CHAPTER 49
Controversies in Liver Transplantation
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Key concepts

- The institution of liver allocation based on the model for end-stage liver disease (MELD) score was created to alleviate problems that developed under previous liver allocation schemes.
- Liver allocation based on the MELD score has improved the triage of liver candidates by reducing the waiting list mortality rate.
- Despite these improvements, problems remain with regard to liver allocation and distribution.
- While the MELD score is an objective scoring system, relevant variation in the MELD score exists related largely to interlaboratory variation in measuring the serum creatinine and international normalized ratio.
- The institution of donation after cardiac death organs has increased the number of deceased donor organs available for transplantation.
- The application of living donor liver transplantation has decreased by more than half in the past several years.
- The definition of the expanded criteria donor has helped to identify specific donor and transplant characteristics associated with poor outcome.

Controversy is synonymous with liver transplantation where the stakes are high and the resources, in terms of donors, are limited. Through the years, medical advances in the field of transplantation have vastly improved the outcomes for recipients and the availability of donors. In such a dynamic field, disputes over the most effective application of this procedure are commonplace. Therefore, this chapter will focus on some of the most important current controversies in liver transplantation including liver allocation and distribution, variations in model for end-stage liver disease (MELD) score, donation after cardiac death (DCD), living donor liver transplantation (LDLT), expanded criteria donor (ECD), and MELD exception scores.

Liver allocation and distribution

The equitable allocation and distribution of donor livers has been a controversial issue since liver transplantation became widely available more than a quarter of a century ago. The terms “allocation” and “distribution” reflect different processes and for the purposes of this discussion will be defined as follows. Allocation is the process by which liver candidates are prioritized for transplantation. The allocation scheme is dictated and overseen nationally by the United Network for Organ Sharing (UNOS) and is currently based almost entirely on the MELD score [1,2]. In addition, some patients may also receive a MELD score based on exception diagnoses as described below. Prioritizing patients for transplant has been one of the most controversial areas in the field and is continuously evolving to meet the changing requirements of liver transplant candidates. Distribution is essentially the delivery process; that is, the system by which donor livers are procured, matched, and delivered (transplanted) into prioritized patients within a geographic region. Perhaps more complex than liver allocation, distribution involves the supply (number of donor organs) and demand (number of transplant candidates) within a geographic area, as well as acceptance of specific organs for transplant based on their quality (or lack thereof) and policies regarding organ retention or sharing within the area.

Much of the ongoing controversy related to prioritizing patients and distributing donor organs for transplantation is the result of the increasing demand for the procedure. Since the inception of liver transplantation, the demand for organs has outpaced the supply. Consequently, as the liver transplant list grew over time, the disparity widened between the number of transplant...
candidates and the limited donor pool. As a result, the
collection for organs became increasingly intense and
the prioritization of liver candidates and distribution of
donor organs, in turn, more complicated. Through the
years, three fundamental principles have formed the basis
for liver allocation and distribution: (i) triage – the sickest
liver candidates receive a higher priority for transplant
compared with less sick patients; (ii) “first come, first
served” – patients listed earlier receive a higher priority
than patients listed later; and (iii) local organ utilization –
donor organs are transplanted preferentially in the area
of procurement. Most of the disputes about liver alloca-
tion and the distribution system over time are reflected in
the relative importance given to each of these three prin-
ciples. To understand the current controversies one must
understand how the current system evolved [3].

Liver allocation is in a constant state of evolution. In
the early 1990s when fewer patients were listed and com-
petition for donor organ was less intense, liver alloca-
tion was less complicated. Candidates were prioritized
based on only two criteria: waiting time and severity of
illness as determined by the Child–Turcotte–Pugh (CTP)
score; the higher the score, the higher the priority for
transplant. There were only four gradations of illness (or
statuses): status 3 for stable chronic patients (CTP score
<10), status 2B for decompensated patients (CTP score
≥10), status 2A for critically ill patients (expected to die
in less than 7 days), and status 1 for acute liver failure.
Within each status, patients with the longest waiting time
had the highest priority. Consequently, waiting time was
an important determinant in prioritization for transplant.

This system functioned relatively well during the time
when the waiting list was small. In fact, in the early 1990s,
the number of liver transplants exceeded the number of
listed patients. However, during that decade, the size of
the transplant list increased nearly ten-fold from 1,676 in
1991 to 16,292 in 2000 (Fig. 49.1). With the growing num-
ber of patients listed for transplant, three specific allo-
cation problems became manifest. First, there were too
few grades (statuses) of illness to adequately differenti-
ate and prioritize thousands of patients. Therefore, physi-
cians recognized the need for a more precise and com-
plex prioritization scheme, especially for patients with
decompensated disease whose need for transplant was
rathegr greatest. Second, the inclusion of subjective variables in
the CTP score (i.e., degree of ascites and encephalopa-
thy) led to widespread “gaming” of the system. That
is, physicians could describe the severity of ascites and
encephalopathy in the worst possible terms, thereby
increasing a patient’s priority for transplantation. Third,
waiting time was given too much emphasis. This was
especially true for the lower priority statuses, status 2B
and 3 (which accounted for two thirds of liver transplant
recipients), where patients with longer waiting times
were frequently transplanted ahead of sicker patients.
In addition, because of the importance of waiting time,
patients sought early listing to increase their priority for
transplant. Consequently, the transplant list swelled with
candidates whose need for transplant was quite low.

These problems in allocation were further com-
pounded by flaws that developed in liver distribution.
Until 15 years ago, liver transplantation was primarily
performed in a relatively few, selected, large centers.
Consequently, liver recipients traveled great distances
and, in turn, since many regions did not have a transplant
center, all locally procured donor organs were distributed
out of the local area to these larger transplant centers.
However, as more and more physicians became trained
in transplantation during the 1980s and 1990s, they set
up new transplant centers across the United States. While
increasing access to transplantation, these centers created novel challenges in liver distribution. Start-up centers began to compete with the larger, more established centers for the limited donor pool. The allocation and distribution of these donor livers is directed nationally by UNOS, although the functional unit is the local organ procurement organization (OPO) of which there are 50 across the United States. With few exceptions, preference is given to distributing donor livers to recipients listed within the local OPO. In fact, 70% of donor livers are transplanted into local recipients.

