Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review

OPTN/UNOS Liver and Intestinal Organ Transplantation Committee

Prepared by:
Christine M. Flavin, MPH
UNOS Policy Department

Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review

Affected Policies: None
Sponsoring Committee: Liver and Intestinal Organ Transplantation Committee
Public Comment Period: August 15, 2016 – October 15, 2016

Executive Summary

The MELD[1] or, if less than 12 years old, a PELD[2] score is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. For some patients the risk of death without access to liver transplant is not accurately predicted by the MELD score. In these instances, the liver transplant program may request an exception score.

Most OPTN/UNOS regions have adopted independent criteria used to request and approve exceptions, commonly referred to as "regional agreements." These regional agreements may contribute to regional differences in exception submission and award practices, even among regions with similar organ availability and candidate demographics.[3,4]

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, the Committee) is currently pursuing the establishment of the National Liver Review Board (NLRB) to promote consistent, evidence-based review of exception requests. In support of this project, the Committee has developed guidance for specific clinical situations for use by the NLRB to evaluate common exceptional case requests for adult candidates with ten diagnoses, not all of which are appropriate for MELD exception. This supplements existing national guidance and replaces the regional agreements. Review board members and transplant centers should consult this resource when considering MELD exception requests.

Is the sponsoring Committee requesting specific feedback or input about the proposal?

The Committee welcomes your feedback as it builds clinical consensus for these recommendations. It is particularly interested in receiving feedback to improve the recommendation for Multiple Hepatic Adenomas.

---

[1] Model for End-Stage Liver Disease
[2] Pediatric End-Stage Liver Disease
[3] Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. "Regional Variability in Symptom-Based MELD Exceptions: A Response to Organ Shortage?" Am J Transplant, 11(2011): 2353-2361.
[4] Rodriguez-Luna, H., H.E. Vargas, A. Moss, et al. "Regional variations in peer reviewed liver allocation under the MELD system." Am J Transplant, 5(2005): 2244-2247.

What problem will this proposal solve?

A liver candidate receives a MELD[5] or, if less than 12 years old, a PELD[6] score that is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score. However, for some the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[7] In these instances, the liver transplant program may request an exception score.

In 2009, the OPTN/UNOS Board of Directors approved standardized exceptions for nine diagnoses in which waitlist mortality is not accurately predicted by the MELD. A candidate that meets the criteria for one of these diagnoses is approved for a standardized MELD exception.[8] If the candidate does not meet criteria for standardized exception, the request is considered by the Regional Review Board (RRB) for the region in which the transplant program is located. In June 2015, the Board of Directors approved guidance to promote consistent standards for RRBs when reviewing four of the most common types of exceptions: Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), and Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH).[9]

For non-standardized diagnoses, most OPTN/UNOS regions have adopted independent criteria used to request and approve exceptions, commonly referred to as "regional agreements." These regional agreements may contribute to regional differences in exception submission and award practices, even among regions with similar organ availability and candidate demographics.[10,11] Nationally, exception candidates drop off the waitlist at lower rates, and are transplanted at higher rates, than their peers with the equivalent calculated MELD.[12] In addition, there are differences in the proportion of exception requests that are approved and the proportion of transplants that occur under exception among the various regions. On average, 88.4% of initial, appeal, and extension requests submitted between July 1, 2014 and June 30, 2015 were approved; however, individual regions approved as few as 75.8% and as many as 93.5% of requests during this timeframe.[13] Excluding Status 1 recipients, the proportion of recipients transplanted with an exception score ranged from 32.0% to 56.5% among the regions, and non-standardized exceptions ranged from 3.1% to over 21.0% (see **Table 1** below).[14]

---

[5] Model for End-Stage Liver Disease
[6] Pediatric End-Stage Liver Disease
[7] Waitlist dropout is removal from the waiting list due to death or the candidate being too sick to transplant.
[8] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[9] Organ Procurement and Transplantation Network. *Guidance to Liver Transplant Programs and Regional Review Boards for MELD/PELD Exceptions Submitted for Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH).* Richmond, VA, 2015, available at https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/.
[10] Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. "Regional Variability in Symptom-Based MELD Exceptions: A Response to Organ Shortage?" Am J Transplant, 11(2011): 2353-2361.
[11] Rodriguez-Luna, H., H.E. Vargas, A. Moss, et al. "Regional variations in peer reviewed liver allocation under the MELD system." Am J Transplant, 5(2005): 2244-2247.
[12] Massie, A.B., B. Caffo, S.E. Gentry, et al. "MELD exceptions and rates of waiting list outcomes." Am J Transplant, 11(2011): 2362-2371.
[13] Based on OPTN data presented to the Committee on October 20, 2015
[14] Based on OPTN data as of July 8, 2016

