

Liver Transplantation in 2016: An Update

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Liver transplantation is a lifesaving intervention for patients with decompensated cirrhosis, certain malignancies, and genetic disorders associated with disordered liver metabolism. This commentary will discuss the indications for liver transplantation, the evaluation of liver transplant candidates, prioritization of candidates on the waiting list, and post-transplant care.

Nearly 50 years have passed since the first successful liver transplant surgery was performed. In the interim, liver transplantation has become a standard therapy for the management of end-stage liver disease and its complications, hepatocellular carcinoma, a number of congenital and genetic disorders, and fulminant hepatic failure. Since the United Network for Organ Sharing (UNOS) began standardized reporting of data in 1988, there have been more than 138,000 liver transplants performed in the United States, with more than 5,950 performed in 2015 [1]. Within North Carolina, more than 3,100 liver transplants have been performed since 1988 at the 3 centers doing such procedures: Carolinas Medical Center, Duke University Health System, and UNC Health Care. In 2014, the most recent year for which state-based data are available, a total of 151 liver transplants were performed within the state. Of these, 9 liver transplants were performed in recipients under the age of 18 years.

As the field of liver transplantation has matured, outcomes following transplantation have steadily improved: 1-year graft survival now routinely exceeds 89% (for transplants performed in 2012); 5-year graft survival exceeds 78% (for transplants performed in 2008); and 10-year graft survival exceeds 64% (for transplants performed in 2003) [2] (see Figure 1). Patient survival is even higher, given the opportunity for repeat transplantation if allograft failure develops. We can expect even further improvements in long-term graft and patient survival in the next few years, as the recent availability of direct-acting antiviral agents for treatment of hepatitis C virus (HCV) is expected to have a very favorable impact on allograft survival in HCV-infected liver transplant recipients.

While the number of liver transplants performed in the United States is large, the number of waitlisted liver transplant candidates is even larger. As of February 26, 2016,

there were 14,772 individuals listed for liver transplantation in the United States [3], a number that far exceeds the number of transplants performed each year. Within North Carolina, 222 candidates were awaiting liver transplantation as of that date [3].

Indications for Liver Transplantation

Liver transplantation is most commonly indicated for the management of decompensated cirrhosis. The most common cause of cirrhosis among waitlisted liver transplant candidates remains chronic HCV infection; as previously mentioned, however, the increased availability of direct-acting antiviral agents with very high cure rates is expected to decrease this indication for liver transplantation in the future. It is believed that nonalcoholic fatty liver disease with accompanying cirrhosis may soon become the leading indication for liver transplantation [4]. Other common causes of cirrhosis that result in listing for liver transplantation include, in decreasing order of frequency: alcoholic cirrhosis; cholestatic liver disease such as primary biliary cholangiopathy, previously known as primary biliary cirrhosis; primary sclerosing cholangitis; and chronic hepatitis B virus infection. Fulminant hepatic failure accounts for approximately 2% of transplant listings.

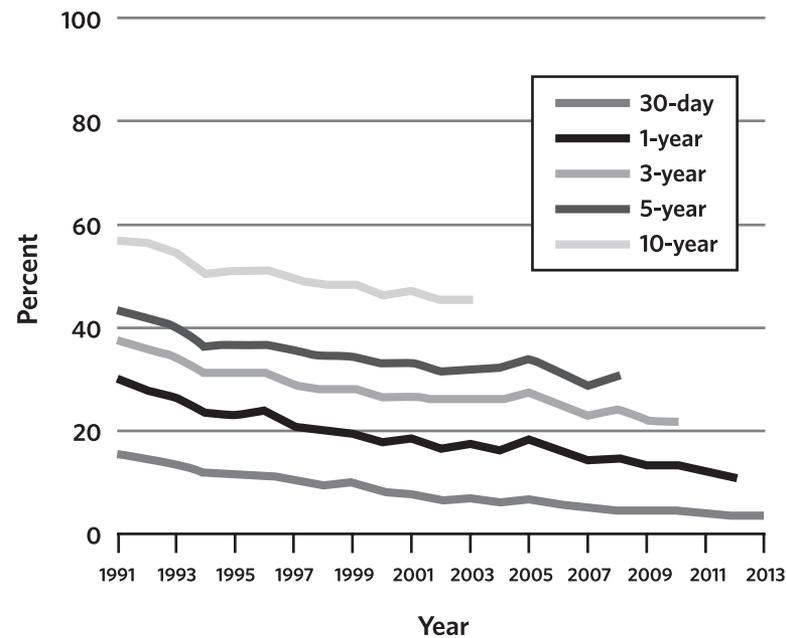
Another common indication for liver transplantation is treatment of hepatocellular carcinoma in patients in whom surgical resection is not feasible due to the presence of underlying compensated cirrhosis with portal hypertension. There are also several less common indications for which liver replacement may be indicated even in the absence of decompensated liver disease: treatment of portopulmonary hypertension, hepatopulmonary syndrome, or localized cholangiocarcinoma; cure of familial amyloidotic polyneuropathy, in which case liver synthetic function is normal but secretion of abnormal transthyretin results in neurologic and cardiac injury; correction of primary hyperoxaluria (in conjunction with simultaneous kidney transplant); and

Electronically published May 6, 2016.