With the proliferation of liver transplant centers, a fundamental debate emerged regarding two competing interests in liver distribution: (i) retaining organs within the OPO of procurement based on considerations of efficiency and local organ ownership, versus (ii) sharing organs over a wider geographic region to expand the potential recipient pool, allowing sicker patients greater access to donor livers. In the debate over liver distribution, the new, smaller centers argued that they could provide excellent local transplant care obviating the need for patients relocating to larger centers. Local distribution of donor livers also has the advantage of faster and more efficient transplantation, which may improve recipient outcomes. In addition, it may permit greater use of ECD livers. Since these organs are particularly sensitive to prolonged cold ischemic time (the time between organ procurement and transplantation), they are less well adapted to regional sharing, which requires time to transport organs over great distances. On the other hand, the larger centers contended that distributing livers to their sicker patients would make better use of a precious resource, especially if the transplant was performed by their experienced team. Local ownership of donor organs was another factor that became a critical component in the debate. The establishment of a new transplant center within a state became an issue of local pride and retention of donor organs a requirement to maintain the center’s viability. As a result, some states attempted to pass laws restricting the transport of organs outside their boundaries. Finally, the debate was further fueled by differences that emerged in the types of patients listed at small and large centers. Compared to the large centers, smaller programs had shorter lists with fewer sick patients. The established larger centers had built long lists with critically ill patients through years of national and international referrals. These differences in patient populations along with the local retention of donor organs led to wide disparities in transplant access across the United States. Less sick patients at small centers were transplanted much faster than sicker patients waiting in larger hospitals.

These systemic problems became increasingly acute as the national waiting list grew and more patients required access to donor organs. The inherent flaws in the liver allocation and distribution scheme led to a national perception amongst professionals and even the lay public that the system did not work properly. By the late 1990s, the discourse grew so intense that the federal government stepped in to perform an independent review of the entire process through the Institute of Medicine [4]. Their conclusions were expressed in regulatory terms through the “final rule” that stipulated three major revisions in allocation (points 1 and 2) and distribution (point 3):

1. Since it was determined to be irrelevant to a patient’s need for transplant, waiting time should be eliminated as a determinant for prioritization.
2. The prioritization of liver candidates for transplantation should be based on an objective and more precise scoring system.
3. In order to provide equitable access to liver transplantation across the country, uniform and larger organ distribution areas, each serving a population base of at least 9 million people, should be established. Organs should be allocated and distributed based on patients’ medical needs with less emphasis placed on keeping organs in the local area where they are procured.

Two of these three recommendations were fully implemented. Most notable, the MELD score was established as the means for prioritizing candidates for transplantation. The MELD score is based on a mathematical model predictive of 90-day mortality and defined by the following equation, which includes only three objective variables (serum creatinine, bilirubin, and international normalized ratio (INR)):

\[ 0.957 \times \ln\text{(creatinine mg/dL)} + 0.378 \times \ln\text{(bilirubin mg/dL)} + 1.120 \times \ln\text{(INR)} + 0.6431. \]

The higher each determinant value, the higher the MELD score and 90-day mortality, and the higher the priority for transplant. Each patient is awarded a MELD score, expressed in whole numbers; the minimum score is 6 and the maximum value is capped at 40. Thus, there are 35 possible MELD scores, compared to four under the prior system. While remaining as a determinant, waiting time serves as a “tie breaker” for candidates with the same MELD score. Since the number of gradations of status increased from four to 35, waiting time was greatly devalued under the MELD system compared with the earlier allocation scheme. In addition, the MELD score offered the possibility of achieving national parity in prioritizing patients for transplantation. Since it was determined solely by objective variables, the MELD score should be the same across the country with little of the subjective variability that plagued earlier allocation schemes.

Following implementation of MELD-based liver allocation in 2002 in the United States, several important
changes occurred. First, the triage of transplant candidates improved and sicker patients were more effectively prioritized and transplanted than under the prior allocation system [5,6]. As a result, sicker patients were transplanted faster and correspondingly the number of patients dying on the waiting list dropped by 16% between 2001 and 2006. As expected, patients were sicker at the time of transplant, and the average MELD score of liver transplant recipients increased from 14 before MELD-based allocation to 22 afterwards. Second, the emphasis on waiting time was greatly reduced. As a result, fewer patients sought early listing and some of those with compensated liver disease were removed from the list. Therefore, the number of listed patients dropped by 13%, from 11,126 in 2001 to 9,646 the following year [7]. Third, unrelated to the implementation of MELD-based allocation, the donor supply improved. The total number of donors increased 30% from 2001 to 2006 due to activity on several fronts (as discussed below) including a nationwide initiative aimed at increasing donor awareness and more aggressive utilization of previously untapped sources of donors. Finally, the allocation system was further amended in 2005 to reduce the transplant priority for less sick patients. The basis for this amendment was the observation that many low MELD score patients (MELD score <15) were still able to receive a liver transplant, particularly in regions of the country with an ample donor supply. In fact, between September 2001 and June 2003, 24% of all US liver recipients had a MELD score <15. Since many of these recipients had compensated liver disease, two concerns were raised. For a patient with compensated liver disease, the benefit of receiving a transplant is not as evident compared to sicker patients. The risk of transplantation in these low MELD recipients could be higher compared to the relatively low mortality risk of remaining on the transplant list. In an analysis from the Scientific Registry of Transplant Recipients (SRTR), the benefit of transplant was analyzed by comparing the 1-year waiting list and post-transplant mortality rates for liver transplant candidates and recipients based on MELD score [8]. This study showed that for low MELD patients (MELD score <15), the 1-year recipient mortality risk was much higher for recipients (who received transplantation) compared with candidates (who remained on the list) (hazard ratio (HR) = 3.64 at MELD 6–11, HR = 2.35 at MELD 12–14, both P<0.001). In response to these data, UNOS amended the allocation scheme to reduce the priority of patients with a MELD score <15. While status 1 patients remain at highest priority, organs are subsequently offered locally within the procuring OPO and then within the UNOS region to patients with MELD scores ≥15. Listed patients with MELD scores <15 are only eligible for deceased donor (DD) livers after these status 1 and MELD ≥15 candidates have been exhausted. After this change, the proportion of low MELD liver recipients dropped by about one fifth [9]. In summary, these improvements in the prioritization of liver candidates along with the increase in donor supply helped to alleviate disparities in access to transplantation and, to a certain extent, quelled the national debate about liver transplantation.

