

# Model for End-Stage Liver Disease (MELD) Exception Guidelines: Results and Recommendations From the MELD Exception Study Group and Conference (MESSAGE) for the Approval of Patients Who Need Liver Transplantation With Diseases Not Considered by the Standard MELD Formula

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Determining need for liver transplantation (LT) can be effectively estimated when the actual liver disease is highly likely to cause death in the near future. However, for many conditions, the liver disease itself does not carry a high risk of short-term mortality, and other factors contribute to defining the need for LT. The existence of these so-called exceptional cases was recognized in the initial development of the Model for End-Stage Liver Disease (MELD)- and Pediatric End-Stage Liver Disease (PELD)-based liver allocation policy,<sup>1</sup> most notably in the case of hepatocellular cancer (HCC). In this instance, the driving imperative for LT is not life-threatening liver failure, but the progression of cancer to a point where a high probability of cure is no longer possible. Using the well-established Milan Criteria<sup>2</sup> as selection criteria for good outcome, policymakers initially equated the risk of HCC progression beyond Milan Criteria to 15% for stage 1 lesions and 30% for

stage 2 lesions within 3 months of listing analogous to MELD-defined mortality risk.<sup>3</sup> These initial estimates proved to be too high based on publications citing much lower risks of progression in cohorts of waiting LT candidates with HCC,<sup>4,5</sup> and subsequently, the risk of HCC progression was reestimated to be much lower. The HCC priority policy was revised accordingly.

The HCC example illustrates two important principles for allocating livers to patients with low mortality risk who fall into these exceptional diagnosis categories. First, a nonmortality endpoint, namely the risk of progression beyond Milan Criteria, where a patient would be removed from the LT waiting list, was defined. For any such endpoint, patient-specific, objective definitions must be used. In the case of HCC, the risk of tumor progression beyond the Milan Criteria meets such standards because the risk of progression does not depend on extrinsic influences like geography, lo-

**Abbreviations:** LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease; HCC, hepatocellular cancer; RRB, Regional Review Board; MESSAGE, MELD Exceptional Case Guideline, HE, hepatic encephalopathy; BCS, Budd-Chiari syndrome; PH, primary hyperoxaluria; CF, cystic fibrosis.

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cation of care, or subjective assessment of symptoms, and the Milan criteria are very well described and reasonably measurable. Policymakers may change the HCC endpoint in the future on the basis of recent evidence that there are some cases beyond Milan Criteria that also carry excellent disease-free survival after LT. Doing so, however, would not require a complete revision of the liver allocation system but would only require reestimation of the risk of progression to this new endpoint. Thus, endpoints can be revised over time if they remain appropriate, objective, and patient-specific estimates of need, and continue to define reasonable success rates relative to the majority of waiting candidates. This process is critical for maintenance of equity of access to the limited donor pool. Second, as evidence accumulated, the original, admittedly arbitrary, estimates of risks of achieving the beyond-Milan Criteria endpoint were not as high as originally thought, and again, the assigned priority was changed based on evidence and without the need to completely readjust the entire system. More recently, with additional accumulated experience, investigators have more directly estimated the risk of HCC progression by using waiting list removal data.<sup>6</sup> In this effort, factors associated with waiting list removal for candidates with HCC were identified and used to construct a predictive model for waiting-list dropout, which can be used to more accurately estimate risk of waiting list removals. This approach can serve as a framework for all LT candidates where the estimated risk of removal can be calculated once criteria for such removals are established. These removal criteria we term “waiting list endpoints” and can be mortality or some other measure like HCC stage. The risk of meeting the waiting list endpoint then becomes the metric for prioritization.

Although the LT community recognized many conditions other than HCC in which mortality risk does not adequately define need for LT,<sup>7</sup> few endpoint criteria and even fewer risk models exist to help quantify this need. A regional peer review system was established so that expert opinion could be brought to bear on making these assessments and currently these Regional Review Boards (RRBs) prospectively review every case (other than HCC within Milan Criteria) where the need for LT is thought to be underestimated by the MELD/PELD defined-mortality risk. However, because there are no well-defined criteria and there has been no comprehensive evidence review to establish guidelines to help RRBs make these assessments, these judgments have been largely based on individual RRB members' expert opinions. Several RRBs around the country have adopted their own systems for making these judgments but there is no consistent national protocol for RRB process. In addition, a systematic examination of the data elements required for better risk assessment studies is required to improve the appropriate prioritization of these exceptional cases.

