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REVIEW

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International Liver Transplantation Society practice guideline update on portopulmonary hypertension

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Abstract

Portopulmonary hypertension (POPH), pulmonary arterial hypertension that develops in the setting of portal hypertension, has long been of significant interest to the pulmonary, cardiology, and hepatology communities. Optimal management of POPH has been challenging to define due to a lack of evidence from clinical trials regarding pulmonary arterial hypertension therapies and uncertainty regarding the role of liver transplantation (LT). Initially, the high risk of intraoperative and early post-transplant death in predominantly untreated patients with POPH tempered consideration of LT. More recently, the observation that POPH can improve, and sometimes even resolve, following LT, has led to reconsideration of the role of LT in selected patients. The first International Liver Transplantation Society (ILTS) POPH and hepatopulmonary syndrome practice guideline was a multidisciplinary consensus of expert opinions based on available evidence. Since that publication, hemodynamic definitions, management approaches, and POPH

Abbreviations: 6MWD, 6-minute walk distance; BMP, bone morphogenetic protein; ECMO, extracorporeal membrane oxygenation; ERA, endothelin receptor antagonist; ERS, European Respiratory Society; ESC, European Society of Cardiology; FC, functional class; FDA, Food and Drug Administration; HPS, hepatopulmonary syndrome; ILTS, International Liver Transplantation Society; IPVD, intrapulmonary vasodilatation; LT, liver transplant; MIF, macrophage migration inhibitory factor; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; RHC, right heart catheterization; RV, right ventricular; RVSP, RV systolic pressure; TEE, transesophageal echocardiogram; TRV, tricuspid regurgitation velocity; TTE, transthoracic echocardiogram; V-A, veno-arterial.

MELD exception criteria have evolved, and there have been new randomized controlled trials in POPH as well as studies regarding long-term outcomes. In order to ensure the guidelines remained current and reflected recent evidence, the original writing committee of the 2016 guidelines, leaders of the ILTS Cardiovascular Special Interest Group, and colleagues active in POPH research were invited to participate in the writing committee. In this document, approved for publication by the ILTS executive council, we provide an update to the prior guidelines with expert recommendations to guide and advance POPH management. Recommendations in these guidelines are based on expert opinion and available evidence and were agreed upon by consensus.

Keywords: liver transplantation, portopulmonary hypertension, treatment

PART 1. DEFINITIONS AND UPDATED DIAGNOSTIC CRITERIA

Key updates to POPH hemodynamic diagnostic criteria

Portopulmonary hypertension (POPH) is a clinical and hemodynamic diagnosis defined by the presence of precapillary pulmonary hypertension (PH) in the setting of portal hypertension without an alternative cause (Figure 1). In the 2016 International Liver Transplantation Society (ILTS) guidelines, POPH was defined according to the contemporary definitions of precapillary PH as measured by right heart catheterization (RHC): mean pulmonary arterial pressure (mPAP) >25 mm Hg with a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a pulmonary vascular resistance (PVR) >3 WU.[1] In 2018, the 6th World Symposium on Pulmonary Hypertension lowered the mPAP threshold to define PH as a mPAP >20 mm Hg.[2] This revised definition was proposed based on accumulating evidence identifying 14 ± 3 mm Hg as the mean $\pm$ SD for mPAP among healthy individuals and evidence from certain conditions, such as systemic sclerosis, that identified worse exercise capacity and increased risk of disease progression among individuals with mPAP of 21–24 mm Hg, previously referred to as "borderline PH."[3–5] The revised definition of PH was also applied to POPH despite limited data regarding normal pulmonary hemodynamics in the setting of portal hypertension. Importantly, it is also necessary to differentiate POPH from other causes of mPAP elevation in liver disease (Figure 2).

In 2022, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines made further modifications to the PH definition by lowering the PVR threshold from 3 to 2 WU and classifying PH as precapillary, postcapillary, and combined pre-postcapillary PH using this threshold[6] (Table 1). This revision was made to reflect an increased mortality risk among patients with PVR >2.2 WU in a large Veterans Affairs cohort as well as other studies suggesting that the upper limit of normal PVR was 2 WU.[7,8] These revised hemodynamic definitions were upheld by the 7th World

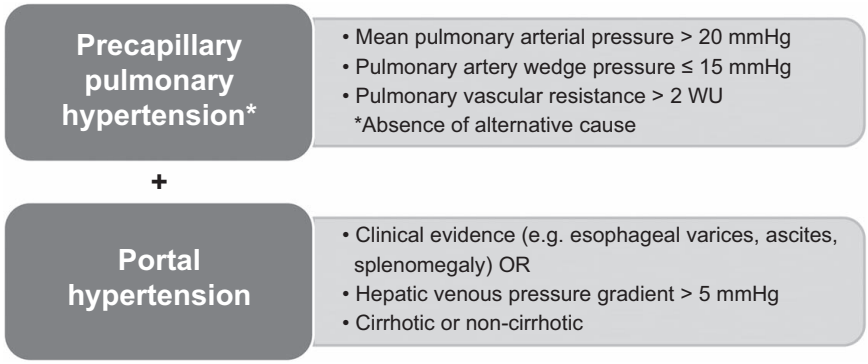

FIGURE 1 Portopulmonary hypertension: definitions and diagnostic criteria. A diagnosis of portopulmonary hypertension requires the presence of both precapillary pulmonary hypertension (without an alternative cause) and portal hypertension.

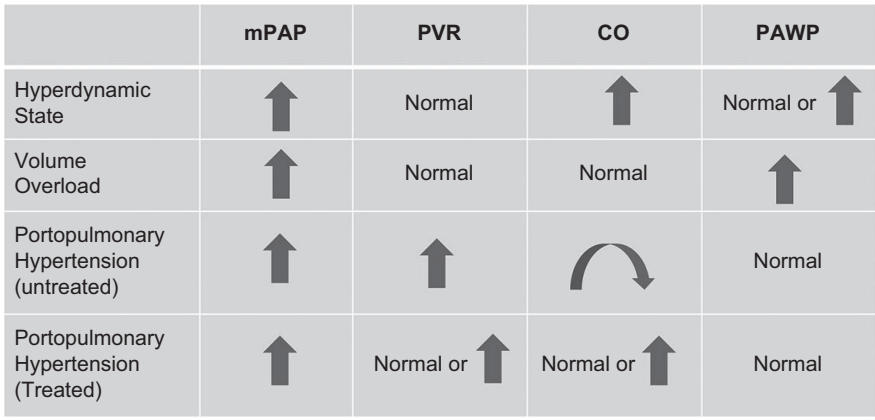

FIGURE 2 Hemodynamic profiles of pulmonary hypertension in liver disease. Among patients with liver disease, an elevated mean pulmonary arterial pressure may be due to a hyperdynamic state, volume overload, or portopulmonary hypertension. Abbreviations: CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance.

Symposium on Pulmonary Hypertension.[9] Notably, current pulmonary arterial hypertension (PAH) therapies have been studied and approved for the treatment of PAH as defined by the older, traditional definitions of PH (mPAP $\geq$25 mm Hg and PVR $>$3 WU). Thus, although the diagnostic criteria for PAH have evolved, it is important to recognize that the role of PAH therapy in patients with milder PH, as defined by the newer thresholds, remains unknown, particularly in POPH.

Among patients with POPH, Certain et al[10] described the clinical significance of a PVR between 2 and 3 WU in a small cohort of patients with mPAP $\geq$25 mm Hg. Out of 16 patients with an initial PVR of 2–3 WU who did not receive PAH therapy, 81% subsequently developed PVR $>$3 WU on follow-up hemodynamic assessments. Among 4 patients who underwent LT, posttransplant RHC demonstrated an increase in PVR to $>$3 WU in all patients, and 2 developed right heart failure in the early posttransplant period requiring initiation of combination PAH therapy, indicating the importance of close monitoring for patients with PVR between 2 and 3 WU.[10]

POPH continues to be a *clinical and hemodynamic* diagnosis, in which precapillary PH is necessary but not sufficient to make the diagnosis. The hemodynamic definitions of PH, initially developed somewhat arbitrarily based on available data, have evolved over the last decade. As the diagnostic criteria for PAH have changed, so have the hemodynamic criteria for POPH. To maintain consistency with the 6th and 7th World Symposium on Pulmonary Hypertension and the 2022 ESC/ERS guidelines and to reflect an increased risk of disease progression associated with PVR of 2–3 WU in patients with POPH, we recommend adopting the revised hemodynamic definitions of precapillary PH for POPH while acknowledging the uncertainty in this specific population. Other diagnostic criteria for POPH, namely the presence of portal hypertension, either confirmed clinically or with measurement of HVPG, and the need to rule out other causes of PH, are unchanged (Figure 1). Although PH severity is dependent on several factors, particularly PVR, prior guidelines have stratified POPH severity by mPAP, and we have maintained that classification for consistency, now with the inclusion of mPAP 21–24 in the mild severity classification (Table 2).