Table 1. Deceased donor adult liver transplants in 2015, by exception type at time of transplant and OPTN/UNOS region.*

Region	No Exception (N)	No Exception (%)	Standard Exception (N)	Standard Exception (%)	Non-Standard Exception (N)	Non-Standard Exception (%)	Total Transplants (N)
1	117	52.7	90	40.5	15	6.8	222
2	421	57.8	216	29.7	91	12.5	728
3	784	66.2	333	28.1	68	5.7	1185
4	358	60.0	207	34.7	32	5.3	597
5	509	59.1	283	32.9	69	8.0	861
6	81	43.5	66	35.5	39	21.0	186
7	279	57.9	188	39.0	15	3.1	482
8	237	58.7	135	33.4	32	7.9	404
9	128	50.4	96	37.8	30	11.8	254
10	363	68.0	121	22.7	50	9.3	534
11	395	62.4	187	29.5	51	8.1	633
US	**3672**	**60.3**	**1922**	**31.6**	**492**	**8.1**	**6086**

***Status 1 recipients excluded from analysis.**

In November 2013, the OPTN/UNOS Board of Directors charged the Liver and Intestinal Organ Transplantation Committee (hereafter, the Committee) with developing a conceptual plan and timeline for the implementation of a national liver review board to promote consistent, evidence-based review of exception requests.

Why should you support this proposal?

The Committee is currently pursuing the establishment of the National Liver Review Board (NLRB). This project has three parts:

1. The proposed structure of a national review board and the operational guidelines that govern it
2. Guidance, which will replace the regional agreements as the resource NLRB members use when assessing requests
3. The optimal method for assigning exception scores

The Committee submitted the proposed structure and operational guidelines for the NLRB for public comment in January 2016. The Committee sought feedback from the community on the method for assigning MELD exception points and is currently gathering evidence to support the proposed change. The Committee anticipates submitting an updated proposal, with the MELD/PELD score assignment, for public comment in January 2017.

The Committee has developed guidance for specific clinical situations for use by the National Liver Review Board (NLRB) to evaluate common exceptional case requests for adult candidates with the following diagnoses, **not all of which are appropriate for MELD exception**:

- Ascites
- Budd Chiari
- GI Bleeding
- Hepatic Encephalopathy
- Hepatic Epithelioid Hemangioendothelioma
- Hepatic Hydrothorax

- Hereditary Hemorrhagic Telangiectasia
- Multiple Hepatic Adenomas
- Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection, Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- Pruritus

This guidance will supplement the existing national guidance for NET, PLD, PSC, and POPH.[15] If supported by the community and approved by the Board of Directors, this guidance would replace any independent criteria that OPTN/UNOS regions used to request and approve exceptions, commonly referred to as "regional agreements." Review board members and transplant centers would consult this resource when considering MELD exception requests for adult candidates with these diagnoses, recognizing that this resource is not exhaustive of all clinical scenarios.

How was this proposal developed?

The MELD Exceptions and Enhancements Subcommittee proposed these recommendations after reviewing the 2006 MELD Exception Study Group (MESSAGE) Conference guidelines, a descriptive analysis of recent MELD exception requests submitted to the OPTN/UNOS, and available peer-reviewed literature.[16] The Committee voted to approve this guidance for public comment on June 29, 2016 (20-Yes, 0-No, 0-Abstentions). The Committee will continue to strengthen the clinical consensus for these recommendations during public comment.

How well does this proposal address the problem statement?

To support a recommendation for MELD exception, the Committee followed the MESSAGE Conference guidelines, which require a measurable end-point such as waitlist drop-out or increased risk of mortality not reflected in the calculated MELD score. The Committee reviewed evidence in existing peer-reviewed literature and developed a consensus recommendation.

The Committee recommends approval of exceptions for recipients of a donation after cardiac death (DCD) donor liver who experience diffuse ischemic cholangiopathy post-transplant, although the data is not conclusive. Waitlist outcomes for these patients suggest that they have a similar or improved waitlist survival compared to donation after brain death (DBD) candidates who are re-listed with similar MELD scores. However, DCD recipients with an approved exception may have been included in the study cohort and thus it is unclear whether the improved survival is due to having received an exception.[17] A subsequent analysis found that DCD recipients who were re-listed and had an approved exception had improved survival compared to DCD recipients who did not have an approved exception. Despite inconclusive evidence, the Committee supports increased priority for prior DCD donor liver recipients, that meet certain criteria for ischemic cholangiopathy, to encourage use of DCD livers when appropriate.

Which populations are impacted by this proposal?

