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Briefing Paper

Liver Review Board Guidance Documents

OPTN/UNOS Liver and Intestinal Organ Transplantation Committee

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Contents

Liver Review Board Guidance Documents

Affected Policies:	*None*
Sponsoring Committee:	*Liver and Intestinal Organ Transplantation*
Public Comment Period:	*January 24, 2016 – March 23, 2016*
BOD Meeting Date:	*June 5 - 6, 2017*

Executive Summary

Medical urgency for liver allocation is determined either by the MELD[1] or PELD[2] score, or by the assignment of a status (1A or 1B). The scores are intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant, and the scores and statuses are good discriminators of death for many candidates with chronic liver disease. However, for some the risk of death without access to liver transplant or the complications of the liver disease are not accurately predicted by the statuses or the MELD or PELD score. In these instances, the liver transplant program may request exceptions.

Liver transplant programs may request exceptions for candidates with hepatocellular carcinoma (HCC), which is the most common diagnosis requiring a MELD or PELD score exception. In 2009, the OPTN Board of Directors adopted additional common diagnoses that often required MELD/PELD exceptions. All of these exceptions in policy are called standardized exceptions, and transplant programs can request a standardized exception for their candidates if the candidates meet the criteria contained within policy.[3] If a standardized exception is approved, the exception scores are determined by policy. Transplant programs are also permitted to request exceptions from the review board for candidates who do not meet the criteria for the standardized MELD/PELD exceptions, but who may have complications of their liver disease not accounted for by the MELD score which increase their waitlist mortality.

Many OPTN/UNOS regions have adopted independent criteria used to request and approve non-standardized 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.[4,5]

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, the Committee) is pursuing the establishment of a National Liver Review Board (NLRB) to promote consistent, evidence-based review of exception requests and award of exception points. 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, pediatric candidates, and candidates with hepatocellular carcinoma (HCC). However, the guidance contained in this proposal can be used by existing review boards upon adoption, independent of the implementation of the NLRB. This supplements existing national guidance and replaces the regional agreements. If adopted, review board members and transplant programs would consult this resource when considering submitting exception requests.

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[1] Model for End-Stage Liver Disease
[2] Pediatric End-Stage Liver Disease
[3] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[4] 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.
[5] 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?

Current liver policy includes standardized exceptions for nine diagnoses in which waitlist mortality is not accurately predicted by the MELD or PELD.[6] A candidate that meets the criteria for one of these diagnoses is approved for a standardized MELD or PELD exception. If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board. In June 2015, the Board of Directors approved guidance to promote consistent standards for review boards 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).[7]

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.[8,9] Nationally, exception candidates drop off the waitlist at lower rates, and are transplanted at higher rates, than their peers with the equivalent calculated MELD.[10] 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.[11] 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).[12]

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

[6] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

[7] 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/.

[8] 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.

[9] 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.

[10] 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.

[11] Based on OPTN data presented to the Committee on October 20, 2015

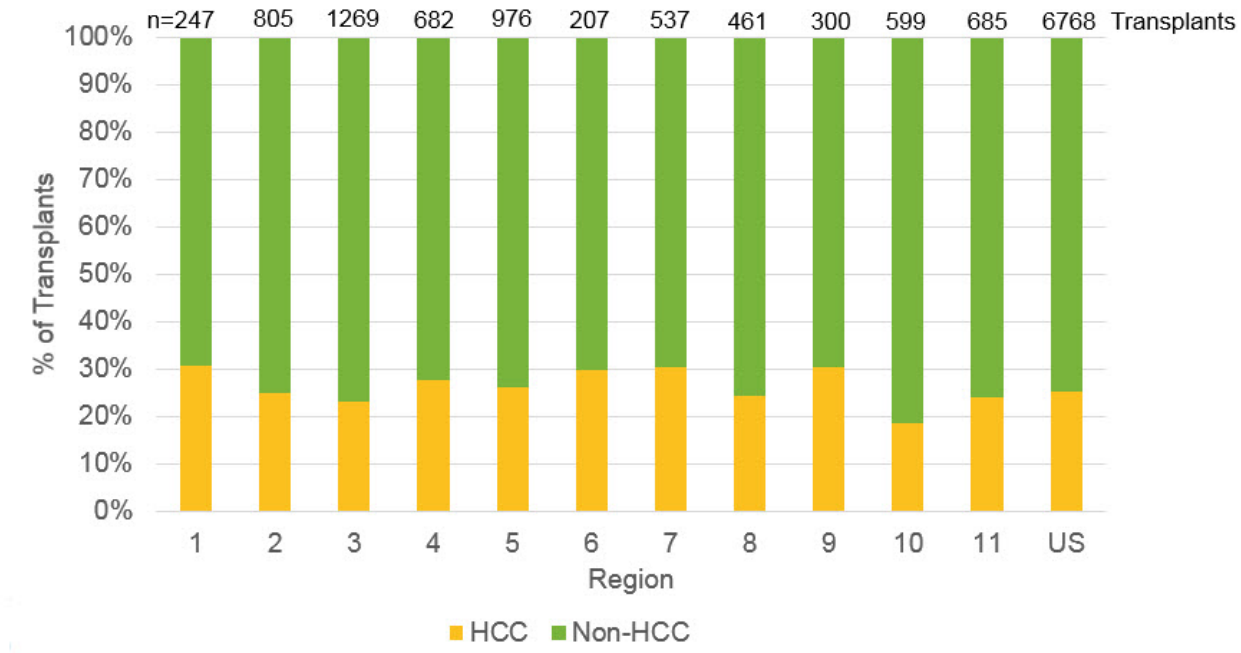
[12] Based on OPTN data as of July 8, 2016

Region	No Exception (N)	No Exception (%)	Standard Exception (N)	Standard Exception (%)	Non-Standard Exception (N)	Non-Standard Exception (%)	Total Transplants (N)
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.**

