Liver transplantation: an update

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Purpose of review

Recent attention in liver transplantation has focused on equity in organ allocation and management of post-transplant complications.

Recent findings

Adoption of the model for end-stage liver disease (MELD) for liver allocation has been successful in implementing a system based on medical urgency rather than waiting time. Refinements are being studied in reducing geographic disparities and improving transplant benefit by balancing pre-transplant mortality and post-transplant survival. With hepatocellular carcinoma becoming a bigger proportion of liver transplants since MELD, emerging literature is examining expansion of the current criteria for transplantation of hepatocellular carcinoma. Hepatitis C virus infection is associated with worse patient and graft survival post-transplantation than other liver diseases. The optimal timing and delivery of current antiviral therapy and immunosuppressive strategies in reducing the severity of hepatitis C virus recurrence post-transplantation are discussed. Chronic renal dysfunction after liver transplantation is a source of considerable morbidity. Nephron-sparing immunosuppression regimens are emerging with encouraging results.

Summary

Organ allocation tends to evolve under MELD with a focus on reducing geographic disparities and maximizing transplant benefit. Hepatitis C virus, hepatocellular carcinoma and chronic renal dysfunction are a major challenge and continued research in these areas will undoubtedly lead to better outcomes for transplant recipients.

Keywords

hepatitis C, hepatocellular carcinoma, liver transplantation, MELD, model for end stage liver disease, renal failure

Curr Opin Gastroenterol 22:272–278. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Gastroenterology 2006, 22:272–278

Abbreviations

CNI	calcineurin inhibitor
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
MELD	model for end-stage liver disease
MFF	mycophenolate mofetil
UNOS	United Network for Organ Sharing

0267-1379

Introduction

Since the introduction of liver transplantation by Starzl in 1967, patient and graft outcomes have improved incrementally, with a 5-year patient survival of 80% and graft survival of 71% [1]. Improvements in surgical technique, organ preservation, immunosuppression, and management of post-transplant complications have resulted in these excellent outcomes.

This paper addresses four issues that are particularly challenging to the clinical practice of liver transplantation currently and for the foreseeable future. These include (1) allocation of donor livers under the current system of using the model for end-stage liver disease (MELD) score; (2) expansion of current criteria for transplantation of hepatocellular carcinoma (HCC) and the impact of the MELD system on transplantation for HCC; (3) outcomes of hepatitis C virus (HCV) infection after liver transplantation: the role of antiviral therapy and immunosuppressive strategies in reducing the severity of HCV recurrence post-transplantation will be discussed; and (4) chronic renal dysfunction, a considerable source of morbidity after liver transplantation.

Model for end-stage liver disease and allocation of livers in the USA

The number of patients on the US waiting list for liver transplantation has grown to 17 285. With 5437 transplants performed in 2005, the increase in donors has not been proportionate [1]. Prior to February 2002, organ allocation was prioritized according to the United Network for Organ Sharing (UNOS) score categories wherein patients were listed in one of four classes (1, 2A, 2B, 3) based mainly on the Child–Turcotte–Pugh (CTP) score and location of patient (intensive care unit). In this system there were a large number of patients in each of the four UNOS strata. Consequently, waiting time became the tie-breaker and the major determinant of organ allocation. As demonstrated by Freeman and Edwards [2] waiting list mortality did not correlate with waiting time. As a result of these

disparities the Department of Health and Human Services issued its Final Rule in 1998 [3] that donor livers should be allocated according to medical urgency.

In response to the Department of Health and Human Services rule, in February 2002 the MELD scoring system was adopted for the allocation of donor livers in the USA. The MELD score was initially developed to predict mortality after the placement of transjugular intrahepatic portosystemic shunt (TIPS) in patients with liver disease [4]. It is based on three objective variables: MELD score = 9.57 ln(creatinine)+3.78 ln(total bilirubin)+11.2 ln(international normalized ratio)+0.643. It is easily calculated from the website of the UNOS, www.UNOS.org. The MELD score has been shown to accurately predict short-term mortality in patients with end-stage liver disease awaiting transplantation [5], with higher scores predicting increasing mortality. It has also been validated for prediction of 1-year mortality in a broad spectrum of patients with chronic liver disease [6•]. Its advantages for organ allocation lie in the fact that it is a statistically weighted, continuous scale with no ceiling or floor effects, thereby reducing the large number of ties and the dependence on waiting time [7].