TABLE 1 Hemodynamic definitions of pulmonary hypertension

Pulmonary hypertension	mPAP $>$20 mm Hg
Precapillary PH	mPAP $>$20 mm Hg PAWP $\leq$15 mm Hg PVR $>$ 2 WU
Isolated postcapillary PH	mPAP $>$20 mm Hg PAWP $>$15 mm Hg PVR $\leq$2 WU
Combined precapillary and postcapillary PH	mPAP $>$20 mm Hg PAWP $>$15 mm Hg PVR $>$2 WU

Abbreviations: mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

Recommendations

1. *POPH is defined by the presence of precapillary PH (mPAP $>$20 mm Hg, PVR $>$2 WU, and PAWP $\leq$ 15 mm Hg) without an alternative etiology in the setting of portal hypertension.*

TABLE 2 Hemodynamic severity of portopulmonary hypertension

Mild	20 $<$ mPAP $<$35 mm Hg
Moderate	35 $\leq$ mPAP $<$45 mm Hg
Severe	mPAP $\geq$45 mm Hg

Abbreviation: mPAP, mean pulmonary arterial pressure.

2. *RHC and clinical evaluation to rule out alternative causes of PH is necessary to make a diagnosis of POPH.*

Impact of new definitions on epidemiology and screening recommendations

The impact of these new hemodynamic criteria on the prevalence and outcomes of POPH has been recently described.[11,12] Atsukawa et al reported an increase in POPH prevalence from 1.1% (2/186) to 2.2% (4/186) using revised criteria among patients with cirrhosis and portal hypertension who underwent RHC. Similarly, Pringuez et al reported an increase in the prevalence of precapillary PH from 1.7% (4/231) to 5.7% (13/231) among patients with cirrhosis referred for LT.[12] Notably, none of the patients with mPAP of 21–25 mm Hg in their cohort had a PVR of >3 WU. This is likely related to the presence of other factors in the setting of liver disease, such as hyperdynamic circulation or volume overload, which contribute to elevations in mPAP (Figure 2). Other studies have suggested that POPH prevalence may be lower than previously reported. According to a multicenter prospective study of transthoracic echocardiogram (TTE) screening in which patients with right ventricular systolic pressure (RVSP) ≥ 50 mm Hg (26/938—2.8%) were referred for RHC, 9/938 (0.96%) of the total cohort (34.6% of those referred for RHC) had POPH as defined as a mPAP >20 mm Hg and PVR ≥ 3 WU.[13] Reasons for the lower prevalence are unknown but may be due to changes in epidemiology, more accurate phenotyping with the exclusion of other causes of PH, or missed diagnoses.

The American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines recommend echocardiographic screening of all liver transplantation (LT) candidates to identify POPH prior to LT.[14,15] Patients undergoing TIPS should also be screened for POPH. Despite screening recommendations, patients with POPH often have severe disease with advanced symptoms and moderate to severe hemodynamic impairment at diagnosis.[16] In the 2016 ILTS guidelines, it was recommended to consider RHC in patients with an estimated RVSP >50 mm Hg. However, the available evidence suggests that a lower threshold has improved sensitivity for identifying POPH. In a prospective study of 152 LT candidates, Raevens et al[17] identified RVSP >38 mm Hg and right ventricular (RV) dilation as optimal echocardiographic criteria for the detection of PH with a specificity of 93% and sensitivity and negative predictive value of 100%.

A lower threshold for screening is also more consistent with ESC/ERS guidelines which recommend further evaluation of PH based on tricuspid regurgitant velocity (TRV) and other signs of PH, such as flattening of the interventricular septum, right ventricle/left ventricle basal diameter ratio >1.0, midsystolic notching, IVC dilation, or right atrial area >18 cm^2.[18] RVSP is calculated from TRV according to the following equation based on Bernoulli's principle: RVSP $= 4(\text{TRV})^2$ + right atrial pressure, estimated based on the diameter and collapsibility of the IVC. TRV >2.8 m/s is associated with an intermediate to high probability of PH (depending on the degree of elevation and the presence of other signs of PH), and further testing such as RHC is recommended for patients with intermediate to high probability of PH, particularly in the presence of PAH risk factors. Given the available evidence and current guidelines, we suggest consideration of PH expert consultation $\pm$RHC for patients with intermediate to high echocardiographic probability of PH or an estimated RVSP >40 mm Hg (rather than 50 mm Hg, as previously recommended). More than mild RV dilation and/or RV dysfunction on echocardiogram should also prompt PH consultation and/or RHC, but the quantitative thresholds for these parameters are not well-defined. In patients with inadequate or unmeasurable TRV, we recommend referral of those with more than mild RV dilation or dysfunction, other signs of PH as detailed in the ESC/ERS guidelines, and/or clinical signs or symptoms of PH. The optimal frequency for screening is also not well-defined.

Recommendations

3. *All LT and TIPS candidates should undergo echocardiography to screen for POPH; although there is little evidence, it is reasonable to perform annual echocardiography while awaiting LT.*
4. *Among LT candidates, a RVSP >40 mm Hg, more than mild RV dilation or dysfunction, or intermediate to high echocardiographic probability of PH according to ESC/ERS guidelines should prompt referral to PH experts with consideration of RHC in appropriate patients.*

PART 2. UPDATES IN PATHOPHYSIOLOGY

In recent years, there has been improved understanding regarding POPH disease pathogenesis, although the lack of a reliable animal model continues to limit our knowledge regarding pathophysiology. Numerous studies have described the importance of estrogen signaling and metabolism in PAH, including POPH. The Pulmonary Vascular Complications of Liver Disease studies (multicenter prospective cohort studies of patients with portal hypertension undergoing evaluation for LT or those with POPH) found that genetic variations in

aromatase and different estrogen metabolites were associated with POPH.[19,20] Applying single nuclear RNA sequencing to cirrhotic livers of patients with and without POPH, Jose et al[21] also found excess estrogen as well as altered arginine metabolism, dysregulated growth differentiation factor signaling, and decreased bone morphogenetic protein-9 (BMP-9) associated with POPH. Given its role in disease pathobiology, future studies of estrogen modulation have been suggested as a possible treatment approach for POPH, although a recent RCT of anastrozole in PAH was null.[22]

It is well-established that POPH can develop in the setting of non-cirrhotic portal hypertension and that portal hypertension and portosystemic shunting rather than cirrhosis itself play a key role in disease pathogenesis.[1,23] It is unclear, however, whether ligation of portosystemic shunts can lead to improvement in POPH. In patients with POPH associated with congenital portosystemic shunts, expert guidelines recommend PAH therapies and shunt closure if feasible.[24] Inflammation, potentially related to the presence of portal hypertension or portosystemic shunts, has been implicated in disease pathogenesis. Macrophage migration inhibitory factor (MIF), a pleiotropic pro-inflammatory cytokine, was elevated in patients with POPH compared to liver disease controls in both the pulmonary and systemic circulation. MIF levels were also correlated with hemodynamic severity as well as clinical outcomes.[25]

The importance of BMP signaling has been recently described in both POPH and hepatopulmonary syndrome (HPS). Biomarkers such as BMP-9 and BMP-10, vascular quiescence factors produced in the liver, are reduced in the setting of cirrhosis and among patients with both HPS and POPH.[18,26] In a mouse model of cirrhosis, BMP-9 levels were reduced and augmentation of BMP-9 signaling was protective against the development of POPH.[26] More recently, however, Robert et al described reduced levels of BMP-9 among patients with concomitant POPH and HPS but similar BMP-9 levels among patients with isolated POPH without HPS compared to cirrhotic controls. This finding suggests that BMP-9 may play a more important role in the pathogenesis of HPS rather than POPH.[27] Since BMP-9 is reduced in the setting of cirrhosis, the reasons why a specific patient with cirrhosis and low BMP-9 levels develops HPS and/or POPH remains unknown.