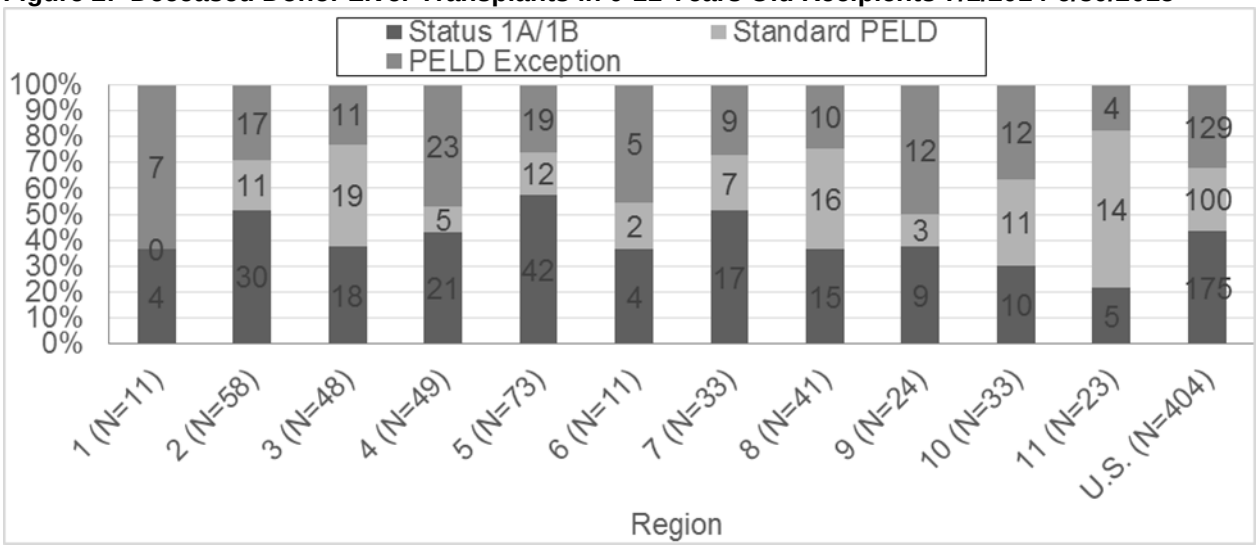
There is also evidence of regional variability in the award of HCC exception requests for candidates who not meet criteria for a standardized exception. In nearly all regions, review boards grant MELD exceptions to patients with lesions beyond T2 though the criteria are not consistently applied across the regions.

Figure 1. Deceased Donor Liver Transplants in 2015: Percentage with Approved HCC Exception at Transplant, by Region.



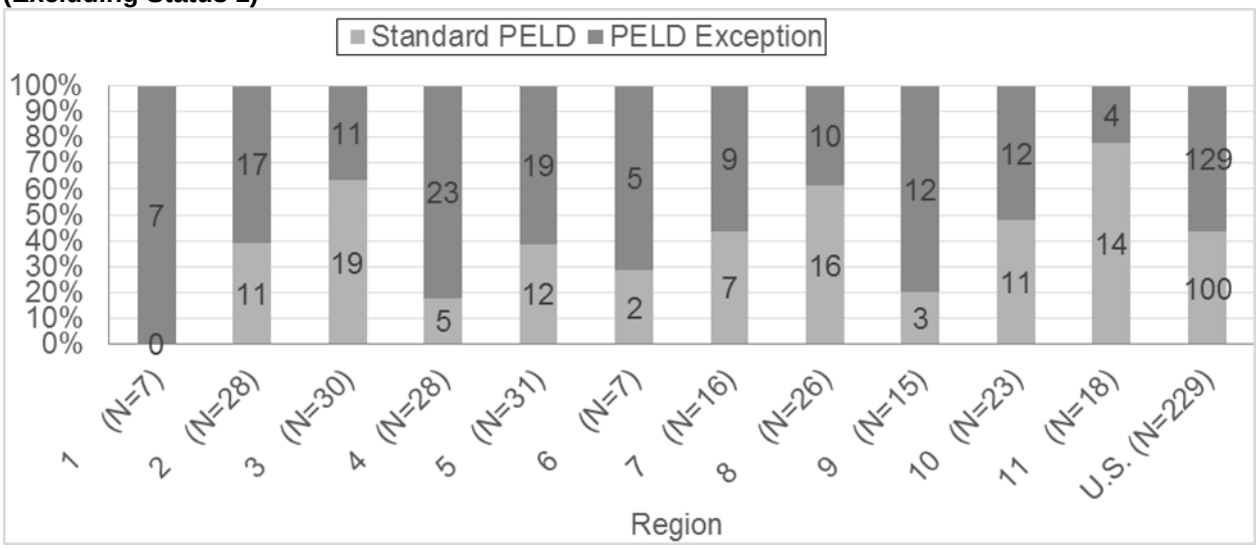
Regional variability exists among young pediatric liver transplant candidates as well. The percentage of pediatric candidates age 0 to 11 years old transplanted while listed with an exception varies widely across regions, from as low as 17% to as high as 64%.

Figure 2: Deceased Donor Liver Transplants in 0-11 Years Old Recipients 7/1/2014-6/30/2015



After excluding any status 1A candidates, the percent of 0 to 11 year old recipients who received PELD exceptions across all regions is 56%, ranging from as low as 22% to as high as 100%.

Figure 3: Deceased Donor Liver Transplants in 0-11 Years Old Recipients 7/1/2014-6/30/2015 (Excluding Status 1)



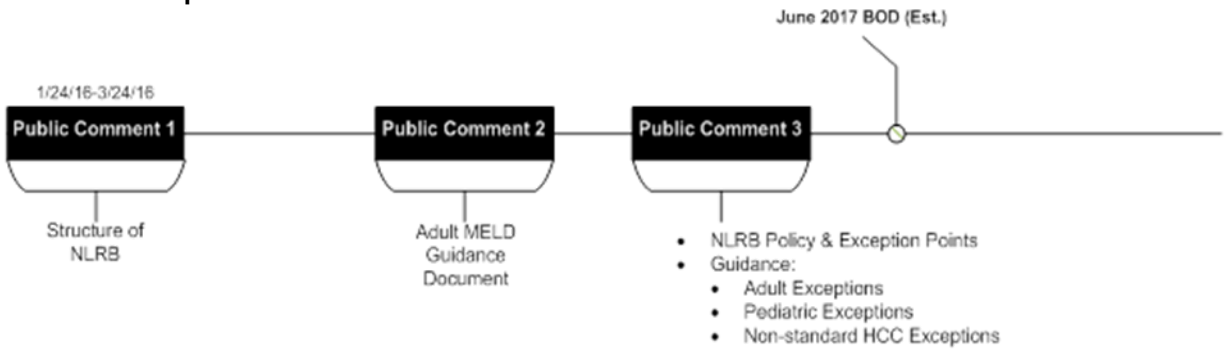
Why should you support this proposal?

This proposal is a companion to the proposal to establish a National Liver Review Board (NLRB). 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 an NLRB to promote consistent, evidence-based review of exception requests. In January 2016, the Committee distributed for public comment the proposed structure of the NLRB and operational guidelines to govern it.[13] 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.

[13] https://optn.transplant.hrsa.gov/governance/public-comment/national-liver-review-board/

The updated proposal is also currently out for public comment during the January to March 2017 public comment cycle.

Figure 4: NLRB Proposal Timeline



An important aspect of the NLRB proposal is the establishment of specialty boards, which will ensure that exception requests are assigned to reviewers with relevant expertise. There will be three specialty boards: a board to review adult MELD exception requests for all non-HCC diagnoses; a board to review pediatric exceptions requests for candidates less than 18 years old; and a board to review HCC exception requests.

The guidance documents contained in this proposal will help the specialty boards make more consistent decisions by providing the reviewers with up-to-date information about the most common conditions for which exceptions are most likely to be submitted. The proposal contains a guidance document for each of the three specialty boards. 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.

