International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension

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Abstract: Two distinct pulmonary vascular disorders, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) may occur as a consequence of hepatic parenchymal or vascular abnormalities. HPS and POPH have major clinical implications for liver transplantation. A European Respiratory Society Task Force on Pulmonary-Hepatic Disorders convened in 2002 to standardize the diagnosis and guide management of these disorders. These International Liver Transplant Society diagnostic and management guidelines are based on that task force consensus and should continue to evolve as clinical experience dictates. Based on a review of over 1000 published HPS and POPH articles identified via a MEDLINE search (1985-2015), clinical guidelines were based on, selected single care reports, small series, registries, databases, and expert opinion. The paucity of randomized, controlled trials in either of these disorders was noted. Guidelines are presented in 5 parts; I. Definitions/Diagnostic criteria; II. Hepatopulmonary syndrome; III. Portopulmonary hypertension; IV. Implications for liver transplantation; and V. Suggestions for future clinical research.

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PREAMBLE

This document presents official recommendations of the International Liver Transplantation Society (ILTS) on the diagnosis and management of hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) in adults and children. These guidelines were approved by the ILTS Practice Guideline Committee (ILTS Eduction.org).

These guidelines are not intended to provide an exhaustive literature review, but rather are based on selecting key published articles from a review of over 1000 articles obtained in a Medline search (OVID); single case reports, small series, databases and registries. The paucity of randomized, controlled trials in either HPS or POPH is noted and, therefore, consensus and expert opinion is often invoked for quality of evidence.

The ILTS Practice Guidelines Committee has adopted the following:

Grading System for Recommendations (Strength and Quality of evidence).

Strength

(1) Strong. There is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.

(2) Weak. There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment.

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Quality

Level A, data derived from multiple randomized clinical trials or meta-analyses.

Level B, data derived from a single randomized trial or nonrandomized studies.

Level C, only consensus opinion of experts, case studies, or standard-of-care.

PART I. DEFINITIONS/DIAGNOSTIC CRITERIA

Hepatopulmonary Syndrome

Diagnostic Criteria:

Hepatopulmonary syndrome is characterized by the triad of abnormal arterial oxygenation caused by intrapulmonary vascular dilatations (IPVD) in the setting of advanced liver disease, portal hypertension, or congenital portosystemic shunts. Abnormal oxygenation is defined by an elevated alveolar-arterial oxygen gradient (≥ 15 mm Hg or ≥ 20 mm Hg if age > 64 years) while breathing room air in the sitting position at rest, Table 1) in the absence of other than mild pulmonary function test abnormalities.[1,2] Intrapulmonary vascular dilatations are optimally detected via contrast-enhanced transthoracic echocardiography (CE-TTE).[1]

Recommendations

1. The European Respiratory Society (ERS) Task Force diagnostic criteria of HPS should be followed in research and clinical settings (1C).
2. Abnormal arterial oxygenation due to HPS should be determined by arterial blood gas (ABG) measurement (1C);
3. In conducting and comparing HPS clinical studies, note that abnormal partial pressure of arterial oxygen (PaO_2) cutoffs for HPS may vary (2C).

Portopulmonary Hypertension

Diagnostic Criteria

Pulmonary artery (PA) hypertension (PAH) in the setting of portal hypertension is termed portopulmonary hypertension.[3] Portopulmonary hypertension diagnostic criteria are satisfied by hemodynamic criteria obtained via right heart catheterization (RHC) measurements (Table 1).[4] Increased mean PA pressure (mPAP) due to increased pulmonary vascular resistance (PVR) in the setting of a normal PA wedge pressure (PAWP) is the hemodynamic cornerstone for the diagnosis of POPH. It is recognized that the hyperkinetic condition in liver disease may impact what is considered a true normal PVR.[4] Other causes of pulmonary hypertension PH may coexist in the setting of liver disease and must be excluded (high flow state, excess volume, diastolic dysfunction, obstructive/restrictive lung disease, sleep disordered breathing).[4] Recommendations are as follows:

4. The ERS Task Force diagnostic criteria of POPH should be followed in research and clinical settings (1C).
5. Right heart catheterization should be done to confirm hemodynamics consistent with diagnosis of POPH: mPAP > 25 mm Hg, PVR > 3 wood units (240 dynes/s per cm^{-5}) and PAWP < 15 mm Hg (1B).
6. Exclude other causes of pulmonary hypertension in the setting of liver disease (2B).

TABLE 1.

Diagnostic criteria

(A) HPS
Liver disease (usually cirrhosis with portal hypertension)
Positive CE-TTE[a]
Abnormal arterial oxygenation:
Alveolar-arterial oxygen gradient (AaO_2) ≥ 15 mm Hg (>20 mm Hg if age > 64)[b]
(B) POPH
Portal hypertension[c]
mPAP > 25 mm Hg
PVR > 3 wood units (240 dynes/s per cm^{-5})
PAWP < 15 mm Hg

[a] Microbubbles in the left heart ≥ 3 cardiac cycles after right heart microbubbles following 10 mL agitated saline injection in a peripheral arm vein

[b] AaO_2 mm Hg = $PAlveolarO_2 - ParterialO_2$.

= $[FIO_2 \times (Patm - PH_20) - PaCO_2/.8] - PaO_2$.

where: FIO_2, inspiratory oxygen fraction; Patm, atmosphere pressure; PH_2O, water vapor partial pressure; $PaCO_2$, arterial carbon dioxide pressure; and PaO_2, partial pressure of oxygen.

[c] A clinical diagnosis (gastroesophageal varices; splenomegaly, ascites) or portal pressure.

