comprising Texas and Oklahoma, "expanded criteria" are utilized (Table 1). These allow patients with larger and more numerous liver tumors than those allowed under the Milan criteria to receive exception points.

Table 1: Region 4 Criteria for Hepatocellular Cancer Exception Points
•T2 HCC •Single lesion up to, but not greater than 6 cm

•Two or three lesions with the largest no greater than 5 cm and the total tumor diameter no greater than 9 cm
•No evidence of vascular invasion or extrahepatic spread of tumor

Less Common Indications for Liver Transplantation:

Most patient undergoing liver transplant in the United States are identified and prioritized by declining hepatic function or hepatocellular cancer. Some patients, however, develop conditions that carry elevated mortality, not captured in the MELD priority scoring (Table 2). It is important to recognize these conditions since, in almost all cases, a waiting time is necessary from the time of transplant listing to transplant. This time allows for accrual of MELD priority points and allows optimization of the underlying condition. For the diagnoses listed below (Table 2), MELD exception points are given and predictably increase over time to reflect the risk of mortality for the underlying condition and allowing timely and safe transplantation.

Hepatopulmonary Syndrome (HPS) is a condition in which the failing liver results in pulmonary vascular change that prevent adequate oxygenation. Patients often have dyspnea out of proportion to their chest imaging or spirometry and have clubbing on physical examination. Patients may display platypnea/orthodeoxia. Evaluation typically includes excluding alternate explanation for dyspnea (COPD, etc.), an ABG, and cardiac echo with bubble study. Oxygen supplementation is the treatment in the short term, and the condition often resolves within months of liver transplant.

Portopulmonary Hypertension (PPH) is a form of pulmonary hypertension classically associated with cirrhosis that can be reversed by liver transplantation. There have been reports of pulmonary hypertension in association with non-cirrhotic portal hypertension. Uncontrolled pulmonary hypertension is a contraindication to transplantation. If the pulmonary pressures can be controlled, the patient can be listed for liver transplantation with close monitoring to ensure that pressures remain well controlled until the time of transplant.

Recurrent Portal Hypertensive bleeding. Cirrhotic patients may develop blood loss from a variety of sources including gastric and esophageal varices and portal hypertensive gastropathy. Despite attempts to manage these issues endoscopically and medically, some patients require recurrent transfusions and hospitalizations. If patients exceed 4 units of blood in one month, priority may be given for transplantation.

Table 2. Conditions for which MELD priority exception points are given

Condition	Criteria
Hepatocellular Cancer	Must be within Region 4 criteria
Hepatopulmonary Syndrome	pAO2 < 60 mmHg and no other pulmonary disease.
Portopulmonary Hypertension	Must be effectively medically treated.

Familial Amyloidosis	After symptoms develop.
Polycystic Liver Disease	Progressive interference with nutrition and overall condition.
Recurrent Portal Hypertensive Bleeding	> 4 units of blood in 1 month
Cholangiocarcinoma	Criteria varies by center protocol.

Additional less common indications for liver transplantation are listed in the guidelines of the American Association for the Study of Liver Diseases (AASLD) [19].

Contraindications to Liver Transplantation

Absolute contraindications:

Conditions that in the past represented absolute contraindications to transplantation can now often be addressed or managed to allow successful transplantation.

Advanced cardiopulmonary conditions such as untreated severe coronary artery disease, congestive heart failure, and pulmonary hypertension represent a contraindication to transplant. Patients over 50, or 45 with risk factors undergo chemical cardiac stress testing as part of their evaluation for transplant. If patients have longstanding diabetes, or other predictors of coronary artery disease, cardiac catheterization is pursued, regardless of stress testing result. The prevalence of CAD (stenosis > 70%) in liver transplant candidates with age > 50 and without cardiac history was 13.3% [20]. Revascularization prior to severe decompensation can often allow successful liver transplantation. Systolic congestive heart failure is generally a contraindication unless a reversible cause can be found in the pre-transplant period. Untreated pulmonary hypertension is also a contraindication, with excess perioperative mortality seen in patients with mean pulmonary artery pressures > 35 mmHg [21]. Pre-transplant medical therapy can often achieve acceptable hemodynamics to allow transplantation.

Active non-hepatic malignancy that is predicted to impact longevity after transplantation or advanced hepatic malignancy have traditionally been a contraindication to transplant. Increasingly, if a non-hepatic malignancy is identified, and a treatment plan can be formulated which is predicted to result in excellent long-term outcomes, transplant may proceed.

Uncontrolled infections represent a barrier to transplant. As sepsis and infections are frequent decompensating events in listed high-MELD patients, close coordination with our transplant infectious disease colleagues is required to determine the point at which transplant may safely proceed.

