OPTN

Briefing to the OPTN Board of Directors on

Clarification of Pre-Existing Liver Disease

OPTN Liver and Intestinal Organ Transplantation Committee

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Clarification of Pre-Existing Liver Disease

Affected Policies:	*9.1.A: Adult Status 1A Requirements*
	9.1.B: Pediatric Status 1A Requirements
Sponsoring Committee:	*Liver and Intestinal Organ Transplantation*
Public Comment Period:	*August 2, 2019 – October 2, 2019*
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Executive Summary

A liver candidate with a diagnosis of fulminant liver failure may qualify to be listed as Status 1A on the liver waiting list. Status 1A is the highest medical urgency category for liver candidates, and is reserved for candidates who have the highest risk of mortality within one week if they do not receive a transplant. In order to qualify for Status 1A based on this diagnosis, the candidate must not have pre-existing liver disease. There has not been a clear policy on whether a candidate who has previously received a liver transplant would be disqualified because of liver disease before that transplant. This policy would clarify that pre-existing liver disease in a prior liver transplant recipient would not disqualify them as a candidate for Status 1A fulminant liver failure unless the candidate had a diagnosis of liver disease following that liver transplant.

Purpose of Proposal

Fulminant liver failure is rare, but when it occurs, liver transplantation can be lifesaving.[1] OPTN Policies *9.1.A: Adult Status 1A Requirements* and *9.1.B Pediatric Status 1A Requirements* allow patients meeting specific criteria for fulminant hepatic failure[2] to be eligible for listing as Status 1A when patients are "without pre-existing liver disease".[3] Current policy regarding whether prior liver disease that has been treated by a prior liver transplant would preclude a candidate from listing as Status 1A is ambiguous. Although in that case there is not a continuing pre-existing liver disease, the candidate has had liver disease in the past. The intent of the Liver and Intestinal Organ Transplantation Committee (Committee) is that the qualification for Status 1A follow the generally accepted definition of fulminant hepatic failure, which is that the rapid decline is the result of a severe liver injury and not a longer progression of liver disease.[4] This would allow listing as Status 1A as long as there was not ongoing, pre-existing liver disease.

Patients who meet the criteria for a Status 1A listing due to fulminant liver failure have the same urgent need for transplant regardless of whether they have received a prior transplant. Because these patients are just as urgent, they should be afforded the same level of priority as other, similar patients who have not received a prior liver transplant.

Background

An OPTN transplant hospital member approached the Committee because they were listing a liver recipient who was experiencing fulminant hepatic failure and they were unsure whether that disqualified him from Status 1A. The Committee agreed that the policy language was not clear as to whether a candidate in that situation would be able to qualify for Status 1A. In order to ensure that the ambiguity surrounding the definition of "pre-existing liver disease" does not inadvertently preclude any candidates from being listed with the appropriate priority, the Committee now seeks to update the definition of pre-existing liver disease in *Policy 9.1.A*.

Under the current policy, a candidate's first signs or symptoms of liver disease must occur no earlier than 56 days before the onset of hepatic encephalopathy, and the candidate must not have liver disease before that in order to qualify for Status 1A.[5]

[1] William Bernal, Georg Auzinger, Anil Dhawan and Julie Wendon, "Acute Liver Failure," *The Lancet* (July 17, 2010): 190-201. Carmi Ounzalan, Curtis Barry, "Acute Liver Failure: Diagnosis and Management," *Journal of Intensive Care Medicine* 31, no. 10 (October 6, 2015), 642-653. https://doi.org/10.1177/0885066615609271.

[2] Fulminant hepatic failure is also referred to as acute liver failure, fulminant liver failure, and acute hepatic failure.

[3] OPTN Policy 9.1.A Adult Status 1A Requirements and OPTN Policy 9.1.B Pediatric Status 1A Requirements.

[4] Fulminant hepatic failure is generally defined as "a potentially reversible disorder that was the result of severe liver injury, with an onset of encephalopathy within 8 weeks of symptom appearance and in the absence of pre-existing liver disease. "Bernal, Auzinger, Dhawan and Wendon, "Acute Liver Failure".

[5] Encephalopathy is brain disease, damage or malfunction. Hepatic encephalopathy us a decline in brain function that occurs as a result of severe liver disease.