PART II. HEPATOPULMONARY SYNDROME

Pathophysiology

Hepatopulmonary syndrome results when alterations in the pulmonary microvasculature impair gas exchange.[1] Dilation of capillary and precapillary vessels up to 100 μm in diameter as well as increased in numbers of dilated vessels have been observed.[5] Evidence in experimental HPS and indirect evidence in humans support that pulmonary angiogenesis also contributes to HPS.[6,7] These vascular changes result in ventilation-perfusion (V/Q) mismatch, diffusion limitation and anatomic shunting that cause hypoxemia. In experimental HPS, several mediators, including TNF-α, nitric oxide and endothelin-1, as well as vascular endothelial growth factor generated by intravascular monocytes that accumulate in the lung, drive microvascular alterations.[8]

Severity Classification:

The severity of HPS is determined by the degree of hypoxemia. Based on the ERS Task Force, severity is graded as mild (PaO_2 ≥ 80 mm Hg), moderate (PaO_2 = 60-79 mm Hg), severe (PaO_2 = 50-59 mm Hg), and very severe (PaO_2 < 50 mm Hg).[1]

Recommendations

7. The ERS severity classification for HPS is appropriate for both clinical and clinical investigative studies to facilitate uniform assessment (2C).
8. Translational studies are needed to define if mechanisms in animal models have relevance for treatment of human disease (2C).

Epidemiology

Clinical Presentation

Hepatopulmonary syndrome most commonly occurs in portal hypertension and cirrhosis. However, it may also occur in patients with acute and chronic hepatitis, acute liver failure and vascular abnormalities that limit hepatic venous outflow to the lungs (cavopulmonary shunts, Abernethy malformation).[8]

Typical symptoms include dyspnea on exertion or at rest. Hepatopulmonary syndrome may coexist with other pulmonary diseases, which aggravate gas exchange abnormalities, such as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, cystic fibrosis, and others.[9] Coexistence of HPS and POPH, based on echocardiography and RHC, is not uncommon.[10]

Digital clubbing and cyanosis are typical findings in advanced HPS, as are diffuse telangiectasias. Platypnea (worsening of dyspnea moving supine to upright position) and orthodeoxia (decrease in PaO_2 of more than 5% or more than 4 mm Hg when the patient moves from supine to upright position) are found in up to 25% of HPS patients.[8] Chest radiography may show bibasilar nodular or reticulonodular opacities, although the majority of HPS patients have normal findings. Pulmonary function testing often reveals decreased diffusing capacity for carbon monoxide.[8]

Natural History/Prognosis

The prevalence of HPS in patients with cirrhosis undergoing evaluation for liver transplantation (LT) ranges from 5% to 30%. In children with cirrhosis, the prevalence of HPS ranges from 3% to 20%.[11-13] The presence of HPS significantly worsens prognosis and quality of life in affected patients. Those with HPS have a double risk of death in comparison to those with liver cirrhosis of similar severity without HPS,[11] which is why patients with HPS may be eligible to receive a higher priority on the transplant waitlist, depending on the allocation system. Moreover, mortality in most centers, with or without LT, appears to be highest in patients with severe hypoxemia (PaO_2 < 50 mm Hg),[13-15] Therefore, screening for severe HPS is advised in individuals otherwise suitable for candidates for LT.[12]

Recommendation

9. The clinical presentation of HPS may be variable, adversely influencing quality of life and survival, therefore screening is appropriate, especially in liver transplant candidates (2B).

Screening and Diagnostic Testing

Screening Evaluation

Pulse oximetry (O_2 saturation < 96%) identifies all patients with hypoxemia (PaO_2 < 70 mm Hg) at sea level (ABG with A grad necessary at high altitudes) and appears to be a cost-effective screening test for detecting otherwise suitable LT candidates to be eligible for model for end stage liver disease (MELD) exception.[16,17] Hyperemic arterialized capillary blood gas determination may be a better screen than pulse oximetry for hypoxemia in cirrhotic children.[18] To detect all patients with HPS, ABG analysis is required. Hepatopulmonary syndrome patients have increased levels of exhaled nitric oxide (NO) (alveolar fraction), but measuring such levels have not been validated for HPS screening.[19]

Noninvasive Testing

The criterion for detection of intrapulmonary shunting is CE-TTE.[20] Normal diameter of the lung vascular capillary vessels is less than 8 to 15 μm. Agitated saline creates microbubbles greater than 10 μm in diameter that normally do not pass through the pulmonary capillary bed. Therefore, delayed appearance of intravenously injected microbubbles in the left heart 3 or more cardiac cycles after visualization in the right heart demonstrates an abnormal vascular dilation in the intrapulmonary capillary bed. Intracardiac shunting (ie, due to persistent foramen ovale or atrial septal defect) demonstrates early appearance of microbubbles in the left heart within 1 to 2 cardiac cycles after appearance in the right heart. Transesophageal echocardiography (TEE) can distinguish intracardiac shunts from intrapulmonary shunts by imaging the source of microbubbles arriving into the left atrium (across the atrial septum versus pulmonary veins).[20]

Nuclear/Invasive Testing

Lung perfusion scanning (peripheral vein injection of 20 μm labeled ^{99m}Tc macroaggregated albumin [MAA] with brain uptake imaging) is another method for detecting and quantifying IPVD. The MAA lung-brain perfusion scan is normal in non-HPS causes of hypoxemia.[21] However, the lung perfusion scan does not distinguish intracardiac and intrapulmonary shunting and has inferior sensitivity compared to CEE for detection of mild or moderate HPS in adults. In children, MAA lung perfusion scans may have favorable sensitivity for detecting mild degrees of IPVD relative to CE-TTE.[22]

In HPS patients with concomitant lung problems (chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, or hepatic hydrothorax), abnormal brain uptake of ^{99m}TcMAA after lung perfusion (uptake > 6%) helps to distinguish the degree of hypoxemia caused by IPVD versus hypoxemia due to nonvascular lung parenchymal abnormalities.[9,22]

Recommendations

10. Pulse oximetry (O_2 saturation < 96%) is a reasonable screening test to detect hypoxemia in adults who are otherwise suitable LT candidates, however ABG determination of oxygenation is necessary to diagnose HPS (1C).
11. CE-TTE is the optimal screening test and criterion in adults for detection of IPVD (1B).
12. MAA scans clarify the contribution of HPS-related hypoxemia in coexistent intrinsic cardiopulmonary disease (1C).