This proposal promotes equitable access to transplant for adult liver candidates whose calculated MELD score does not accurately reflect the severity of their disease. In addition, these changes will improve access to transplant for adult candidates without exception points, who are currently transplanted at

---

[15] Organ Procurement and Transplantation Network. *Guidance to Liver Transplant Programs and Regional Review Boards for MELD/PELD Exceptions Submitted for Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH).* Richmond, VA, 2015, available at https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/.

[16] Freeman, R.B., R.G. Gish, A. Harper, et al. "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." Liver Transpl 12(2006): S128-S136.

[17] Allen, A.M., W.R. Kim, H. Xiong, et al "Survival of recipients of livers from donation after circulatory death who are relisted and undergo retransplant for graft failure." Am J Transplant 15 (2014): 1120-8.

higher MELD scores than those with approved exceptions (**Table 2**). In some cases, the proposed recommendations are more conservative than some current RRB exception practices, meaning that some candidates that currently receive non-standardized exceptions may not in the future.

This proposal also affects current RRB members and prospective NLRB members (see "How will members implement this proposal?").

Table 2. Deceased donor adult liver transplants in 2015, by OPTN/UNOS region, exception status, and median MELD score at transplant.

Region	No Exception	HCC Exception	Other Exception
1	23	31	34
2	34	28	29
3	27	25	22.5
4	33	27	27
5	39	31	33
6	36	25	29
7	34	28	29.5
8	28	25	27
9	36.5	31	31
10	23	22	25
11	27	25	22
US	**31**	**25**	**27**

How does this proposal support the OPTN Strategic Plan?

1. *Increase the number of transplants:* There is no impact to this goal.

2. *Improve equity in access to transplants:* The primary goal for this proposal is to improve equity in access to transplant. Nationally, exception candidates are less likely to die while waiting for a liver transplant or be removed from the waitlist because they are too sick to transplant, and more likely to be transplanted, than their peers with the equivalent calculated MELD.[18] There are also regional differences in whether similar candidates are awarded exception points.[19,20] This guidance replaces any independent criteria OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements," and promotes national standards for review.

3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* Decisions made using this guidance will contribute to better waitlist and post-transplant outcomes for adult exception candidates, as well as those who will be transplanted on the basis of the calculated MELD score.

4. *Promote living donor and transplant recipient safety:* There is no impact to this goal.

[18] Massie, A.B., B. Caffo, S.E. Gentry, et al. "MELD exceptions and rates of waiting list outcomes." A J Transplant, 11(2011): 2362-2371.
[19] Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. "Regional variability in symptom-based MELD exceptions: A response to organ shortage?" Am J Transplant, 11(2011): 2353-2361.
[20] Rodriguez-Luna, H., H. E. Vargas, A. Moss, et al. "Regional variations in peer reviewed liver allocation under the MELD system." Am J Transplant, 5(2005): 2244-2247.

5. *Promote the efficient management of the OPTN:* There is no impact to this goal.

How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

The OPTN/UNOS will assess the impact of these policy changes using a pre versus post analysis at 6-month intervals, up to 24 months after implementation. At the Committee's request, analyses beyond 24 months may be performed. The Committee will monitor several metrics, including, but not limited to, the following:

- Waiting List
    - Number of non-standardized exception requests
    - Number of non-standardized exception requests approved
    - Distribution of MELD/PELD scores among approved requests
    - Outcomes (probability of removals for transplant, death, too sick) for approved requests
- Transplant
    - Number of approved non-standardized exceptions
    - Distribution of MELD/PELD scores among approved non-standardized exceptions
    - Variance in the median MELD/PELD score among approved non-standardized exceptions
    - Outcomes (graft/patient survival) for non-standardized approved exceptions compared to recipients with standardized exceptions and no exceptions

Results will be presented for the US and where applicable, by region.

How will the OPTN implement this proposal?

If public comment is favorable, the Committee plans to bring this guidance with the final NLRB proposal to the Board of Directors in June 2017. Upon Board approval, the OPTN/UNOS will publish this guidance to the resources section of both the OPTN and other websites.

The OPTN/UNOS will work with the Committee to develop the orientation training all NLRB representatives and alternates must complete before beginning their term of service. The content of this guidance will be included as part of that training.

This proposal will not require programming in UNet^{SM}.

How will members implement this proposal?

Transplant Hospitals

Review board members should consult this resource when assessing adult MELD exception requests. Liver programs should also consider this guidance when submitting exception requests for adult candidates with these diagnoses. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice.

Will this proposal require members to submit additional data?

This proposal does not require additional data collection; however, the OPTN/UNOS will provide exception templates upon implementation to encourage programs to include the recommended information for the candidate's diagnosis.

How will members be evaluated for compliance with this proposal?