Psychosocial issues are perhaps the most common absolute barrier to transplantation. Medical compliance and ability to care for the allograft liver are required for successful outcomes after liver transplantation. Substance use, including alcohol, is evaluated in a multidisciplinary manner. Patients are not evaluated solely by their duration of sobriety from alcohol or recreational drugs, but by risk of harmful relapse, and insight required to avoid behaviors harmful to themselves and their allograft liver. Increasingly, it is recognized

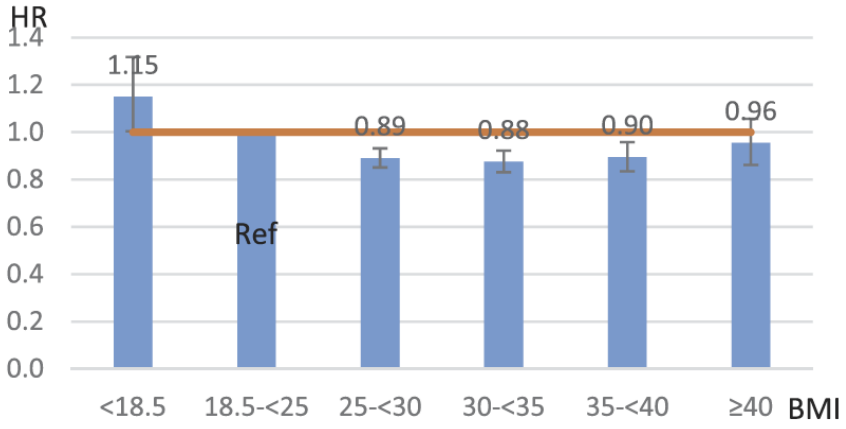
that duration of sobriety alone should not be the sole criteria for liver transplant eligibility as excellent long-term outcomes after liver transplant can be achieved in carefully selected candidates with shorter duration of sobriety [22].

Relative contraindications:

There is no specific age beyond which transplant is not performed. In general, transplantation beyond age 70 requires that the patient is otherwise in good health.

Traditionally, BMI > 35 has been a relative contraindication to transplantation. Presently, liver transplantation is routinely performed on patients with BMI of 40, and sometimes above, depending on medical comorbidities and body habitus. The risk of mortality after transplantation with low body mass index exceeds the risk of transplantation with high BMI (Figure 4) [23]. We work closely with a nutritionist to address these issues in the pre and post-transplant period.

Figure 4. Hazard Ratio for Death After Liver Transplant by BMI



BMI categorization using WHO

Other relative contraindications included extensive portal vein thrombosis, previous malignancy, or mild to moderate pulmonary hypertension.

Post-Transplant Management of the Liver Transplant Recipient

Issues in the immediate post-transplant period are generally surgical in nature, and include hemorrhage, vascular and biliary complications, infections and early rejection. In general, these issues are managed by the transplant team in the hospital setting.

Immunosuppression

Induction immunosuppression in the immediate perioperative period is used in about 25% of liver transplant programs. Medicines used include anti-thymocyte globulin (ATG) and IL-2 receptor antibodies (basilixumab and daclizumab). For liver transplant alone, our program currently uses IV solumedrol with early initiation of antimetabolite therapy (mycophenolate). Typically, within several days post-transplant, calcineurin inhibitor therapy (tacrolimus or cyclosporine) is initiated with the timing somewhat dependent on renal function and indication for transplantation. Steroids are generally weaned off within

three months post-transplant, and calcineurin inhibitor with or without antimetabolite continued for long-term immunosuppression. Occasionally, an mTOR inhibitor (sirolimus or everolimus) is added or substituted depending on side effects or rejection. Common side effects of these medicines are listed in (Table 3, adapted from [24]).

Table 3. Common side effects of post liver transplant immunosuppression

	Steroids	Tacrolimus	Cyclosporine	Mycophenolate
Diabetes	***	**	*	-
Hypertension	***	**	***	-
Dyslipidemia	**	*	**	-
Renal Dysfunction	-	***	***	-
Osteoporosis	***	*	*	-
Malignancy	-	**	**	*
Headaches	*	**	**	*
Gastrointestinal	*	*	*	**

Drug-drug interactions are an important consideration when treating patients after liver transplant. Several commonly used medications that alter tacrolimus trough levels are shown in table 4.