As part of ongoing organ allocation policy assessment and development, the United Network for Organ Sharing, the federal contractor for administration of the national Organ Procurement and Transplantation Net-

work, constituted an effort to evaluate the non-HCC exceptional cases under the MELD/PELD liver allocation system. The MELD Exceptional Case Guideline (MESSAGE) Committee and recent MESSAGE conference participants were charged with two main tasks in an effort to improve ranking of candidates with these exceptional diagnoses where the need for LT might be defined by other endpoints. The specific goals in this exercise were: (1) to identify conditions for which a specific, objective, endpoint exists that defines need for LT such that assignment of additional priority can be automatic (without RRB peer review) and recommend the amount of additional priority so assigned, and (2) for those conditions where there is insufficient evidence, to recommend specific, objective data elements to be collected for individual conditions for which there was insufficient evidence for granting increased priority.

Since HCC has been well addressed in other forums, the MESSAGE subcommittee was directed to focus on all other areas of exceptional diagnoses and RRB requests for priority upgrades and state where there was no data and identify data elements to be collected. The MESSAGE subcommittee presented the results of their literature review at an international meeting of experts in the field held March 1 and 2, 2006, in Chicago, IL, at which final recommendations were formulated. The preceding articles in this supplement summarize these deliberations. In this article, we summarize the conclusions reached for individual exception conditions regarding LT waiting-list endpoints, the priority magnitude recommended, and the data required to develop endpoints in cases where no clear endpoint has been defined. We will offer some conclusions for future development of policy to address exceptional cases.

## SPECIFIC RECOMMENDATIONS

Current evidence and expert opinion regarding exceptional conditions where MELD/PELD alone may be inadequate for prioritization for LT are listed in Table 1. Waiting list endpoints are indicated for all exceptional case diagnoses. For most diagnoses, a risk of mortality is deemed most appropriate, but since the evidence suggests that the MELD/PELD score does not adequately measure wait-list removals as too ill, mortality risk or risk of no liver disease end organ damage for these cases, additional data are needed. Automatic assignment of priority is indicated based on sufficient evidence, expert opinion, or established practice.

### Ascites

Biggins et al.<sup>8</sup> cite studies indicating that mortality risk is the appropriate endpoint when considering ascites as an additional criterion for assigning priority for LT. These studies indicate that ascites is associated with increased mortality risks but subjective measurements, even those defined by the International Ascites Club, are not dependent on intrinsic patient characteristics and are more a reflection of physician practice patterns/preferences and reporting biases. Serum so-

TABLE 1. Summary of MESSAGE Guidelines for MELD Point Allocation

Diagnosis	Waiting list endpoint	Additional data	Automatic points	Comments
Ascites	Mortality risk	Serum sodium + MELD score	No	There is inadequate evidence for increased mortality to support increased priority in most cases.
Hepatic encephalopathy	Mortality risk	ICP; need for endotracheal intubation for airway protection	No	Evidence for increased mortality risk is confounded by subjective measures and patient compliance issues. The West Haven criteria are subjective.
Polycystic liver disease	Malnutrition	Nutritional parameters; vascular studies; infection history	No	Quality of life justifications are not sufficient for increased priority.
Gastrointestinal bleeding	Mortality risk	Amount of blood transfused over time; contraindications to standard medical or interventional treatments	No	Prospective application should include specific contraindication to TIPS, endoscopic, or medical treatments.
Hepatopulmonary syndrome	Hypoxemia	PaO <sub>2</sub> <60 mm Hg while sitting; bubble echocardiography	Yes	A correlation between progressive hypoxemia and mortality is not well established. There is a need for standardized intrapulmonary shunt testing.
Portopulmonary syndrome	MPAP,PVR	Prostacyclin therapy; RV function	No	A correlation between progressive MPAP and waiting list mortality needs to be established in large prospective studies.
BCS	Mortality risk	None	No	MELD points define severity of disease for chronic BCS. Acute BCS should use 1A designation.
Pruritis	Not justified	None	No	Quality-of-life justifications are not sufficient for increased priority.
Primary Hyperoxaluria	Mortality risk	Renal failure; progressive oxalate deposition; liver biopsy	Yes	A liver biopsy sample documenting PH is sufficient evidence for automatic MELD/ PELD award.
Familial amyloid polyneuropathy	Mortality risk;polyneuropathy score; left ventricular wall thickness	Cardiac parameters; modified BMI (self-reported height at age 25 years); polyneuropathy disability score	Yes	Evidence needs to be accumulated to document increased waiting list disease progression that results in dropout and increased mortality.
Cystic fibrosis	Mortality risk	FEV <sub>1</sub> < 40% predicted	Yes/No	Automatic priority increases justified for patients listed for LT alone who have progressive pulmonary deterioration justified by documented increase in mortality. Quantification of risk is not well characterized.
Cholangiocarcinoma	Tumor markers; mortality risk	Protocol variables; imaging data; IRB-approved treatment protocol needs to be documented at each institution	No	Neoadjuvant protocols must be approved by UNOS/OPTN Liver Committee to meet increased priority. Automatic upgrades are only permissible for approved neoadjuvant protocols. Dysplasia has no evidence for increased waiting list death or removal.