Medical/Nonsurgical Management

Principles of Management

Management of HPS is supportive because there are no medical therapies, and genetic predisposition may exist.[6,23] The administration of supplemental oxygen to maintain O_2 saturations above 88% is advised based on experience in treating nonspecific pulmonary vascular and parenchymal disorders.[23] However, increased mortality in HPS is not confined to those with severe hypoxemia, thus potential medical treatments may be appropriate in all stages of disease.[11] Liver transplantation should be considered before the development of severe or very severe disease.

Medications/Nonsurgical Therapy

Although no clearly effective medical therapy for HPS is available, somatostatin, almitrine, indomethacin, norfloxacin, inhaled (nebulized) L-NAME, aspirin, and plasma exchange have all been tried in small studies without clear benefit.[23-26] The norfloxacin randomized, crossover, pilot study in 9 HPS patients was negative for an improvement in alveolar-arterial

oxygen gradient.[26] Garlic extracts have shown some benefit in HPS.[27-30] More recently, pentoxifylline, a phosphodiesterase inhibitor with known mild inhibitory effects on TNF-α and NO, has been linked to improved oxygenation in experimental HPS.[31-34] However, results of small uncontrolled studies in human HPS with pentoxifylline are conflicting.[32,33] Other interventions have included inhaled prostacyclin derivatives to improve ventilation-perfusion matching[35] and withdrawal of chronic methadone.[36]

Lowering of portal pressure with transjugular intrahepatic portosystemic shunt (TIPS) has had variable effect on HPS.[37,38] Inferior vena cava stenting in the setting of spontaneous inferior vena cava portal vein shunting and ligation of congenital portosystemic shunts in the Abernethy malformation associated with HPS have resulted resolution of HPS.[39,40]

The effect of 100% inspired oxygen (PaO_2 < 300 mm Hg) and chest computed tomography scanning can determine which patients should proceed to pulmonary angiography.[41] Discrete abnormalities are rare in HPS and are likely to be visible on high-resolution chest computed tomography. Rarely, coil embolization has been used successfully in improving hypoxemia in both type I (discrete) and type II (diffuse) HPS vascular patterns.[42,43] In children, mesenteric angiography may identify a congenital portosystemic shunt that may be approached by embolization and dilation of portal vein remnants to treat the underlying cause of the HPS.[44]

Monitoring/Follow-Up

No standard guidelines regarding oxygenation monitoring exist. Sequential pulse oximetry appears prudent.[45]

Recommendations

13. Aside from supplemental oxygen (rest, exercise and sleep), no medical therapies are definitively established or FDA approved for HPS (2B).
14. Portal decompression with TIPS is of uncertain benefit in HPS in adults (2C).
15. Rarely, coil embolization may improve oxygenation in selected HPS patients (2C).
16. Correction of congenital portosystemic shunts in children appears beneficial (2B).
17. Sequential pulse oximetry is advised for oxygenation monitoring (1C).

PART III. PORTOPULMONARY HYPERTENSION

Pathophysiology

Portopulmonary hypertension results when there is obstruction to arterial flow in the pulmonary arterial bed. Obstruction can be due to contributions of vasoconstriction, proliferation of endothelium/smooth muscle, and platelet aggregation. Mediators associated with POPH include increased circulating endothelin-1 and estradiol levels and deficiency of prostacyclin synthase in pulmonary endothelial cells.

Severity Classification

The severity of POPH is based on mean PA pressures (in the setting of increased PVR) determined via RHC data at rest. Based on the ERS Task Force, it is graded as mild (25 ≤ mPAP < 35 mm Hg), moderate (35 ≤ mPAP < 45 mm Hg), and severe (mPAP ≥ 45 mm Hg).[1]

Clinical Features

A clinical diagnosis of POPH can be made with the documentation of compatible hemodynamics in a patient with portal hypertension in the absence of coexisting conditions associated with pulmonary hypertension.[46] However, fulfilling hemodynamic criteria alone is not sufficient to make a diagnosis of POPH, which requires ruling out other causes for PA or pulmonary venous hypertension. Exertional dyspnea is invariably present with findings of right heart failure as the disorder progresses.[46]

Recommendation

18. Severity of POPH can be described in terms of mPAP (assuming increased PVR) as follows: mild 25 ≤ mPAP < 35); moderate (35 ≤ mPAP <45) and severe 45 ≤ mPAP) (1B).

Epidemiology and Natural History

Portopulmonary hypertension incidence is reported as at least 1 case per 3 million inhabitants per year.[47] An autopsy study of more than 17 000 decedents identified changes suggestive of a pulmonary arteriopathy in 0.13%; 0.73% in cirrhosis.[48] A prospective study of 1235 patients evaluated for LT (all with Child-Turcotte-Pugh score ≥ 7) showed that 5% met current hemodynamic criteria for POPH (4). Previous retrospective analyses have generally yielded similar estimates.[49-51] Portopulmonary hypertension accounts for approximately 5% to 10% of the overall PAH population and is one of the most common form of PAH.[47] Although uncommon, POPH does occur in childhood.[52,53] In a multicenter case-control study, female sex and a diagnosis of autoimmune hepatitis were independent risk factors for POPH in patients evaluated for LT; genetic variants involved in estrogen signaling increased the risk of POPH.[54] A case-control study identified a higher prevalence of large spontaneous portosystemic shunts and hepatofugal portal blood flow among patients with moderate-to-severe POPH compared with milder or no POPH.[55]