However, despite the advancements, some problems have persisted. Of the three recommendations by the US Institute of Medicine, only the two regarding liver allocation (the creation of an objective scoring system and the de-emphasis of waiting time) were implemented. There has been no change in liver distribution relative to increasing the organ allocation area, simply because the liver transplant community could not reach a consensus on this topic. Consequently, some disparities in access to transplantation have persisted. A recent analysis demonstrated a wide geographic variation in the severity of illness of liver recipients [10]. This analysis found that OPOs serving a small population transplant significantly less sick patients. Twelve of the nation’s 50 OPOs have fewer than 100 patients listed, representing the bottom quartile in OPO size. In fact, the mean number of patients listed in these small OPOs (43) is less than one tenth that of the remaining larger OPOs (462). However, the distribution of MELD scores within all of these OPOs is the same, with only 2% of listed patients with a MELD score >24. Therefore, in small OPOs in which a mean of 43 patients are listed for transplantation, none or only one patient is likely to have a MELD score >24 at any given time. However, in large OPOs, where more than 400 patients on average are listed, the number of patients with a MELD score >24 is likely to be eight or more. The national distribution policy dictates that, in general, livers should be allocated to the patient with the highest MELD score within the OPO where the organs are procured. Therefore, when an organ becomes available, large OPOs are more likely to have a patient with a higher MELD score (>24) compared with a small OPO. Consequently, the proportion of patients who received a transplant with a MELD score >24 is more than 2.5 times higher in large OPOs than in small OPOs (49% versus 19%; P<0.001). In addition, patients are transplanted faster within the small OPOs. The rate of transplantation (per years listed) was 2.5-fold higher for patients listed in small OPOs versus large OPOs (1.03 versus 0.41; P<0.001). Despite transplanting less sick patients faster, the 1-year patient and graft survival rates for small OPOs and large OPOs are not statistically different and waiting list mortality rates are similar in both.

The consequences of this disparity have important implications for individual patients as well as for the liver distribution system as a whole. For the individual patient,
selection of a transplant center within a small OPO will result in a faster transplant at a lower MELD score, but no better outcome in terms of pretransplant waiting list mortality rate or post-transplant survival. For the liver distribution and allocation system, transplantation of less sick patients within these selected OPOs represents a failure to fulfill the Institute of Medicine mandate, which states that organs should be distributed based on patients' medical needs with less emphasis placed on keeping organs in the local area where they were procured.

In response to this problem, UNOS is in active discussion with the liver community about widening the area of organ distribution, that is, regional sharing. While most transplant professionals support the concept of regional sharing, there is no consensus on its implementation.

Another problem in implementing regional sharing is that in general, smaller programs in remote regions are less supportive of increasing the organ distribution area because their local organs would preferentially be shared over a larger base of patients. On the other hand, big transplant programs in large metropolitan cities are more favorably inclined towards regional sharing since they could access more organs from a larger catchment area. Lack of consensus is the result of each center supporting the regional sharing system that would provide its center with the greatest number of transplants. Another problem in implementing regional sharing is the disparity in the distribution of patients and transplant centers across the United States. The large metropolitan population centers (mainly on the east and west coasts) have more transplant candidates and transplant centers compared to smaller cities, mostly located within the middle of the country. In addition, the largest cities have more transplant candidates per population because of better access to medical care and the relocation of sick patients to large, inner-city transplant centers. Were the Institute of Medicine mandate followed, creating uniform organ distribution areas of 9 million people would encompass an area as small as metropolitan New York City (with five liver programs and 1,500 listed patients) and a region as large as 1 million square miles in the Rocky Mountain West (with one program and 120 listed patients). Establishing uniform allocation areas with such stark differences in geographic characteristics and population density is obviously difficult and probably impossible. In addition, there are significant logistic problems in sharing organs across wide expanses of sparsely populated regions. The time, and attendant cost, required to transport organs over vast areas are of particular concern since cold ischemic time is an important determinant of graft function. Therefore, at the time of this writing, the likelihood of adopting a national system for regional sharing of all donor livers in the near future seems remote. However, in the near future, there will likely be implementation of an incremental shift towards a limited regional sharing plan, e.g., for the relatively few liver candidates with extremely high priority for transplant (i.e., MELD score >34). Ultimately, most transplant professionals believe that some form of regional sharing will likely be implemented throughout the country. Because of the inability of the liver community to reach a consensus on this important issue, development of a regional sharing plan may require a governmental mandate following an independent review, similar to what was required prior to the implementation of the MELD system.