TABLE 1. (Continued)

Diagnosis	Waiting list endpoint	Additional data	Automatic points	Comments
Cholangitis	Mortality risk;bacteremia;septic complications	Bacteremia; structural bile duct diagnosis; antibiotic use; septic complications	No	There is no evidence that cholangitis is directly associated with waiting list mortality risk. Predictors for septic complications such as antibiotic resistance would help RRBs select patients likely to have waiting list mortality or waiting list removal as too ill to undergo LT.
Unusual tumor	None	Metastatic survey; biopsy data	No	Prospective RRB review is required on a case-by-case basis.
Unusual metabolic disease	Complications that are specific to the metabolic defect that may include: neurologic, nutritional, renal, and other organ system involvement	Neurologic testing; nutritional parameters	No	Rare cases with multiple manifestations result in lack of definitive evidence for automatic upgrade. Prospective RRB review is required on a case-by-case basis, taking into account wait-list removal for progression of non-liver-related organ failure or injury and the documentation that LT will obviate disease progression.
Small-for-size syndrome	Mortality risk	Biopsy	Yes	Expert opinion recommends automatic upgrade. Need validation of MELD/PELD for these cases.
Hereditary hemorrhagic telangiectasia	Mortality risk	Cardiac failure; portal hypertension	No	Mortality risk is likely not reflected by MELD/PELD because of lack of deterioration in liver synthetic function.

**Abbreviations:** MELD, Model for End-Stage Liver Disease; MESSAGE, MELD Exception Study Group and Conference; ICP, intracranial pressure; TIPS, transjugular intrahepatic portal systemic shunt; MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RV, right ventricular; BCS, Budd-Chiari syndrome; PH, primary hyperoxaluria; PELD, Pediatric End-Stage Liver Disease; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume at 1 second; LT, liver transplantation; IRB, institutional review board; UNOS, United Network for Organ Sharing; OPTN, Organ Procurement Transplantation Network; RRB, regional review board.

dium in association with MELD score has shown improved accuracy for estimating mortality risk, especially for patients with low MELD scores, although the absolute increase in predictive value is small.<sup>9</sup> The United Network for Organ Sharing/Organ Procurement Transplantation Network waiting list data collection process has accumulated a large amount of serum sodium values and these data should be analyzed for prospective validation in association with the MELD score. At present, in the absence of a clear contribution of objectively measured ascites to the mortality risk defined by MELD, no automatic assignment of additional priority points can be made. There is little additional objective evidence that ascites changes the MELD-defined mortality risk, especially at the higher range of MELD scores where liver allocation is most likely to occur, and most measures of severity of ascites remain physician-specific. Therefore, there is little evidence to support additional priority for patients with severe ascites and those referred for RRB approval should be extremely rare and unusual.