Portopulmonary hypertension is associated with a 1-year survival of 35% to 46% without treatment.[56,57] A retrospective study[58] as well as a large, multicenter prospective US registry both suggested worse survival for patients with POPH relative to idiopathic pulmonary artery hypertension patients (5 years, 40% vs 64%) despite higher cardiac output (CO) and lower PVR in POPH.[52] A retrospective cohort study of POPH patients from France showed better survival, which was similar to that of IPAH, but reported an increased risk of death with more severe cirrhosis and lower cardiac index.[59]

Neither the severity of liver disease nor the degree of portal hypertension (as measured by the hepatic venous pressure gradient) predicts the presence or severity of POPH.[54,60] Patients often die of right ventricular failure or from complications from hepatic disease (gastrointestinal bleeds, sepsis, hepatocellular carcinoma), though the relative frequencies with which each occurs vary by study. Lower cardiac index or higher right atrial pressure is associated with an increased risk of death.[60,61] A CO in the "normal" range in a patient with POPH may be the manifestation of significant right ventricular afterload and dysfunction.[61]

Recommendations

19. Risk factors for POPH exist and include female sex, autoimmune liver disease, but these should not be used for screening (2B).
20. Natural history of POPH may be affected by either cardiac limitation or direct complications of liver disease; simultaneous clinical monitoring of both should be accomplished (1C).

Screening and Initial Evaluation

Transthoracic Doppler echocardiography (TDE) plays an important role in the evaluation of symptomatic cirrhotic patients with suspected POPH and in the screening of candidates for LT and TIPS.[62-64] In a prospective study of LT candidates, a cutoff for pulmonary artery systolic pressure > 30 mm Hg had a negative predictive value of 100%, but the positive predictive value was only 59%.[63] There is less consensus surrounding the cutoff and TDE criteria to trigger RHC; LT and TIPS candidates with an right ventricular systolic pressure greater than 50 mm Hg and/or with significant right ventricular (RV) hypertrophy or dysfunction likely require RHC to measure hemodynamics and consistency with POPH.[4,64] Transthoracic Doppler echocardiography is recommended by the American Association for the Study of Liver Diseases for all patients being considered for LT.[65]

Recommendations

21. Screening for POPH should be performed with TDE in patients with portal hypertension who are candidates for TIPS or LT (1B).
22. Screening for POPH in patients with portal hypertension who are candidates for LT with TDE should be repeated while waiting, however the optimal interval is unclear (2C).

Medical Treatment

Histopathologic and clinical similarities between POPH and other forms of PAH have provided a rationale for the use of PA-targeted therapies in POPH, though this patient subset has been excluded from virtually all clinical trials of these therapies, as well as those using anticoagulation.[66-69] Cirrhosis-related varices likely present strong contraindications to therapeutic anticoagulation in POPH although no clinical trials have been conducted.

Lack of response and potential for calcium channel blockers to increase fluid retention, reduce right ventricular function, and increase portal pressures suggest that these drugs should be avoided in POPH.[70-72] Acute vasodilator testing in POPH appears unlikely to be helpful in POPH; however, there is lack of consensus.[73]

Patients with cirrhosis and esophageal varices are often treated with β-blockers. In patients with more advanced POPH (mean PAP ≥ 35-40 mm Hg), withdrawal of β-blocker therapy may increase CO (via release of chronotropic response), as well as exercise capacity.[74] Therefore, the risk-benefit ratio of β-blocker therapy should be considered along with alternative means of controlling variceal bleeding risk (eg, band ligation) in patients with POPH.

Prostacyclin Analogues

Prostacyclin analogues possess vasodilator, antithrombotic, and antiproliferative properties. Numerous case reports/series have reported improvements in hemodynamics with the use of intravenous epoprostenol in POPH.[75-80] Progressive splenomegaly and thrombocytopenia have been documented[81,82]; slower titration and target doses lower than those used in other forms of PAH may prevent the former issue. Favorable short-term hemodynamic effects have been reported with intravenous or subcutaneous treprostinil[83,84] and inhaled iloprost as well.[85] Improved 5-year survival using intravenous prostacyclin compared with those in the Registry to Evaluate Early and Long-term Pulmonary Artery Hypertension (71% vs 40%) was reported in a single-center study (n = 21).[86]

Phosphodiesterase Inhibitor Subtype 5 Inhibitors

Phosphodiesterase inhibitor subtype 5 inhibitors prevent the metabolism of cyclic guanosine monophosphate, which mediates the vascular effects of NO. Small series suggest that oral sildenafil improves functional capacity decreases PVR, mPAP, and increase in CO in POPH.[87-91] Although there were significant hemodynamic improvements, there were no changes in 6-minute walk distances in the largest reported series of POPH patients (n = 20).[91] Esophageal variceal hemorrhage related to the use of sildenafil has been reported.[92]

Endothelin Receptor Antagonists

Bosentan, an oral dual endothelin receptor antagonist (ERA), leads to improvements in exercise capacity and hemodynamics in POPH.[93-100] Improvements were noted regardless of the Child-Turcotte-Pugh severity of liver disease. A 3-year survival rate of 89% in a retrospective study of 18 POPH patients treated with bosentan has been reported.[99] A recent retrospective study included 34 POPH patients treated with bosentan; after 5 months, there was a 31% reduction in PVR and 39% increase in cardiac index. Seven patients (5.5%) developed elevations in liver transaminases greater than 3 times the upper limit of normal, which resolved with dose reduction or discontinuation.[100]

A cohort of 13 POPH patients (62% Child-Pugh class A) were successfully treated with the selective ERA, ambrisentan (median exposure 390 days).[101] Patients demonstrated improved functional class, increased CO, and a mean reduction in PVR of 61%. No significant changes in liver function parameters were observed.

The first ever multicenter, placebo controlled trial in POPH using the nonselective ERA, macitentan, has recently begun.[102] It should be noted the FDA labelling recommends avoiding any ERA in patients with moderate to severe liver dysfunction or elevated transaminases.

