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.¹ 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 Review Board 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
- Neuroendocrine Tumors (NET)
- Polycystic Liver Disease (PLD)
- Portopulmonary Hypertension
- Primary Sclerosing Cholangitis (PSC)
- Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection, Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- Pruritus

These guidelines are intended to promote consistent review of these diagnoses and summarize the Committee’s recommendations to the OPTN 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 Review Board.

Background

A liver candidate receives a MELD² or, if less than 12 years old, a PELD³ 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 the candidate’s medical urgency, 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.⁴ If the candidate does not meet criteria for standardized

¹ Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.
² Model for End-Stage Liver Disease
³ Pediatric End-Stage Liver Disease
exception, the request is considered by the Review Board. The OPTN Liver and Intestinal Organ Transplantation Committee (hereafter, “the Committee”) has developed guidance for adult MELD exception candidates. 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.

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-year mortality rate of approximately 50%.\(^5\,6\,7\,8\) Hyponatremia is common in patients with cirrhosis and refractory ascites from portal hypertension.\(^9\,10\,11\) 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.\(^12\) 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

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hydrothorax) among others. Medical management may include diuresis and anticoagulation; or more aggressive management with Transjugular Intrahepatic Portosystemic Shunt (TIPS), portosystemic shunting, or liver transplant. Anticoagulation and pharmacologic management is the cornerstone treatment. 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)
- Etiology of hypercoagulable state
- 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 empyema, and negative cytology or any evidence of infection).
- Documentation that extrahepatic malignancy has been ruled out

**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). 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.

**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

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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 extrahepatic 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 prolonged survival.24,25

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.26,27,28 Hepatic hydrothorax can occur in either or both pleural spaces and can occur with or without portal hypertensive ascites.29 By definition, hepatic hydrothorax is a transudative 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.\textsuperscript{22,30} 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.\textsuperscript{31} 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 in the majority of circumstances.

Adult liver transplant candidates with chronic, recurrent, confirmed hepatic hydrothorax could be considered on an individual basis for a MELD exception provided that infectious and malignant causes have been ruled out. Documentation submitted for case review should include the following:

- At least 1 thoracentesis over 1 L weekly in last 4 weeks; report date and volume of each thoracentesis
- Pleural fluid is transudative by pleural albumin-serum albumin gradient of at least 1.1 and by cell count
- 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
- Diuretic refractory

**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.\textsuperscript{32,33}

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 (the reason must be provided), and one or more of the following:**

- Malignant transformation proven by biopsy
- Presence of glycogen storage disease which increases the risk for malignant transformation

The identification of these criteria is mandatory to aid in the decision-making process.34,35,36,37

**Neuroendocrine Tumors (NET)**

A review of the literature supports that candidates with NET are expected to have a low risk of waiting list drop-out. Initial recommendations included age less than 60. Older patients with a lot of disease burden may be referred to transplant as a last resort, leading to poor outcomes, while data presented at the AASLD show that very young patients with NET and early stage disease do well. Committee members believed that these initial guidelines could include strict criteria that could be expanded based upon the experience of the Review Board.

Transplant programs should also be aware of these criteria when submitting exceptions for NET. The Review Board should consider the following criteria when reviewing exception applications for candidates with NET.

- Recipient age <60 years.
- Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.
- Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.

Tumors in the liver should meet the following radiographic characteristics on either CT or MRI:

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1. If CT Scan:
   a. Triple phase contrast Lesions may be seen on only one of the three phases
   b. Arterial phase: may demonstrate a strong enhancement
   c. Large lesions can become necrotic/calcified
2. If MRI Appearance:
   a. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
   b. Diffusion restriction
   c. Majority of lesions are hypervascular on arterial phase with wash-out during portal venous phase
   d. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

1. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.
2. Lower - intermediate grade following the WHO classification. Only well differentiated (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20 per 10 HPF with less than 20% ki 67 positive markers.
3. Tumor metastatic replacement should not exceed 50% of the total liver volume.
4. Negative metastatic workup should include one of the following:
   a. Positron emission tomography (PET scan)
   b. Somatostatin receptor scintigraphy
   c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododecane-N, N', N'', N‴-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

Note: Exploratory laparotomy and or laparoscopy is not required prior to MELD exception request.

1. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD exception request (submit date).
2. Recheck metastatic workup every 3 months for MELD exception increase consideration by the Review Board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
3. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion criteria

Polycystic Liver Disease (PLD)

Certain patients with PLD may benefit from MELD exception points. Indication for an exception include those with PCLKD (Mayo type D or C) with severe symptoms plus any of the following:

- Hepatic decompensation
- Concurrent hemodialysis
- GFR less than 20 ml/min

Transplant programs should provide the following criteria when submitting exceptions for PLD. The Review Board should consider the following criteria when reviewing exception applications for candidates with PLD.
1. Management of PLD

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2. Surgical Management of PLD
   - Indications:
     a. Types C* and D and at least 2 of the following:
        o Hepatic decompensation
        o Concurrent renal failure (dialysis)
     b. Compensated comorbidities

   **Note:** Prior resection/fenestration, alternative therapy precluded.

Patients who meet the criteria above should be considered for MELD exception points such that transplantation may be expected within the year.

**Portopulmonary Hypertension**

Candidates meeting the criteria in *Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* are eligible for MELD or PELD score exceptions that do not require evaluation by the full Review Board. The transplant program must submit a request for a specific MELD or PELD score exception with a written narrative that supports the requested score. Templates were developed for these exceptions to aid the transplant programs in the process of submitting the required information to justify the exception.

The Committee recommends that the following three elements be considered in reviewing the exception application in addition to the requirements listed in policy for the purposes of policy research:

1. Although policy only requires reporting of the MPAP and PVR, complete Hemodynamics should be reported, including MPAP, PVR, PWAP and CO.
2. To be considered abnormal, the initial mean pulmonary artery pressure (MPAP) should be >35 mmHg and pulmonary vascular resistance (PVR) levels should be > 240 dynes.s.cm-5.
3. The initial transpulmonary gradient (MPAP-PVR) to correct for volume overload should be > 12 mmHg

As noted in policy, these candidates will receive a MELD score of 22/ PELD score of 28. In order to qualify for MELD/PELD extensions and a 10% mortality equivalent increase in points, the required documentation must be resubmit every three months and the mean pulmonary arterial pressure (MPAP) must remain below 35 mmHg, confirmed by repeat heart catheterization.
Primary Sclerosing Cholangitis

Candidates with PSC historically have low mortality rates, and therefore do not need exception scores. Based on clinical experience and a review of the available literature, the Committee recommends that four specific elements be considered.

Transplant programs should provide the following criteria when submitting exceptions for PSC. The Review Board should consider the following criteria when reviewing exception applications for candidates with PSC.

The candidate must meet both of the following two criteria:
1. The candidate has been admitted to the intensive care unit (ICU) two or more times over a three month period for hemodynamic instability requiring vasopressors
2. The candidate has cirrhosis

In addition the candidate must have one of the following criteria:
- The candidate has biliary tract stricture which are not responsive to treatment by interventional radiology (PTC) or therapeutic endoscopy (ERCP) or
- The candidate has been diagnosed with a highly-resistant infectious organism (e.g. Vancomycin Resistant Enterococcus (VRE), Extended Spectrum Beta-Lactamase (ESBL) producing gram negative organisms, Carbapenem-resistant Enterobacteriaceae (CRE), and Multidrug-resistant Acinetobacter.)

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. Typical findings include worsening cholestasis and ascites. With optimal care, some patients may recover while others may require re-transplantation.

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

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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. 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 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. Patients with biliary injuries and need for biliary interventions also have been demonstrated to have an increased risk of graft loss and death. Therefore, patients with a prior DCD transplant that demonstrated two or more of the following criteria within 12 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. 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

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42Policy 9.1.A: Adult Status 1A Requirements, Organ Procurement and Transplantation Network Policies.

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. The frequency ranges from 80-100% for patients suffering from Primary Biliary Cirrhosis; 20-40% for patients with primary Sclerosing Cholangitis and Chronic Viral Hepatitis among other diseases. 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. 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 is 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.

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