### Hepatic Encephalopathy

Ham et al.<sup>10</sup> rightfully point out that there are no patient-specific, well-documented objective measures of hepatic encephalopathy (HE), although there are data suggesting that HE (if consistently measured) can be associated with increased mortality, independent of the MELD score. Potential objective variables to be assessed for future refinement of the contribution of HE to mortality risk are: endotracheal intubation for airway protection in severe HE, and/or increased intracranial pressure. The West Haven Criteria are subject to observer bias and are based on subjective assessments of mental status. Endotracheal intubation is also dependent on physician practice patterns. Thus, although there is evidence for increased mortality risk for patients with chronic liver disease and HE, the lack of objective methods for quantification of its severity makes it extremely difficult to accept increased priority for this condition in a consistent and equitable manner. Thus, the available evidence does not support auto-

matic increases in priority and case-by-case approvals by the RRBs also should be extremely rare unless supported by intracranial pressure measurements or endotracheal intubation justifications.

### Polycystic Liver Disease

Polycystic liver disease rarely carries an increased mortality risk, although these patients can have severe deterioration in their quality of life.<sup>11</sup> There are many nontransplant options that may temporarily or rarely, permanently, relieve symptoms. In extreme cases, malnutrition resulting from inanition and early satiety can develop and profoundly impair affected patients' immune responses to infection and their ability to survive surgery. There is insufficient evidence to warrant automatic priority increases for patients with polycystic liver disease. Individual prospective requests to RRBs for increased priority should include information on nutritional parameters and history of cyst infection. Requests based on quality-of-life justifications cannot be supported because there is no correlation with quality of life. Some regions have assigned a moderate increase in priority to cases where severe starvation can be documented by liver size and biochemical nutritional parameters. A modest initial score can then be increased by 2 or 3 points every 3 months until the patient gets transplanted. This approach gives these cases some increase in priority, but does not allow for transplantation in such cases without substantial waiting time, making it fair for all patients waiting.

### Gastrointestinal Bleeding

Bleeding from increased portal pressure is a common complication of chronic liver disease and has been associated with increased mortality in these patients.<sup>12</sup> Although there are highly effective surgical and medical treatments for acute portal hypertensive bleeding, there are also contraindications to each of these measures. Currently, there are no prospectively validated measures of the severity of bleeding or objective measures for contraindications for interventions, although serum bilirubin may be a helpful prognostic marker for success of transjugular intrahepatic portal systemic shunt. Because the vast majority of cases of portal hypertensive bleeding can be controlled with nontransplant measures, and there are no well-established, objective, patient-specific measures of refractory bleeding, no automatic increase in priority can be justified at this time. Individual prospective applications to RRBs for increased priority based on recurrent bleeding should include documentation of contraindications to medical and surgical therapy, quantity of blood transfused over a given period of time, use of mechanical tamponade devices, and requirement for endotracheal intubation.

### Hepatopulmonary Syndrome

Hepatopulmonary syndrome is increasingly diagnosed in patients with cirrhosis. Established MELD/PELD liver al-

location policy allows increased priority, in theory, because the pulmonary component of this disease conferred a risk of dropping out that was beyond that calculated by the MELD score alone. Fallon et al. indicate that there are data suggesting that progressive hypoxemia in patients with documented intrapulmonary shunting and cirrhosis is associated with increased mortality, but these results are derived from small retrospective analyses.<sup>13</sup> Hypoxemia appears to be an appropriate waiting list variable in that it is patient specific, easily and objectively measured, and has been associated with mortality. The degree to which this is independent from MELD only defined risk remains to be established and incorporating PaO<sub>2</sub> with MELD might be feasible. Based on these data and the experience with the current MELD/PELD-based policy for increased priority for Hepatopulmonary syndrome patients with PaO<sub>2</sub> < 60 mmHg and documented intrapulmonary shunting with no other cause for the pulmonary disease found, expert opinion recommends an automatic increase in MELD priority calibrated to the severity of hypoxemia. Additional data on pulmonary parameters will be helpful in better defining the limits of waiting list dropout and LT success for these patients.