Table 3. Common medications that may alter tacrolimus trough levels

Drugs that increase tacrolimus trough levels	clarithromycin, erythromycin, azithromycin, fluconazole, grapefruit, some protease inhibitors, amiodarone, lansoprazole, omeprazole, reglan
Drugs that decrease tacrolimus trough levels	Rifampin, phenytoin, carbamazepine, St. John's Wort, prednisone

Liver-Related Complications after Transplantation

Rejection

Acute liver allograft rejection occurs in between 10-20%, most commonly within the first 30 days, and generally does not impact long-term allograft survival. Rejection is signaled by rising liver biochemistries in the absence of biliary or vascular causes. A liver biopsy is required for diagnosis, and can distinguish between rejection, infection, allograft steatosis, and other less common causes for enzyme elevation. Treatment typically involves oral or intravenous steroids and overall intensification of immunosuppression. During periods of

treatment of rejection, prophylactic antimicrobials may be temporarily restarted. Chronic rejection, characterized by bile duct loss and vascular injury, is a more indolent process, but may lead to allograft loss and need for re-transplantation. Liver chemistries are monitored on a regular basis by the transplant program to screen for rejection and monitor immunosuppression levels.

Biliary Obstruction and Leaks

Bile leaks occur in 5-32% of liver transplant recipients, most often in the immediate perioperative period and are managed by biliary stenting and dilation [25]. These may be related to surgical anastomotic leaks or ischemic scarring. If a biliary stricture cannot be adequately managed endoscopically, conversion to a roux-en Y hepatocojejunostomy may be required. The allograft bile duct is dependent on hepatic artery blood flow. If hepatic artery blood flow is interrupted, focal or diffuse stricturing can occur and re-transplantation may be necessary.

Vascular complications

The most threatening hepatic vascular complication after liver transplant is hepatic artery thrombosis [26]. Early hepatic artery thrombosis occurs in ~3-4% of allograft recipients and leads to allograft loss or death in > 50% of patients. Patients suffering hepatic artery thrombosis within the first week post liver transplant are prioritized for immediate re-transplantation given the poor predicted outcome. Portal vein, hepatic vein, and caval thrombosis or stenosis can also occur and may require vascular intervention or anticoagulation. Fortunately, these complications rarely lead to allograft loss.

Medical complications

Infections

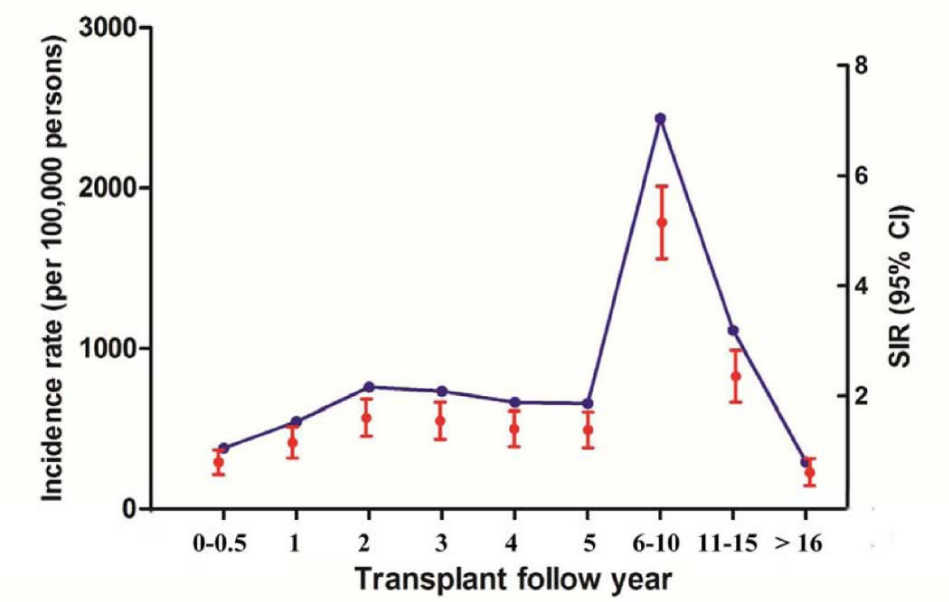
Infections after liver transplantation generally fall within three time periods, with differing etiologies [27]. Within the first month after transplantation, most infections are either surgery related, or related to active infections in the donor or recipient at the time of liver transplant. These can include surgical site infections, infections related to anastomoses, line infections and aspiration. Between months 1-6, most infections are caused by reactivation of latent infections, relapse of infections, or opportunistic infections. This may include CMV reactivation, HBV recurrence, HCV, clostridium difficile, and PCP. Prophylactic use of antimicrobials (to prevent p. jirovecii and fungal infections) and antivirals (to prevent CMV and HBV reactivation) has dramatically reduced morbidity due to these pathogens. Infections beyond 6 months post liver transplant generally reflect infections in the non-transplant population.

Cancer

Malignancies are much more common in solid organ transplant recipients compare with non-transplant populations. The standardized incidence ratio is > 11-fold elevated [28]. Skin cancers affect approximately 30% of solid organ transplant recipients. Solid organ cancers and hematologic malignancies are also common. Patients are counseled to avoid excessive sun exposure, use hats and SPF > 15 sunscreen, and are advised to have annual

dermatologic exams. De-novo malignancies can occur years after transplantation highlighting the importance of preventative care and screening (Figure 5 [28]).