This study of BMP-9 in POPH and HPS also highlights a finding that has been increasingly observed and reported—the concomitant presence of both POPH and HPS among individuals. Fussner et al[28] described the presence of intrapulmonary vascular dilatations (IPVD), a key diagnostic feature of HPS, among half of the patients with POPH. The presence of IPVD was also associated with worse survival. Olsson et al[29] also described a case of HPS developing in a patient with POPH who was treated with PAH therapy. These reports have raised awareness that POPH and HPS are not mutually exclusive and may exist simultaneously or sequentially within individuals. Evaluation for HPS should be considered in POPH patients, both at

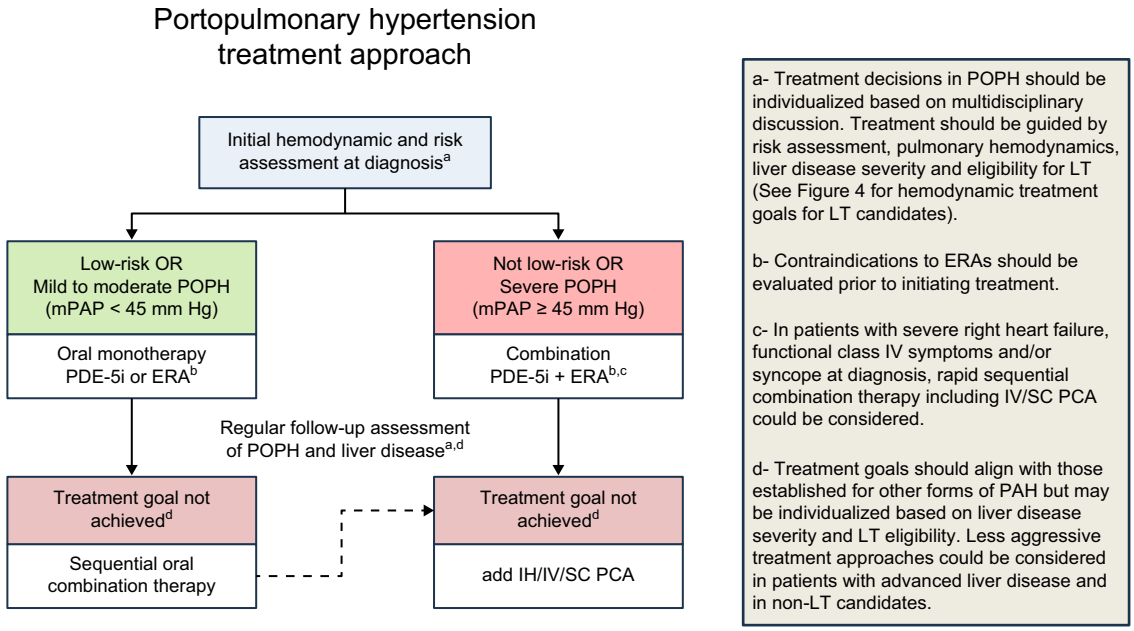

FIGURE 3 Treatment approach for portopulmonary hypertension. A general approach to medical treatment of portopulmonary hypertension. Treatment decisions should be individualized and guided by multidisciplinary evaluation with consideration of several factors, including liver disease severity, eligibility for liver transplantation, risk stratification, and pulmonary hemodynamics (see text). Abbreviations: ERA, endothelin receptor antagonist; IH, inhaled; IV, intravenous; LT, liver transplantation; mPAP, mean pulmonary arterial pressure; PCA, prostacyclin analog; PDE5i, phosphodiesterase-5 inhibitor; POPH, portopulmonary hypertension; SC, subcutaneous.

the time of diagnosis and during follow-up assessments. De-novo PH post-LT has also been reported in the setting of pretransplant HPS, recurrent portal hypertension, and in the absence of other risk factors.[30] For future studies, recognition of coexistent HPS and POPH is important to distinguish pathways involved in disease pathogenesis.

PART 3. UPDATES IN POPH MANAGEMENT

POPH clinical practice variation

Despite previously published guidelines, there remains significant practice variation regarding POPH management, as highlighted by 2 recent multidisciplinary (pulmonologists, cardiologists, and hepatologists) surveys. A survey by DuBrock et al highlighted controversial opinions regarding whether POPH should be considered an indication for LT, as well as disagreement among providers with the contemporaneous MELD exception criteria.[31] The results of this survey helped to bolster support for modification of the POPH MELD exception criteria as described below. The surveys also identified variation by specialty and region regarding use of PAH therapies in POPH and differences in how providers manage patients post-LT.[32]

An analysis of the multicenter Pulmonary Hypertension Association Registry also identified socioeconomic and treatment differences between patients with idiopathic PAH and POPH.[33] Compared to idiopathic PAH, patients with POPH had lower income, were less likely to have graduated from college, less likely to be employed, less likely to be treated with combination therapy and endothelin receptor antagonists and had increased healthcare resource utilization. Similarly, an analysis of patients with portal hypertension in the Optum database found that PH was associated with a higher annual cost and greater risk of hospitalization compared to those without PH.[34] These studies highlight the variability in POPH management, the existence of socioeconomic disparities that may affect access to care, and the impact of POPH on the healthcare system. They also underscore the need for standardized recommendations to guide POPH management to ensure equitable care.

Recommendations

5. *There is substantial practice variation regarding POPH management; clinicians should follow updated guidelines to ensure standardized, equitable care.*

Treatment goals and strategies

Treatment of POPH has unique goals and considerations. In idiopathic and other types of PAH, the goals of treatment are to improve symptoms, functional class (FC), quality of life, exercise capacity, RV function, pulmonary hemodynamics, risk-status and survival.[35] In POPH, an additional goal that often drives treatment decisions is to achieve hemodynamic acceptability for LT. Achievement of these criteria is important to ensure the safety of LT in the setting of POPH. Importantly, PAH therapy is reasonably effective at achieving this goal. According to a meta-analysis by Deroo et al,[36] 44% of treated patients became eligible for LT. Furthermore, 50% were able to discontinue PAH therapy posttransplant and outcomes were overall best in patients treated with a combination of LT and PAH therapy.[36] In this section, we focus on the medical management of POPH. The role of LT in POPH management is discussed in Part 4.

Risk stratification in POPH

Guidelines suggest the use of multiparametric risk stratification tools to guide prognostic assessment and treatment approaches in PAH.[6,35] There is little evidence regarding risk stratification tools in POPH, but they may be helpful to guide therapy, particularly in patients with compensated cirrhosis who are not eligible for LT (Figure 3). Risk stratification tools use a combination of clinical observations and modifiable variables including symptoms, biomarkers, exercise capacity, echocardiography, and hemodynamics. Key variables in validated risk prediction tools include World Health Organization FC, an assessment of symptoms and activity limitation related to PH, 6-minute walk distance (6MWD), and natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] or BNP).[35] The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) 2.0 risk score, developed based on data from the multicenter U.S.-based REVEAL registry, provides risk assessment and estimates of 1-year mortality and assigns patients with POPH a higher score to account for their increased mortality.[37] While a higher score is predictive of a worse prognosis, treatment decisions in POPH should be guided by modifiable risk factors that may improve with therapy as well as the urgency of LT and hemodynamics. Notably, PH risk scores do not account for liver disease severity which has an important impact on survival, particularly in advanced liver disease.[38] A more detailed discussion of risk stratification in PAH/POPH is beyond the scope of these guidelines but has been recently summarized.[35]

Medical therapy

The medical management and treatment options for PAH have evolved over time with an increasing number of therapeutic pathways and medications and an increase in the use of combination therapy.[39] There are currently 12 Food and Drug Administration (FDA) approved PAH therapies delivered via oral, inhaled, subcutaneous, and intravenous routes (Table 3), many of which are also used to treat POPH. These medications target nitric oxide, endothelin, prostacyclin, and activin signaling pathways related to vasoconstriction and vascular remodeling and have unique side effect profiles, some of which are of particular concern in the setting of liver disease (Table 3).