### Portopulmonary Hypertension

Portopulmonary hypertension (POPH) has been associated with increased rates of posttransplant mortality and untreated, the median survival is approximately 18 months. The degree to which the severity of liver disease and the severity of the pulmonary hypertension each contribute to the poor outcomes before and after liver LT remains poorly understood, but MELD scores do seem to correlate well with the degree of portopulmonary hypertension.<sup>14</sup> Experts recommend that screening for pulmonary hypertension with echocardiography should be required as many cases of portopulmonary hypertension are diagnosed only at the time of anesthesia induction for LT. In addition, right heart catheterization is required to accurately characterize the portopulmonary hypertension so that measurements of pulmonary systolic, diastolic, vascular resistance, occlusion pressure, and cardiac output can be performed. Mean pulmonary artery pressure (mPAP) is emerging as a potentially acceptable waiting list variable since it is objective and patient-specific and may be correlated with pretransplant mortality, but more data needs to be accumulated including the role of prostacyclin analogue treatment in altering the pulmonary hemodynamics and waiting list mortality.

Expert opinion recommends that increased priority is justified for patients with documented mean pulmonary artery pressure > 35mmHg (prior to treatment) with an estimated 26 MELD points awarded. However, since there is clear evidence that patients with mPAP > 45 mmHg have extremely poor post transplant outcomes,<sup>15</sup> every effort should be made to treat this degree of POPH prior to LT. Cases where the mPAP remains > 45 mmHg despite treatment should receive extra priority only in extremely unusual instances, since the results with LT remain very poor for these

patients. Requests for increased priority for POPH cases should include documentation of the mPAP and pulmonary vascular resistance and the effects of any treatment given to reduce the mPAP prior to LT. Because there is little data on the magnitude of increased risk related to MPAP, quantification of increased need on the basis of MPAP remains arbitrary at this time.

### Budd-Chiari Syndrome

Indications for LT for patients with Budd-Chiari syndrome (BCS) generally fall into two categories. Most patients develop progressive cirrhosis and portal hypertensive symptoms that, ultimately result in loss of hepatic synthetic function. In rare cases, BCS can present with features of fulminant hepatic failure where emergent intervention is required. The available evidence suggests that patients with chronic progressive BCS are well served by the MELD score as the parameters associated with mortality cited in previous studies closely parallel those included in the MELD score.<sup>16</sup> Patients with acute, fulminant BCS should be prioritized by using acute liver failure polices such as the IA designation. Thus, exception points should not be necessary for patients with BCS.

### Pruritus

There have been applications to RRBs justifying increased priority on the waiting list due to intractable pruritus. While this can be an aggravating problem, there are no data associating pruritus with waiting list mortality or premature dropout from the list.<sup>17</sup> While pruritus may be a patient-specific complaint, there are no measures developed for objectively quantifying this problem. For all of these reasons, we conclude that there is no evidence to support automatic or prospective RRB approval for increased priority based on pruritus symptoms.

### Primary Hyperoxaluria

Primary hyperoxaluria (PH) causes progressive deposition of oxalate in affected individuals that eventually results in renal failure. In this inborn error of metabolism, the deficient enzyme resides in the liver and failure to correct the enzymatic defect results in continued oxalate deposition that can result in cardiac and other peripheral tissue destruction in addition to the inevitable oxalate stones and subsequent renal failure. Generally, PH patient's mortality risk is not defined by their liver disease and is not reflected by their MELD/PELD score. Their need for LT is defined by progressive oxalate deposition. The development of renal failure in patients with PH has been associated with increased mortality before transplantation, as has extremely young age, but there are no quantitative studies identifying risk factors for dropping out from the waiting list. Since the introduction of the MELD/PELD system, approximately 8 or 9 patients with PH have received liver transplants per year.

Expert opinion has determined that analysis of liver biopsy samples alone (a patient-specific variable) documenting the PH enzymatic defect is sufficient to justify automatic award of increased priority above the calculated MELD/PELD score without prospective RRB review.<sup>18</sup> The recommended amount of increased priority for patients with PH, however, is not based on a quantitative assessment of increased risk. In addition, because PH patients with established renal failure as defined by the need for renal replacement therapy have increased mortality risk, expert opinion recommends automatic award of additional increased priority, again without solid evidence for determining the magnitude of increased priority. Children less than one year of age with this condition have the highest mortality risk while waiting and therefore, should be allowed an automatic award of 40 PELD points. The very few cases overall, and rare numbers of small children with PH will make statistical validation of dropout risks difficult.