Another potential improvement under consideration by UNOS is liver allocation based on the survival benefit of transplant [11]. Transition to such a system would represent a fundamental change in organ allocation, but has many attractive features. There are essentially three means by which liver candidates may be prioritized for transplantation, each with distinct advantages and disadvantages. The current allocation system is devised to prioritize patients based on their need or urgency for transplant independent of transplant outcome. The advantage of this system is that the patients with the greatest risk of death receive the highest priority for transplant. However, the disadvantage is that some patients with a high pretransplant priority have a high post-transplant mortality risk. Allocating livers to such patients would not represent the most utilitarian use of organs. A second means of prioritization is based on a utilitarian approach. That is, patients with the greatest chance of post-transplant survival would receive the highest transplant priority. The benefit of this allocation scheme is that only the best transplant candidates would receive organs thereby maximizing the lifespan of each patient and organ. However, many of the ideal candidates for transplant have a low urgency for transplant. Therefore, adoption of this system would likely increase the pretransplant waiting list mortality.

The third organ allocation scheme, and the one under current consideration, would be a combination of the two systems and is termed “transplant benefit” or “survival benefit.” Under this proposed system, for each donor liver that becomes available, the transplant survival benefit score would be computed for each candidate on the waiting list based on their specific characteristics as well as those of the particular donor. This benefit is calculated based on the difference in 5-year mean survival with the transplant compared to the survival rate of remaining on the list. Proponents of this system contend that survival-based allocation makes the best use of each donor organ. In addition, they point to modeling projections that 2,000 life-years would be saved were such a scheme implemented. However, there are problems with this system, the greatest of which is that the current means of predicting post-transplant survival is inaccurate. The $r^2$
statistic for survival benefit liver allocation is only 0.6 (where 1 is the perfect prediction of the modeling for post-transplant survival). Many experts believe that this is too low to permit its implementation for liver allocation. (By comparison, the $r^2$ statistic for the predictive capacity of MELD is approximately 0.82.) In addition, opponents contend that the projected number of lives saved by survival benefit liver allocation each year (102) is minimal compared to the nearly 17,000 patients listed for transplant. Finally, changing the entire allocation scheme would likely create new unforeseen problems that could be worse. While survival-based organ allocation has been implemented for lung transplantation, its application in liver transplantation remains under intense review and consideration. As the financial resources in all fields of medicine are becoming increasingly restricted, expensive medical procedures such as liver transplantation will be required to demonstrate sufficient benefit to warrant continued funding from payors. Allocating and distributing livers under a "survival benefit" system could potentially provide for a more effective application of liver transplantation in such a financially constrained environment.

### Variation in MELD score

Since it was developed more than 10 years ago, the MELD score has received intense scrutiny on virtually every aspect of its effect on liver allocation. One area of interest is the variation in two of its determinants (INR and serum creatinine) and the potential impact on liver allocation. The INR was devised primarily to standardize the anticoagulation effects of warfarin and not to provide a reproducibly precise assessment of severity of illness in patients with end-stage liver disease. Standardization of therapeutic anticoagulation became necessary when clinicians noted that the various thromboplastin reagents used to determine prothrombin time differed markedly in their responsiveness to the anticoagulant effects of warfarin. To rectify this problem, the World Health Organization (WHO) proposed the INR, which is a correction factor that adjusts for the variable sensitivities of different thromboplastin reagents. The INR can be defined by the following equation:

$$\text{INR} = \frac{\text{mean normal prothrombin time}}{\text{patient's prothrombin time}^2}$$

where $x$ is the international sensitivity index. The INR allows for the standardization of the prothrombin time ratio (determined by any thromboplastin reagent) to a reference WHO thromboplastin standard. With this standardization, the INR allows safe and effective dosing of warfarin, independent of the sensitivity of the thromboplastin reagent.

In liver patients, however, there has never been a formal demonstration of reproducibly precise INR values. In fact, wide INR variations in liver patients have been recognized for years based on the selection of the thromboplastin reagent [12]. (Whether this interlaboratory INR variation was recognized when MELD was developed is unclear.) The reason(s) for the wide variation in INR in liver patients compared with patients receiving oral anticoagulants is not known. One explanation may be the different mechanisms of prothrombin time elevation caused by warfarin and liver disease. Warfarin causes prolonged prothrombin time through inhibition of the vitamin K-dependent $\gamma$-carboxylation of coagulation factors II, VII, IX, and X. In liver disease, the elevated prothrombin time is due in large part to a decreased production of coagulation factors. A recent study evaluated the effect of INR variation on MELD score in liver transplant candidates. These investigators found that based on the selection of clinical laboratory, the same blood sample can yield up to a 2.1-fold difference in INR, which corresponds to a change in MELD score of up to 9 points (Fig. 49-2) [13]. The importance of these findings is underscored by the observation that the greatest variations in INR (and corresponding MELD score) occurred in the patients with the highest INR and highest MELD score. That is, the patients with the highest priority for transplant have the greatest variation in MELD score. Similar findings have been replicated in other studies [14–16]. The fundamental problem with this interlaboratory variation in INR and MELD score is its impact of parity, especially since the greatest differences are noted in patients with the highest MELD scores. Patients with an urgent need for transplant could be advantaged or penalized by changes in their MELD score based on the selection of the clinical laboratory where the INR is measured. Similarly, if one center were using an INR assay yielding lower INR values than another center, all of its patients would be correspondingly disadvantaged. Several possible responses regarding this issue have been proposed [17].

1. The problem could be ignored, with the recognition that clinically relevant variations in the MELD score are acceptable. This seems to be the most likely response.
2. Uniform reagents and measuring devices could be utilized by all laboratories across the country measuring the INR for the MELD score. Given the virtually infinite variety in the combination of reagents and devices, such a response seems impractical.
3. A central laboratory for measuring INR could be developed within the local allocation area to minimize the INR variation. While possible, this solution would be logistically difficult especially when MELD scores are urgently required for all patients.
4. A correction factor could be devised to normalize the MELD score between different clinical laboratories.
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5 The INR could be removed from the MELD score. An analysis has demonstrated that removal of the INR from the MELD score would only minimally impact its predictive capacity; the c-statistic of the MELD-XI (without the INR) was comparable (0.829) to the MELD (0.842) [18].