Consistent with the NLRB policy proposal currently out for public comment, the Committee recommends that the NLRB award exception points for non-standardized exceptions in a uniform manner. The Committee recommends that the NLRB award adult candidates exception scores equal to three points below the median MELD at transplant in the DSA, and pediatric exception scores equal to the median MELD at transplant in the DSA. The NLRB can use its discretion to assign more or less points depending on the candidate’s medical urgency.

Importantly, the guidance contained in this proposal can be used immediately, independent of the implementation of the NLRB.

How was this proposal developed?

The three guidance documents were developed separately. The MELD/NLRB Subcommittee of the Liver Committee developed the adult MELD exception guidance document and the HCC guidance document, while a group of pediatric liver transplantation experts, including members of the Liver Committee and the OPTN/UNOS Pediatric Committee, formed a work group to develop the pediatric exception guidance document. The groups performed extensive literature searches to find evidence in peer-reviewed journals to support their positions. They also met via teleconference on multiple occasions to reach clinical consensus on questions that may not be explicitly answered by data or literature alone.

Adult MELD Exception Guidance Document

The MELD/NLRB Subcommittee proposed some modifications to the adult MELD exception guidance in response to feedback received during the first round of public comment in January 2016. The Board previously approved guidance for four standardized exceptions: Neuroendocrine Tumors (NET); Polycystic Liver Disease (PLD); Primary Sclerosing Cholangitis (PSC); and Portopulmonary

Hypertension.[14] Because this guidance was approved in June 2015, the Committee did not include those sections in the proposed guidance in the August 2016 version. However, that may have led to some confusion, particularly for people concerned about PSC, because it may have created the impression that the Committee was proposing removing guidance for PSC. That was not the intent. Therefore, in this version of the proposal, guidance for all conditions, including the guidance previously approved, are combined into one document. The Committee also proposes clerical and grammatical changes to the existing PLD section to make it more understandable.

The Committee proposes a few changes based on feedback received during public comment. It proposes clarifying that the exception is for *chronic* Budd Chiari, and included that transplant programs should submit the etiology for the hypercoagulable state the exception request, as well as documentation ruling out extrahepatic malignancy. The Committee disagreed with some commenters who suggested that Budd Chiari should not be eligible for exception points because Budd Chiari patients already have a MELD that reflects their severity of illness, because MELD sometimes does not reflect the severity of illness for Budd Chiari and therefore an exception may be needed.

Similar to Budd Chiari, the Committee disagreed with comments that said hepatic adenoma exceptions were not needed because MELD accurately reflects the severity of illness. However, the Committee proposes minor changes to the criteria in the guidance document based on public comment, specifically, that the tumor must be unresectable with two of the following characteristics:

- Malignant transformation proven by biopsy
- Presence of beta-canenin gene mutation
- Presence of glycogen storage disease

Finally, the Committee discussed feedback regarding diffuse ischemic cholagniopathy. Some commenters suggested that the guidance should not be limited to candidates that previously received a donation after cardiac death (DCD) liver transplant. However, as discussed in the previous public comment proposal, the Committee believes the data supports limiting the guidance to those candidates that are re-listed for a liver transplant with diffuse ischemic cholagniopathy that previously received a DCD liver transplant. Those candidates have waitlist outcomes that have a similar or improved waitlist survival compared to donation after brain death (DBD) candidates who are relisted who similar MELD scores.[15] Though evidence is not conclusive, the Committee supported limiting the guidance to candidates that previously received a DCD liver transplant, and noted that this guidance document does not preclude a transplant program from applying for an exception for candidates with diffuse ischemic cholagniopathy after receiving a donation after DBD liver transplant.

<u>Pediatric Exception Guidance Document</u>

The Liver Committee convened a joint working group with the OPTN/UNOS Pediatric Transplantation Committee to develop guidance for assessing exceptions for pediatric liver candidates (less than 18 years old) to promote consistent, evidence-based review of pediatric MELD/PELD exception requests and status 1B requests. The working group categorized the proposed guidance into different sections:

- Status 1B
- Neoplasms
- Chronic Liver Disease
- Congenital Portosystemic Shunts
- Post-Transplant Complications

The working group systematically evaluated the clinical criteria that a transplant program should provide as evidence to the review board when requesting an exception for all of the conditions under each

[14] https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/

[15] 7Allen, 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.

category. When clinically appropriate, the working group agreed that the adult MELD guidance and pediatric exception guidance should be consistent. The working group largely relied on literature to support its proposal, but also evaluated OPTN data and SRTR analyses[16,17] to inform its decisions when relevant. Finally, absent conclusive evidence in literature or in data, the working group reached clinical consensus to determine its final recommendations.

HCC Exception Guidance Document

In December 2016, the OPTN/UNOS Board of Directors approved policy changes to the criteria for standardized HCC exceptions. In the development of this proposal, the Committee identified the need for a subsequent guidance document to the NLRB for HCC exception candidates falling outside of standard criteria. The Committee addressed specific scenarios in which guidance on a decision would be helpful to NLRB reviewers. These include:

- Contraindications for HCC exception score
- History of HCC in candidates
- HCC progression while undergoing local-regional treatment
- Alpha-fetoprotein (AFP) level in candidates
- Candidates beyond standard down-staging criteria

The guidance also includes recommendations for dynamic contrast-enhanced CT or MRI of the liver. These recommendations previously existed in policy, but recommendations, rather than rules, are not appropriate for policy. In the development of the HCC proposal in 2016, the Committee agreed to remove these two tables from policy that describe the recommended CT and MRI characteristics, and put them in the guidance document instead.

Was this proposal changed in response to public comment?

Yes, during the public comment period, the Committee made changes to the originally proposed guidance, and voted (14-Approve, 0-oppose, 0-abstenstions) to send the modified proposal to the OPTN/UNOS Board of Directors for consideration during its June 2017 meeting.

Post-public Comment Changes

HCC Guidance Document

In the public comment proposal, the Committee included guidance regarding contraindications for Hepatocellular Carcinoma (HCC) exception requests. This included language stating that an exception may be appropriate for patients with macro-vascular invasion of branch portal vein, and ruptured HCC. Following public comment, the committee clarified this guidance by specifying *primary* portal vein branch invasion. The use of “primary” is more in line with appropriate clinical terminology. Within this section of guidance, the Committee also clarified that patients should remain stable for a prolonged (minimum of 12 months) interval after treatment.

Following a recommendation by the MELD Enhancements and Exceptions Subcommittee, the Committee has added additional guidance regarding the six month delay for HCC candidates that have recurrent tumor following resection. The Committee discussed this topic and ultimately feel that it is appropriate that candidates who presented with T2 HCC, who underwent complete resection and subsequently developed T1 (biopsy proven) tumor recurrence, should be considered for a MELD score exception without a six month delay period. The Committee concluded that candidates that pursue resection in contrast to transplant, and subsequently recur, should be considered for deviation from the normal 6 month delay.

[16] Analysis Report: Data request from the OPTN Liver and Intestinal Organ Transplantation Committee, July 29, 2016. Presented to the Pediatric Liver Working Group on September 29, 2016. Data Request ID# LI2016_02 (Data Request 1).