### Familial Amyloid Polyneuropathy

Familial amyloidotic polyneuropathy is another enzyme defect that results in progressive deposition of amyloid into various tissues. In the most common type, there is a point mutation in a primarily hepatic enzyme that results in amyloid deposition into neurologic, cardiac, and ophthalmic tissues that is ultimately fatal. Liver transplantation restores normal enzyme function and can partially resolve the end-organ dysfunction. These patients' mortality risk is not dependent on their liver disease and the MELD score is not reflective of their need for LT. There are no good analyses of factors associated with mortality or waiting-list dropout in these patients, although cardiac parameters (i.e., ventricular wall thickness, ejection fraction, arrhythmias, and New York Heart Association class), nutritional parameters, and the polyneuropathy disability score have the potential to define a risk of waitlist removal analogous to MELD/PELD for other candidates because they are patient-specific and reasonably objective variables. These diagnoses are patient-specific, reasonably objective, and these variables would be good candidates for future liver allocation policy adjustments.<sup>19</sup>

The original MELD/PELD-based liver allocation policy recognized the lack of natural history data for patients with familial amyloidotic polyneuropathy and the difficulty of correlating risk of dropout for these patients with the standard MELD risk of mortality. Arbitrarily, a MELD priority equivalent to 15% risk of 3-month mortality was assigned. The current expert opinion recommends that this be automatic if the application contains biopsy-proven evidence of amyloid deposition and documentation of the most common TTR gene mutations, but recognizes that this amount of increased risk is still completely arbitrary. There are no organized efforts for collecting other data such as echocardiographic variables or polyneuropathic disability or nutritional scores that are possibly associated with deterioration beyond a transplantable stage, and no endpoints defining futile transplant stage have been developed.

## Cystic Fibrosis

Cystic fibrosis (CF) results in progressive pulmonary and liver disease. The liver disease resembles chronic biliary cirrhosis. CF patients with isolated liver disease develop all of the manifestations of chronic cirrhotic liver disease and their need for LT is reasonably estimated by their mortality risk defined by MELD/PELD. However, the evidence suggests that CF patients with liver disease who also have progressive pulmonary disease face increased risks of death before (and after) LT and some will require combined liver-lung transplant procedures.<sup>20</sup> Forced expiratory volume (FEV<sub>1</sub>), an objective, patient-specific measure, has been helpful identifying CF patients with pulmonary disease and can be used to screen waiting LT candidates. Formal collection of the FEV<sub>1</sub> data has not been accomplished by the United Network for Organ Sharing/Organ Procurement Transplantation Network data collection system but the evidence is strong enough to justify automatic award of increased priority for patients waiting for LT alone with progressive pulmonary disease due to CF. Quantification of the amount of increased priority is arbitrary at this time and how patients in need of combined liver-lung transplantation should be accurately ranked will require many more cases to be accumulated before statistical validity can be achieved. The impact of new lung allocations policies also needs to be monitored to see if those policies obviate the need for any additional automatic MELD points to be assigned on the basis of progressive liver disease and its associated risks.

## Cholangiocarcinoma and Biliary Dysplasia

Recent neoadjuvant protocols that include operative staging for cholangiocarcinoma confined to the hepatic hilum have improved the previously dismal success rates for LT in patients with this condition.<sup>21</sup> However, these results have only been achieved via rigorous application of well-designed protocols. Current evidence suggests that, for properly-selected patients with primary sclerosing cholangitis-associated cholangiocarcinoma in whom surgical resection is not possible, LT offers a reasonable chance at cure and that alternative therapies have little benefit. In addition, tumor recurrence rates are high for patients fulfilling protocol criteria who come to LT longer than 140 days after listing. Unfortunately, published reports do not describe pre-transplant predictors of cancer recurrence other than waiting time. The results from these prospective, neoadjuvant protocols provide evidence for justification of increased priority for patients enrolled in these trials especially in light of the poorer results obtained when patients waiting longer. Though the recommended quantity of increased priority has not been calibrated to the risk of dropout as yet, this should become possible as more data accumulates.