6 The maximum INR value in the calculation of the MELD score could be capped, similar to the serum creatinine (Cr), which is capped at 4.0. Capping the INR would minimize the contribution of high values to the MELD score and would help to reduce interlaboratory variation [19]. This solution is currently under consideration and would likely be an important and easily implemented remediation of the INR problem.

The serum Cr is also subject to variation relative to the methodology selected for its measurement as well as patient gender. In particular, investigators have shown that elevated bilirubin levels may interfere with colorimetric assays for Cr [20]. They evaluated four different Cr assays in liver patients to assess changes in MELD score. Agreement was found to be poor among all Cr assays and the variation in MELD score was greatest for the patients with the highest bilirubin. For those whose bilirubin was < 5.8 mg/dL, only 3% had a difference of ≥ 2 MELD points. However, in patients with higher values (bilirubin ≥ 23.4 mg/dL), 78% had a difference of ≥ 3 MELD points. This variability among different assays, especially in patients with high bilirubin levels (and therefore high MELD scores and transplant priority) could have a relevant impact on prioritization for liver transplantation.

The same investigators also reported the importance of the differences in Cr relative to the glomerular filtration rate (GFR) between the genders [21]. Compared to men, women have long been recognized to have lower serum Cr for the same GFR. Therefore, for the same degree of renal impairment, females would have a lower Cr, a lower corresponding MELD score, and lower priority for transplantation. These investigators used a correction formula to compensate for this difference and reported that correcting the Cr increases MELD score by 2 or 3 points in 65% of female liver candidates. Whether this variation in Cr relative to MELD score is sufficiently important...
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to address through changes in the allocation system is unclear. However, the variation in MELD score relative to serum Cr and INR point out potential flaws in this carefully constructed allocation system.

**Donation after cardiac death**

Despite an overall shortage of donor organs, the number of donor livers has increased dramatically over the past decade due to changes in medical as well as administrative practice. Between 2000 and 2006 the number of donor livers increased by 33% from 4,997 to 6,653 in the United States [7]. Perhaps the most important reason for this increase was a change in administrative practices promulgated by the Organ Donation Breakthrough Collaborative in 2003, which facilitated the creation of systems within acute care hospitals and OPOs to ensure accurate and timely referral, screening, consent, organ recovery, and successful placement of organs [22].

In addition to these administrative changes, there have been three important medical innovations that have tapped into previously unavailable or underutilized sources of donors: DCD, ECD, and LDLT. The conventional deceased donor, donation after brain death (DBD), is a patient on a ventilator with a devastating brain injury whose death is declared based on the fulfillment of the strict criteria for brain death. On the other hand, DCD donors, while on a mechanical ventilator with irrecoverable brain injury (usually from trauma or hemorrhage), do not meet the strict criteria for brain death [23]. Prior to the development of DCD, such patients had not been eligible for donation. The protocol for DCD was therefore developed as a very controlled and regulated process through which these patients could be legally utilized for donation. The means of acquiring DCD donors fundamentally compromises the quality and function of the donor organ. At the time of extubation and cessation of heart function (donor warm ischemic time), there is a period of hypotension and hypoperfusion of the donor organ that negatively impacts its viability and function. While quite variable, the donor warm ischemic time is the single most important determinant of donor organ quality. In some cases, the warm time is so prolonged that the quality of the donor organ is compromised to the extent that the donor organ is discarded. In general, the outcomes with DCD liver recipients are inferior to those in DBD liver recipients. Specifically, two analyses from the SRTR (one between 1993 and 2001 and another from 1996 to 2003) reported virtually identical results with a mean 50% higher 1-year graft loss rate with DCD compared with DBD (29.4% versus 19.8%; P < 0.01) [24,25]. Perhaps the greatest progress towards improving outcomes is the identification of risk factors associated with graft loss with DCD. These include donor age >35 years (HR = 1.17), donor warm ischemia time >30 minutes (HR = 2.34), and donor cold ischemia time >10 hours (HR = 1.18), as well as recipient factors of age >60 years (HR = 1.17), life support (HR = 1.54), prior transplant (HR = 1.84), hemodialysis (HR = 1.26), and Cr >2.0 mg/dL (HR = 1.23) (P < 0.001). As these risk factors became recognized, the protocols for DCD procurement improved along with better selection of recipients for these marginal organs.

With these changes, some investigators found that patient outcomes with DCD are similar to DBD. For example, in a study where low-risk recipients were paired with low-risk DCD donors (warm ischemic time <30 minutes and cold ischemic time <10 hours), 1-year graft survival rates (81%) were not significantly different than those in DBD recipients (80%). However, despite these favorable results, the overall performance of DCD grafts is clearly inferior to DBD. The most important clinical complication associated with DCD is biliary strictures. Because the cause of biliary disease in DCD recipients is different to that in DBD recipients, so is the characteristic distribution of strictures within the liver. The biliary tree receives its critical perfusion through the arterial system and is therefore quite sensitive to hypoperfusion that may occur during DCD organ procurement. Consequently, DCD recipients are more likely to develop diffuse biliary strictureing throughout the liver, whereas most strictures in DBD recipients are at the biliary anastomosis. In fact, biliary disease is twice as common in DCD compared to DBD recipients and may frequently lead to significant graft dysfunction and/or failure [26,27]. The diffuse nature of the strictures in many DCD recipients makes them less amenable to interventional drainage and patients may be rendered as “biliary cripples,” with serious chronic intractable biliary disease.