Recent randomized controlled trials in POPH

Patients with POPH have been typically excluded from PAH clinical trials. Despite limited evidence, PAH therapies are commonly used to treat POPH. Only 2 PAH medications (macitentan [Opsumit] and riociguat [Adempas]), however, have been studied in POPH in prospective RCTs.

Macitentan is an oral once daily dual endothelin receptor antagonist (ERA) approved by the FDA in 2013 for PAH. In PORTICO, a multicenter prospective phase 4 RCT designed to evaluate the safety and efficacy of macitentan in POPH, adult patients from 36 centers in 7 countries were randomly assigned in a 1:1 fashion to receive macitentan 10 mg once daily (n = 43) or placebo (n = 42).[40] Inclusion criteria included a diagnosis of POPH with mPAP ≥25 mm Hg and PVR >4 WU. POPH patients with advanced liver disease, defined as a MELD score >19 or Child–Pugh class C, were excluded. The study met its primary endpoint with a 35% reduction in PVR at 12 weeks. Macitentan was not associated with significant changes in 6MWD or NT-proBNP. The most frequent adverse event was peripheral edema and there were no hepatic safety concerns. In a post hoc analysis, macitentan also improved waitlist and perioperative risk stratification.[41]

Riociguat is a soluble guanylate cyclase stimulator. It was approved in 2013 for the treatment of group 1 (PAH) and group 4 PH (chronic thromboembolic pulmonary hypertension). In the PATENT-1 study, a phase 3 RCT of riociguat versus placebo among patients with PAH, 13 patients with POPH were included[42,43]; 11 patients received riociguat while 2 patients received placebo. Among patients with POPH, riociguat was associated with improvements in 6MWD, FC, and PVR.[42]

Other studies regarding PAH therapies in POPH

In the last decade, numerous case reports and case series, as well as systematic reviews, have described

TABLE 3 Currently approved pulmonary arterial hypertension therapies and adverse effects

Pathway	Therapeutic class	Drug	Route	Adverse effects
Nitric oxide	Phosphodiesterase-5 inhibitors	Sildenafil Tadalafil	PO	• Headache, flushing, dyspepsia, visual changes, **epistaxis**
	Soluble guanylate cyclase stimulators	Riociguat	PO	• **Hypotension, lightheadedness, syncope**, headache, flushing, dyspepsia • Teratogenic, requires monthly pregnancy tests
Endothelin	Endothelin receptor antagonists	Bosentan Ambrisentan Macitentan	PO	• **Edema**, nasal congestion, **elevated aminotransferases and/or bilirubin (bosentan)**, anemia • Teratogenic; requires monthly pregnancy test
Prostacyclin	Prostacyclin analogs	Epoprostenol Treprostinil Iloprost	PO, IH, IV, SC	• Headache, nausea, vomiting, diarrhea, jaw pain, flushing, hypotension • Side effects also depend on the mode of administration • Inhaled: throat irritation, cough • PO: GI predominant side effects • SC/IV: site pain (SC), **thrombocytopenia, worsening ascites or splenomegaly,** catheter-associated thrombosis (IV), bloodstream infection (IV)
	Prostacyclin IP receptor agonist	Selexipag	PO	• Headache, nausea, vomiting, diarrhea, jaw pain
Activin signaling	Activin signaling inhibitor	Sotatercept	SC	• Increases in hemoglobin, **thrombocytopenia, bleeding, epistaxis,** headache, telangiectasias

Note: Bold font indicates side effects that may be of particular concern in the setting of liver disease.
Abbreviations: IH, inhaled; IV, intravenous; PO, oral; SC, subcutaneous.

the successful use of PAH therapies in POPH. Several studies have also reported "real-world" evidence of PAH therapies in POPH. Acknowledging publication bias, most of these studies describe improved hemodynamics and facilitation of LT with PAH therapy[44] and also address concerns regarding safety in POPH.[45]

Ambrisentan, a highly selective endothelin A receptor antagonist, was studied in an open-label, prospective multicenter study of 31 POPH patients.[46] Ambrisentan was associated with an improvement in PVR from 7.1 to 3.8 WU at 24 weeks, an improvement in mPAP from 46 to 38 mm Hg and an improvement in cardiac index with no change in 6MWD. Edema (38%) and headache (23%) were the most common side effects, and 1 patient withdrew from the study due to edema.

The efficacy and safety of tadalafil, a phosphodiesterase-5 inhibitor (PDE5i), was described in a retrospective study of 38 consecutive POPH patients.[47] Tadalafil was associated with improvements in FC, mPAP, and PVR (a decrease of 38% from baseline). Similar to other studies in POPH, there was no change in 6MWD. This finding of improvement in hemodynamics without an improvement in 6MWD has been replicated in several studies and may be due to the impact of comorbid liver disease on exercise capacity.

Sotatercept is a novel activin signaling inhibitor that was recently FDA-approved for the treatment of PAH.[48] Sotatercept targets BMP-9 signaling, which is known to be altered in POPH and liver disease.[18,26] Among patients with PAH, sotatercept was associated with improvements in the primary composite endpoint of morbidity and mortality as well as improvement in secondary endpoints, including PVR, patient-reported outcomes, NT-proBNP, and 6MWD. Similar to other PAH clinical trials, patients with POPH were excluded from RCTs of sotatercept. Side effects of sotatercept which may be of concern in the setting of liver disease include telangiectasias, thrombocytopenia, and bleeding events, particularly epistaxis.[48] Notably, sotatercept was associated with improvements in PVR without a significant effect on cardiac output.[48,49] This hemodynamic treatment effect has potential utility in POPH since patients with liver disease can often develop a hyperdynamic state with PAH therapy, particularly prostacyclins[50] (Figure 2). At this time, the safety and efficacy of sotatercept in POPH are unknown.

Recommendations

6. *POPH is a significant and unique subset of PAH. We recommend the inclusion of patients with POPH in clinical trials in order to better understand the safety and efficacy of PAH therapy in POPH.*
7. *Despite limited evidence, several FDA-approved drugs for PAH (PDE5i, soluble guanylate cyclase stimulators, ERAs, and prostacyclin analogs) are reasonable to use in the treatment of POPH.*

Medical treatment approaches in POPH

Patients with POPH were not included in the 7th World Symposium PAH treatment algorithm as there is little evidence regarding POPH medical management. According to the ESC/ERS guidelines, upfront combination therapy with a PDE5i and ERA is recommended for most patients with low or intermediate risk PAH at diagnosis although there may be a residual role for monotherapy in some patients, such as those with POPH.[6] According to the French Registry, monotherapy was the most common initial treatment approach for patients with POPH.[38] Changes in PVR and 6MWD at first follow-up were similar in patients treated with an ERA or PDE5i, although there is less evidence regarding the safety of ERAs in advanced liver disease.[38] Compared to idiopathic PAH, patients with POPH are less likely to be treated with combination therapy and ERAs.[33,51] Although POPH patients were excluded from RCTs of upfront combination therapy in PAH, such as the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study, upfront combination therapy in POPH has been associated with greater improvements in pulmonary hemodynamics compared to monotherapy.[52] In the French PH registry, patients treated with upfront dual oral combination therapy had a greater improvement in PVR than patients whose initial treatment was monotherapy with either a PDE5i or ERA.[38]

The 2022 ESC/ERS guidelines highlight this knowledge gap regarding the safety and efficacy of combination therapy in POPH and recommend initial monotherapy followed by sequential combination therapy if necessary.[6] The approach to POPH treatment is complex, requires multidisciplinary discussion, and may vary based on PH and liver disease severity and LT candidacy and urgency. There is no "one-size-fits-all" algorithm for all patients, but a general approach to treatment guided by risk assessment and hemodynamics is outlined in Figure 3. Importantly, mPAP needs to be considered in the context of other hemodynamic values, such as PVR. Upfront monotherapy with a PDE5i or ERA with sequential combination therapy, if necessary, can be considered for low-risk patients or those with mild to moderate POPH (mPAP <45 mm Hg) with a preference for PDE5i as initial therapy in patients with more advanced liver disease (Child–Pugh class C or MELD >19). For patients with severe POPH (mPAP ≥ 45 mm Hg) or those not considered low-risk, upfront combination therapy should be considered with consideration of parenteral prostacyclin analogs for those with dyspnea at rest, syncope, or right heart failure (Figure 3). Less

aggressive treatment approaches could be utilized in patients with advanced liver disease who are not LT candidates. Additional data is needed to determine the optimal treatment approach, and there is no evidence for treatment of POPH with mPAP <25 mm Hg. Regardless of the initial treatment approach, patients with POPH require close follow-up to assess for side effects, disease progression, or decompensation of liver disease.