[17] Analysis Report: Data request from the OPTN Liver and Intestinal Organ Transplantation Committee, August 31, 2016. Presented to the Pediatric Liver Working Group on September 29, 2016. Data Request ID# LI2016_02 (Data Request 2).

This guidance will serve as a resource for NLRB reviewers assigned to the HCC specialty board to use when reviewing cases that meet this clinical situation.

Which populations are impacted by this proposal?

This proposal promotes equitable access to transplant for all liver candidates whose status or MELD or PELD scores do not accurately reflect the severity of their disease. The proposal may also benefit liver candidates without exceptions, as the guidance in some instances is more conservative than current review board practices and some candidates currently receiving exceptions may not in the future.

How does this proposal impact the OPTN Strategic Plan?

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

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.

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

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

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

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 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?

Review board members should consult this resource when assessing exception requests.

Transplant Hospitals

Liver programs should also consider this guidance when submitting exception requests for their adult and pediatric liver transplant candidates with these diagnoses. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice.

[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.

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.

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
    i. Number of non-standardized exception requests
    ii. Number of non-standardized exception requests approved
    iii. Distribution of MELD/PELD scores among approved requests
    iv. Outcomes (probability of removals for transplant, death, too sick) for approved requests
- Transplant
    i. Number of approved non-standardized exceptions
    ii. Distribution of MELD/PELD scores among approved non-standardized exceptions
    iii. Variance in the median MELD/PELD score among approved non-standardized exceptions
    iv. 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.

Guidance Documents

RESOLVED, that the guidance documents entitled *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review*, *Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review*, and *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC)*, as set forth below, are hereby approved, effective pending implementation and notice to OPTN members.

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.[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

[1] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

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 Review Board.

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

Background

A liver candidate receives a MELD[2] or, if less than 12 years old, a PELD[3] 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 exception, the request is considered by the Review Board.

The OPTN/UNOS 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

[2]Model for End-Stage Liver Disease
[3]Pediatric End-Stage Liver Disease
[4]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[5]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.
[6]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.
[7]Runyon, B.A., Committee APG. "Management of adult patients with ascites due to cirrhosis: an update." Hepatology 49 (2009): 2087-107.
[8]Gines P., A. Cardenas, V. Arroyo, et al. "Management of cirrhosis and ascites." N Engl J Med 350 (2004):1646-54.
[9]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.
[10]Porcel, A., F. Diaz, P. Rendon, et al. "Dilutional hyponatremia in patients with cirrhosis and ascites." Arch Intern Med 162 (2002):323-8.
[11]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.

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 hydrothorax) among others.[13] Medical management may include diuresis and anticoagulation; or more aggressive management with Transjugular Intrahepatic Portosystemic Shunt (TIPS), portosystemic shunting, or liver transplant.[14] Anticoagulation and pharmacologic management is the cornerstone treatment.[15,16] 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).[17] However, due

[12]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.
[13]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.
[14]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.
[15]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.
[16]DeLeve, L.D., D.C. Valla, G. Garcia-Tsao. “Vascular disorders of the liver AASLD practice guidelines.” Hepatology 49 (2009): 1729-64.
[17]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.

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.[18,19]

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.[20,21,22,23]

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 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.

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[18]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.
[19]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.
[20]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.
[21]García-Martínez, R., M. Simón-Talero, J. Córdoba. “Prognostic assessment in patients with hepatic encephalopathy.” Dis Markers 31 (2011): 171-9.
[22]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.
[23]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.
[24]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.
[25]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.

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.[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.[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

[26]Norvell, J.P., J.R. Spivey. "Hepatic hydrothorax." Clin Liver Dis 18 (2014): 439-49.
[27]Baikati, K., D.L. Le, I.I. Jabbour, et al. "Hepatic hydrothorax." Am J Ther 21 (2014): 43-51.
[28]Cardenas, A., T. Kelleher, S. Chopra. "Review article: hepatic hydrothorax." Aliment Pharmacol Ther 20 (2004): 271-9.
[29]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.
[30]Porcel, J.M. "Identifying transudates misclassified by Light's criteria." Current Opinion Pulmonary Medicine 19 (2013): 362-7.
[31]Hewett, L.J., M.L. Bradshaw, L.L. Gordon, et al. "Diagnosis of isolated hepatic hydrothorax using peritoneal scintigraphy." Hepatology (2016).

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.[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.

[32]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.
[33]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.

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:

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:

[34]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.
[35]Chiche, L., A. David, R. Adam, et al. “Liver transplantation for adenomatosis: European experience.” Liver Transplantation 22 (2016): 516-526.
[36]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.
[37]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.

   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-tetraazacyclododedcane-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

PLD Classification – *Mayo Modification*

Types	A	B	C	D
Symptoms	0 - +	++/+++	++/+++	++/+++
Cyst Findings	Focal	Focal	Diffuse	Diffuse
Spared Remnant Volume	≥ 3	≥ 2	≥ 1	< 1
PV/HV Occlusion	No	No	No	Yes

2. Surgical Management of PLD
    - Indications:
        a. Types C* and D ***and*** at least 2 of the following:
            - Hepatic decompensation
            - 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.[38] 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

[38]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.

- 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.[39] 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.[40] Patients with biliary injuries and need for biliary interventions also have been demonstrated to have an increased risk of graft loss and death.[41] **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.[42][43] Cases of late hepatic artery thrombosis which do not meet these criteria are not eligible

[39]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.
[40]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.
[41]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.
[42]Policy 9.1.A: Adult Status 1A Requirements, Organ Procurement and Transplantation Network Policies.
[43]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

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.[44] 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.[45] 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.[46] 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.

[44]Pruritus in chronic cholestatic liver disease. Bunchorntavakul C, Reddy KR Clin Liver Dis. 2012 May;16(2):331-46.
[45]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
[46]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.

Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review

Summary and Goals

The MELD[1] or PELD[2] score and status (1A or 1B) are used to prioritize candidates on the waiting list, and are good discriminators of death without a transplant for many pediatric patients with chronic liver disease. However, for some patients, complications of the liver disease and not the degree of liver dysfunction determine the need for liver transplant. Statuses and MELD or PELD scores do not reflect these complications, which have an increased risk of mortality or waitlist dropout without access to timely transplant.[3] This document summarizes available evidence to assist clinical reviewers in approving candidates for status 1B exceptions and MELD or PELD exceptions. It contains guidance for use by the Review Board or the OPTN/UNOS Liver & Intestinal Organ Committee (hereafter, "the Committee") to evaluate common exceptional case requests for pediatric candidates with the following diagnoses, not all of which are appropriate for an exception:

- Status 1B exceptions (including neoplasms)
- Neoplasms
  - Metastatic Neuroendocrine Tumor (NET)
  - Hepatocellular Carcinoma (HCC)
  - Hilar Cholangiocarcinoma
- Complications of Liver Disease
  - Growth failure or nutritional insufficiency
  - Infections
  - Complications of portal hypertension, including ascites

[1] Model for End-Stage Liver Disease
[2] Pediatric End-Stage Liver Disease
[3] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

    - Encephalopathy
    - Hepatopulmonary syndrome
    - Developmental delay
    - Pruritus
    - Metabolic bone disease
- Congenital Portosystemic Shunts
- Post-transplant complications
    - Chronic Rejection
    - Cholangiopathy
    - Vascular Complications

These guidelines 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 Review Board.