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N C Med J. 2016;77(3):194-197. ©2016 by the North Carolina Institute of Medicine and The Duke Endowment. All rights reserved. 0029-2559/2016/77310

FIGURE 1.
Graft Failure Among Adult Deceased Donor Liver Transplant Recipients, 1991-2013.



Note. These data include all adult recipients of deceased donor livers, including multi-organ transplants.
 Source: Reprinted with permission from Kim WR et al [2].

management of cystic fibrosis-related cirrhosis with declining lung function.

For pediatric liver transplant recipients, the indications are quite different than for adults. In children, transplantation is most commonly performed for management of biliary atresia, management of fulminant hepatic failure, treatment of controlled hepatoblastoma, or correction of urea cycle defects or organic acidemias.

Evaluation for Liver Transplantation Listing

Evaluation for liver transplant listing is comprehensive and is largely focused on the provision of scarce donor organs to candidates in whom medical and psychological health is such that long-term function of the liver can be anticipated. Patients referred for transplantation typically undergo an extensive multidisciplinary evaluation with assessments performed by transplant hepatologists, transplant surgeons, social workers, nutritionists, financial counselors, transplant coordinators, and often a psychologist or psychiatrist. The team assesses a candidate's medical health and physical fitness with regard to his or her ability to survive a complex surgery with significant cardiac stress, as well as his or her physical ability to participate in weeks to months of physical recovery. Particular attention is paid to a history of compliance with prior medical regimens, given the considerable number of medications required post-transplantation and the risks of significant organ injury if immunosuppression is not administered in a regimented fashion. Social work

and psychiatry or psychology team members assess the risks for decompensation of mental health associated with the stresses of waiting for transplantation as well as the challenges that will be encountered post-transplantation. Identification of responsible family members or friends who can actively participate in caregiving during the medical and physical recovery from transplantation is also required.

Given that a prior history of drug use is often associated with the diagnosis of HCV infection and that alcoholic cirrhosis is prevalent in the transplant waiting list population, careful attention is focused on previous substance abuse, and risks for relapse are identified. While it is commonly believed that 6 months of alcohol abstinence are required for liver transplant listing, there is actually no required duration of abstinence mentioned in the policies of UNOS or the Centers for Medicare & Medicaid Services (CMS), so transplant teams may make exception to this common practice if patients have strong support systems and appear to be engaged in, and responding well to, relapse prevention counseling.

Prioritization for Liver Transplantation

Since 2002, the system for prioritization of candidates on the waiting list for liver transplantation has been based on medical urgency; that is, those patients on the list who are at the greatest risk of death are afforded the highest priority. Patients with fulminant hepatic failure are afforded the highest priority, known as status 1, and then candidates with

other liver diseases are ordered below them on the waiting list. This approach replaced the older system that prioritized patients based on a combination of medical urgency and accumulated wait time.

Since the change to the system in 2002, adult patients have been prioritized based on their Model for End-Stage Liver Disease (MELD) score (see Table 1). This score has been very well validated for patients with cirrhosis, and it predicts the risk of death without transplantation while on the waiting list. Scores range from 40 (high) to 6 (low). For patients whose indication for transplantation is a condition other than decompensated cirrhosis, MELD exception points are assigned so that these patients' MELD scores reflect their risk of waitlist mortality or morbidity (see Table 2). Importantly, the presence of hepatic encephalopathy, gastrointestinal bleeding, problematic ascites, or hepatic hydrothorax does not routinely afford patients extra priority on the waiting list. In contrast, the presence of hyponatremia in cirrhotic patients has been recognized to convey excess mortality beyond that calculated by the MELD score alone [5]; thus, as of January 11, 2016, the system for liver allocation in the United States was changed to utilize the MELD-Na score (see Table 1). This modification now gives increased priority to cirrhotic patients with hyponatremia.

For patients with lower MELD scores, the survival benefits gained from liver transplantation remain uncertain [6, 7], so the allocation system is designed such that waiting list candidates with MELD scores less than 15 are afforded little priority for transplantation. Candidates with low MELD scores who face considerable morbidity related to their liver disease can attempt to gain increased priority for transplantation by applying for a MELD score exception through a UNOS Regional Review Board.

In North Carolina, there has been a steady increase over the past 5 years in the MELD scores needed to achieve

TABLE 2.
Standard Adult MELD Exceptions

Cholangiocarcinoma
Hepatocellular carcinoma
Portopulmonary hypertension
Hepatopulmonary syndrome
Familial amyloidotic polyneuropathy
Primary hyperoxaluria
Cystic fibrosis
Note. MELD, Model for End-Stage Liver Disease.

access to donor organs. As such, it is not unusual for waitlist candidates with common blood types (A and O) to achieve MELD scores in the middle to upper 20s before they begin to receive offers for deceased donor organs [2]. Waitlist candidates in North Carolina with uncommon blood types (B and AB) may receive organ offers at lower MELD scores. Extra access to organs is afforded to patients of all blood types who are at highest risk of death through a national mechanism known as Share 35; this program gives patients in North Carolina with MELD scores greater than 35 priority for organ offers from the 5 states assigned to UNOS Region 11 (North Carolina, South Carolina, Virginia, Kentucky, and Tennessee).