Since the implementation of MELD, audits of the UNOS system have revealed significant changes in the dynamics of organ allocation. The average MELD score at transplant now is higher compared to the pre-MELD era (20.5 compared with 17) [8•]. Despite the shift to sicker patients there has been no difference in 1-year patient and graft survival since the implementation of MELD, as originally feared [8,9]. There has also been a reduction in the median waiting time, from 656 to 416 days [10]. Perhaps the best indicator of the superiority of MELD as an efficacious prediction model is the reduction in waiting-list mortality of 3.5% since its implementation [11•]. These changes meet the requirement of the Department of Health and Human Services that organs should be allocated based on medical urgency rather than waiting time.

Current emphasis is in continuous improvement in the MELD-based allocation scheme. Based upon further audits of the UNOS data, a survival benefit in the first year post-transplant was seen in patients whose MELD was more than 18. For patients whose MELD scores were lower than 15 the risk of dying in the first year post-transplant was higher than remaining on the waiting list [12•]. Subsequent changes in the allocation policy were made so that a MELD of at least 15 is required for transplantation if on the waiting list.

An area for improvement is the disparity of the MELD at transplant between various regions and organ-procurement organizations. Smaller organizations (< 100 patients listed) had more organs available per listed patient and patients listed in these organizations received organs faster and at lower MELD scores [13••]. As a solution to this geographic disparity some have advocated making more uniform-sized organ-procurement organizations so that each serves a population of roughly 9 million.

Addition of other objective parameters may increase the predictive ability of MELD. Serum sodium, which is correlated with refractory ascites, has been reported as such [14•]. At listing for transplant a serum sodium of less than 126 mM was associated with a 6.3–7.8-fold increased risk of death while on the waiting list [15•]. This is being studied further and UNOS is now prospectively collecting data on serum sodium in transplant-listed patients to see if they correlate with pre-transplant mortality.

Longitudinal changes in the MELD (Delta MELD) may provide additional prognostic information compared to a single-time-point MELD alone. In several studies Delta MELD demonstrated a high sensitivity and specificity in predicting mortality [16–18]. However, a recent study failed to confirm that Delta MELD is predictive of waiting-list mortality [19]. Delta MELD has not yet been incorporated into allocation schemes [20••].

Although the MELD score is a good predictor of pre-transplant survival, it is only a weak predictor of post-transplant survival [8•,21•,22]. Donor factors, surgical factors and post-transplant complications play a significant role in post-transplant outcomes. Further changes to liver-allocation schemes should include the investigation and incorporation of other objective parameters that add to the post-transplant prediction of mortality. To maximize the utility of organ allocation a system that balances both pre-transplant medical urgency and post-transplant survival is needed.

Hepatocellular carcinoma and liver transplantation – current allocation rules and expansion of criterion for transplantation

The incidence of HCC and mortality is increasing in the USA as the hepatitis C epidemic of the 1970s and 1980s matures [23]. In patients with cirrhosis and HCC liver transplantation remains the best option for long-term survival. Using stringent selection criteria (often referred to as the Milan criteria), limiting transplantation to patients with a single nodule of less than 5 cm or up to three nodules with none bigger than 3 cm [24], an actuarial 4-year survival rate of 75% and recurrence-free survival rate of 83% was achieved. Subsequent studies have confirmed the excellent survival after transplant for HCC meeting the Milan criteria [25,26].

Under the UNOS system, the reliance on waiting time meant that many patients with HCC advanced beyond

the Milan criteria while awaiting transplantation. One of the key elements in introduction of allocation based on MELD score was the recognition that an arbitrary priority score would be necessary for exceptional patients at risk of death from liver disease not identified by changes in serum bilirubin, creatinine or prothrombin time. HCC is the most common of these exceptions. An additional advantage of MELD is that it has facilitated adjustment of the exceptional attribution of points according to the effect of particular priority scores on donor liver allocation in practice. After a few initial modifications [5], the current system does not attribute priority points to patients with stage 1 HCC, whereas stage 2 HCC is currently allocated 24 priority points. With these provisions, in the first year after MELD implementation, the number of patients with HCCs that were transplanted increased from 167 (7% of total transplants) to 408 (22%) [8•,27•]. Waiting time to deceased-donor transplant for HCC patients decreased from a mean of 2.3 to 0.69 years. The 5-month dropout rates due to cancer progression also decreased from 25.9 to 6.7%.