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt placement should be considered cautiously in the patient with POPH. The typical postprocedure hemodynamic changes of increased right ventricular filling pressures and increased CO may be poorly tolerated with significant elevations in PVR and right ventricular volume or pressure overload.[103,104] Congestive heart failure and severe pulmonary hypertension (mPAP ≥ 45 mm Hg) are absolute contraindications to TIPS; moderate POPH (35 ≤ mPAP < 45 mm Hg) is considered a relative contraindication.[104]

Recommendations

23. The safety of anticoagulation in POPH has not been studied, but such therapy is not advised (2C)

24. Treatment with calcium channel blockers should not be initiated for treatment of POPH (2C).
25. Acute vasoreactivity testing during RHC to guide treatment in POPH is not required (2C).
26. Beta-blockers use should be minimized and varices treated by other means in POPH (2B).
27. Treatment with agents approved for PAH may be useful in improving hemodynamics and exercise capacity in patients with POPH (1C).
28. Severe POPH (mPAP ≥ 45-50 mm Hg) is an absolute contraindication to elective TIPS (1C).

PART IV. IMPLICATIONS FOR LT

Hepatopulmonary Syndrome

Indications

Starzl et al described LT in 3 children with evidence of intrapulmonary shunting and severe hypoxemia, but survival was short-lived.[105] Right to left intrapulmonary shunts (now known as HPS) were previously considered an absolute contraindication for LT if hypoxemia was severe (PaO_2 < 50 mm Hg).[106]

With reduction of intrapulmonary shunting, normalization of ventilation/perfusion abnormalities and HPS resolution following LT reported through the mid-1990s, investigators espoused progressive hypoxemia due to HPS as an indication for LT.[107-111] That concept was bolstered by poor correlation between severity of liver disease and severity of HPS, as well as dismal outcome (20-26% 5- year survival) if LT was not conducted in HPS.[13]

Recommendation

29. Severe hypoxemia due to HPS (PaO_2 < 60 mm Hg) should be considered an indication for LT and such individuals should have expedited LT consideration (1B).

High risk/Contraindications

Despite HPS being an indication for LT, very severe hypoxemia (PaO_2 < 50 mm Hg) portends an increased risk for complications and mortality after LT.[14,112-114] In the multicenter, multivariate analysis of HPS patients from the Pulmonary Vascular Complications of Liver Disease Study Group), an increased risk of death associated with HPS (HR = 2.41) persisted after adjusting for LT, age, sex, race, and MELD score.[11]

A multivariate analysis of United Network for Organ Sharing (UNOS) data regarding MELD exception granted to HPS patients from 2002 to 2012 concluded no association between waitlist mortality and severe hypoxemia, but a pre-LT PaO_2 < 45 mm Hg was associated with increased post-LT mortality.[15]

Recent series of HPS patients (n = 70) transplanted from 2 experienced centers suggest that the post-LT risk/mortality has dramatically improved in severe HPS.[115,116] Severity of hypoxemia (pre-LT PaO_2 < 50 mm Hg which was documented in 34/70) was not associated with increased mortality. In 49 HPS patients transplanted since the initiation of MELD exception for HPS, only 3 post-LT deaths (6%) were reported.

Recommendations

30. Multicenter data and recent UNOS data suggest that pre-LT PaO_2 less than 45 to 50 mm Hg, has been associated with increased risk of transplant hospital mortality, morbidity, and severe hypoxemia post-LT (1B).
31. Prospective center-specific data show that selected HPS patients with pre-LT PaO_2 less than 50 mm Hg may have good outcomes, suggesting center-specific excellence (1C).

MELD/Pediatric End-Stage Liver Disease Exception

Priority for LT in the setting of HPS was reviewed in the 2006 MESSAGE conference.[117] Model for end stage liver disease exception granted for HPS patients from 2002 through 2007 suggested a pre-LT HPS survival advantage followed by similar post-LT survival when compared to non-exception controls. Waitlist death occurred in 1.6% versus 14.5% in controls.[118] However, a key limitation in the analysis was the lack of specific PaO_2 values for analysis in the exception group.[119]

As of December 2010, the UNOS has allocated standard exception points to the MELD/pediatric end-stage liver disease (PELD) score for HPS patients if the PaO_2 is less than 60 mm Hg, and no other clinical significant pulmonary condition exists. Hepatopulmonary syndrome exception MELD (22 points)/PELD (28 points) are automatically increased every 3 months if the repeat PaO_2 remains less than 60 mm Hg breathing room air in the sitting position https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.

Recent UNOS analysis of HPS patients granted MELD exception documented a waitlist mortality of 8% and significantly worse post-LT survival if pre-LT PaO_2 was < 44 mm Hg) (15). Future studies are needed to define whether modification of the HPS MELD exception policy (granting higher MELD points if PaO_2 is less than 50 mm Hg may optimize waitlist and post-LT outcomes for HPS candidates.

Recommendations

32. Standard MELD exception scores should be given if PaO_2 is less than 60 mm Hg due to HPS (1B).
33. Increased MELD exception score (higher MELD points if PaO_2 < 50 mm Hg) should be considered in view of recent UNOS post-LT data analysis (1B).

Intraoperative Issues

The major issue in managing HPS patients during the LT is maintaining satisfactory arterial oxygenation.[120] Even in the setting of severe HPS (PaO_2 < 50 mm Hg), most patients can significantly improve PaO_2 with 100% inspired oxygen.[23] Monitoring mixed venous oxygen saturation (SvO_2) is potentially important. SvO_2 monitoring may guide the need to initiate venovenous bypass (if SvO_2 drops below 65%).[120]

Hepatopulmonary syndrome patients are usually orally intubated and mechanically ventilated with lung protective ventilation (tidal volumes, 6-8 mL/kg). Of unique interest in HPS is the characteristic of orthodeoxia (worsening PaO_2 in the upright position/better PaO_2 supine).[121] Therefore, supine patient positioning in the operating room may be favored by the existence of HPS. The difference between inhalational and intravenous anesthesia in HPS patients has been studied; although general anesthesia decreased oxygen capacity in all patients, the differences in oxygenation by method of delivery were not significant 30 minutes after induction.[120] There are no established cutoffs regarding

degree of pre-LT arterial oxygenation that dictates cancellation of a case.