This resource is not OPTN/UNOS Policy, so it does not carry the monitoring or enforcement implications of policy. It will not change the current routine monitoring of OPTN/UNOS members. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This is a resource intended to provide guidance to transplant programs and the NLRB, and is for voluntary use by members. Any data entered by members on exception forms is still subject to OPTN/UNOS review, and members are still required to provide documentation as requested.

Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review

Summary and Goals

For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score, which is used to prioritize candidates on the waiting list. However, for some patients the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[21] This document summarizes available evidence to assist clinical reviewers in approving candidates for MELD exceptions. It contains guidance for specific clinical situations for use by the National Liver Review Board (NLRB) to evaluate common exceptional case requests for adult candidates with the following diagnoses, not all of which are appropriate for MELD exception:

- Ascites
- Budd Chiari
- GI Bleeding
- Hepatic Encephalopathy
- Hepatic Epithelioid Hemangioendothelioma
- Hepatic Hydrothorax
- Hereditary Hemorrhagic Telangiectasia
- Multiple Hepatic Adenomas
- Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection, Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- Pruritus

This document supplements existing exception guidance for candidates with Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension.[22] These guidelines are intended to promote consistent review of these diagnoses and summarize the Committee's recommendations to the OPTN/UNOS Board of Directors.

This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the NLRB.

[21] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.
[22] Organ Procurement and Transplantation Network. *Guidance to Liver Transplant Programs and Regional Review Boards for MELD/PELD Exceptions Submitted for Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH).* Richmond, VA, 2015, available at https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/.

Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review

Contents

Background

A liver candidate receives a MELD[23] or, if less than 12 years old, a PELD[24] score that is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. When the calculated score does not reflect disease severity, a liver transplant program may request an exception score. A candidate that meets the criteria for one of nine diagnoses in policy is approved for a standardized MELD exception.[25] If the candidate does not meet criteria for standardized exception, the request is considered by the National Liver Review Board (NLRB). In June 2015, the OPTN/UNOS Board of Directors approved national guidance to promote consistent standards when reviewing three of the most common types of exceptions: Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), and Primary Sclerosing Cholangitis (PSC).

To supplement the existing guidance, the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exception candidates with ten other diagnoses. The MELD Exceptions and Enhancements Subcommittee proposed these recommendations after reviewing the 2006 MELD Exception Study Group (MESSAGE) Conference, a descriptive analysis of recent MELD exception requests submitted to the OPTN, and available peer-reviewed literature. To support a recommendation for approving additional MELD exception points, there must have been adequate evidence of increased risk of mortality associated with the complication of liver disease. The Committee voted to approve these additional recommendations for public comment on June 29, 2016 (20-Yes, 0-No, 0-Abstentions), during which time it will work to strengthen the clinical consensus for these recommendations.

This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements." Review board members and transplant centers should consult this resource when considering MELD exception requests for adult candidates with the following diagnoses.

Recommendation

Ascites

There is inadequate evidence to support granting a MELD exception for ascites in adult candidates with the typical clinical symptoms associated with this diagnosis. Ascites is a common clinical finding in liver transplant candidates. Refractory ascites, as defined by the International Ascites Club, occurs in 5-10% of patients with portal hypertension and has a 1-

[23]Model for End-Stage Liver Disease
[24]Pediatric End-Stage Liver Disease
[25]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

year mortality rate of approximately 50%.[26,27,28,29] Hyponatremia is common in patients with cirrhosis and refractory ascites from portal hypertension.[30,31,32] In January 2016, the OPTN implemented a modification to the MELD score to incorporate serum sodium for candidates with a calculated MELD greater than 11.[33] Much of the excess mortality risk related to ascites is similar to portal hypertension and hepatorenal syndrome and will be accurately reflected in the lab values used to calculate the MELD score, specifically the serum creatinine and serum sodium. Therefore, MELD exception for ascites is not recommended.

Budd Chiari

Approval of MELD exception points for adult candidates with Budd Chiari may be appropriate in some instances. Budd Chiari syndrome is an uncommon manifestation of hepatic vein thrombosis and patients might present with evidence of decompensated portal hypertension (ascites and hepatic hydrothorax) among others.[34] Medical management may include diuresis and anticoagulation; or more aggressive management with Transjugular Intrahepatic Portosystemic Shunt (TIPS), portosystemic shunting, or liver transplant.[35] Anticoagulation and pharmacologic management is the cornerstone treatment.[36,37] Patients with severe portal hypertension not controlled with the standard of care might have evidence of hyponatremia or renal impairment, but these will be accurately reflected by the calculated MELD score.