Beyond PAH therapy, there are other important aspects to the supportive management of POPH. Diuretics should be used to optimize volume status. TIPS should be avoided as it can precipitate right heart failure,[53] and beta-blockers should be avoided as they can worsen exercise capacity.[54]

Recommendations

8. *POPH is complex and should be managed by multidisciplinary expert teams.*
9. *Medical treatment of POPH should take into consideration hemodynamic disease severity, liver disease severity, and LT candidacy.*
10. *We recommend close monitoring of patients with POPH after initiation of PAH therapy to assess for side effects, disease progression, and/or decompensation of liver disease.*
11. *TIPS and beta-blockers should be avoided in patients with POPH.*

PART 4. IMPLICATIONS FOR LIVER TRANSPLANTATION (LT)

Waitlist and perioperative risk assessment

POPH has significant implications for LT eligibility with a well-documented waitlist and perioperative mortality risk. Risk is dependent on both pulmonary hemodynamics and liver disease severity, and PAH therapy can improve hemodynamics to minimize risk. Among 190 waitlist candidates who received POPH MELD exceptions in the UNOS/OPTN database from 2006 to 2014, 23% were removed from the waitlist for clinical deterioration or death.[55] Liver disease severity, as assessed by the MELD score and baseline PVR was associated with waitlist mortality, while patients with both a low MELD below the median of 12 and low PVR below the median of 450 dynes/s/cm^{-5} (5.6 WU) had excellent waitlist survival. Among these patients with predominantly treated POPH, there was no association between mPAP and waitlist mortality.

Perioperative risk stratification in POPH has been based upon early transplant experiences suggesting that intraoperative elevations in mPAP were associated with perioperative death. Prior to formal recommendations regarding routine echocardiographic screening for POPH among LT candidates, identification of severe POPH intraoperatively was not uncommon.[14] A literature review of 43 published cases and a multicenter POPH database report of 66 cases[56] concluded that mPAP >35 mm Hg with a PVR >250 dynes/s/cm^{-5} (3.1 WU) posed a high risk of intraoperative and postoperative death.[57] Hemodynamic eligibility for LT, as well as MELD exception criteria, were developed based on this data with a focus primarily on reducing mPAP to ≤ 35 mm Hg as a treatment goal. Importantly, these outcomes were predominantly reported in the era prior to the use of many of the current PAH therapies.

More recently, the relationship between elevated pulmonary arterial pressures (mPAP >20 mm Hg) regardless of cause during LT and postoperative complications was reported among 942 patients.[58] In total, 68%, 36%, and 6.2% of patients had a mPAP >20, ≥ 25, and >35 mm Hg, respectively. Although elevated mPAP was highly prevalent during LT, it was not associated with a higher risk of posttransplant pulmonary complications or mortality. These findings were similar to a study by DeMartino et al[59] in which elevations in mPAP among LT recipients were predominantly caused by a hyperdynamic cardiac output and were not associated with adverse outcomes. In a small cohort study of treated POPH patients, pretransplant mPAP >35 mm Hg was also not associated with an increased risk of adverse events when the PVR was <3 WU.[50] The overall evidence suggests that mPAP thresholds to assess perioperative risk need to be considered in the context of PVR and cardiac output and that mPAP >35 mm Hg with a normal PVR and satisfactory RV function should not preclude LT.[50,59]

Pretransplant PVR is an important aspect of perioperative risk stratification. According to a series of 50 POPH patients who underwent LT, PVR >3 WU was associated with a nearly 3-fold higher risk of posttransplant death.[60] An analysis of 269 POPH patients from the UNOS database granted MELD exception (2006–2020) found that pretransplant PVR ≥ 1.6 WU was associated with a 2-fold higher risk of posttransplant death or re-transplantation, suggesting that lower pretransplant PVR is preferable, although PVR <1.6 WU may not be a feasible goal for many patients.[61]

Absolute contraindications to LT due to unacceptably high perioperative risk include mPAP >45–50 mm Hg, PVR >5 WU, and severe RV dysfunction. Although mPAP needs to be considered in the context of PVR and CO, there have been no studies refuting the previous recommendation that mPAP >45–50 mm Hg should be a contraindication to LT. Additionally, no studies to date have addressed RV function and its impact on waitlist or perioperative mortality risk. This represents an important area for future research. There

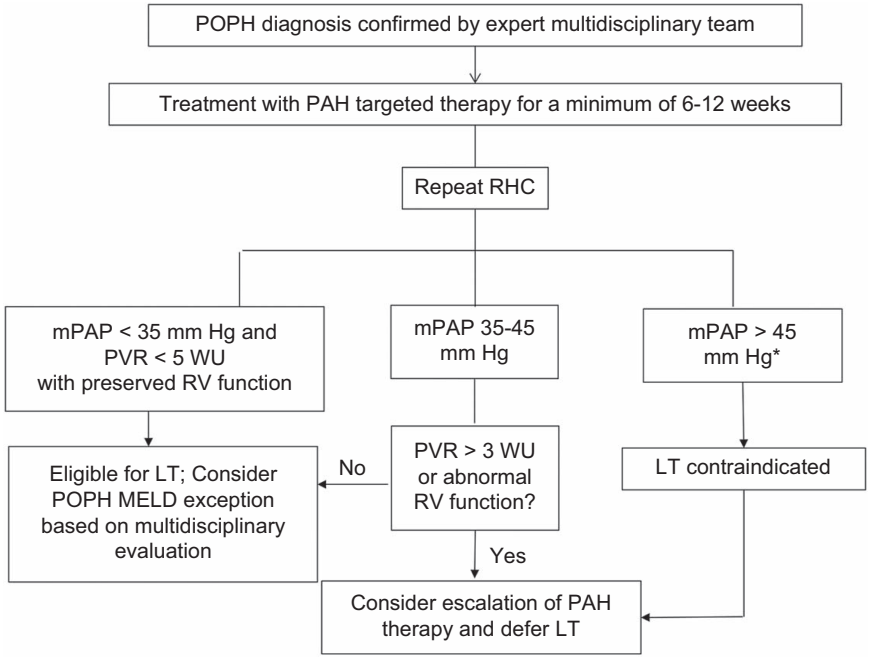

FIGURE 4 General approach to liver transplant evaluation and consideration of MELD exception in patients with portopulmonary hypertension. Specific criteria for MELD exceptions vary by country (Table 4). Abbreviations: LT, liver transplantation; mPAP, mean pulmonary arterial pressure; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricular.

is a need to standardize and quantify RV function in POPH but also to understand the impact of RV function on perioperative risk. An overview of the approach to LT evaluation and consideration of POPH MELD exception is depicted in Figure 4.

Recommendations

12. *To minimize waitlist and perioperative risk, PAH treatment should be utilized to reduce mPAP and PVR.*
13. *Absolute contraindications to LT include any of the following: mPAP >45–50 mm Hg, PVR > 5 WU, or severe RV dysfunction.*

POPH MELD exception

Numerous case reports and case series have documented the resolution or improvement of POPH following LT.[1] This chance of improvement is balanced by an increased perioperative risk in the setting of POPH, particularly among those who do not achieve an acceptable hemodynamic response to PAH therapy. Due to the successes documented with LT in selected patients and the increased mortality in POPH underestimated by the MELD score, a POPH MELD exception to expedite organ allocation prior to POPH disease progression was developed and adopted by several international transplant groups with some variation in specific criteria[62,63] (Table 4). A brief overview of the evolution of the UNOS POPH MELD exception is depicted in Figure 5.

