

Notice of OPTN Policy and Guidance Changes

Updating National Liver Review Board Guidance and Policy Clarification

Sponsoring Committee:	OPTN Liver and Intestinal Organ Transplantation
Policy Affected:	<i>Policy 9.5.A: Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions</i>
Guidance Affected:	<i>Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD or PELD Exception Review</i> <i>Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review</i>
Public Comment:	January 21, 2021 – March 23, 2021
Board Approved:	June 14, 2021
Guidance Effective Date:	July 15, 2021
Policy Effective Date:	Pending implementation and notice to OPTN Members

Purpose of Policy and Guidance Changes

The National Liver Review Board (NLRB) was implemented on May 14, 2019.¹ The purpose of the NLRB is to provide equitable access to transplant for liver candidates whose calculated model for end-stage liver disease (MELD) score or pediatric end-stage liver disease (PELD) score does not accurately reflect the candidate's medical urgency for transplant. Since the implementation of the NLRB, the OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) has continued to evaluate the effectiveness of the system and has identified a number of ways in which the NLRB could be improved. The purpose of this proposal is to improve the NLRB by incorporating feedback from the transplant community. The proposed changes are anticipated to create a more efficient and equitable system for the review of exception requests.

Proposal History

Prior to the implementation of the NLRB, MELD and PELD exception requests were reviewed by regional review boards (RRBs). The implementation of the NLRB was a significant change in the process for reviewing MELD or PELD exception requests and because of the significance and complexity of the change, the Committee has continued to receive feedback on areas for improvement to the NLRB guidance and policy. This proposal represents the Committee's commitment to continue to improve the NLRB.

¹ Proposal to Establish a National Liver Review Board, OPTN Liver and Intestinal Organ Transplantation Committee, June 2017, Available at <https://optn.transplant.hrsa.gov/>

Summary of Changes

The proposal includes the following changes:

- **CCA policy:** Expand diagnostic criteria for standardized exceptions to include candidates with a hilar mass less than three centimeters in radial diameter.
- **Pediatric guidance:** Expand guidance for candidates with growth failure or nutritional insufficiency; add language that outlines information that should be submitted for candidates with gastrointestinal bleeding with ongoing transfusion requirement and information that should be submitted for candidates with serum sodium less than 130 g/dL on two occasions more than two weeks apart; add language that states a candidate should have at least two thoracenteses in the last 60 days not including the diagnostic thoracentesis; add guidance that recommends an exception for candidates requiring a hospitalization of at least five days with ascites not adequately controlled by oral diuretics and requiring IV diuretic therapy; add guidance for candidates with rare metabolic disorders; update conclusion section to allow submission and consideration of clinical details not currently included in guidance.
- **Neuroendocrine tumor guidance:** Clarify language and remove recommendation that candidates be less than 60 years old.
- **Primary and secondary sclerosing cholangitis guidance:** Update guidance to recommend candidates be admitted to hospital two or more times in previous year with a document blood stream infection or evidence of sepsis including hemodynamic instability requiring vasopressors.

Implementation

Liver transplant programs and NLRB reviewers will need to be familiar with the changes when submitting and reviewing MELD or PELD exception requests.

The OPTN will implement changes in UNetSM for updating the CCA criteria. Changes to guidance will need to be communicated and published.

Affected Policy Language

New language is underlined (example) and language that is deleted is struck through (~~example~~).

9.5.A Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions

A candidate will receive a MELD or PELD score exception for CCA, if the candidate's transplant hospital meets *all* the following qualifications:

1. Submits a written protocol for patient care to the Liver and Intestinal Organ Transplantation Committee that must include *all* of the following:
 - Candidate selection criteria
 - Administration of neoadjuvant therapy before transplantation
 - Operative staging to exclude any patient with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease
 - Any data requested by the Liver and Intestinal Organ Transplantation Committee

2. Documents that the candidate meets the diagnostic criteria for hilar CCA with a malignant appearing stricture on cholangiography and at least *one* of the following:
 - Biopsy or cytology results demonstrating malignancy
 - Carbohydrate antigen 19-9 greater than 100 U/mL in absence of cholangitis
 - Aneuploidy
 - Hilar mass, which is less than 3 cm in radial diameter.

The tumor must be considered un-resectable because of technical considerations or underlying liver disease.

3. Submits cross-sectional imaging studies. If cross-sectional imaging studies demonstrate a mass, the mass must be single and less than three cm in radial (perpendicular to the duct) diameter. The longitudinal extension of the stricture along the bile duct is not considered in the measurement of a mass.
4. Documents the exclusion of intrahepatic and extrahepatic metastases by cross-sectional imaging studies of the chest and abdomen within 90 days prior to submission of the initial exception request.
5. Assesses regional hepatic lymph node involvement and peritoneal metastases by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neo-adjuvant therapy is initiated.
6. Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative or percutaneous approaches) must be avoided because of the high risk of tumor seeding associated with these procedures.

A candidate who meets the requirements for a standardized MELD or PELD score exception will be assigned a score according to *Table 9-2*.