Implementation of DCD has expanded the total number of donor livers available for transplantation. The number of DCD donors in the United States increased more than ten-fold from just 23 in 1999 (~1% of liver transplants) to 307 in 2007 (4.9% of liver transplants) (Fig. 49.3). However, there was a slight decrease in the number of cases in 2008 to 276 cases (4.5% of all liver transplants) [28]. The reason(s) for the slight decline is not known, but is likely due to increased awareness of the associated risks and perhaps more careful selection of donors and recipients. Due to the higher risk of graft failure associated with DCD as well as the inherent complexities in organ procurement, some centers have not fully embraced the concept of DCD as a source of additional...
donor livers. Consequently, the application of DCD is quite variable amongst transplant centers across the country. In some regions of the United States, DCD accounts for nearly 10% of all adult deceased donor liver transplantation (DDLT) and in other areas fewer than 1%. DCD will likely remain as an important, but limited, means of expanding the donor pool, especially in areas where the donor supply is most limited. The effective application of DCD for liver transplantation requires cooperation between the OPO and the local transplant center(s) to ensure maximal utilization of these higher risk organs as well as careful application of the donor procurement protocols.

**Living donor liver transplantation**

The use of living donors has been another important development to partially alleviate the shortage of donor organs [29]. The first successful case was reported in 1989 and over the subsequent decade the procedure was largely limited to Asia where cultural mores prohibit the widespread application of deceased donation. At that time, the procedure utilized the left hepatic lobe or one of its segments. In the United States, relatively few cases were performed until 1999, largely in pediatric recipients where the parental donors readily accepted the procedural risk of donation and the small size of the left hepatic lobe provided a sufficient hepatic reserve. After 1999, LDLT was more widely applied and its rapid growth was due primarily to two factors. First, the growing shortage of deceased donors intensified in the late 1990s, forcing transplant centers to seek innovative strategies to increase the donor pool. Second, selected centers reported successful LDLT with the right hepatic lobe, which is larger than the left lobe and provided adequate hepatic volume to support full-size adults. The subsequent growth in LDLT was rapid; in 1998, fewer than 100 cases were performed while the number increased to 524 in 2001, remarkably accounting for 11% of adult liver transplants in the United States (Fig. 49.3) [7]. There were initial projections that LDLT would constitute up to 50% of all liver transplants, although this has never been realized.

The choice to pursue LDLT for a specific patient is a complex consideration of the advantages and disadvantages of the procedure. The primary advantage associated with LDLT is speed and timing. Patients with an urgent need for transplant and no immediate prospects for DDLT are the best candidates for LDLT – such as patients with low MELD scores with hepatocellular carcinoma or primary sclerosing cholangitis with recurrent sepsis. While awaiting a deceased donor, such patients are at risk for dying or suffering decompensation, thereby jeopardizing the success of the DDLT. The primary risk for the LDLT recipient is associated with the immediate perioperative risk of complications, which are higher compared with DDLT, including death. In short, the patient who chooses to pursue LDLT incurs a potentially higher short-term risk related to an expedited transplant with the potential benefit of improved long-term survival by avoiding the risk of death while on the waiting list or decompensation which could ultimately jeopardize the success of DDLT. In fact, a recent study by the Adult-to-Adult Living Donor Liver Transplant Study Group (A2ALL) compared outcomes of LDLT versus DDLT [30]. The starting point for this study (from the time of donor evaluation) was carefully selected to encompass the clinical scenario (described above) related to the risks and benefit associated with the procedure. Of the 807 potential living donor recipients, 389 underwent LDLT, 249 underwent DDLT, 99 died without transplantation, and 70 were awaiting transplantation at last follow-up. Compared to
waiting for DDLT, the receipt of an LDLT organ was associated with a significant survival benefit with an adjusted mortality HR of 0.56 (P < 0.001). The benefits were even greater at centers performing more than 20 LDLTs, with a mortality HR of 0.35 (P < 0.001). Therefore, this study demonstrated for the first time that the choice to pursue LDLT is associated with at least a 44% reduction in mortality risk compared to waiting for DDLT.

Despite these data supporting its use, LDLT has been negatively impacted by several recent developments. Consequently, the initial enthusiasm surrounding the procedure has waned, the number of cases in the United States has dropped significantly, and its role in the field of liver transplantation is being reconsidered. After the implementation of MELD-based liver allocation in 2002, there was less need for LDLT. As discussed above, better access to DDLT due to improvements in liver allocation along with better donor supply, obviated the need for a living donor. In fact, a recent study found that 11% of LDLT donor candidates could not even finish their evaluation, because the recipient underwent DDLT prior to its completion [31]. Another reason for the decline in LDLT is the emergence of data showing inferior outcomes compared to DDLT. The rate of allograft failure in a risk-adjusted analysis was shown to be increased with LDLT (HR = 1.66, P <0.05) compared with DDLT [32]. In addition, the complication rate was significantly higher with LDLT. Data from the A2ALL study found that the following complications occurred at a higher rate after LDLT versus DDLT: biliary leak (31.8% versus 10.2%), reexploration (26.2% versus 17.1%), hepatic artery thrombosis (6.5% versus 2.3%), and portal vein thrombosis (2.9% versus 0.0%) (P < 0.05) [33]. The reduction in LDLT cases over time was also due in part to a front-loaded effect. That is, at the inception of LDLT at each center, the most ideal donor-recipient pairs were identified and transplanted. However, after these cases were expended, it became apparent that many potential LDLT recipients were unable to identify a suitable donor and therefore were ultimately rejected for the procedure. This is reflected in the A2ALL study where the overall rate of donor acceptance was significantly higher during the early experience (47% in 1998-2000) compared with a later era (35% in 2001-2003; P <0.0002) [31]. Finally, the full extent of donor risk did not become apparent until several years after the widespread application of the procedure. Initial reports of donor complications were relatively low (less than 20%) [34]. However, a more comprehensive report of donor complications reported a complication rate of 38% that was nearly twice as high. While 27% of complications were minor, the remaining 11% were more serious, including 2% that were considered life threatening and 0.8% that led to death [35]. Reports began to surface of donor deaths and aborted donations (patients who underwent anesthesia in the operating room, but had the donor operation aborted prior to successf ul donation). Twelve (3%) aborted donors were reported from the A2ALL series and an additional 12 (4.7%) from Toronto [35,36]. While the risk of donor death is not known due to the absence of a comprehensive database, there are at least 13 worldwide donor deaths “definitely” related to the donor operation, making an estimated risk of 0.15% [37]. Because of all of these concerns, the number of LDLTs performed in the United States decreased by one half from its peak year of 2001 when 524 cases were performed, to only 219 adult recipients in 2009, representing just 3.5% of all liver transplants.