Recently, published data supported modification to the original UNOS POPH MELD exception post-treatment hemodynamic criteria. This data included survey-based studies of clinicians who disagreed with this aspect of the MELD exception criteria, as well as several studies demonstrating the safety of LT in the setting of an elevated mPAP >35 mm Hg if the PVR was <3 WU.[31,50,59] That update and subsequent policy modification resulted in revised UNOS "MELD Exception Criteria," which now allow a posttreatment mPAP <35 mm Hg with a PVR <5 WU OR a mPAP of 35–45 mm Hg with a PVR <3 WU (Table 4).[64] With this modification, POPH patients who were not previously eligible, usually due to the development of mPAP >35 mm Hg secondary to a high cardiac output after starting PAH therapy, are now eligible for standardized exceptions.

Serial RHCs are also required by UNOS every 3 months to maintain MELD exception points and to ensure patients continue to have acceptable hemodynamics for LT. Notably, RHCs are not typically performed clinically in PAH at such a frequent interval and other countries do not have this requirement (Table 4). Multicenter or international collaborative

TABLE 4 A comparison of selected international portopulmonary hypertension MELD exception policies

	United Network for Organ Sharing/Organ Procurement Transplantation Network	French	Eurotransplant	Spanish
Country	United States	France	Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands, Slovenia	Spain
MELD Exception Criteria	Initial Diagnostic Criteria 1. Initial mPAP $\geq$35 mm Hg and PVR $>$3 WU on RHC from same date 2. Other causes of PH assessed and deemed not to be a significant contributing factor **Posttreatment criteria** Either of the following documented on RHC within 90 days: 1. Posttreatment mPAP $<$35 mm Hg and PVR $<$5 WU OR 2. Posttreatment mPAP $\geq$35 mm Hg and $<$45 mm Hg and PVR $<$3 WU	No established criteria to access the MELD exception. A posttreatment mPAP $<$50 mm Hg must be achieved. In patients with mPAP $<$50 mm Hg, the decision is left to expert opinion, generally based on hemodynamic United Network for Organ Sharing criteria and right ventricular function assessment	All of the following need to be met: 1. mPAP 25–35 mm Hg with or without therapy 2. PVR $\geq$240 dynes/s/cm^{-5} 3. PCWP $\leq$15 mm Hg 4. The above values are documented by RHC 5. Proven liver disease	Not standardized: case by case assessment. In general, previous UNOS criteria (baseline mPAP $\geq$35 mm Hg that decreases to $<$35 mm Hg with PVR $<$5 WU and preserved RV function after at least 12 weeks of treatment)
Liver Disease Severity	Documentation of portal hypertension at the time of initial exception; no comment on severity	Documentation of portal hypertension at the time of initial exception; no comment on severity	Proven liver disease as above; no comment on severity	
Extension Criteria	Repeat right heart catheterization since the last exception that continues to meet the treatment response criteria above	No specific criteria. In general, patients are evaluated every 3 months	Accrue points every 3 months without specific additional requirements	

Note: A comparison of key criteria from selected international portopulmonary hypertension MELD exception policies.
Abbreviations: mPAP, mean pulmonary arterial pressure; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

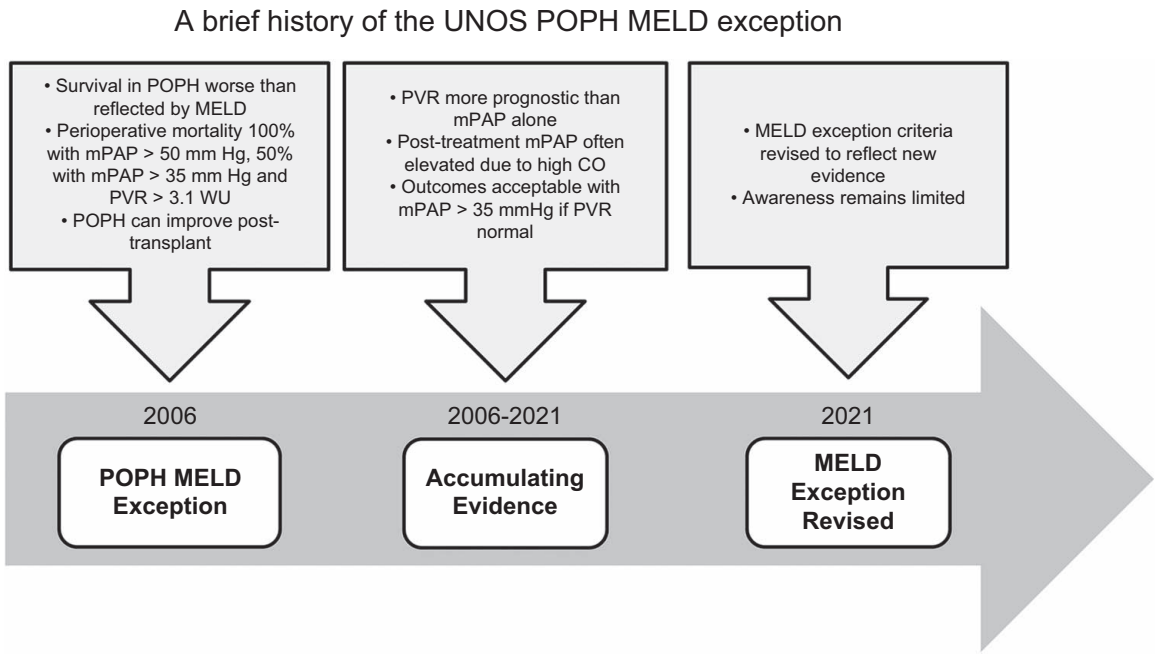

FIGURE 5 Brief history and overview of the United Network for Organ Sharing (UNOS) portopulmonary hypertension (POPH) MELD exception. Abbreviations: CO, cardiac output; LT, liver transplantation; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

studies are needed to determine if echocardiogram and clinical evaluation could decrease the frequency of serial RHCs in appropriate patients.

Between 2006 and 2019, 504 patients with predominantly mild liver disease (mean MELD 12.9–14.4) have received POPH MELD exceptions in the US.[16] Over time, there has been an increase in age and liver disease severity (mean MELD 12.9 in the 2006–2010 era, 14.4 in the 2016–2019 era) among patients with approved POPH MELD exceptions but no change in waitlist or posttransplant mortality.[16] These trends potentially reflect delays in seeking MELD exceptions and may reflect changes in practice as a result of recommendations from the 2016 ILTS guidelines, which stated that POPH should *not* be considered an indication for LT.

The question of whether MELD exceptions should be pursued in patients with mild liver disease remains largely unanswered since there have been no prospective RCTs of LT, and observational studies are limited by bias. The French Registry showed that patients who underwent LT had better outcomes than non-transplanted patients, regardless of liver disease severity. Even patients with mild liver disease (MELD score < 15 and Child–Pugh class A) had improved survival with LT compared to non-transplanted patients. Whether improvements in survival are related to improvement in the liver disease itself or improvements in POPH post-LT (or a combination of both) is unknown. These findings of improved survival among patients treated with a combination of PAH therapy and LT versus either alone were also replicated in a meta-analysis.[36] Compared to non-transplanted patients, patients who underwent LT likely had fewer comorbidities and less severe PH, suggesting that confounding could also account for the results.

Given the paucity of evidence, the decision to pursue POPH MELD exception and LT in the setting of compensated liver disease and a low MELD score needs to be an individualized, multidisciplinary decision that takes into consideration liver disease severity, complications of liver disease, PH severity, and treatment response. Patients with evidence of decompensated liver disease should proceed to LT if they meet appropriate hemodynamic criteria and the consideration of POPH being an "indication" for transplant, *under those conditions* is supported. If patients have a low MELD score with no evidence of decompensated liver disease, continued POPH medical management without LT is favored, even if MELD exception criteria are fulfilled. Priority and desirability for LT in that scenario require a multidisciplinary approach, taking into consideration both the individual patient with POPH and the scarcity of organs as a limited resource. There is insufficient evidence to define a specific MELD threshold in which POPH MELD exceptions should not be granted.