## Cholangitis

Bacterial cholangitis is a common problem in patients with structural biliary disease and can cause severe

complications. However, there is essentially no evidence for cholangitis being associated with mortality risk.<sup>22</sup> Patients who have cholangitis and recurrent bacteremia or its complications (i.e., osteomyelitis, endocarditis) may be ineligible to receive LT and thus may be at increased risk of dropout, although this has not been conclusively proven. For this reason, expert opinion recommends that prospective RRB application be allowed for such cases and that an increased priority can be awarded if specific criteria are met. Again, the amount of increased priority is not based on quantified endpoint risks, since neither an endpoint nor the risk factors have been established.

## Unusual Tumors

There are several different types of non-HCC tumors, primary or metastatic, for which LT has been reported. However, these are very few in number and there is essentially no data on dropout risk for these cases. For this reason, automatic award of increased priority cannot be justified. Metastatic tumors where the primary disease has not been controlled generally have very poor outcomes and should not receive increased priority through prospective review. Other cases should receive individual attention via the RRB process. Expert opinion recommends that primary hepatic hemangiomas, carcinoid tumors confined to the liver and multiple hepatic adenomas in glycogen storage disease are acceptable cases for prospective RRB applications and review.<sup>23</sup> The extremely small number of these cases makes it unlikely that enough data will be obtained for evidence-based decision-making regarding correct priority ranking for these patients on the basis of their dropout rates.

## Unusual Metabolic Diseases

All of these conditions are rare, which makes development of evidence-based recommendation on prioritizing these patients nearly impossible.<sup>24</sup> Some defects such as Wilson's disease, hemochromatosis, and alpha-1-antitrypsin disease result in progressive liver fibrosis and cirrhosis and biliary transport diseases (e.g., Byler's disease) result in jaundice and secondary biliary cirrhosis. In these cases, the MELD/PELD score is an adequate reflection of the need for LT. For other conditions where there is no structural liver disease, liver-based mortality endpoints are not appropriate and other parameters such as risk of neurologic deterioration, risk of renal failure, nutritional compromise, hyperammonemia, and HCC risk should be taken into account. There is insufficient evidence to justify automatic upgrade by RRBs for these conditions and they should be managed on a case-by-case basis. Several of these conditions qualify for advancement to status 1B priority.

## Small-For-Size Syndrome

Small-for-size syndrome develops after primary living-donor transplantation of a liver graft that either is of

insufficient liver mass for the recipient or has a significant mismatch of vascular inflow to outflow. In both cases, severe synthetic dysfunction occurs, which has been associated with increased risk of death.<sup>25</sup> There are no data available indicating whether these patients have different risks of dropout relative to other cases listed for retransplantation or whether the MELD/PELD score underestimates these patients' mortality risk relative to other waiting LT candidates. It is clear, however, that mortality risk is the correct waiting list endpoint for these cases.

In the absence of these data, expert opinion has recommended that cases where a partial graft has been transplanted in which hyperbilirubinemia, coagulopathy, and/or ascites is evident in the early posttransplant period should receive automatic increase in priority equal to 50% mortality risk. There are no quantitative data indicating that this estimate accurately reflects the true degree of increased risk these recipients face and such data needs to be prospectively collected.

### Hereditary Hemorrhagic Telangiectasia

Although hereditary hemorrhagic telangiectasia, also known as Rendu-Osler-Webber Disease, is a systemic disease, the liver is often the major area of involvement. These cases can develop high output cardiac failure and portal hypertension from the arteriovenous malformation in the liver. There are a few reported series of LT performed for this condition with varying success rates related to other comorbidities and degree of extra-hepatic disease. Natural history studies also indicate that although some cases progress to fatal outcomes, other cases regress spontaneously with or without medical or surgical intervention. Thus, mortality risk progression may be the correct waiting list endpoint for hereditary hemorrhagic telangiectasia, but the lack of documented prognostic risk factors makes prediction of this impossible at this time. For this reason, there is insufficient evidence to justify automatic increases in MELD/PELD score priority and these cases should be evaluated by RRBs on an individual basis. Since these patients usually do not develop synthetic liver failure, it is unlikely that their MELD/PELD scores will adequately estimate their mortality risk. However, since these are rare cases, there is no available evidence on which to base a quantification of mortality risk at this time.