Figure 5. Incidence of malignancies after liver transplantation by year

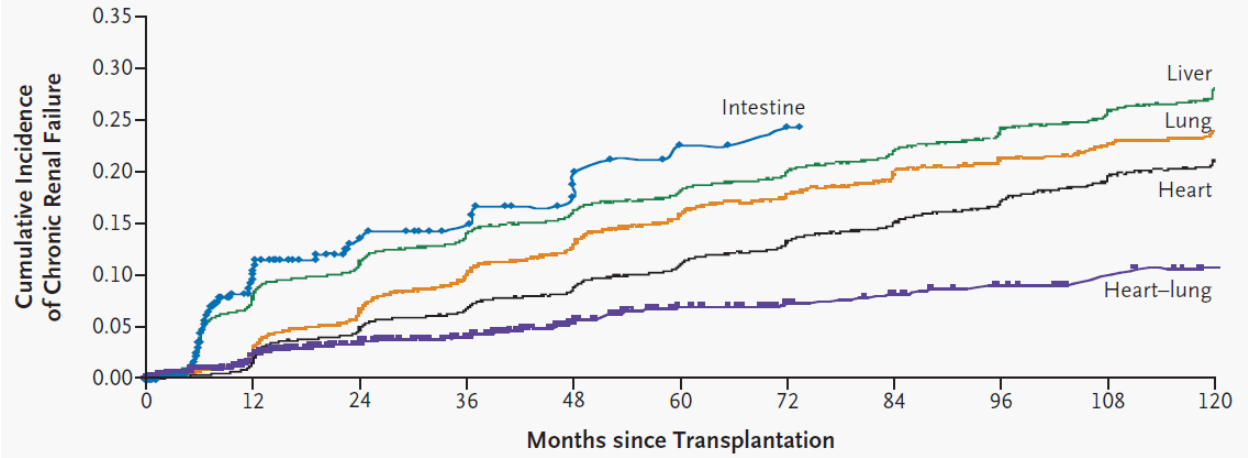


Post-transplant lymphoproliferative disorder (PTLD) is the most common hematologic malignancy, with a standardized incidence ratio of 52. PTLD is often related to Epstein Barr virus infection. Initial treatment is reduction of immunosuppression and chemotherapy. In some cases, radiation and surgery is required.

Renal

Chronic kidney disease (CKD) is common the pre-transplant cirrhotic patient population, often related to hypertension, diabetes, and other conventional renal insufficiency risk factors. Furthermore, patients have often had multiple contrasted diagnostic studies leading up to liver transplantation. Renal transplant following liver transplant is higher than in most other solid organ transplant recipients (Figure 6 [29]) and the rate of end-stage renal disease or renal transplant in liver transplant recipients is 5-8% at 10 years post-transplant [30]. Minimization of calcineurin inhibitor exposure, control of hypertension and other traditional risk factors are the hallmarks of management in the setting of post liver transplant CKD.

Figure 6. Incidence of chronic renal failure after solid organ transplant



Hypertension and Dyslipidemia

The risk of cardiovascular disease after liver transplantation greatly exceeds the non-transplant population with the risk of a cardiovascular event post-OLT being 64% greater compared with a control population [31]. Dyslipidemia, a common side effect of immunosuppression is also common after liver transplant. The AASLD guidelines recommend a target blood pressure of 130/80 in liver transplant recipients with hypertension and treatment of dyslipidemia if the LDL remains > 100 mg/dL and triglycerides are not well controlled after lifestyle changes [30]. Though calcium channel blockers have been used for mechanistic reasons, ACE and ARBs are recommended for use in patients with diabetes, CKD, or proteinuria though patients need to be monitored for hyperkalemia.

Obesity

Most liver transplant programs have an upper BMI limit, though this may not be absolute, depending on the weight distribution and comorbidities of the patient. Despite the requirement in many patients to lose weight to be listed for transplant, recurrence of obesity is almost universal post-transplant. Furthermore, de-novo obesity is exacerbated by steroids and resolution of some of the cachexia that accompanies liver failure. In a report of 98 patients undergoing liver transplant for NAFLD, recurrent steatosis has been reported in 70% of patients, and allograft NASH in 25% [32]. Fortunately, allograft loss is uncommon.

Bone Density

Low bone density is common after liver transplant, and is a frequent side effect of immunosuppressive regimens, which, at least in the early post-transplant period, includes prednisone. Bone density is often lowest in the 6 months post liver transplant before rebounding [33]. Treatment with bisphosphonates should be considered when indicated to minimize risk of fractures

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