Recommendations

14. *LT with MELD exception for POPH should be considered in appropriate patients with decompensated liver disease without contraindications to LT who meet either of the below hemodynamic criteria with PAH therapy*:

TABLE 5 Phases of liver transplantation, potential issues, and management

Phase of LT	Physiologic considerations	Management
Anesthetic induction	• Development of hypoxemia and hypercarbia after intubation with potential increase in pulmonary pressures • Drop in systemic vascular resistance (SVR) from anesthetics with hypotension secondary to drop in SVR and initiation of positive pressure	• Controlled induction with optimization of oxygenation and ventilation • Early use of vasopressors or inotropes based on right ventricular (RV) function on TEE
Prehepatic	• Hypotension secondary to decrease in preload from bleeding and loss of ascitic fluid as well as vasodilation of cirrhosis	• Judicious volume resuscitation and vasopressor use
Anhepatic	• Decreased preload and cardiac output due to clamping of the IVC • Progressive hypothermia and multifactorial acidosis, which worsen pulmonary hemodynamics and right ventricular function	• Maintenance of normothermia and preload • Consider the use of venovenous bypass if an option
Reperfusion/ neohepatic	Characterized by multifactorial hypotension (post-reperfusion syndrome), bleeding, thromboembolism, arrhythmias, increased RV preload, and depressed RV contractility. • These changes may result in cardiac arrest • RV overload may also occur due to volume overload secondary to the management of coagulopathy	• TEE-guided hemodynamic management • Availability of anticoagulants and cardioversion/ defibrillation capability • Early consideration for ECMO with decompensation

Abbreviations: ECMO, extracorporeal membrane oxygenation; IVC, inferior vena cava; LT, liver transplantation; RV, right ventricular; TEE, transesophageal echocardiogram.

- *mPAP < 35 mm Hg and PVR < 5 WU,*
- *mPAP 35–45 mm Hg and PVR < 3 WU.*

Intraoperative management

There are unique risks confronted by POPH patients across various phases of LT,[65,66] as detailed in Table 5. Anticipation of potential issues during each phase of LT and review of the pretransplant echocardiogram and hemodynamic data are essential to guide intraoperative management. Intraoperative pulmonary artery catheter hemodynamic monitoring is generally advised in the setting of PH. Transesophageal echocardiogram (TEE) is a safe and effective tool to complement the assessment of invasive pulmonary hemodynamics and should be used to assess RV function and to detect and intervene upon intraoperative complications related or unrelated to POPH.[67]

All continuous intravenous or subcutaneous pretransplant prostacyclin analogs should be continued throughout LT, and oral and/or inhaled PAH therapies should be continued in the postoperative setting as feasible. The use of inhaled pulmonary vasodilators (nitric oxide or prostacyclin analogs), dobutamine, or milrinone may be helpful to facilitate additional pulmonary vasodilatation and RV inotropic support. Norepinephrine, vasopressin, and epinephrine are preferred vasopressors to use in the setting of PAH if needed to maintain systemic perfusion.[65,68]

The evolving use of extracorporeal membrane oxygenation (ECMO) in LT, including for patients with POPH, has been recently reviewed.[69,70] Veno-arterial (VA) ECMO can be used as a "rescue" therapy for cardiovascular collapse due to RV failure in the setting of POPH. A high risk of complications (bleeding and thrombosis) during ECMO therapy for POPH has been noted, requiring a multidisciplinary approach by hematologists, hepatologists, perfusionists, and intensivists. Although routine use of pretransplant ECMO is not advised, successful use of pretransplant VA-ECMO has been reported following the failure of POPH medications to facilitate a safe LT.[71] In high-risk POPH cases undergoing LT, the option of ECMO as a rescue therapy is recommended if available.

Recommendations

15. *Intraoperative hemodynamic monitoring with a pulmonary artery catheter and TEE, performed by experienced LT anesthesiologists, should be utilized in POPH in the absence of contraindications.*
16. *Intravenous and subcutaneous PAH therapies should be continued throughout the LT procedure; oral medications should be continued perioperatively.*
17. *If available, VA-ECMO can be employed as a rescue intervention in cardiovascular collapse due to acute RV failure in POPH.*

Posttransplant and outpatient follow-up

In the immediate posttransplant period, all PAH therapy should be continued under the supervision and guidance of a PH expert. The initial 6 months post-LT pose a high risk for patients with POPH. According to recent

studies, the majority of deaths occur during this vulnerable time period when pulmonary hemodynamics can worsen.[72] For this reason, we do not advise weaning or discontinuation of PAH therapy within the initial posttransplant period. Patients with POPH should have follow-up clinical evaluation with TTE within 3 months post-LT. Weaning of PAH therapy can be considered at outpatient follow-up at a minimum of 3–6 months post-LT if patients demonstrate clinical and echocardiographic improvement or if they are experiencing treatment-related adverse effects.

Importantly, LT is not a cure for all patients with POPH, and only half of patients are able to safely discontinue PH therapy. Treatment de-escalation is a process that should not be rushed to ensure it is done safely.[36,60,72] Typically, intravenous or subcutaneous prostacyclin analogs are the first drugs to be weaned as these therapies are often the most burdensome for patients. Oral and inhaled PAH medications can subsequently be weaned or discontinued over time if patients demonstrate clinical improvement. Periodic TTE ± RHC should be used to follow POPH posttransplant.

Recommendations

18. *Patients with POPH should have an echocardiogram and clinical evaluation with a PH expert within 3 months post-LT or sooner if clinically indicated.*
19. *Weaning of PAH therapy post-LT cannot be performed in all individuals and should be a slow process that is initiated in the outpatient setting at a minimum of 3–6 months post-LT as guided by clinical assessment, TTE ± RHC.*
20. *Intravenous or subcutaneous prostacyclin therapy should typically be weaned first, as tolerated, followed by weaning of oral or inhaled medication over time based on TTE results, clinical parameters, and hemodynamics.*

PART 5. PROGNOSTIC FACTORS AND OUTCOMES

Prognostic factors

Pulmonary hemodynamics, particularly PVR and CO/cardiac index (CI), and liver disease severity are important prognostic factors in POPH.[38,73,74] Aggarwal et al identified liver disease severity, as assessed by the MELD-Na score, in addition to resting heart rate and hepatic encephalopathy, as significant predictors of survival.[73] Savale et al[38] identified MELD score or Child–Pugh stage, age, sex, and 6MWD as independent prognostic factors. Sex may also influence outcomes. In an analysis of LT candidates with POPH MELD exceptions, females had worse pulmonary hemodynamics with a higher baseline and posttreatment PVR. Females and males had similar survival but female sex was associated with worse survival among younger patients.[75] To summarize, several factors, including age, sex, PH severity (PVR, CI), liver disease severity (MELD score, Child–Pugh score), complications of liver disease, and exercise capacity impact the prognosis of patients with POPH.

Long-term outcomes

Since the 2016 guidelines, several studies have described long-term outcomes in POPH with and without LT. The overall results of these studies and a recent meta-analysis suggest that patients treated with a combination of PAH therapy and LT have the best overall outcomes and survival.[36]

As recently reviewed, there have been several single-center and national studies describing posttransplant outcomes in POPH patients transplanted over varying time intervals.[76] The 5-year median survival in those studies ranged from 60% to 87%, and

TABLE 6 Portopulmonary hypertension survival post-liver transplantation in modern treatment era[a]

Authors	Cohort	Era	Number	Survival (%)		
				1 year	3 years	5 years
Verma et al[77]	United Kingdom	1992–2012	28	63	59	54
Cartin-Ceba et al[60]	Mayo Clinic	1996–2019	50	72	63	60
Savale et al[72]	French PH Registry	1999–2013	35	80	77	77
Rajaram et al[78]	Emory	2005–2015	13	69		
Sadd et al[79]	Univ. of WI	2005–2019	24	87	87	87
DuBrock et al[55]	United States	2006–2019	103	86		
Savale et al[38]	French PH registry	2007–2017	63	92	83	81
Reymond et al[80]	French transplant centers	2008–2016	23	83	83	

[a]Studies included outcomes reported for more than 10 individuals.