Recommendations

34. Continuous monitoring of mixed venous oxygen saturation (SvO_2) should be accomplished. If the SvO_2 falls below 65% on vascular exclusion of the liver, venovenous bypass maybe beneficial (2C).
37. Intraoperative oxygenation is not adversely affected by different anesthetic deliveries (1B).

Posttransplant/Intensive care issues

It is expected that in the immediate HPS posttransplant hours, arterial oxygenation may worsen due to the effects of narcotics/sedation, subcostal incision, volume overload and atelectasis. Abrupt reversal of the process driving the HPS-associated pulmonary vasodilatation may result in transient pulmonary arterial vasoconstriction and worsen ventilation/perfusion matching.[121,122]

Early extubation after LT remains a goal to minimize the effects of ventilator- associated pneumonia; prolonged use of 100% inspired oxygen via intubation or close fitting face mask has been well tolerated in HPS.[123,124] The use of Trendelenburg positioning, continuous lateral rotation, noninvasive ventilation, and transtracheal oxygen has been used to improve persistent severe hypoxemia experienced due to HPS.[125-129] Continuous inhaled nitric oxide (up to 40 ppm, ranging from 2 to 14 days) as a means to improve perfusion of the aerated parts of the lung without increasing flow through the intrapulmonary vascular dilatations can improve O_2 post-LT.[130,131] Intravenous methylene blue has been used successfully in improving PaO_2 post-LT presumably by vasoconstricting areas of impaired ventilation, thus improving V/Q matching.[132] Extracorporeal membrane oxygenation to provide adequate arterial oxygenation has been successfully used pre-LT and post-LT when all other oxygenation maneuvers and medication attempts have failed.[133]

Importantly, posttransplant severe hypoxemia (100% FIO_2 needed to maintain hemoglobin saturation $\geq$ 85%) was associated with a 45% mortality in those with pretransplant PaO_2 less than 70 mm Hg.[113]An algorithm to medically treat severe hypoxemia associated with HPS post-LT has been proposed.[134]

Recommendations

36. Early extubation should be accomplished to prevent ventilator associated pneumonia (1B).
37. 100% inspired oxygen via face mask/noninvasive ventilation/nasal oxygen should be used to maintain O_2 saturation $\geq$ 85% (1C).
38. Goal directed fluid therapy should be conducted to avoid fluid overload and pulmonary congestion (2C).
39. Inhaled pulmonary vasodilators (nitric oxide) can be used to improve post-LT oxygenation (2B).
40. ECMO can be used to as a bridge to LT and reduce the need for mechanical ventilation in severe HPS (2B).

Expected Outcomes

Resolution of HPS after LT can be expected if the patient survives the transplant hospitalization.[23] Experience has shown that the more severe the pre-LT arterial hypoxemia, the longer the post-LT recovery in terms of resolving hypoxemia and prolonged need for supplemental oxygen.[135]

Liver transplantation candidates with severe hypoxemia (PaO_2 < 50 mm Hg) can have reduced waitlist mortality, HPS resolution, and long-term survival.[115,116,136-138] Living donor LT results in resolution of HPS and long-term survival in both the pediatric and adult age groups.[139-141] Recurrence of HPS post-LT is rare and related to the recurrence of the liver disease.[142,143]

Uncommonly, post-LT resolution of HPS has been associated with the evolution of clinically significant pulmonary arterial hypertension; the latter can be managed in a manner similar to POPH. Whether this form of post-LT pulmonary hypertension occurs de novo or results from the unmasking of coexistent pre-LT POPH as the vascular dilatations of HPS resolve is unknown.[144]

Post-LT outcomes in patients with IPVD (without arterial hypoxemia) are similar to those without vascular dilatations.[145] No studies have addressed optimal follow-up testing in HPS patient's post-LT, but periodic assessment by pulse oximetry seems prudent. Aside from research studies, there is no clinical role for repeat CE-TTE or ^{99m}TcMAA lung perfusion scanning post-LT in patients with satisfactory oxygenation by oximetry (Sat $\geq$ 96%) or ABG PaO_2 > 80 mm Hg).

Recommendations

41. Resolution of HPS after LT (deceased or living donor) is expected, temporally related to pre-LT severity, and may take several months and require continued supplemental oxygen use (1B).
42. Periodic oxygenation assessments via pulse oximetry should be done to decide need for supplemental oxygen (2C).
43. Supplemental oxygen should be discontinued when O_2 saturation remains greater than 88% (rest, exercise, and sleep) (2C).
44. Post-LT contrast-enhanced echocardiography CE-TTE is not routinely advised unless clinically indicated (2C).

Portopulmonary Hypertension

Indications

Fatal outcome following LT in the setting of severe POPH was first reported in 1991.[146] Subsequent case reports suggested nonreversibility and unacceptably high risk for LT in the setting of severe POPH unresponsive to pulmonary vasodilators.[147,148]

However, 2 distinct organ transplant outcomes in the setting of portopulmonary hypertension provided important insight into POPH transplant outcomes.[149] In case 1, successful LT in the setting of severe POPH treated with pre and post-LT continuous intravenous prostacyclin was described with normal pulmonary hemodynamics, off prostacyclin, reported 22 months post-LT. In case 2, a single-lung transplant, due to severe pulmonary hypertension in the setting of portal hypertension due to portal vein thrombosis was accomplished. Normalization of the right ventricular function within 3 months, but by 9th month postlung transplant, the pulmonary hemodynamics were similar to the pretransplant levels. The resolution of portal hypertension (case 1) and persistence of same (case 2) suggested a functional relationship between the consequences of portal hypertension and PAH.