Background

For allocation purposes, a liver candidate is either registered in a status or receives a MELD or, if less than 12 years old, a PELD score. Candidates are registered in either status 1A or 1B if the candidate meets certain clinical criteria defined by policy, and transplant programs may request to register a candidate in a status if the candidate does not meet the policy requirements. The Committee retrospectively reviews candidates registered in a status by exception.

The MELD and PELD scores are intended to reflect the candidate's disease severity, based on 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 for a higher score. A candidate that meets the criteria for one of the diagnoses in policy is approved for a standardized MELD or PELD exception.[4] If the candidate does not meet criteria for standardized exception, the Review Board considers the request. Pediatric candidates with approved exceptions who turn 18 while still waiting with an approved exception continue to be eligible to receive pediatric exceptions unless or until the candidate is removed from the waiting list.[5]

The Committee has developed guidance for pediatric status and MELD or PELD exception candidates. To support a recommendation for approving an exceptional status registration or additional MELD or PELD 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 use to request and approve exceptions, commonly referred to as "regional agreements." Review Board members, transplant

[4] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[5] Policy 9.1: Status and Score Exceptions, Organ Procurement and Transplantation Network Policies.

centers, and the Committee should consult this resource when considering status or MELD/PELD exception requests for pediatric candidates less than 18 years old. Any guidance contained within this document that differs from the guidance offered for adult MELD exceptions is intentional, and is based on peer-review literature and/or clinical practice.

Recommendation

Status 1B

Status 1B - Chronic liver disease

Generally candidates that do not meet criteria in *Policy 9.1.C: Pediatric Status 1B Requirements* should not receive a status 1B exception. Candidates that meet criteria in *Policy 9.1.C.2.c* or *9.1.C.2.d* but without a PELD score of at least 25 may be considered for status 1B exception if the candidate is critically ill and admitted in the Intensive Care Unit (ICU). Candidates without renal replacement therapy may be considered for a status 1B exception if they meet all other criteria in policy and require a liver support device (such as Molecular Adsorbent Recirculating System (MARS), albumin dialysis, plasmapheresis).

Status 1B – Neoplasm

Under *Policy 9.1.C.2*, candidates with biopsy-proven hepatoblastoma without evidence of metastatic disease qualify for status 1B. In some instances, it may also be appropriate to consider the following pediatric candidates with hepatoblastoma for a status 1B exception:

- Candidates less than 8 years old with hepatoblastoma[6] but not biopsied with radiographic criteria consistent with unresectable hepatoblastoma, and all of the following:
    - No evidence of metastasis at time of listing
    - AFP greater than 100
- Candidates with a biopsy-confirmed embryonal sarcoma that has not metastasized[7,8,9]
- Candidates with vascular malformation (congenital, infantile, or other) and hospitalized with presence of Kasabach-Merritt syndrome or presence of high output cardiac failure requiring pressor or ventilatory support

There is inadequate evidence to support approving Status 1B exception for pediatric candidates

[6] Meyers et al, in press, Lancet Oncology, 2016
[7] Ismail H, Dembowska-Baginska B, Broniszczak D, et al. Treatment of undifferentiated embryonal sarcoma of the liver in children--single center experience. J Pediatr Surg 2013;48:2202-6.
[8] Plant AS, Busuttil RW, Rana A, Nelson SD, Auerbach M, Federman NC. A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. J Pediatr Hematol Oncol 2013;35:451-5.
[9] Walther A, Geller J, Coots A, et al. Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. Liver Transpl 2014;20:191-9.

with rhabdoid tumors.[10,11,12,13] There is also inadequate evidence to support approving Status 1B exception for pediatric candidates with angiosarcoma.[14]

Neoplasms

Hepatoblastoma

Candidates with non-metastatic hepatoblastoma are eligible for status 1B under *Policy 9.1.C Pediatric Status 1B Requirements*.

Epithelioid Hemangioendothelioma (HEHE)

Candidates with (HEHE) with unresectable lesions unresponsive to therapy may be considered for exceptions.[15]

Metastatic Neuroendocrine Tumor (NET)

A review of the literature supports that candidates with NET are expected to have a low risk of waiting list drop-out, though they benefit from transplantation.[16]

The Review Board should consider the following criteria when reviewing exception applications for candidates with NET:

1. Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD or PELD exception request.
2. Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.
3. Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:
    a. If CT Scan: Triple phase contrast
        i. Lesions may be seen on only one of the three phases
        ii. Arterial phase: may demonstrate a strong enhancement
        iii. Large lesions can become necrotic/calcified
    b. If MRI Appearance:
        i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
        ii. Diffusion restriction
        iii. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase
        iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

[10] Kachanov D, Teleshova M, Kim E, et al. Malignant rhabdoid tumor of the liver presented with initial tumor rupture. Cancer Genet 2014;207:412-4.
[11] Agarwala S. Primary malignant liver tumors in children. Indian J Pediatr 2012;79:793-800.
[12] Sugito K, Uekusa S, Kawashima H, et al. The clinical course in pediatric solid tumor patients with focal nodular hyperplasia of the liver. Int J Clin Oncol 2011;16:482-7.
[13] Marzano E, Lermite E, Nobili C, et al. Malignant rhabdoid tumour of the liver in the young adult: report of first two cases. HPB Surg 2009;2009:628206.
[14] Xue M, Masand P, Thompson P, Finegold M, Leung DH. Angiosarcoma successfully treated with liver transplantation and sirolimus. Pediatr Transplant 2014;18:E114-9.
[15] Rodriguez, J.A., Becker, N.S., O'Mahony, C.A. et al. J Gastrointest Surg (2008) 12: 110. doi:10.1007/s11605-007-0247-3
[16] V. Mazzaferro, C. Sposito, J. Coppa, et. al., The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors, Am. J. Transplantation, 16:(10), DOI 10.1111/ajt.13831

4. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage.

   Note: NET with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.

5. 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.
6. Tumor metastatic replacement should not exceed 50% of the total liver volume
7. 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-tetraazacyclododedcane-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 or PELD exception request.

8. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD or PELD exception request (submit date).
9. Recheck metastatic workup every 3 months for MELD or PELD 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.
10. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion criteria

Hepatocellular Carcinoma (HCC)[17,18,19,20]

Status 1B exceptions may be considered for pediatric candidates with HCC in the presence of metabolic liver disease (such as hereditary tyrosinemia).