## DISCUSSION

Ideally, medical decision-making, especially decisions of the magnitude of liver allocation, would be made with the highest quality clinical evidence derived from randomized controlled trials and would be consistent through UNOS. However, obtaining this kind of evidence is obviously not possible in the field of liver allocation. The MELD/PELD allocation system for standard cases is based mostly on level 2 evidence, derived from retrospective and prospective case-controlled and cohort studies. More problematic as far as evidence-based policy making is concerned are these so-called

"exceptional cases". Many of these conditions, as outlined above, occur so infrequently that valid cohort studies producing statistically or clinically relevant results that are reproducible will never be possible and prioritization policy will always have to rely on expert opinion alone. However, as indicated above for some conditions, there are potential endpoints that might be addressed and data that might be accumulated to provide a more objective assessment of these patients' need for transplantation.

For many of these cases, there may be enough occurrences where mortality risk may serve as a reasonable prioritization endpoint and could be easily equated to the MELD/PELD score mortality risk estimates employed for the standard cases. Unfortunately, there is a near complete lack of data from which risk factors that would accurately define the mortality risk, or wait list removals for progressive disease, for these various conditions might be developed and validated. Outside data collection efforts funded by entities with interests in specific diseases should be sought as in the case of the pulmonary complications in hepatic disease effort funded by the National Institutes of Health. Moreover, in the majority of these cases, factors other than those included in the MELD/PELD score are likely to play a role, and a concerted effort to collect these data will be necessary. Possible data elements to be addressed are included in Table 1. For most cases a risk of mortality is deemed to be most appropriate, but since the evidence suggests that the MELD/PELD score does not adequately measure mortality risk for these cases, additional data are needed. Automatic assignment of priority is indicated based on sufficient evidence, expert opinion, or established practice as indicated. For a few of the conditions (e.g., small-for-size syndrome), MELD/PELD might be a reasonable estimate of mortality risk and these instances should be analyzed and validated.

For other conditions, mortality risk is not an appropriate estimation of LT need and risk for waiting list removals and progression of nonliver-related diseases must be considered.<sup>26</sup> We have suggested potential endpoints already indicated in the literature that might serve to prioritize these patients. For example, using the polyneuropathy disability score, which is somewhat analogous to the MELD/PELD score in patients with familial amyloid polyneuropathy, might be a more continuous and evidence-based method for assigning priority instead of the arbitrarily designed methods we currently use. Incorporating some measure of hypoxia with the appropriate coefficients into a MELD score for patients with hepatopulmonary syndrome might also be appropriate and more reflective of need than the arbitrary, one-size-fits-all method we currently use. What is clear though, is that quality-of-life endpoints alone are not sufficient for prioritization because they are subjective and cannot be fairly equated to mortality risk.<sup>27</sup>

In all of the cases where automatic priority increases are recommended, a single uniform amount of MELD/PELD points to be awarded has been advocated. These



black and white distinctions generally are not reflective of the spectrum of clinical disease and varying rates of progression and do not adequately characterize the need for LT, regardless of the endpoint used. For these reasons, less arbitrary, more granular, continuous stratifications of LT need must be developed to more precisely represent the actual situations.

All of these refinements, however, require a much more standardized data collection system. Developing a national review board process that uses standardized data collection methods and analysis protocols and that assigns priority on a consistent basis seems to be mandatory to achieve these goals. Only with this standardized approach can consistent priority be assigned, either by RRBs applying national standards to the local reality or using a national system that accounts for regional variations. The MESSAGE study group has provided an excellent synthesis of the available data for these diagnostic categories, but just as importantly, it has clearly illuminated the significant evidence gaps that exist. Closing these gaps may not be possible for some of the rarer conditions, but our patients deserve a much more evidenced-based approach to prioritizing most of these cases. This can only be achieved with a rational approach on a national level that targets the more common exceptional diagnostic groups for focused data collection, similar to the HCC example cited above. Waiting list endpoints need to be designed and risk factors for progression to these endpoints must be identified.

The MESSAGE committee members and the members of the Liver and Intestinal Committee who were involved in this project would like to emphasize that the Regional Review Boards across the country have held widely divergent opinions on which conditions should receive additional MELD points if any, and on how much priority should be given for exceptional case requests. The purpose of the MESSAGE group's work was to provide a consistent, evidence-based approach to listing of patients with additional MELD points across the United Network for Organ Sharing regions.

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