Unlike HPS, unpredictability of POPH post-LT even with current PA targeted therapies precludes POPH from being considered an indication for LT. However, with improved pulmonary hemodynamics and RV function due to evolving therapies, LT can be successfully accomplished in highly selected patients (see below).[150]

Recommendation

45. Unlike HPS, there are no data to support the concept that POPH (treated or untreated) should be an indication for LT (2C).

High Risk/Contraindications

Before the routine use of PA-targeted therapy for POPH, several studies[50,111,150-153] reported no increase in perioperative mortality if mPAP was less than 35 mm Hg. POPH with mPAP of 35 to 50 mm Hg or greater poses higher risk for LT,[150,151] longer post-LT ventilation and length of hospital stay.[151,153] Portopulmonary hypertension patients with mPAP of 35 mm Hg or greater should be treated aggressively to improve the mPAP, PVR, and right ventricular function, especially if LT is to be considered.[112,150,154,155]

Regardless of therapy, mPAP greater than 50 mm Hg (≥45 mm Hg in some centers) remains an absolute contraindication to LT in most centers.[61,150,156] Rarely, patients with mPAP greater than 50 mm Hg can survive LT without pulmonary targeted therapy, as long as cardiac index is preserved.[157]

Recommendations

46. PA targeted therapy should be initiated in POPH if mPAP of 35 mm Hg or greater (2B).
47. Patients should be informed that pre-LT mPAP of 35 mm Hg or greater and increased PVR is associated with increased morbidity and mortality (1B).
48. POPH with mPAP of 45 to 50 mm Hg or greater should be considered as an absolute contraindication to LT (1C).

MELD/PELD

POPH/MELD exception has been granted to prevent the progression pulmonary hemodynamics that would preclude successful LT.[158] Since December 2010, standardized MELD (22 points)/PELD (28 points) exception has been awarded to POPH patients (mPAP > 25 mm Hg and PVR > 240 dynes/s per cm^{-5}) with at least moderate severity (baseline mPAP > 35 mm Hg) who attain, with PA targeted therapy, improved mPAP (<35 mm Hg) and PVR (<400 dyne/s per cm^{-5}). https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.

Baseline (pretreatment) transpulmonary gradient (mPAP – PAWP) should be determined to correctly classify the effect of increased PAWP associated with volume overload (due to various reasons such as renal insufficiency or diastolic dysfunction).[4,158] Transpulmonary gradient < 12 mm Hg suggests pulmonary venous hypertension, not true portopulmonary hypertension, thus, does not warrant MELD/PELD exception.[4]

In those with POPH MELD exception granted from 2006 to 2014 (n = 190), the waitlist mortality was 7.0%.[159] At the time of transplant, mPAP that ranges between 35 and 43 mm Hg, with therapy and normal PVR, does not appear to be associated with adverse outcomes.[160] That study did include POPH patients who qualified for MELD exception and otherwise had normalization of PVR and RV function with treatment, but did not meet the mPAP criteria (<35 mm Hg).[160] Continued high mPAP pressure was attributed to treatment-induced improvement in flow, as opposed to obstruction in flow, a favorable effect of therapy.

Recommendations

49. MELD exception should be considered in correctly diagnosed POPH patients with at least moderate hemodynamic severity (baseline mPAP > 35 mm Hg), if PA targeted therapy results in mPAP less than 35 mm Hg and PVR less than 400 dynes/s per cm^{-5} (1C).
50. MELD exception can be considered if treated POPH does not reduce mPAP to less than 35 mm Hg, but there is normalization of PVR (<240 dynes/s per cm^{-5}) and RV function (2C).

Intraoperative Issues

Until the mid-2000s, it was not uncommon to first diagnose POPH (65% in 1 retrospective series) in the operating room.[151] With advent of screening TDE and pretransplant practice guidelines, such an event is now uncommon.[4,148,160]

Pulmonary artery catheter placement/monitoring before the abdominal incision is the usual standard of care. Cancellation of cases in the OR occurs most commonly when mPAP is greater than 50 mm Hg or when acute therapy fails to reduce mPAP to less than 40 mm Hg and normal PVR. Under those circumstances, further management has been needed to initiate or modify PA targeted therapy. Outcomes in such circumstances have been unpredictable.[161,162]

Pulmonary artery–targeted therapy should be continued through the transplant procedure. Major changes in pulmonary hemodynamics with reperfusion remain a clinical challenge.[16] There is an unpredictable increase in CO (5-18% and even larger at times) causing additional strain on a preexisting stressed RV.[163,164] The intraoperative management of the POPH patient may be aided by using TEE to assess RV function throughout the procedure.[164] The time of reperfusion is extremely critical because the reperfusion syndrome that is seen in 30% of liver transplants can result in an acute rise in PA pressures and may precipitate acute RV failure leading to graft congestion and failure.[164] Under those circumstances, a variety of interventions have been reported including the use of inhaled nitric oxide, intravenous prostacylin, milrinone, and ECMO.[165-169] The development of pulmonary thromboembolism during liver transplant is uncommon (4%), presenting with cardiac arrest (75%), occurring after reperfusion (85%), and is associated with increased PA pressures and a 20% intraoperative mortality.[170] Intuitively, right ventricular assist devices are not advised due to the potential for PA rupture and immediate death.

Recommendations

51. PA catheter monitoring should be conducted prior to and during LT in all adult cases (1C).
52. Intraoperative, pre-abdominal incision mPAP ≥ 35 mm Hg should be assessed with CO, PAWP, and PVR measurements (2C).
53. If mPAP exceeds 45 to 50 mm Hg before abdominal incision, deferment of LT is advised while assessment of RV function and reversibility of the POPH is made (1C).