Policy 9.5.I: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions also permits the Review Board to award exceptions for candidates with HCC in

17 Jacfranz J. Guiteau, Ronald T. Cotton, Saul J. Karpen, Christine A. O'Mahony, John A. Goss, Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: The UNOS experience, Pediatric Transplantation, 2010, 14, 3, 326

18 Beaunoyer, Mona and Vanatta, Jason M. and Ogihara, Makoto and Strichartz, Debra and Dahl, Gary and Berquist, William E. and Castillo, Ricardo O. and Cox, Kenneth L. and Esquivel, Carlos O. Outcomes of transplantation in children with primary hepatic malignancy Pediatric Transplantation 11(6) url =http://dx.doi.org/10.1111/j.1399-3046.2007.00751.x}, p655—660, 2007

19 Mazzaferro, V. and Sposito, C. and Coppa, J. and Miceli, R. and Bhoori, S. and Bongini, M. and Camerini, T. and Milione, M. and Regalia, E. and Spreafico, C. and Gangeri, L. and Buzzoni, R. and de Braud, F. G. and De Feo, T. and Mariani, L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors}, American Journal of Transplantation},16 (10) doi = {10.1111/ajt.13831},{2892--2902},2016

20 Pham TA, Gallo AM, Concepcion W, Esquivel CO, Bonham CA. Effect of Liver Transplant on Long-Term Disease-Free Survival in Children with Hepatoblastoma and Hepatocellular Cancer. JAMA Surg 150(12): 1150-8, 2015)

certain circumstances. In the absence of metabolic disease, data from the Pediatric Liver Unresectable Tumor Observatory (PLUTO) registry and other single center experience suggests criteria may be expanded beyond Milan and University of California – San Francisco (UCSF) criteria. Extrahepatic metastasis should be an absolute contraindication but exception points for unresectable HCC limited to liver may be considered on a case by case basis in pediatric candidates.

- Children do not need to be within Milan criteria
- Documentation of metastatic work up (including cross-sectional imaging of the chest and bone scan or PET) and no evidence of tumors outside the liver

Hilar Cholangiocarcinoma

Candidates with hilar cholangiocarcinoma may be considered for a MELD or PELD exception if the candidate meets the requirements in *Policy 9.5.A: Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions.*

Chronic Liver Disease[21,22,23,24,25,26,27]

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, exceptions should be considered for candidates who meet any of the following criteria:

- Growth parameters[28]
  - For candidates over 1 year of age, <5th percentile for: height, weight (may adjust to estimated dry weight if ascites)[29,30]
  - Z-score (Weight for height) less than 2 standard deviations
- Anthropometrics
  - Skin fold thickness < 5th percentile for age and gender for children > 1 year[31]
- 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[32]
- Requirement for TPN nutrition to allow for growth or to maintain euglycemia

[21] Tamir M et al pediatric liver Transplantation for Primary Sclerosing Cholangitis Liver Transplantation 17:925-933 2011
[22] Elgendy H et al The outcome of critically ill children afterliving donor liver transplant Exp Clin Transplant Suppl 1 : 100-7 2015
[23] Malatack etal Choosing a pediatric recipient for orthotopic liver transplantation J Pediatr 111: 479-489 1987
[24] Sarin SK etal Young adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival Gut 29: 101-107 1988
[25] Matloff RG The Kidney in Pediatric Liver Disease Curr Gastroenterol Rep 17: 36
[26] Dara N et al Liver function, paraclinical tests, and mortality risk factors in pediatric liver transplant candidates Comparative clinical Pathology 25 (1) : 189-195 2015
[27] Keating et al Clinical course of cirrhosis in young adults and therapeutic potential of liver transplantation Gut 26: 1359-1363 1985
[28] Sokol RJ etal Anthropometric evaluation of children with chronic liver diseases Am J Nutrition 52:203-208 1980
[29] World Health Organization global Database on Child Growth and Malnutrition
[30] Yang etal Living donor liver transplantation with body weight more or less than 10 kilograms world J Gastroenterol 21 (23) 7248-53 2015
[31] UptoDate 2016. Table for skin fold thickness percentiles.
[32] Chin SE the nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation Am J Clin Nutr 56:164-168 1992

Infections

Approval of MELD or PELD exception points for pediatric candidates with recurrent cholangitis or other life-threatening infection may be appropriate in some instances. Documentation submitted for case review should indicate one of the following:

- Two or more episodes of spontaneous bacterial peritonitis (SBP)[33] (specify date of each episode)
- At least one episode of other life-threatening infection with sepsis requiring ICU stay
- Two or more episodes of cholangitis within 6 months requiring IV antibiotics requiring placement of a PICC or central line for > 2 continuous weeks for ongoing administration of antibiotics (specify date of each episode)

Complications of portal hypertension, including ascites

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[34]
- 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[35]
- Multiple therapeutic paracenteses (at least 2 in the previous 30 days, not including diagnostic paracentesis)
- Hydrothorax requiring chest tube or therapeutic thoracentesis

Encephalopathy

Approval of MELD or PELD exception points for hospitalized pediatric candidates with symptomatic encephalopathy may be appropriate in any of the following instances:

- Clinically refractory to medical management with lactulose or rifaximin
- Infant Glasgow coma score less than 12

[33] Larcher VF Spontaneous bacterial peritonitis in children with chronic liver disease, clinical features jpediatr 106: 907-912 1985

[34] Iwatsuki S et al: Liver transplantation in the treatment of bleeding esophageal varices Surgery 104 (4) : 697-705 1988

[35] Pugliese R et al Ascites and serum sodium are markers o increased waiting list mortality in children with chronic liver failure Hepatology 59: 1964-7 2014

Hepatopulmonary Syndrome

Approval of additional MELD or PELD exception points for pediatric candidates who meet the standardized criteria for hepatopulmonary syndrome according to *Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* may be appropriate in some instances, such as if the candidate is hospitalized, or if the candidate is debilitated or exhibits progressive decompensation.

Developmental Delay

There is insufficient evidence to support approval of exception points for pediatric candidates with developmental delay.

Pruritus

Approval of MELD or PELD exception points for pediatric candidates with pruritus may be appropriate in some instances. Documentation submitted for case review should indicate that the candidate has evidence of cutaneous mutilation with bleeding and scratching nonresponsive to medications such as rifampin, ursodiol and naltrexone.

Candidates should not be awarded additional MELD or PELD exceptions points on the basis of xanthomas or an indwelling biliary catheter.

Metabolic Bone Disease

Approval of MELD or PELD exception points for pediatric candidates with metabolic bone disease may be appropriate in some instances. Documentation submitted for case review should indicate:

- Documented pathologic fractures or bone deformity
- Patient is unresponsive to vitamin D, mineral supplementation

Congenital Portosystemic Shunts

Pediatric patients with congenital portosystemic shunts as Abernathy syndrome may be evaluated on the basis of their complications (hyperammonemia and encephalopathy or hepatopulmonary syndrome) rather than as a unique disease category.

Post-Transplant Complications

Chronic rejection

Chronic rejection (CR) may cause long-term graft dysfunction and fibrosis. The Banff group defined the minimal histological features of CR as biliary epithelial changes affecting a majority of bile ducts with or without duct loss, foam cell obliterative arteriopathy, or bile duct loss affecting greater than 50% of portal tracts.[36,37]

[36] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.