As experience grows with transplantation for small HCC, individual centers have analyzed their data for transplantation of tumors exceeding the Milan criteria. Yao *et al.* [28] retrospectively analyzed the outcome of 70 patients with HCC undergoing transplantation. Those that on pathologic exam of the explant exceeded the Milan criteria but met expanded criteria (single lesion less than or equal to 6.5 cm, two or three nodules, with the largest less than or equal to 4.5 cm, and total tumor diameter 8 cm or less) had a 75% 5-year survival rate. Patients exceeding these criteria however had a 50% 1-year survival rate after transplant.

Even though these results are encouraging, these data were based on patients that met the Milan criteria radiographically even if they exceeded them pathologically. Prospective application of these expanded criteria to radiographically staged tumors has yet to be reported. In other studies, predictors of dropout from the waiting list have included a single lesion greater than 3 cm or three nodules. MELD allocation should be studied further to refine prioritization for HCC based on similar characteristics and different risks of dropout [29]. Further prospective study should be done for other potential predictors of HCC outcomes, including tumor grade, microvascular invasion and tumor markers.

Liver transplantation in hepatitis C virus patients – outcomes, antiviral strategies and immunosuppression

Hepatitis C is the single most common indication for liver transplantation in the USA [30]. Recurrent HCV-related cirrhosis is accelerated in the immunosuppressed individual and develops in 8–44% of patients within 5–7 years [31•]. Outcomes for patients with recurrent HCV are significantly worse than non-HCV recipients with a 23% increased risk of death and 30% increased risk of graft failure over a follow-up of more than 700 days [32]. Retransplantation for HCV is controversial with worse outcomes (up to 50% mortality at 1 year) as compared to other causes of liver disease [33,34••].

The best strategy to prevent severe post-transplant recurrence of HCV is to eliminate the virus before transplantation. Antiviral therapy of HCV with interferon and ribavirin is however difficult to tolerate and associated with poor response rates in patients with decompensated cirrhosis. Using a low-dose escalating drug regimen (LADR) approach to improve tolerability in patients with advanced chronic HCV, sustained response rates of 24% overall were achieved [35]. In this single-center clinical experience, of the 15 patients who became HCV RNA-negative before liver transplant, 12 remained HCV RNA-negative at 6 months post-transplant. Treatment was difficult to tolerate with only 36 of the 124 completing a full course of therapy, and with cytopenias, infections and decompensation of liver disease occurring as the most frequent adverse events. Other studies have achieved similar sustained virologic response rates of 20–24% in patients with decompensated cirrhosis [36,37]. The International Liver Transplant Society consensus conference suggested that patients with decompensated cirrhosis and a MELD score of less than 18 could be considered for antiviral therapy [38].

Two approaches can be taken for antiviral therapy of HCV after transplantation. Typically these approaches utilize interferon and ribavirin, and can be either pre-emptive (started before identification of biochemical or histologic disease, usually at the second or third months) or after identification of patients with histologic and biochemical disease. Pre-emptive therapy has the potential advantage of prevention of recurrent disease before liver disease is advanced. There are no published trials comparing pre-emptive post-transplant antiviral combination with the usual approach of treating after histological demonstration of recurrent disease. However pre-emptive therapy is more difficult to tolerate since patients are still recovering from their surgery and are on higher doses of immunosuppression. Results of controlled trials have shown sustained virologic responses of 0–17% in most trials [39•,40,41•,42] with a sustained viral response, which is equivalent to viral eradication, of 39% being achieved in one trial involving living-donor liver transplants. Treatment discontinuations or dose reductions were performed in 28–85% of cases.

Antiviral treatment of recurrent disease usually occurs later in the post-transplant course when the patient is on

lower doses of immunosuppression. This approach has the advantage of selecting the subset that has progressive disease, avoiding therapy patients without progressive disease. Patients usually have more advanced fibrosis by this time (often stage 2 or greater). Sustained virologic response rates in these controlled trials have ranged from 12 to 34% [41•,43,44]. Treatment dose reductions ranged up to 61% and discontinuations from 0 to 43%, with patients requiring growth factors for cytopenias as well. Prolonged interferon therapy after transplantation has not been described in controlled trials and warrants study. Trials of novel better-tolerated antiviral agents (protease inhibitors) with and without interferon are needed in transplant patients in an attempt to improve the dismal outcomes associated with recurrent hepatitis C disease.