Table 1: Current Policy Standard

If the candidate meets the other requirements, and the onset of hepatic encephalopathy is	Then the candidate
Within 56 days after the first signs or symptoms of new liver disease	Qualifies for Status 1A
More than 56 days after the first signs and symptoms of new liver disease	Does NOT qualify for Status 1A

This change will clarify the prioritization of liver candidates who have already received a liver transplant and then experience fulminant liver failure. It will make it clear that these candidates receive the same priority for transplantation as other candidates with the same acute liver failure. Without transplantation, the chances of survival for patients with fulminant hepatic failure are approximately 15%.[6] However, receipt of a liver transplant increases their short-term survival rate to more than 65%.[7]

Overview of Proposal

Under this proposal, the rules for when a candidate who has had a prior transplant will be clearer.

Table 2: Proposed Policy Standard

If the candidate meets the other requirements, and is	and the onset of hepatic encephalopathy is	Then the candidate
Not a prior liver recipient	Within 56 days after the first signs or symptoms of new liver disease	Qualifies for Status 1A
A prior liver recipient	Within 56 days after the first *post-transplant* signs or symptoms of new liver disease	Qualifies for Status 1A
Not a prior liver recipient	More than 56 days after the first signs and symptoms of new liver disease	Does NOT qualify for Status 1A
A prior liver recipient	More than 56 days after the first *post-transplant* signs and symptoms of new liver disease	Does NOT qualify for Status 1A

This proposal will ensure that candidates for re-transplant who are experiencing fulminant hepatic failure receive the same access to organ transplant as one another and as candidates with fulminant hepatic failure who are listed for their first liver transplant. Fulminant hepatic failure affects an estimated 2,000 patients in the United States annually. The most common causes are drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion, although many cases have no discernible cause.[8]

[6] Julie Polson and William Lee, "AASLD position paper: The management of acute liver failure", *Hepatology* (April 19, 2005): 1179-1197, available at https://doi.org/10.1002/hep.20703.
[7] Id.
[8] Id.

Community Feedback

This proposal was supported during public comment. All of the regions (see **Figure 1**) and all types of members (see **Figure 2**) were supportive. The American Society of Transplantation, American Society of Transplant Surgeons, and Society for Pediatric Liver Transplant were all supportive.

Figure 1: Sentiment at Regional Meetings

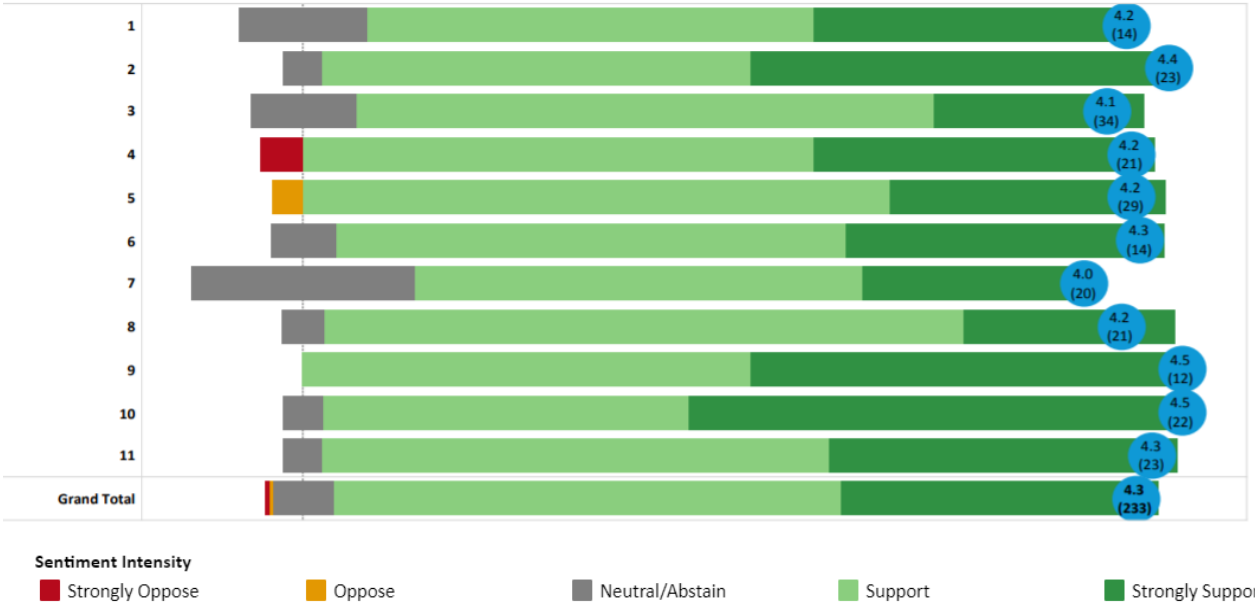
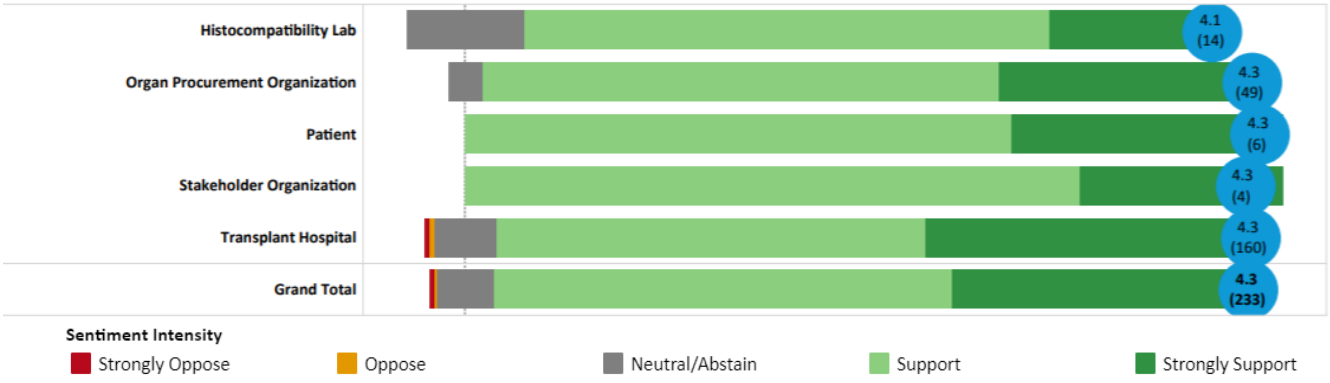