Liver transplant candidates with Budd Chiari syndrome could be considered on an individual basis for a MELD exception based on severity of liver dysfunction and failure of standard management. Documentation submitted for case review should include all of the following:

- Failed medical management (please specify)
- Any contraindications to TIPS or TIPS failure; specify specific contraindication
- Decompensated portal hypertension in the form of hepatic hydrothorax requiring thoracentesis more than 1 liter per week for at least 4 weeks (transudate, no evidence of

[26]Moore, K.P., F. Wong, P. Gines, et al. “The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club.” Hepatology 38 (2003): 258-66.
[27]Runyon, B.A., AASLD. “Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012.” Hepatology 57 (2013): 1651-3.
[28]Runyon, B.A., Committee APG. “Management of adult patients with ascites due to cirrhosis: an update.” Hepatology 49 (2009): 2087-107.
[29]Gines P., A. Cardenas, V. Arroyo, et al. “Management of cirrhosis and ascites.” N Engl J Med 350 (2004):1646-54.
[30]Biggins, S.W., W.R. Kim, N.A. Terrault, et al. “Evidence-based incorporation of serum sodium concentration into MELD.” Gastroenterology 130 (2006):1652-60.
[31]Porcel, A., F. Diaz, P. Rendon, et al. “Dilutional hyponatremia in patients with cirrhosis and ascites.” Arch Intern Med 162 (2002):323-8.
[32]Gines, A., A. Escorsell, P. Gines, et al. “Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites.” Gastroenterology 105 (1993):229-36.
[33]Biggins, S.W. “Use of serum sodium for liver transplant graft allocation: a decade in the making, now is it ready for primetime?” Liver Transpl 21 (2015):279-81.
[34]Janssen, H.L., J.C. Garcia-Pagan, E. Elias, et al. “Budd-Chiari syndrome: a review by an expert panel.” Hepatology 38 (2003): 364-371.
[35]Seijo, S., A. Plessier, J. Hoekstra, et al. “Good long-term outcome of Budd-Chiari syndrome with a step-wise management.” Hepatology 57 (2013): 571962-8.
[36]Plessier, A., A. Sibert, Y. Consigny, et al. “Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome.” Hepatology 44 (2006):1308-16.
[37]DeLeve, L.D., D.C. Valla, G. Garcia-Tsao. “Vascular disorders of the liver AASLD practice guidelines.” Hepatology 49 (2009): 1729-64.

empyema, and negative cytology or any evidence of infection).

Gastrointestinal Bleeding

There is inadequate evidence to support granting a specific MELD exception for gastrointestinal bleeding in adult candidates who experience acute or chronic blood loss independent of their calculated MELD. There is also inadequate evidence to support a MELD exception for transfusion dependence independent of MELD with one exception, spur cell hemolytic anemia (SCHA).[38] However, due to the infrequent occurrence of SCHA in a transplant candidate, and its common association with recent alcohol use or active infection, MELD exception is not recommended. Similarly there is no evidence to support that candidates with transfusion dependence who develop antibodies while waiting warrant a MELD exception. [39,40]

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complication of chronic liver disease associated with significant morbidity. There is an absence of evidence of sufficient quality to support MELD exception for complications of HE. [41,42,43,44]

Hepatic Epithelioid Hemangioendothelioma

Approval of MELD exception points for adult candidates with unresectable Hepatic Epithelioid Hemangioendothelioma (HEHE) may be appropriate in some instances. Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma.

HEHE is a rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity of the diagnosis, as well as the variability in presentation, the optimal treatment strategies are not fully established. However, for lesions which cannot be resected, liver transplant is associated with 1, 5, and 10-year patient survival rates of 97%, 83%, and 74%; with more favorable results occurring in patients without microvascular invasion. The presence of extra-hepatic disease has not been associated with decreased survival post liver transplant and therefore should not be an absolute contraindication. Controversy regarding the role of liver transplant in treating HEHE relates to the variable course of disease in the absence of liver transplant, with some patients demonstrating regression or stabilization of disease and

[38]Alexopoulou, A., L. Vasilieva, T. Kanellopoulou, et al. “Presence of spur cells as a highly predictive factor of mortality in patients with cirrhosis.” J Gastroenterol Hepatol. 4 (2014):830-4.
[39]Lyles, T., A. Elliott, D.C. Rockey. “A risk scoring system to predict in-hospital mortality in patients with cirrhosis presenting with upper gastrointestinal bleeding.” J Clin Gastroenterol 48 (2014):712-20.
[40]Flores-Rendón, A.R., J.A. González-González, D. García-Compean, et al. “Model for end stage of liver disease (MELD) is better than the Child-Pugh score for predicting in-hospital mortality related to esophageal variceal bleeding.” Ann Hepatol 7 (2008):230-4.
[41]Cordoba J., M. Ventura-Cots, M. Simón-Talero, et al. “Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF).” Hepatology 60 (2014): 275-81.
[42]García-Martínez, R., M. Simón-Talero, J. Córdoba. “Prognostic assessment in patients with hepatic encephalopathy.” Dis Markers 31 (2011): 171-9.
[43]D'Amico, G., G. Garcia-Tsao, L. Pagliaro. “Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies.” Hepatology 44 (2006): 217-31.
[44]Brandman, D., S.W. Biggins, B. Hameed, et al. “Pretransplant severe hepatic encephalopathy, peritransplant sodium and post-liver transplantation morbidity and mortality.” Liver Int 32 (2012): 158-64.