What does the future hold for LDLT? It will likely remain a viable procedure where the supply of DD organs is limited. In Asia, where LDLT remains the predominant means of providing liver transplantation, its application remains robust. In fact, the Asan Medical Center in Seoul, Korea—a country with less than one quarter the population of the United States—performs over 300 cases annually, which is more than the entire volume of LDLTs in the United States. In the latter, LDLT may remain a viable means to provide access to liver transplantation in selected patients, particularly in regions where the donor shortage is especially acute such as Boston, New York, Chicago, and California. However, in most other parts of the United States, the application of LDLT will likely remain quite limited. In addition, unless a program performs approximately ten or more cases each year, it seems unlikely that they would be able to maintain adequate performance standards for this technically complex procedure. In 2009, only seven hospitals in the United States had performed such a volume.

**Expanded criteria donors**

The use of ECDs, defined as donors who are not ideal or standard, is another strategy to increase the donor pool. While marginal liver grafts have been transplanted for decades, the concept of ECD is to objectively define the characteristics and associated risk of using these organs. By doing so, clinicians may learn how to mitigate these factors and select the best recipients for these marginal grafts, thereby maximizing organ utility. Perhaps the most detailed description of the ECD procedure was by Feng et al., who identified seven donor and graft factors associated with graft failure: donor age >40 years, DCD, split/partial grafts, African-American race, less height, cerebrovascular accident, and “other” causes of brain death [38]. Using these specific features, they devised the donor risk index (DRI), which is the relative risk of graft loss for an organ with a specific set of donor
and transplant characteristics compared with a reference case, where DRI = 1.0. The higher the DRI, the higher is the 1-year graft loss rate. For example, the 1-year graft loss rate for a high DRI liver (DRI > 2.0) is 28.6%, which is more than twice that of an ideal donor (DRI < 1.0) at 12.4%.

Over the past decade, transplant centers have utilized an increasingly high proportion of marginal or high DRI livers. Between 1999 and 2008, there was a 36% increase in donors with a DRI > 1.8, with a corresponding 17% decrease in donors with a DRI < 1.3 (Fig. 49.4) [28]. When selecting recipients to receive a high DRI liver, transplant centers have developed a utilitarian approach towards graft disposition. Surgeons have learned through experience that transplanting high DRI livers into high MELD score patients is associated with higher rates of graft loss. Specifically, when using a liver with DRI ≥ 1.7, the 1-year graft loss rate is 37% higher in recipients with a MELD score ≥ 27 compared with a better liver (DRI < 1.7) [39]. Therefore, high DRI organs are frequently rejected for use in high MELD recipients and are utilized in low MELD recipients where graft loss rates are lower. One-year graft loss rates in these low-risk patients (MELD score < 15) are 21% lower than in high-risk recipients (MELD score ≥ 27) (20.9% and 26.6%, respectively). A recent SRTR analysis confirmed the widespread use of this strategy where investigators demonstrated an inverse relationship between DRI and recipient MELD score [40]. The liver DRI decreased as MELD score increased and the highest median DRI (1.22) occurred in patients transplanted with a MELD score of 40. While this strategy may provide the most utilitarian use of a wide spectrum of donor livers, the benefit to specific recipients is less clear. Low MELD recipients (MELD score < 12) receiving a high DRI liver suffer a significantly higher mortality with transplant, compared to remaining on the waiting list. In fact, the highest relative risk of mortality occurred in recipients with the lowest MELD scores (score 6–8) who received high DRI organs (HR = 3.70, P < 0.0005). So, which patients benefit the most from receiving high DRI livers? All recipients with a MELD score ≥ 20 had a significant survival benefit from transplantation, regardless of DRI. However, the patients who had the greatest relative benefit from high DRI organs were those with the highest MELD scores, due to their significant risk of death without transplantation. Even with the highest quartile risk DRI, recipients with the highest MELD score (score = 40) had a significantly lower mortality rate with transplant compared to remaining on the list. However, the impact of implementing such a practice would probably not have its intended result. In Schaubel et al.’s analysis, only 1% of all recipients had a MELD score of 40 and received a high DRI graft [40]. Therefore, these donor-recipient matches were likely selected for favorable outcome. Without selection mechanisms in place, the outcomes of high MELD/high DRI transplants might be very poor.

Currently, the liver transplant list is filled with a wide range of liver candidates, from those with minimal or no decompensation, to patients whose 90-day mortality is virtually 100%. The spectrum of quality in donor organs is equally wide. One of the greatest unmet challenges is devising a system that effectively matches specific organs and recipients to maximize the utilization of marginal grafts without impacting recipient outcomes.

MELD exception scores

Another area of considerable controversy is that of MELD exception scores. MELD exception scores are awarded to patients whose mortality risk is not adequately reflected by their laboratory MELD score. Assignment of MELD
exception scores occurs through the regional review board for one of two broad indications: hepatocellular carcinoma (HCC) and non-HCC diagnoses. For HCC, candidates within the Milan criteria (or, in some regions, other similar specified criteria) receive a standard MELD exception score (22 points) to limit the risk of removal from the waiting list due to cancer progression. The number of transplant recipients with HCC increased from 999 in 2002 to 1,656 in 2008 or 27% of all liver transplants. Patients beyond the Milan criteria are also awarded MELD exception scores if approved by their regional review board. Some of these candidates meet prespecified tumor specifications – International Registry of Hepatic Tumors in UNOS region 4 [41] or University of California, San Francisco (UCSF) criteria [42] – both of which are slightly over the Milan criteria. Other patients with nonstandardized criteria for HCC are evaluated on a case-by-case basis by the regional review boards. The proportion of HCC patients on the waiting list (at the year’s end) with a nonstandard HCC MELD exception score increased from 1.0% in 2002 to 20.6% in 2008 [28]. Many such patients may have been successfully downstaged with loco-regional therapies.