TABLE 2.

Liver transplant outcomes in the setting of moderate to severe POPH

Outcomes	References[a]
• POPH waitlist mortality	150, 174, 175
• Case canceled in operating room due to pulmonary artery pressures	88, 155, 161[b], 162[b]
• Intraoperative death	52[b], 57, 59, 151
• Transplant hospitalization death due to RV failure	78, 112, 148, 152, 155, 157
• Post-LT POPH	
○ POPH resolved/PAT discontinued	77, 112, 148, 152, 155, 157
○ POPH improved/PAT continued	77, 78, 84, 149, 173, 176, 177
○ POPH progressive despite PAT	147, 155
• Late death due to POPH (RV failure)	59, 155
• Late death not due to POPH	57, 78, 155, 173
• De novo PAH post-LT	172

[a] Most references selected are small series since 2002 in which N ≥ 3 POPH cases were described.
[b] Single case reports selected because of thorough hemodynamic/clinical description.
PAT, pulmonary artery targeted therapy (ie, medications in the prostacyclin, endothelin receptor antagonist, and phosphodiesterase inhibitor families).

54. PA targeted therapy should be continuously administered during LT (1C).
55. TEE should be readily available for RV monitoring in the setting of POPH (1C).
56. Especially during reperfusion, inhaled nitric oxide or intravenous milrinone can be used to enhance pulmonary vasodilation (2C).
57. ECMO can be used if an acute rise in mPAP occurs at reperfusion and RV dysfunction occurs (2C).
58. Right ventricular assist devices should not be used in POPH due to potential for PA rupture (2C).

Posttransplant/Intensive Care Unit Issues/Outpatient Follow-Up

Unless clinically indicated, major changes in pulmonary hypertension medications are not advised immediately post-LT.[171] Portopulmonary hypertension monitoring is usually accomplished by serial TDE at varying intervals post-LT, usually every 4 to 6 months. Repeat RHC is not routinely advised unless such data will facilitate PA-targeted therapy changes. Weaning from these medications can be safely accomplished by monitoring serial TDE.[77,78,84] No controlled studies have addressed the process of weaning from pulmonary vascular–targeted therapy for POPH post LT. As a caveat, de novo development of PAH post-LT has been reported in patients after LT in both adults and children.[172]

Recommendation

59. PA-targeted therapy should be continued in the immediate post-LT period unless contributing to hemodynamic instability (1C).

Expected Outcomes

No controlled, prospective trials have addressed long-term, post-LT outcomes in the setting of POPH. Single institution experiences have reported that 29% to 64% of moderate to severe POPH patients (n = 39) who were dismissed post-LT have been able to discontinue PA-targeted therapy over varying time.[57,77,78,84,173] Transthoracic Doppler echocardiography follow-up over time has demonstrated normal RV size and function, suggesting a hemodynamic cure of POPH with pre-LT therapies and LT.[57,77,84] The spectrum of POPH outcomes waiting for and after LT, have recently been reviewed and are summarized in Table 2.[62]

In the early LT experience, 1 multicenter database described 35% transplant hospitalization mortality with 5 intraoperative deaths and 8 post-op deaths. Only 1 patient had pre-LT treatment with prostacyclin.[151] Recent post-LT survival data for POPH MELD exception patients have been reported in over 4 different periods since 2002.[150,159,174,175] Waitlist mortality ranged from 7.0% to 10.3%; 1- and 3-year post-LT survivals ranging from 86.4% to 64.0%. Portopulmonary hypertension MELD exception patients had worse (within 1 year) adjusted post-LT mortality/graft failure compared with non-POPH, no-exception patients.[175] Although the experience is limited, successful outcomes after living donor LT[176,177] and multiorgan transplantation for portopulmonary hypertension have been reported.[178-180] An overall summary comparing HPS to POPH is provided in Table 3.

Recommendations

60. POPH PA targeted therapies should be weaned, rather than stopped abruptly (1C).
61. TDE should be conducted every 3 months to guide weaning decisions (2C).
62. Post-LT RHC is not routinely advised unless clinically indicated (2C).
63. POPH counseling should emphasize higher LT risk, regardless of hemodynamics (1B).

PART V. SUGGESTIONS FOR FUTURE CLINICAL RESEARCH

1. Update MELD exception criteria for HPS and POPH:
   a. HPS—indexed by duration and degree of hypoxemia;
   b. POPH—indexed by calculated MELD, PVR, and RV function.

TABLE 3.

Clinical distinctions between HPS and POPH

Parameter	HPS	POPH
Genetic predisposition	Documented	Documented
Screening advised	Yes	Yes
Correlation with liver disease severity	No	No
Adults and pediatrics	Yes	Pediatrics, uncommon
Lung biopsies needed for diagnosis	No	No
ABG required for diagnosis	Yes	No
RHC required for diagnosis	No	Yes
Pulmonary hypertension	High flow only	Flow obstruction
Severe hypoxemia (PaO_2 < 50 mm Hg)	Common	Rare
Right heart failure	Not reported	Well described
Randomized drug studies	None done	In progress
Poor 5-y survival if not treated	Yes	Yes
Indication for liver transplant	Yes	No
Resolution after liver transplant	Common	Variable

2. Formalize HPS/POPH phenotyping and multicenter data collection, including biologic samples.
   a. Develop a multicenter HPS and POPH registry;
   b. Consider/study a lower cutoff of the PVR definition used for POPH;
   c. Develop prognostic risk scores for HPS and POPH based on hepatic dysfunction severity, coexistent lung conditions, oxygenation, and hemodynamics.
3. Initiate prospective, multicenter drug studies.
   HPS: angiogenesis inhibitors;
   POPH: endothelin receptor antagonists/growth factor inhibitors/estrogen blockers and prostacyclin receptor agents (Table 3).

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