[37] Wallot MA, Mathot M,Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience.Liver Transpl 2002;8:615-622.

In the Studies of Pediatric Liver Transplantation (SPLIT) database, CR remains at a less than 5% incidence; however 38% of reported patients proceeded to retransplanation.[38] When evaluating late graft loss (more than one year after transplant), 37% of all lost grafts in SPLIT were due to CR. Retransplantation is indicated for those patients who do not respond to treatment of rejection.

Chronic rejection alone is not sufficient for an exception. Exceptions for clinical complications or manifestations of chronic rejection may be appropriate if the transplant program submits evidence of a comorbid condition from the Chronic Liver Disease section above, as well as other evidence including:

- Evidence of chronic rejection on liver biopsy
- Recurrent infections – cholangitis, spontaneous bacterial peritonitis (SBP) (similar criteria regarding quantification and severity of infections to cholestatic patients)
- Growth failure/nutritional insufficiency, complication of portal hypertension, hyponatremia – sodium less than 130, intractable ascites, intractable pruritis

Cholangiopathy

The rates for biliary strictures range from 5% to 25% in pediatric liver graft recipients (Duffy, Tanaka).[39,40] The main cause of late biliary strictures is graft ischemia; ischemic biliary strictures are frequently multiple and affect all aspects of the biliary tree. In contrast, solitary anastomotic strictures are usually short and may respond to percutaneous or endoscopic dilatation. Non-anastomotic strictures are harder to manage, and often result from Hepatic Artery Thrombosis (HAT) or ischemia-reperfusion injury. Some can also be due to primary immune injury. Cholangitis remains the most common manifestation along with progressive fibrosis. Retransplantation may be required for diffuse and multiple biliary strictures and particularly for those associated with late HAT; retransplantation should be considered in patients with diffuse cholangiopathy.[41]

Exceptions for clinical complications or manifestations of chronic graft dysfunction due to biliary cause may be appropriate if the transplant program submits evidence of a comorbid condition from the Chronic Liver Disease section above, as well as other evidence including:

- Radiological evidence (imaging study such as MR; percutaneous or endoscopic findings of cholangiopathy) of cholangiopathy is required specify:
- Recurrent infections/cholangitis, including:
    - development or evolution of bacterial resistance
    - SBP (similar criteria regarding quantification and severity of infections to

[38] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.

[39]Duffy JP, Kao K, Ko CY,Farmer DG, McDiarmid SV,Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652-661.

[40] Tanaka H, Fukuda A,Shigeta T, Kuroda T,Kimura T, Sakamoto S,Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. J Pediatr Surg2010;45:1668-1675.

[41] Sunku B, Salvalaggio PR,Donaldson JS, Rigsby CK,Neighbors K, Superina RA,Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. Liver Transpl2006;12:821-826.

309 cholestatic patients)
310 o Growth failure/nutritional insufficiency
311 o Complication of portal hypertension
312 o Hyponatremia – sodium less than 130
313 o Intractable ascites
314 o Intractable pruritis
315
316 **Vascular complications**[42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]

317 Exceptions for clinical complications/manifestations of late vascular complications may be
318 appropriate if the transplant program submits evidence of a cobmorbid condition from the
319 Chronic Liver Disease section above, as well as other evidence including:

320 • Recurrent infections, including:
321 o cholangitis
322 o SBP (similar criteria regarding quantification and severity of infections to
323 cholestatic patients)
324 o Growth failure/nutritional insufficiency
325 o Complication of portal hypertension
326 o Hyponatremia – Sodium less than 130

[42] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.
[43] Wallot MA, Mathot M,Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience.Liver Transpl 2002;8:615-622.
[44] Duffy JP, Kao K, Ko CY,Farmer DG, McDiarmid SV,Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652-661.
[45] Tanaka H, Fukuda A,Shigeta T, Kuroda T,Kimura T, Sakamoto S,Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. J Pediatr Surg2010;45:1668-1675.
[46] Sunku B, Salvalaggio PR,Donaldson JS, Rigsby CK,Neighbors K, Superina RA,Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. Liver Transpl2006;12:821-826.
[47] Yazigi NA.Long term outcomes after pediatric liver transplantation. Pediatr Gastroenterol Hepatol Nutr. 2013 Dec;16(4):207-18
[48] Marshalleck F. Pediatric arterial interventions. Tech Vasc Interv Radiol2010;13:238-243
[49] Kelly DA, Bucuvalas JC, Alonso EM, et al Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013 Aug;19(8):798-825.
[50] Buell JF, Funaki B, Cronin DC, Yoshida A, Perlman MK, Lorenz J, et al. Long-term venous complications after full-size and segmental pediatric liver transplantation. Ann Surg2002;236:658-666.
[51] iraglia R, Maruzzelli L,Caruso S, Marrone G,Carollo V, Spada M, et al.Interventional radiology procedures in pediatric patients with complications after liver transplantation.Radiographics2009;29:567-584.
[52] Cheng YF, Chen CL,Huang TL, Chen TY, Chen YS, Wang CC, et al.Angioplasty treatment of hepatic vein stenosis in pediatric liver transplants: long-term results. Transpl Int 2005;18:556-561.
[53] Skaro AI, Jay CL, Baker TB, et al. The impact of ischemic cholangiopathy in liver transplantation using donors after cardiac death: the untold story. Surgery. 2009;146(4):543-553.
[54] Berrocal T, Parrón M,Alvarez-Luque A, Prieto C,Santamaría ML. Pediatric liver transplantation: a pictorial essay of early and late complications.Radiographics2006;26:1187-1209.
[55] Maheshwari A, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. Liver Transpl. 2007;13(12):1645-1653.
[56] Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. Surgery. 2011;150(4):692-702.
[57] Hong JC, Venick R, Yersiz H, et al. Liver transplantation in children using organ donation after circulatory death: a case-control outcomes analysis of a 20-year experience in a single center.JAMA Surg. 2014 Jan;149(1):77-82
[58] Bartlett A, Vara R, Muiesan P, et al. A single center experience of donation after cardiac death liver transplantation in pediatric recipients. Pediatr Transplant. 2010;14(3):388-392.

- Intractable ascites
- Intractable pruritis

Specific criteria for arterial, or vascular cause of graft dysfunction requiring transplantation are listed below.

Late HAT

Late HAT (greater than 30 days post-transplant) are underrecognized and are usually due to ischemic or immunologic injuries.[59] The liver function is usually fairly preserved due to the presence of extensive collateralization, and bile ducts complications are the defining morbidities. Because the blood supply to transplanted bile ducts is derived solely from the hepatic artery, HAT is frequently associated with biliary pathology – typically non-anastomotic strictures, often in the hilum and complex in nature. Bilomas and biliary sepsis are common.