Figure 2: Sentiment by Member Type



The Committee reviewed and discussed the results of public comment and concluded the public sentiment supports sending the proposal to the Board with no substantive changes. The proposed language has been edited for further clarity without impact to the requirements.

Compliance with the Final Rule and NOTA

The OPTN Final Rule[9] sets requirements for allocation policies developed by the OPTN. This proposal complies with the following aspects of the Final Rule:

- **Shall be based on sound medical judgment:** The Committee proposes this change based on the medical judgment that all candidates with fulminant liver failure should have the same access to transplantation.
- **Shall seek to achieve the best use of donated organs:** The Committee believes that maximizing the gift of organ donation by using each donated organ to its full potential achieves the best use of donated organs. This proposal seeks to make the best use of donated organs by using them for the most medically urgent candidates first.
- **Shall be designed to…promote patient access to transplantation:** This proposal promotes liver candidate access to transplants by providing the same access to transplantation for candidates with fulminant liver failure regardless of whether they have had a prior liver transplant.
- **Shall not be based on the candidate's place of residence or place of listing, except to the extent required [by the aforementioned criteria]:** This proposal is not based on the candidates' place of residence.

Although the proposal outlined in this briefing paper addresses certain aspects of the Final Rule listed above, the Committee does not expect impacts on the following aspects of the Final Rule:

- Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e);
- Shall be designed to avoid wasting organs, to avoid futile transplants, … and to promote the efficient management of organ placement;
- Shall be reviewed periodically and revised as appropriate;
- Shall include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program.

Additionally, this proposal is aligned with the OPTN Strategic Plan goal of promoting the efficient management of the OPTN by ensuring that the criteria to qualify for Status 1A are understandable and consistently used.

Potential Fiscal Impact of Proposal

Members

No fiscal impact.

OPTN

Programming modifications will require a small effort (under 300 hours) to create changes in UNet℠, while Communications will inform members of changes through targeted emails and notices.

[9] 42 C.F.R §121.8

Implementation and Operational Considerations

OPTN actions

This proposal will require programming in UNet℠ to update data labels and help documentation.

Member actions

Liver transplant programs will need to ensure that their transplant teams are aware of the updated criteria for Status 1A. This proposal does not require additional data collection.

Post-implementation Monitoring

Member compliance

The proposed language will not change the current routine monitoring of OPTN members. Site surveyors will continue to verify that the Status 1A qualifying criteria reported in UNet are consistent with documentation in the candidate's medical record, and that all lab results reported for Status 1A qualifying criteria were the most recent available at the time they were entered into UNet.

Policy evaluation

The Committee will monitor the volume of Status 1A candidates meeting criteria, specifically surrounding pre-existing liver disease, and will evaluate the effect of the policy six months after implementation. Further post-implementation analyses will be performed as requested by the Committee.