In recent years the rate of severe recurrence of HCV after transplantation appears to have increased [45]. This study identified shorter courses of azathioprine and prednisone as well as induction with mycophenolate as being associated with more rapid progression of fibrosis. Other factors for more severe recurrence include multiple steroid pulses for treatment of rejection, high pre-transplant HCV viral load, older donor age and increased histological activity early after transplant in the first year [46–49, 50••,51,52]. More potent recent immunosuppressants such as tacrolimus and mycophenolate mofetil (MMF) may be detrimental for hepatitis C [53]. However, some authors have advocated MMF as beneficial in HCV patients. In a retrospective study, patients on a MMF+ calcineurin inhibitor combination were compared to patients on calcineurin inhibitors (CNIs) only [54••]. Fibrosis progressed only in the non-MMF group over 24 months. However, it is difficult to say if the benefit was due to the lower doses of CNIs in the combination group or the use of mycophenolate. There is no good evidence of any antiviral effect of MMF in HCV patients [55]. Recent intriguing reports have shown that cyclosporine may have an additive antiviral effect on HCV when combined with interferon, an effect that is not seen with tacrolimus [56••]. This study as well as others have also shown an antiviral effect of cyclosporine in HCV replicon models [57]. Azathioprine has also been shown to have an anti-HCV effect in the replicon model [58•]. However, most studies have reported no differences in HCV outcomes post-transplantation between cyclosporine and tacrolimus [59,60,61•]. Confirmation of the potential for specific immunosuppressant combinations to have a salutary effect on HCV progression in liver transplant recipients awaits better clinical trials of appropriate power and duration.

Long-term renal failure after liver transplantation

With improving survival after liver transplantation, the long-term effects of immunosuppression are becoming prevalent. According to a recent large UNOS database study, the cumulative incidence of chronic renal failure after liver transplant is 18.1% after 5 years [62]. Renal failure leads to a significantly increased risk of mortality as well as increased costs of healthcare [62,63,64•].

Progressive decline in renal function is predicted by a decline in renal function over the first 3–12 months after transplant [63,65]. Other predictors of chronic renal failure include older recipient, pre-transplant renal failure, female sex, cyclosporine (compared to tacrolimus), hepatitis C pre-transplant and pre-transplant diabetes as predictive of chronic renal failure [62]. Late toxicity associated with CNIs is associated with typical renal histologic lesions [66]. A recent retrospective review of the first 3 years in more than 1000 liver-transplant recipients from 11 US centers showed that prevailing serum creatinine and blood pressure measures were higher in subjects treated with cyclosporine rather than tacrolimus as the principal immunosuppressant [67•].

The first step when managing patients with progressive decline in renal function after liver transplantation is to minimize the dose of CNIs. Addition of MMF with lower CNI doses may be just as effective as standard blood levels, with less nephrotoxicity. In a controlled study, patients with chronic renal dysfunction randomized to a strategy of MMF introduction with reduction in CNI (Tac trough < 4 or cyclosporine < 50), had significant improvement in renal function compared to a conventional CNI dose along with improvements in blood pressure and lipid profile [68•]. Other studies have shown similar results with this strategy of CNI reduction as well [69•,70–72]. Some studies have shown no improvement in biopsy-proven CNI renal dysfunction 6 months after CNI withdrawal and replacement by MMF in late severe renal dysfunction [66].

The other alternatives are CNI-free regimens. Although there has been some success in selected patients with mycophenolate monotherapy [73,74], a high rate of rejection has been seen in other studies [75], including graft failure [76]. Sirolimus monotherapy may be safe but experience is limited and side effects such as hyperlipidemia must be monitored. However, in small series there have been improvements in renal function in patients where CNI was withdrawn and replaced by sirolimus due to progressive nephrotoxicity [77,78]. The combination of mycophenolate and sirolimus is being studied after CNI withdrawal early after transplantation.

Other nephrotoxic medications should be avoided in these patients and related metabolic complications such as diabetes, hypertension and dyslipidemia should be aggressively treated to minimize their impact on renal function.

Conclusions

Since the adoption of the MELD score for liver transplantation, important advances have been made in organ allocation. Donor livers are now allocated according to medical urgency. Further challenges include reducing geographic disparities in waiting times and MELD scores at transplantation. Refinements in organ allocation will continue to occur with audits of outcomes of waiting list candidates and post-transplant outcomes.

Transplantation for HCC has benefited from prioritization under the MELD system. Expansion of current criteria for liver transplantation in HCC should be prospectively studied. Large multicenter trials of antiviral therapy and immunosuppressive strategies in patients transplanted for HCV are needed. Rapid changes in immunosuppression should be avoided in these patients. Chronic renal dysfunction is a prevalent long-term complication after liver transplantation. Nephron-sparing immunosuppressive strategies should be studied in large prospective trials.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 326–331).

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