A definitive diagnosis of late HAT requires more advanced imaging (e.g. CT, MR, or standard angiographies). If treatment is required, thrombolysis and anticoagulation are rarely effective, and surgical reconstruction is contraindicated. Radiological treatment of biliary strictures is indicated if necessary, and drainage of intrahepatic abscesses/bilomas is required. For symptomatic late HAT with cholangitis, hepatic abscesses, or diffuse biliary stricturing, retransplantation is frequently necessary.

Specific information regarding the following is helpful to substantiate the request:

- Radiological or angiographic evidence of HAT complicated by both of the following:
  - Recurrent infections – cholangitis, sepsis
  - Failure or inapplicability of percutaneous or endoscopic biliary interventions: specify

Patients with early HAT just beyond the 7 day status 1A cut off or the 14 day standard exception cut off with evidence of severe graft dysfunction may be considered for MELD exception, depending on the clinical scenario.

Portal Vein Thrombosis (PVT)[60,61]

PVT is estimated at 2-10% in all pediatric recipients. Portal hypertensive complications manifest mostly as hypersplenism and gastrointestinal (GI) bleeding. Currently scarce systematic data is available on those patients' outcomes. Surgical shunts (selective distal splenorenal, systemic mesocaval, and meso-Rex) are useful, but retransplantation may be indicated. A REX shunt (meso-rex bypass) is favored when technically feasible.

[59] Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. Liver Transpl 2009: 15(Suppl 2): S12–S18

[60] Jensen MK, Campbell KM, Alonso MH, Nathan JD, Ryckman FC, Tiao GM. Management and long-term consequences of portal vein thrombosis after liver transplantation in children. Liver Transpl. 2013;19:315–321

[61] de Ville de Goyet J, Gibbs P, Clapuyt P, Reding R,Sokal EM, Otte JB. Original extrahilar approach for hepatic portal revascularization and relief of extrahepatic portal hypertension related to later portal vein thrombosis after pediatric liver transplantation. Long term results. Transplantation1996;62:71-75.

Endovascular interventions should be attempted in patients with portal vein stenosis.

Data requested to substantiate exception requests include:

- evidence of PVT on imaging study or angiography required with complication requiring retranplantation (i.e. refractory complications of portal hypertension, hepatopulmonary syndrome)
- Contraindication to surgical shunt: specify
- Failure of surgical shunt: specify

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.

Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC)

Background

A liver candidate receives a MELD[1] or, if less than 12 years old, a PELD[2] 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.[3] If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board.

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exceptions for Hepatocellular Carcinoma (HCC). This guidance document is intended to provide recommendations for the review board considering HCC cases which are outside standard policy.

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

1. Patients with the following are contraindications for HCC exception score:

    - Macro-vascular invasion of main portal vein or hepatic vein
    - Extra-hepatic metastatic disease
    - Ruptured HCC
    - T1 stage HCC

While in most cases, ruptured HCC and primary portal vein branch invasion of HCC would be contraindications, some patients who remain stable for a prolonged (minimum of 12 months) interval after treatment for primary portal vein branch invasion or after ruptured HCC may be suitable for consideration.

2. Patients who have a history of prior HCC >2 years ago which was completely treated with no evidence of recurrence, who develop new or recurrent lesions after 2 years should generally be considered the same as those with no prior HCC, in order to

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

determine the current stage suitability for MELD exception, and MELD exception score assignment.

3. Patients beyond standard criteria who have continued progression while waiting despite LRT are generally not acceptable candidates for HCC MELD exception.
4. Patients with AFP>1000 who do not respond to treatment to achieve an AFP below 500 are not eligible for standard MELD exception, and must be reviewed by the HCC review board to be considered. In general, these patients are not suitable for HCC MELD exception but may be appropriate in some cases.
5. Patients with HCC beyond standard down-staging criteria who are able to be successfully downstaged to T2 may be appropriate for MELD exception, as long as there is no evidence of metastasis outside the liver, or macrovascular invasion, or AFP >1,000. Imaging should be performed at least 4 weeks after last down-staging treatment. Patients must still wait for 6 months from the time of the first request to be eligible for an HCC exception score.
6. Patients with cirrhosis who presented with stage T2 resectable HCC (one lesion >2 cm and <5 cm in size, or two or three lesions >1 cm and <3 cm in size, based on resection specimen pathology) who underwent complete resection but developed T1 (biopsy proven), or T2 HCC (LI-RADS 5) following complete resection should be considered for MELD score exception, without a six month delay period.

Patients with cirrhosis and HCC beyond T2 but within generally accepted criteria for down-staging (such as up to 5 lesions, total tumor volume <8 cm based on resection pathology) who underwent complete resection with negative margins and developed T1 (biopsy proven) or T2 recurrence (LI-RADS 5) may also be considered for MELD score exception for HCC. Because the larger tumor size, the 6 month delay is appropriate to ensure favorable tumor biology.

Recommendations for Dynamic Contrast-enhanced CT or MRI of the Liver

Table 1: Recommendations for Dynamic Contrast-enhanced CT of the Liver

Feature:	CT scans should meet the below specifications:
Scanner type	Multidetector row scanner
Detector type	Minimum of 8 detector rows and must be able to image the entire liver during brief late arterial phase time window
Slice thickness	Minimum of 5 mm reconstructed slice thickness; thinner slices are preferable especially if multiplanar reconstructions are performed
Injector	Power injector, preferably dual chamber injector with saline flush and bolus tracking recommended
Contrast injection rate	3 mL/sec minimum, better 4-6 mL/sec with minimum of 300 mg I/mL or higher, for dose of 1.5 mL/kg body weight
Mandatory dynamic phases on contrast-enhanced MDCT	1. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein 2. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins 3. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast

Feature:	CT scans should meet the below specifications:
Dynamic phases (Timing)	Use the bolus tracking or timing bolus

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Table 2: Recommendations for Dynamic Contrast-enhanced MRI of the Liver

Feature	MRIs should meet the below specifications:
Scanner type	1.5T Tesla or greater main magnetic field strength. Low field magnets are not suitable.
Coil type	Phased array multichannel torso coil, unless patient-related factors precludes its use.
Minimum sequences	Pre-contrast and dynamic post gadolinium T1-weighted gradient echo sequence (3D preferable), T2 (with and without fat saturation), T1-weighted in and out of phase imaging.
Injector	Dual chamber power injector with bolus tracking recommended.
Contrast injection rate	2-3 mL/sec of extracellular gadolinium chelate that does not have dominant biliary excretion, preferably resulting in vendor-recommended total dose.
Mandatory dynamic phases on contrast-enhanced MRI	1. Pre-contrast T1W: do not change scan parameters for post contrast imaging. 2. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein. 3. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins. 4. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast.
Dynamic phases (Timing)	The use of the bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal vein phase images should be acquired 35 to 55 seconds after initiation of late arterial phase. Delayed phase images should be acquired 120 to 180 seconds after the initial contrast injection.
Slice thickness	5 mm or less for dynamic series, 8 mm or less for other imaging.
Breath-holding	Maximum length of series requiring breath-holding should be about 20-seconds with a minimum matrix of 128 x 256. Technologists must understand the importance of patient instruction about breathholding before and during scan.

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