While the severity of illness needed to generate organ offers for liver transplant candidates waitlisted in North Carolina has increased in recent years, candidates listed at the North Carolina centers are in a much more favorable position than are those in other parts of the United States, where the imbalance between deceased donor organ supply and demand for transplantation is much greater. Patients awaiting liver transplantation in the Northeast, upper Midwest, and portions of Texas, Oklahoma, and California must often achieve MELD scores in the 30s before they begin to receive offers for donor organs.

Pediatric patients awaiting liver transplantation are assigned a Pediatric End-Stage Liver Disease (PELD) score (see Table 1). This score incorporates the patient's creatinine level, bilirubin level, and prothrombin time (PT) international normalized ratio (INR), as well as taking into account the presence of growth retardation.

Living Donor Liver Transplantation

Approximately 5% of liver transplantations performed in the United States utilize partial allografts from living donors. As the imbalance between the availability of deceased donor organs and the number of waitlisted candidates continues, living donor liver transplantation provides an option that does not require patients to achieve a MELD score high enough to reach the top of the waiting list. Liver transplantation has shown a survival benefit in cirrhotic patients with MELD scores as low as 10 [8]. Thus, use of a living donor may be considered when a transplant candidate is thought to have a low likelihood of reaching the top of the waiting list or they face risks of death while waiting that are not reflected

TABLE 1.
MELD, MELD-Na, and PELD Calculations

MELD score ^a = 0.957 × Log _e (creatinine mg/dL) + 0.378 × Log _e (bilirubin mg/dL) + 1.120 × Log _e (INR) + 0.643
MELD-Na score ^b = Initial MELD + 1.32 × (137 - Na) - [0.033 × MELD(initial) × (137 - Na)]
PELD score ^c = 0.436 (Age (<1 YR.)) - 0.687 × Log _e (albumin g/dL) + 0.480 × Log _e (total bilirubin mg/dL) + 1.857 × Log _e (INR) + 0.667 (Growth failure (≤ 2 standard deviations present))
For all scores, calculation will be rounded to the tenth decimal place and then multiplied by 10 to achieve waitlist score. All scores capped at 40 for allocation purposes. All laboratory values of less than 1 will be set to 1.0.
Note. INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.
^a MELD score employed for candidates 12 years of age and older. Creatinine value caps at 4 mg/dL and is set at 4 mg/dL if patient is on renal replacement therapy.
^b MELD-Na score calculated such that if serum sodium is less than 125 mmol/L, then value in equation is set to 125 mmol/L. MELD-Na adjustment is not applicable to candidates with initial MELD score of 11 or less.
^c PELD score for candidates less than 12 years old at time of listing.

in their MELD or PELD score (ie, refractory encephalopathy, recurrent episodes of infection, etc).

For pediatric liver transplant recipients, living donor transplantation often entails the use of a small segmental graft, such as the left lateral segment, from a living adult donor. For adults, a larger volume of liver is needed, so most frequently the right lobe of the liver is utilized. Recent data suggest that, for adult waitlisted candidates with MELD scores greater than 10 but less than 25, receipt of a living donor liver transplant decreases the risk of death compared to remaining on the waiting list and hoping to receive a deceased donor graft [8]. The assessment and care of the potential donor requires careful anatomic assessment of liver vasculature and biliary anatomy, as well as assessment of general and psychological health. In addition, a thorough discussion of the risks associated with living donation [9], including the small but nonzero risk of death, is essential for appropriate informed consent of potential living donors.

Care of Liver Transplant Recipients

There are hundreds of thousands of Americans living with an organ transplant, so medical practitioners from nearly every background are likely to encounter transplant recipients in their practices. It is essential for these practitioners to recognize the role of immunosuppression in transplant recipients and to understand the risk of complications related to management of other medical problems in the setting of immunosuppression. A recent comprehensive review of this topic is available and may prove helpful to medical providers who see liver transplant recipients in their practice [10]. Important topics in the care of transplant recipients include a focus on preventive vaccinations (with avoidance of live-virus vaccines such as zoster); assessment for cutaneous malignancy, which is common in the setting of immunosuppression; routine cancer screening as recommended by the American Cancer Society; and diligent management of the diabetes and hyperlipidemia that often accompany the use of calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus). It is also critical to understand the potential drug interactions that may cause serious side effects in patients taking cal-

cieneurin inhibitors. Lastly, as mTOR inhibitors result in poor wound healing, clinicians should consider whether it is necessary to change immunosuppression prior to elective surgery or immediately after urgent surgery.

Transplant centers are eager to partner with local providers and routinely assist with such matters. Such long-term partnerships maximize the opportunities for long-term graft and patient survival following liver transplantation. **NCMJ**

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Acknowledgments

Potential conflicts of interest. C.L.B. is the immediate past president of the United Network of Organ Sharing/Organ Procurement and Transplantation Network.

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