prolonged survival.[45,46]

Hepatic Hydrothorax

There is inadequate evidence to support granting a MELD exception for hepatic hydrothorax in adult candidates with the typical clinical symptoms associated with this diagnosis. Liver transplant candidates with chronic, recurrent, confirmed hepatic hydrothorax could be considered on individual basis for a non-standard MELD exception.

Hepatic hydrothorax is a relatively uncommon complication of endstage liver disease occurring in only 5-10% of patients with cirrhosis and portal hypertension.[47,48,49] Hepatic hydrothorax can occur in either or both pleural spaces and can occur with or without portal hypertensive ascites.[50] By definition, hepatic hydrothorax is a transudatative pleural effusion due to portal hypertension without a cardiopulmonary source. Infectious and malignant pleural effusions must be excluded. In this context, a serum pleural fluid albumin gradient (SPAG) of at least 1.1 g/dL may be more accurate in identifying hepatic hydrothorax than the more traditional Light's criteria for a transudative pleural effusion.[22,51] The mostly like explanation for hepatic hydrothorax is passage of fluid from the peritoneal space to the pleural space through diaphragmatic defects which can be documented by intraperitoneal injection of 99MTc-tagged nannocolloids followed by scintigraphy.[52] Unlike ascites, relatively small amounts of fluid in the pleural space (1 to 2 L) lead to severe symptoms such as shortness of breath and hypoxia. Initial management with dietary sodium restriction, diuretics, intravenous albumin, and therapeutic thoracentesis can be successful. Hepatic hydrothorax can be complicated by spontaneous bacterial empyema or iatrogenic complication of thoracentesis (infections, pneumothorax, or hemothorax). For chronic, recurrent, confirmed hepatic hydrothorax, transjugular intrahepatic portosystemic shunt, indwelling pleural catheter, and surgical repair of diaphragmatic defects can be effective in some patients yet risk additional complications. Like ascites, hepatic hydrothorax is similar to portal hypertension and hepatorenal syndrome and will be accurately reflected in the lab values used to calculate the MELD score, specifically the serum creatinine and serum sodium**.** Therefore, MELD exception for hepatic hydrothorax is not recommended.

Adult liver transplant candidates with chronic, recurrent, confirmed hepatic hydrothorax could be considered on an individual basis for a MELD exception. Documentation submitted for case review should include the following:

- At least 4 thoracentesis over 1 L in last 3 months; report date and volume of each thoracentesis

[45]Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry." Ann Surg 246 (2007): 949-57.
[46]Nudo, C.G., E.M. Yoshida, V.G. Bain, et al. "Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience." Can J Gastroenterol 22 (2008):821-4.
[47]Norvell, J.P., J.R. Spivey. "Hepatic hydrothorax." Clin Liver Dis 18 (2014): 439-49.
[48]Baikati, K., D.L. Le, I.I. Jabbour, et al. "Hepatic hydrothorax." Am J Ther 21 (2014): 43-51.
[49]Cardenas, A., T. Kelleher, S. Chopra. "Review article: hepatic hydrothorax." Aliment Pharmacol Ther 20 (2004): 271-9.
[50]Badillo, R., D.C. Rockey. "Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature." Medicine (Baltimore) 93 (2014): 135-42.
[51]Porcel, J.M. "Identifying transudates misclassified by Light's criteria." Current Opinion Pulmonary Medicine 19 (2013): 362-7.
[52]Hewett, L.J., M.L. Bradshaw, L.L. Gordon, et al. "Diagnosis of isolated hepatic hydrothorax using peritoneal scintigraphy." Hepatology (2016).