Table 9-2: CCA Exception Scores

Age	Age at registration	Score
At least 18 years old	At least 18 years old	3 points below MMaT
At least 12 years old	Less than 18 years old	Equal to MMaT
Less than 12 years old	Less than 12 years old	Equal to MPaT

In order to be approved for an extension of this MELD or PELD score exception, transplant hospitals must submit an exception extension request according to *Policy 9.4.C: MELD or PELD Exception Extensions*, and provide cross-sectional imaging studies of the chest and abdomen that exclude intrahepatic and extrahepatic metastases. These required imaging studies must have been completed within 30 days prior to the submission of the extension request.

Guidance to Liver Transplant Programs and the National Liver Review Board for:

Pediatric MELD/PELD Exception Review

Growth Failure or Nutritional Insufficiency

There is insufficient evidence to support approval of exception points for pediatric candidates with any broadly defined growth failure or nutritional insufficiency. However, It is now known that the PELD score, as currently calculated, does not accurately capture growth failure for all children. Exceptions should be considered for candidates who meet any of the following criteria:

- Growth parameters
 - ~~For candidates over 1 year of age,~~ < 5th percentile for: height, weight (may adjust to estimated dry weight if ascites)
 - Z-score (~~Weight for height~~) (weight, height, or BMI/weight-for-length) less than 2 standard deviations below the mean for age and gender
- Anthropometrics
 - Triceps skin fold thickness or mid-arm muscle circumference < 5th percentile for age and gender ~~for children > 1 year~~
- Failure of nasoenteric tube feedings as evidenced by failure to demonstrate improvement in growth failure in the previous month based on either weight or anthropometrics
- Requirement for TPN nutrition to allow for growth or to maintain euglycemia

Complications of portal hypertension, including ascites and gastrointestinal bleeding

Approval of MELD or PELD exception points for hospitalized pediatric candidates with complications of portal hypertension may be appropriate in some instances. Documentation submitted for case review should indicate:

- Gastrointestinal bleeding with on-going transfusion requirement, specification of interventions and treatments attempted or contraindications to their use, and the amount and dates of transfusions
- ~~Transjugular intrahepatic portosystemic shunt (TIPS) placement as a bridge to transplant. Indicate if TIPS is not an option or variceal bleeding unresponsive to ablative therapy~~
- ~~Ongoing octreotide administration~~

There is insufficient evidence to support approval of exception points in the presence of splenomegaly or varices without bleeding. There is also insufficient evidence to support approval of exception points for pediatric candidates with ascites controlled by diuretics in the outpatient setting. Exception points may be considered for candidates with severe or complicated ascites in at least one of the following clinical scenarios:

- Serum sodium less than 130, two times greater than 2 weeks apart (specify dates, values, and treatment required to demonstrate persistence and severity)
- Multiple therapeutic paracenteses (at least 2 in the previous 30 days, not including diagnostic paracentesis)
- Hydrothorax requiring chest tube or therapeutic thoracentesis (at least 2 in the previous 60 days, not including diagnostic thoracentesis)

- Patients requiring a hospitalization of at least 5 days with ascites not adequately controlled by oral diuretics and requiring IV diuretic therapy

Metabolic Liver Disease

In addition to the standard metabolic indications for transplant, there are rare metabolic diseases that present in childhood with liver failure, cirrhosis, or other life-threatening complications that may be successfully ameliorated by liver transplant. An exhaustive list of rare disorders that could be appropriate for a MELD or PELD exception is beyond the scope of this guidance. Approval of MELD or PELD exceptions may be appropriate in cases of rare metabolic disease in which liver transplant can ameliorate the life-threatening risk of the disease.

Transplant programs should submit:

- How liver transplant addresses disease complications and mortality risk
- Reference to other comparable MELD or PELD exception categories as appropriate, to justify points requested
- Experience from other cases in which liver transplant was utilized, from published literature or other.

Conclusion

Liver transplant programs, Review Board members and the Committee should consult this resource when assessing pediatric MELD, PELD and status exception requests. Liver programs should also consider this guidance when submitting exception requests for pediatric candidates with these diagnoses. However, these guidelines are not prescriptive of clinical practice.

This guidance may not be reflective of all available evidence pertinent to a specific case. Additional evidence pertinent to a child's clinical course can also be considered when reviewing exception applications.

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

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~~ the following 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:

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-Tyr3-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

Primary Sclerosing Cholangitis or Secondary Sclerosing Cholangitis

Candidates with Primary Sclerosing Cholangitis (PSC) or Secondary Sclerosing Cholangitis (SSC) historically have low mortality rates, and therefore do not need exception scores. may be at risk of adverse outcomes secondary to sepsis from cholangitis, which may not be reflected in the candidate's calculated MELD score.

Based on clinical experience and a review of the available literature, transplant programs should provide the following elements when submitting exceptions for PSC or SSC and the Review Board should consider the following elements when reviewing exception applications for candidates with PSC or SSC: the Committee recommends that four specific elements be considered.

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

The candidate must meet both of the following two criteria:

1. The candidate has been admitted to the intensive care unit (ICU) to the hospital two or more times over a three month period for hemodynamic instability requiring vasopressors within a one year period with a documented blood stream infection or evidence of sepsis including 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.)