TABLE 7 Summary of recommendations

Definitions and diagnostic criteria
(1) *POPH is defined by the presence of precapillary PH (mPAP > 20 mm Hg, PVR > 2 WU, and PAWP ≤ 15 mm Hg) without an alternative etiology in the setting of portal hypertension.*
(2) *RHC and clinical evaluation to rule out alternative causes of PH is necessary to make a diagnosis of POPH.*
(3) *All LT and TIPS candidates should undergo echocardiography to screen for POPH; although there is little evidence, it is reasonable to perform annual echocardiography while awaiting LT.*
(4) *Among LT candidates, a RVSP > 40 mm Hg, more than mild RV dilation or dysfunction, or intermediate to the high echocardiographic probability of PH according to ESC/ERS guidelines should prompt referral to PH experts with consideration of RHC in appropriate patients.*
Updates in POPH management
(5) *There is substantial practice variation regarding POPH management; clinicians should follow updated guidelines to ensure standardized, equitable care.*
(6) *POPH is a significant and unique subset of PAH. We recommend the inclusion of patients with POPH in clinical trials in order to better understand the safety and efficacy of PAH therapy in POPH.*
(7) *Despite limited evidence, several FDA-approved drugs for PAH (PDE5i, soluble guanylate cyclase stimulators, ERAs, and prostacyclin analogs) are reasonable to use in the treatment of POPH.*
(8) *POPH is complex and should be managed by multidisciplinary expert teams.*
(9) *Medical treatment of POPH should take into consideration hemodynamic disease severity, liver disease severity, and LT candidacy.*
(10) *We recommend close monitoring of patients with POPH after initiation of PAH therapy to assess for side effects, disease progression, and/or decompensation of liver disease.*
(11) *TIPS and beta-blockers should be avoided in patients with POPH.*
Implications for liver transplantation
(12) *To minimize waitlist and perioperative risk, PAH treatment should be utilized to reduce mPAP and PVR.*
(13) *Absolute contraindications to LT include any of the following: mPAP > 45–50 mm Hg, PVR > 5 WU, or severe RV dysfunction.*
(14) *LT with MELD exception for POPH should be considered in appropriate patients with decompensated liver disease without contraindications to LT who meet either of the below hemodynamic criteria with PAH therapy.* • *mPAP < 35 mm Hg and PVR < 5 WU,* • *mPAP 35–45 mm Hg and PVR < 3 WU.*
(15) *Intraoperative hemodynamic monitoring with a pulmonary artery catheter and TEE, performed by experienced LT anesthesiologists, should be utilized in POPH in the absence of contraindications.*
(16) *Intravenous and subcutaneous PAH therapies should be continued throughout the LT procedure; oral medications should be continued preoperatively.*
(17) *If available, VA-ECMO can be employed as a rescue intervention in cardiovascular collapse due to acute RV failure in POPH.*
(18) *Patients with POPH should have an echocardiogram and clinical evaluation with a PH expert within 3 months post-LT or sooner if clinically indicated.*
(19) *Weaning of PAH therapy post-LT cannot be performed in all individuals and should be a slow process that is initiated in the outpatient setting at a minimum of 3–6 months post-LT as guided by clinical assessment, TTE ± RHC.*
(20) *Intravenous or subcutaneous prostacyclin therapy should be weaned first, as tolerated, followed by weaning of oral or inhaled medication over time based on TTE results, clinical parameters, and hemodynamics.*
Prognostic factors and outcomes
(21) *Prognostic factors in POPH include age, sex, PH severity as assessed by PVR and CO/CI, liver disease severity and complications, and 6MWD; these parameters should be routinely assessed to guide management and prognostication.*
(22) *PAH therapy and LT evaluation should be considered in POPH patients as this combination is associated with the best long-term outcomes.*

approximately half of patients came off all PH medications posttransplant (Table 6). In most cases, posttransplant death has been due to infection, recurrent liver disease, or non-PH–related cardiac dysfunction rather than POPH.[60,81,82] Among 637 POPH patients in the French Registry, overall survival rates were 84%, 69%, and 51% at 1, 3, and 5 years, respectively.[38,72] Survival from POPH diagnosis was significantly better in the subgroup of patients who underwent LT (92%, 83%, and 81% at 1, 3, and 5 years, respectively), suggesting a survival benefit for LT. Other studies have also described excellent long-term outcomes post-LT. A single-institution retrospective study of 50 post-LT POPH patients at Mayo Clinic had a 5-year survival of 60%.[60] Those patients had a baseline mPAP of 45 mm Hg, PVR of 5.9 WU, and CO of 6.2 L/min with a median MELD of 14, and 42% came off all PAH therapy at a median of 13 months post-LT. Sadd et al also reported excellent posttransplant survival among treated POPH patients in a single-center study.[79] Among transplanted patients, 5-year posttransplant survival was 86.9%, and all patients were able to discontinue parenteral therapy post-LT, while 61.9% discontinued all PAH therapy.[79]

POPH is typically a progressive disease. Overall survival in non-transplanted POPH patients is worse, likely related to several factors, including the natural progression of disease in the absence of LT. A cohort of 160 non-transplanted patients with severe POPH (mean mPAP 49 mm Hg, PAWP 12 mm Hg, CO 5.3 L/min, and PVR 6.4 WU) diagnosed between 1988 and 2019[81] had a median survival of 27.5 months with overall survival of 77%, 51%, and 38% at 1 year, 3 years, and 5 years, respectively. Most patients did not receive a LT due to uncontrolled POPH. Causes of death were documented in 66% and due to complications of liver disease (38%), progressive right heart failure (23%), and sepsis/multisystem failure (10%). Causes of death also vary by liver disease severity, where patients with mild liver disease are more likely to die from cancer (HCC or extrahepatic cancer) or PAH rather than liver disease.[38]

In addition to LT, PAH treatment also impacts long-term outcomes. Recent studies have described worse survival compared to idiopathic PAH and poor outcomes in untreated patients. A prospective registry from Spain, which included 237 POPH patients enrolled between 1998 and 2017, found that patients with POPH had worse survival compared to idiopathic and familial PAH (49.3% versus 68.7% age and sex-adjusted 5-year survival) despite better hemodynamics.[83] Treated POPH patients had better survival than non-treated. Notably, a minority of patients in this cohort underwent LT 8/237 (3.4%).[83]

Recommendations

21. *Prognostic factors in POPH include age, sex, PH severity as assessed by PVR and CO/CI, liver disease severity and complications, and 6MWD; these parameters should be routinely assessed to guide management and prognostication.*
22. *PAH therapy and LT evaluation should be considered in POPH patients as this combination is associated with the best long-term outcomes.*

PART 6. FUTURE DIRECTIONS

Since the publication of the 2016 ILTS guidelines, there have been significant advances in the diagnosis and management of POPH. Overall, the field has evolved with respect to the development of more refined, evidence-based definitions of PH, revised criteria for MELD exceptions that better reflect risk stratification, and an improved understanding of the role of PAH therapy and LT in management. A summary of our updated recommendations regarding POPH diagnosis and management is detailed in Table 7. Despite recent advances, there remain several unanswered questions and priorities for future research. These areas include the following: (1) POPH pathophysiology and understanding of the relationship between HPS and POPH, (2) RV function assessment in POPH and its association with outcomes, (3) optimal treatment strategies, (4) predictors of posttransplant outcomes, (5) the role of mechanical circulatory support to facilitate safe LT, and (6) the role of LT for patients with POPH and mild liver disease. Ongoing studies and research in these priority areas are needed to improve understanding of POPH pathophysiology and to better define optimal management.

CONFLICTS OF INTEREST

Outside of the submitted work, Hilary M. DuBrock consults for and advises Merck, Janssen, and MSD. She advises United Therapeutics. She received grants from Bayer. Outside of the submitted work, Laurent Savale received personal fees and received grants from MSD and Janssen. He received personal fees from Bayer. He received grants from Acceleron. Outside of the submitted work, Olivier Sitbon consults for and received grants paid to his institution from MSD, Janssen, Gossamer Bio, Aerovate, Ferrer, and AOP Orphan. He consults for Liquida, Respira Therapeutics, Roivant, and United Therapeutics. The remaining authors have no conflicts to report.

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