- Pleural fluid is transudative by pleural albumin-serum albumin gradient of at least 1.1
- No evidence of heart failure; provide objective evidence excluding heart failure
- Pleural fluid culture negative on 2 separate occasions
- Pleural fluid cytology is benign on 2 separate occasions
- There is contraindications to TIPS; specify specific contraindication

Hereditary Hemorrhagic Telangiectasia

Approval of MELD exception points for adult candidates with high output cardiac failure due to multiple arteriovenous (AV) malformations may be appropriate in some instances. Hereditary hemorrhagic telangiectasia is an uncommon, autosomal dominant genetic disorder characterized by mucocutaneous telangiectasias, as well as arteriovenous malformations in the brain, spine, lungs, gastrointestinal tract, and liver. The AV malformations can progress to high output cardiac failure, which eventually may be irreversible. In the future, there may be effective non-transplant options, and if such agents become widely available, the recommendation to offer MELD score exception will need to be revisited. [53,54]

Documentation submitted for case review should include both of the following:

- Documentation of high output cardiac failure by echocardiography
- Imaging supporting intra-hepatic AV malformations or severe diffuse bilobar hepatic necrosis in the setting of hepatic AV malformation

Multiple Hepatic Adenomas

Hepatic adenomas (HA) are rare benign nodules occurring principally in women taking oral contraceptives, are solitary or multiple, and highly variable in size; there is no consensus for their management except that once their size exceeds 5 cm nodules are resected to prevent 2 major complications: bleeding and malignant transformation. An exception to this is in men where it is recommended to remove smaller nodules. The presence of HCC in HA is a well-documented observation, the risk ranging from 5 to 9%; gene coding for β-catenin mutations (15-18% of cases) are associated with a high risk of malignant transformation (together with cytologic atypia). HA are a frequent mode of presentation in some genetic diseases, particularly Glycogen Storage Disease (GSD) and congenital or acquired vascular anomalies. **Orthotopic liver transplantation for HA remains an extremely rare indication; however, it is a valid therapeutic option in select patients with adenoma with risk of malignant transformation, not amenable to resection, and one or more of the following:**

- Reason not amenable to resection
- Malignant transformation suspected or proven by biopsy
- Disease progression (size and number of adenomas)
- One or more hepatic resections (incomplete resection or recurrence) or other management (embolization)

---

[53]Lee, M., D.Y. Sze, C.A. Bonham, et al. “Hepatic arteriovenous malformations from hereditary hemorrhagic telangiectasia: treatment with liver transplantation.” Dig Dis Sci 55 (2010): 3059-62.
[54]Boillot, O., F. Bianco, J.P. Viale, et al. “Liver transplantation resolves the hyperdynamic circulation in hereditary hemorrhagic telangiectasia with hepatic involvement.” Gastroenterology 116 (1999): 187-92.

- Presence of underlying liver disease (GSD, vascular anomalies, fibrosis or cirrhosis)

The identification of these criteria is mandatory to aid in the decision-making process. [55,56,57,58]

Post-Transplant Complications

Small for Size Syndrome

Small for size syndrome refers to graft dysfunction of varying severity occurring in the early post-operative period, less than 30 days, following transplantation of a size-reduced liver allograft, with no other identified cause of graft dysfunction such as vascular thrombosis, prolonged ischemia, or other etiology.[59] Typical findings include worsening cholestasis and ascites. With optimal care, some patients may recover while others may require retransplantation. **In many cases, the calculated MELD score will provide adequate priority. However, mortality risk may not be adequately reflected by the calculated MELD score in cases of severe dysfunction, and an exception may be appropriate.**

Documentation submitted for case review should include all of the following:

- Risk factor for small for size syndrome
- Interventions used to treat small for size syndrome
- Clinical status of the patient (hospitalized, requiring ICU care, intubated)

Chronic Rejection

There is inadequate evidence to support granting a MELD exception for chronic rejection in adult candidates with the typical clinical symptoms associated with this diagnosis. In cases where re-transplantation is being considered, it is anticipated that progressive injury of the allograft due to rejection will be reflected in the development of liver dysfunction, and prioritization by MELD score may be appropriate. Cases with atypical clinical scenarios in which the degree of liver dysfunction and risk of waitlist mortality are not reflected by the MELD score may be considered on an individual basis.

Diffuse Ischemic Cholangiopathy

Diffuse ischemic cholangiopathy is a complication associated with donation after cardiac death (DCD) donors. Analysis of waitlist outcomes for patients re-listed after undergoing liver transplant from a DCD donor demonstrates that these patients have a similar or improved waitlist survival compared to donation after brain death (DBD) candidates who are re-listed with similar MELD scores.[60] However, patients with ischemic cholangiopathy may have significant morbidity and require multiple repeat biliary interventions and repeat hospitalizations for cholangitis. Despite similar waitlist outcomes as DBD donor liver recipients who are listed for

