

### Candidates for liver transplantation with portopulmonary hypertension

Patients with portopulmonary hypertension (POPH) are a unique group of high risk patients that present for transplant evaluation. Approximately 5% of patients with portal hypertension are affected. There are no patient characteristics or medical tests that reliably predict mortality risk in this patient population. This can give rise to varying opinions within the transplant selection committee regarding the benefit and risk of liver transplantation in an individual candidate. The University of Colorado Liver Transplant multidisciplinary team therefore developed recommendations to help guide candidate selection. Evidence derived from our center experience and observations from the peer reviewed literature were used in developing these recommendations.

#### **Background**

##### *POPH Definition:*

1) Hemodynamic measures: mean pulmonary artery pressures (mPAP) >25 mm Hg at rest; pulmonary vascular resistance > 3 Wood units (WU) and a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg determined by right heart catheterization. In cases of volume overload, a Transpulmonary gradient (mPAP-PCWP) > 12 mm Hg indicates greater than normal pulmonary pressures due to vascular resistance. Presence of portal hypertension established by clinical symptoms or portal venous pressure measurements.

*MELD Exception points:* Data supporting prioritization of patients with POPH specified the following criteria: mPAP > 35 mm Hg and PVR > 3 WU who had an mPAP ≤ 35 mm Hg and PVR < 5 WU following 12 weeks of an FDA-approved pulmonary hypertension therapy **AND satisfactory right ventricular function (defined by the transplant center)** (Krowka et al 2006).

When the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network (OPTN) formulated the exception points, the policy was simplified and did not include a prescribed time for treatment with pulmonary vasodilators or the inclusion of criteria for right ventricular function (UNOS/OPTN).

##### *National Outcomes:*

An analysis of US outcome data for patients with POPH using the Scientific Registry of Transplant Recipients (SRTR) showed that these patient are at significantly higher mortality risk than other waitlisted patients. Increased mortality occurs at all phases of transplant care with the highest rates occurring in the intraoperative period. This is highlighted in the following observations:

## Portopulmonary Hypertension

Examination of OPTN database (SRTR) shows patients with POPH who met UNOS/OPTN criteria for receiving exception points had an increased risk of death with a HR of 2.46 (CI 1.73-3.52) compared to waitlisted patients without exception MELD points (Goldberg 2014).

25% of POPH deaths occurred on the day of surgery

Investigators conclude that patients with POPH have increased waitlist and transplant mortality even when the current UNOS upgrade criteria for transplant prioritization are met (Goldberg et al 2014).

Data from a 2006 study found earlier access to transplant did not improve survival (Verma et al 2016). Evidence suggest there is no survival benefit to patients with POPH who need a transplant for pulmonary vascular disease rather than liver disease. Rather, recent evidence suggests patients without a hepatic indication for liver transplantation have better survival when they are treated medically for POPH (Verma et al 2016).

### *Remaining questions:*

No single patient characteristic predicts disease resolution following transplantation. This may influence patient selection. No patient at the University of Colorado with POPH has achieved disease resolution following successful transplantation.

To date studies have measured the effect of other comorbidities on POPH transplant outcomes. However, increased mortality risk is associated with a number of comorbid conditions. These may exert additive or synergistic effects on mortality and patients with comorbidities in addition to POPH need special consideration by the Transplant Selection Committee. Member of the Committee have firsthand knowledge of the effects of other disease processes on recipient and graft survival. .

### *Considerations based upon current findings:*

*Listing:* Listing of patients with POPH for transplantation is based upon the treatment of liver disease that cannot be medically managed.

*Candidacy:* The Multidisciplinary Transplant Selection Committee has a unique and detailed understanding of how patient characteristics influence overall transplant and graft survival within the context of our practice at the University of Colorado. Therefore, the committee considers the following during decision-making:

Adherence to previously published recommendations that include at least 12 weeks of FDA approved vasodilator therapy, normal myocardial function in addition to the UNOS published guidelines.

Patients with echocardiographic signs of myocardial dysfunction or pressure overload are not optimal candidates and may be deferred for medical therapy.

The added effects of additional comorbid conditions and age on mortality risk are considered in a discussion of candidacy. As outlined, at least 25% mortality occurs on the day of transplantation. Therefore additional factors that predict poor outcome will influence decisions about wait listing patients with POPH.

## Portopulmonary Hypertension

Cases identified at the time of transplant will be deferred for further evaluation. This is based upon a high mortality rate with 11 of 14 intraoperative deaths occurring in previously undiagnosed patients (Krowka 2000).

### Wait list surveillance:

All patients listed with diagnosis of PH need to be seen and followed by the University of Colorado pulmonary hypertension service.

Patients on the top 10 list will be seen by Hepatology every 3 months to provide the multidisciplinary team with regular updates that may change a candidate's priority for organ allocation.

Information from right heart catheterization are submitted to UNOS every three months for the candidate to qualify for MELD exception points. Echocardiography will be repeated during the same visit to provide additional information about right ventricular function.

Patients with any echocardiographic evidence of myocardial systolic or diastolic dysfunction or signs of pressure overload will be inactivated until further evaluated. Therefore, all resting transthoracic echocardiograms should include Tissue Doppler Imaging.

### Intraoperative Care:

The Surgical Fellow will contact the Pulmonary Hypertension attending or their designate and the cardiac catheterization laboratory when a patient with POPH is called in for transplantation.

All patients with POPH will have a pulmonary artery catheter placed in the cardiac catheterization lab so the position can be confirmed by fluoroscopy. Any change in pulmonary pressures from those recorded on the wait list will lead to an immediate discussion between the surgeon and anesthesiologist.

In circumstances when the cardiac catheterization laboratory team is not available, the position of the catheter will be confirmed by TEE in the operating room and then by X-ray.

All pulmonary vasodilators will be given using the dispensing instruction for each medication. Oral medications will be given by oral-gastric tube while parenteral medication will be administered on schedule.

Inhaled NO in the range of 20-40 ppm is used intraoperatively in patients with documented POPH.

### Standard Monitors for patients with POPH include:

- Pulmonary artery catheter

- An arterial catheter placed in the operating room. Catheterization of a larger artery may be performed in patients with co-existing Raynaud's disease.

- Access for use of the Rapid Infuser

## Portopulmonary Hypertension

Extubation is considered in all patients who meet standard published criteria

All patients are transferred directly from the operating room to the STICU

### References

Krowka M, Fallon M, Mulligan D, et al. Model for end stage liver disease (MELD) exception for portopulmonary hypertension. Liver Transpl 2006; 12: S114-S116.

UNOS/OPTN <https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/#PH>

Goldberg D, Batra S, Sahay S, et al. MELD exceptions for portopulmonary hypertension. Current policy and future implementation. Am J Transpl 2014; 12: 20181-2087.

Verma S, Hand F, Armstrong M, et al Portopulmonary hypertension, still an appropriate indication for liver transplantation? Liver Transpl 2016; 22: 1637-1642.