Conclusion

This policy would clarify that pre-existing liver disease in a prior liver transplant recipient would not disqualify them as a candidate for Status 1A fulminant liver failure unless the candidate had a diagnosis of liver disease following that prior liver transplant.

Policy Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

9.1 Status and Score Assignments

9.1.A Adult Status 1A Requirements

To assign a candidate adult status 1A, the candidate's transplant hospital must submit a *Liver Status 1A Justification Form* to the OPTN Contractor. A candidate is not registered as status 1A until this form is submitted. When reporting laboratory values to the OPTN Contractor, transplant hospitals must submit the most recent results including the dates of the laboratory tests.

The candidate's transplant program may assign the candidate adult status 1A if *all* the following conditions are met:

1. The candidate is at least 18 years old at the time of registration
2. The candidate has a life expectancy without a liver transplant of less than 7 days and has at least *one* of the following conditions:

    a. Fulminant liver failure, ~~without pre-existing liver disease, and currently in the intensive care unit (ICU),~~ defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. In addition the candidate:~~, and has~~
        i. Must not have a pre-existing diagnosis of liver disease. For purposes of this section, any diagnoses of liver disease that occurred prior to a subsequent liver transplant do not constitute pre-existing liver disease.
        ii. Must currently be admitted in the intensive care unit
        iii. Must meet at least *one* of the following conditions:
            1. Is ventilator dependent
            2. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
            3. Has an international normalized ratio (INR) greater than 2.0

    b. Anhepatic

    c. Primary non-function of a transplanted whole liver within 7 days of transplant, with aspartate aminotransferase (AST) greater than or equal to 3,000 U/L and at least *one* of the following:
        1. International normalized ratio (INR) greater than or equal to 2.5
        2. Arterial pH less than or equal to 7.30
        3. Venous pH less than or equal to 7.25
        4. Lactate greater than or equal to 4 mmol/L

        All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

d. Primary non-function within 7-days of transplant of a transplanted liver segment from a deceased or living donor, evidenced by at least *one* of the following:
   1. INR greater than or equal to 2.5
   2. Arterial pH less than or equal to 7.30
   3. Venous pH less than or equal to 7.25
   4. Lactate greater than or equal to 4 mmol/L

e. Hepatic artery thrombosis (HAT) within 7-days of transplant, with AST greater than or equal to 3,000 U/L and at least *one* of the following:
   1. INR greater than or equal to 2.5
   2. Arterial pH less than or equal to 7.30
   3. Venous pH less than or equal to 7.25
   4. Lactate greater than or equal to 4 mmol/L

   All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

f. Acute decompensated Wilson's disease

9.1.B Pediatric Status 1A Requirements

To assign a candidate pediatric status 1A, the candidate's transplant hospital must submit a *Liver Status 1A Justification Form* to the OPTN Contractor. A candidate is not assigned pediatric status 1A until this form is submitted.

The candidate's transplant program may assign the candidate pediatric status 1A if *all* the following conditions are met:

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.
2. The candidate has at least *one* of the following conditions:
   a. Fulminant liver failure, ~~without pre-existing liver disease, and currently in the intensive care unit (ICU),~~ defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. In addition the candidate:~~, and has~~
      i. Must not have a pre-existing diagnosis of liver disease. For purposes of this section, any diagnoses of liver disease that occurred prior to a subsequent liver transplant do not constitute pre-existing liver disease.
      ii. Must currently be admitted in the intensive care unit
      iii. Must meet at least *one* of the following conditions:
         1. Is ventilator dependent
         2. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
         3. Has an international normalized ratio (INR) greater than 2.0

b. Diagnosis of primary non-function of a transplanted liver within 7 days of transplant, evidenced by at least *two* of the following:
   i. Alanine aminotransferase (ALT) greater than or equal to 2,000 U/L
   ii. INR greater than or equal to 2.5
   iii. Total bilirubin greater than or equal to 10 mg/dL
   iv. Acidosis, defined as *one* of the following:
      1. Arterial pH less than or equal to 7.30
      2. Venous pH less than or equal to 7.25
      3. Lactate greater than or equal to 4 mmol/L

   All laboratory results reported for any tests required for the primary non-function of a transplanted liver diagnosis above must be from the same blood draw taken between 24 hours and 7 days after the transplant.

c. Diagnosis of hepatic artery thrombosis (HAT) in a transplanted liver within 14 days of transplant

d. Acute decompensated Wilson's disease

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