MELD exception scores are also awarded by the regional review board for indications other than HCC. Such patients have a risk of death, as subjectively judged by their transplant team, that is not reflected by their laboratory MELD score. These may be recognized diagnoses that include specific disorders (e.g., familial amyloidosis, hepatopulmonary syndrome, portopulmonary hypertension) or complications of liver disease (e.g., ascites, encephalopathy, biliary complications). The number and percentage of liver candidates with non-HCC MELD exception scores has increased every year since the institution of MELD-based allocation, from 382 in 2002 to 990 in 2008 [28]. However, the number of candidates with MELD exceptions on the waiting list (at the year’s end, 2008) varies widely between UNOS regions, with only 16 in region 10 compared to 48 in region 5. Special concern relates to patients receiving non-HCC MELD exception points, particularly in regions where organs are in the highest demand, namely region 5 (California) and region 9 (New York), because these patients receive a very high priority for transplantation. For example, in New York, which runs a single list for the entire state (and region), there are 33 such patients, whose mean score is 27.2 points. In region 5, 48 patients have a mean score of 24.3. The high MELD scores awarded to these patients enhance the likelihood of them receiving a transplant. In fact, the rate of transplant is nearly three-fold higher than for patients with standard laboratory MELD scores [43]. There is concern that these non-HCC MELD exclusion scores may reflect another version of subjective upgrading that plagued previous allocation scheme (as described above).

To address this concern, UNOS organized a conference (MELD Exception Study Group and Conference [MESSAGE]) where standard criteria were developed and published for 17 exceptional medical conditions frequently encountered by the US regional review boards. The recommendations were researched, discussed utilizing an evidenced-based format, and ultimately published in 2006 to provide guidelines for regional review boards [44]. While these recommendations are not binding, they have been implemented in varying degrees within each region. The national impact of the MESSAGE guidelines on non-HCC MELD exception points is difficult to assess, but an analysis shows some improvement after their publication in 2006. There was a slight increase in the proportion of patients receiving a DDLT with a MELD exception other than HCC, from 7.6% in 2003 to 8.6% in 2007 [45]. The fraction of each region’s total DDLTs with non-HCC exceptions has become more uniform. In 2003, the percentage of regional DDLTs with non-HCC exceptions ranged from 2% to 21%. By 2007, this range had narrowed to between 5% and 10% for all regions. There have been discussions about creating a national review board to ensure national uniformity in the diagnosis and scoring of these patients as well as normalizing the points awarded to each patient, but none has been formed as yet.

One of the problems related to implementing a national review board is the wide disparity in MELD scores for liver recipients between regions. In regions that transplant at lower MELD scores, the number of MELD points requested for non-HCC MELD exception points would be lower than in regions where MELD scores are higher. This is reflected in the wide range of MELD scores given for non-HCC MELD exceptions, which range from a mean of 19.1 in UNOS region 3 to 28.5 in region 2.

Annotated references


This is the first study that demonstrated the potential benefit for LDLT recipients compared with the option of remaining on the transplant list for a DD transplantation.

The authors describe specific risk factors associated with graft loss in live transplant recipients and in doing so define the donor risk index (DRI), which serves as a point check to objectively assess the quality of a donor graft in liver transplantation.


This paper describes the significant risk factors for graft loss associated with liver transplant recipients of DCD organs. The authors describe a means to match the recipients and DCD donors to maximize patient outcomes.

This study demonstrates the lower limit for the survival benefit for liver transplantation at a MELD score of 15. The findings in this study changed the liver allocation policy known as the “shell 15” rule.


The development of a liver allocation system based on the survival benefit described. While such a system has been adopted for lung transplantation, the liver allocation scheme remains under review.

References

Part XI: Elements of Liver Transplantation


Multiple choice questions

49.1 Which of the three following determinants in the model for end-stage liver disease (MELD) score has the highest multiplicative factor?
   a. Bilirubin.
   b. International normalized ratio (INR).
   c. Serum creatinine.
   d. Both b and c.

49.2 Which of the following have helped to increase the number of deceased donor organs for liver transplantation?
   a. Expanded criteria donors (ECDs).
   b. Donation after cardiac death (DCD).
   c. Living donors.
   d. a, b, and c.
   e. a and b.

49.3 Which of the following factors is associated with the decline in the number of living donor liver transplantations (LDLTs) performed in the United States?
   a. The availability of deceased donor livers.
   b. Donor complication rates.
   c. Recipient complication rates.
   d. All of the above.

49.4 As a means to increase access to transplantation for sick patients, the United Network for Organ Sharing has implemented a widely accepted regional sharing plan for deceased donor livers across the United States.
   a. True.
   b. False.

49.5 The donor risk index (DRI) is which of the following?
   a. The ratio of observed versus expected graft loss.
   b. The relative risk of graft loss for an organ with a specific set of donor characteristics compared with reference case.
   c. Is only applicable to kidney transplantation.
   d. The relative risk of graft loss for an organ with a specific set of donor and graft characteristics compared with a reference case.

49.6 What is the basis for the liver allocation currently under active consideration?
   a. Pretransplant survival.
   b. Utilitarian.
   c. Survival benefit of the transplant.
   d. The donor risk index.

Answers to the multiple choice questions can be found in the Appendix at the end of the book.
These multiple choice questions are also available for you to complete online. Visit http://www.schiffsdiseasesoftheliver.com/