---

[55]Blanc, J.F., N. Frulio, L. Chiche, et al. “Hepatocellular adenoma management: call for shared guidelines and multidisciplinary approach.” Clinics and research in hepatology and gastroenterology 39 (2015): 180-187.
[56]Chiche, L., A. David, R. Adam, et al. “Liver transplantation for adenomatosis: European experience.” Liver Transplantation 22 (2016): 516-526.
[57]Alagusundaramoorthy, S. S., V. Vilchez, A. Zanni, et al. “Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set.” JAMA Surgery 150 (2015): 337-342.
[58]Dokmak, S., V. Paradis, V. Vilgrain, et al. “A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas.” Gastroenterology 137 (2009): 1698-1705.
[59]Uemura, T., S. Wada, T. Kaido, et al. “How far can we lower graft-to-recipient weight ratio for living donor liver transplantation under modulation of portal venous pressure?” Surgery 159 (2016): 1623-30.
[60]Allen, A.M., W.R. Kim, H. Xiong, et al “Survival of recipients of livers from donation after circulatory death who are relisted and undergo retransplant for graft failure.” Am J Transplant 15 (2014): 1120-8.

retransplant, the Committee supports increased priority for prior DCD donor liver recipients to encourage use of DCD livers when appropriate.

In addition, analyses has shown that patients with a prior DCD transplant and an approved MELD score exception had an improved survival compared to those who never had an exception approved.[61] Patients with biliary injuries and need for biliary interventions also have been demonstrated to have an increased risk of graft loss and death.[62] **Therefore, patients with a prior DCD transplant that demonstrated 2 or more of the following criteria within 6 months of transplant should be considered for MELD exception:**

- Persistent cholestasis as defined by abnormal bilirubin (greater than 2 mg/dl)
- Two or more episodes of cholangitis with an associated bacteremia requiring hospital admission
- Evidence of non-anastomotic biliary strictures not responsive to further treatment

Late Vascular Complications

Patients with hepatic artery thrombosis occurring within 7 days of transplant with associated severe graft dysfunction may be eligible for Status 1A, or occurring within 14 days of transplantation without severe graft dysfunction may be eligible for a standard exception of 40.[6364] Cases of late hepatic artery thrombosis which do not meet these criteria are not eligible for standard MELD exception. **Due to the highly variable outcomes associated with late hepatic artery thrombosis, there is inadequate evidence to support granting a MELD exception in adult candidates with the typical clinical symptoms, including hepatic abscess and intrahepatic biliary strictures that may be associated with late HAT. However, patients with atypical severe complications may be considered for MELD exception on an individual basis.** Complications that warrant consideration of MELD exception are similar to those criteria noted for DCD cholangiopathy (with 2 or more episodes of cholangitis requiring hospital admission over a 3 months period plus biliary strictures not responsive to further treatment or bacteremia with highly resistant organisms). Patients with early HAT just beyond 7 or 14 day cut off with evidence of severe graft dysfunction may be considered for MELD exception, depending on the clinical scenario.

Pruritus

There is inadequate evidence to support granting a MELD exception for pruritus in adult candidates with the typical clinical symptoms associated with this diagnosis. Pruritus is a manifestation of predominantly cholestatic liver diseases. It had been reported that chronic pruritus may lead to a decreased quality of life, prolonged wound healing, skin infections, and sleep disturbance.[65] The frequency ranges from 80-100% for patients suffering from Primary Biliary Cirrhosis; 20-40% for patients with primary Sclerosing Cholangitis and Chronic Viral

[61]Makuda, R.C., P.L. Abt, D.S. Goldberg. “Use of Model for End-Stage Liver Disease exceptions for donation after cardiac death graft recipients relisted for liver transplantation.” Liver Transpl 21 (2015):554-60.
[62]Axelrod, D.A., K.L. Lentine, H. Xiao, et al. “National assessment of early biliary complications following liver transplantation: incidence and outcomes.” Liver Transpl. 20 (2014): 446-56.
[63]Policy 9.1.A: Adult Status 1A Requirements, Organ Procurement and Transplantation Network Policies.
[64]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[65]Pruritus in chronic cholestatic liver disease. Bunchorntavakul C, Reddy KR Clin Liver Dis. 2012 May;16(2):331-46.

Hepatitis among other diseases.[66] The pruritus increases as the disease is progresses. So far data have failed to support an endpoint related to quantity but rather of quality of life and were considered inappropriate for additional MELD points.[67] Due to inadequate evidence of increased risk of pre-transplant mortality, or a widely-accepted threshold for access to liver transplant, MELD score exception for isolated clinical finding of pruritus are not recommended.

Conclusion

Review board members should consult this resource when assessing adult MELD exception requests. Liver programs should also consider this guidance when submitting exception requests for adult candidates with these diagnoses. However, these guidelines are not prescriptive of clinical practice.

[66]Elman, S., L.S. Hynan, V. Gabriel, et al. "The 5-D itch scale: a new measure of pruritus." Br J Dermatol 162 (2010): 587-93
[67]Martin, P., A. DiMartini, S. Feng, et al. "Evaluation for liver transplantation in adults: 2013 practice guideline by the AASLD and the American Society of Transplantation." (2013): 61.