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REVIEW

# Pulmonary Complications in Chronic Liver Disease

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**The association of chronic liver disease with respiratory symptoms and hypoxia is well recognized. Over the last century, three pulmonary complications specific to chronic liver disease have been characterized: hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH), and hepatic hydrothorax (HH). The development of portal hypertension is fundamental in the pathogenesis of each of these disorders. HPS is the most common condition, found in 5%-30% of cirrhosis patients, manifested by abnormal oxygenation due to the development of intrapulmonary vascular dilatations. The presence of HPS increases mortality and impairs quality of life, but is reversible with liver transplantation (LT). POPH is characterized by development of pulmonary arterial hypertension in the setting of portal hypertension, and is present in 5%-10% of cirrhosis patients evaluated for LT. Screening for POPH in cirrhosis patients eligible for LT is critical since severe POPH is a relative contraindication for LT. Patients with moderate POPH, who respond adequately to medical therapy, may benefit from LT, although sufficient controlled data are lacking. HH is a transudative pleural effusion seen in 5%-10% of cirrhosis patients, in the absence of cardiopulmonary disease. Diagnosis of HH should prompt consideration for LT, which is the ultimate treatment for HH. Conservative management includes salt restriction and diuretics, with thoracentesis and transjugular intrahepatic portosystemic shunt (TIPS) as second-line therapeutic options. (HEPATOLOGY 2014;59:1627-1637)**

## Hepatopulmonary Syndrome

The hepatopulmonary syndrome (HPS) is defined by an oxygenation defect caused by the development of intrapulmonary vascular dilatation (IPVD) in patients with either advanced liver disease and/or portal hypertension. Impaired oxygenation in HPS is reflected by a widened age-corrected alveolar-arterial oxygen gradient ($P[A\text{-}a]O_2$) on room air, with or without hypoxemia.[1] Cirrhosis, irrespective of the underlying cause, is the most common hepatic condition associated with HPS. However, HPS may also develop in noncirrhotic portal hypertension and ischemic hepatitis.[2,3] HPS may occur in patients with coexisting cardiopulmonary conditions and further exacerbate existing respiratory symptoms and hypoxemia in these patients.[4]

### *Pathogenesis*

The appearance of IPVD underlies the development of HPS. This vascular abnormality consists of diffuse or localized dilated abnormal pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications which result in impaired oxygenation of venous blood as it passes through the pulmonary circulation.[5] Nitric oxide (NO), a potent vasodilator, has been linked to IPVD. Increased levels of exhaled NO derived from the lung are seen in cirrhosis patients with HPS, which normalize after liver transplantation (LT).[6]

Chronic common bile duct ligation in the rat results in biliary cirrhosis, and recapitulates the physiologic changes of human HPS. The majority of what is

*Abbreviations: ABG, arterial blood gas; CTEE, contrast-enhanced transesophageal echocardiography; CTTE, contrast-enhanced transthoracic echocardiography; $CX_3CL1$, fractalkine; DLCO, diffusion capacity for carbon monoxide; eNOS, endothelial nitric oxide synthase; ERA, endothelin receptor antagonist; ET-1, endothelin-1; HH, hepatic hydrothorax; HPS, hepatopulmonary syndrome; iNOS, inducible nitric oxide synthase; IPVD, intrapulmonary vascular dilatation; LT, liver transplantation; NO, nitric oxide; MAA, technetium-labeled macroaggregated albumin; MELD, model for end-stage liver disease; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; $P[A\text{-}a]O_2$, alveolar-arterial oxygen gradient; $PaO_2$, partial pressure of oxygen; PAOP, pulmonary artery occlusion pressure; POPH, portopulmonary hypertension; PMN, polymorphonuclear cell count; PVR, pulmonary vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SBPL, spontaneous bacterial pleuritis; SBP, spontaneous bacterial peritonitis; SPAG, serum-to-pleural fluid albumin gradient; $SpO_2$, oxygen saturation; TPG, transpulmonary pressure gradient; UNOS, United Network for Organ Sharing; VATS, video assisted thoracoscopy.*

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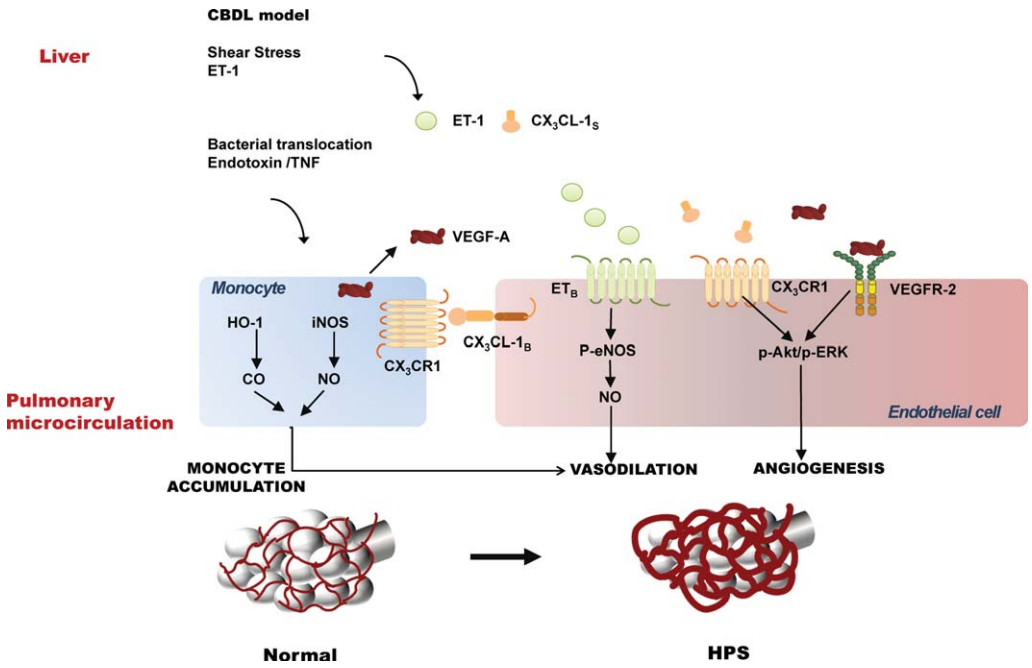


Fig. 1. Pathophysiology of hepatopulmonary syndrome. The salient features of experimental HPS induced by CBDL cirrhosis are pulmonary microvascular alterations including vasodilation, intravascular monocyte accumulation, and angiogenesis. Pulmonary vasodilation is induced by excessive NO production through ET-1/$ET_B$-driven eNOS activation and iNOS induction in intravascular monocytes, in addition to the increased CO production (caused by altered levels of HO-1) in monocytes. Moreover, monocytes bind to the pulmonary vasculature producing growth factors such as VEGF-A, which contribute to angiogenesis by activating angiogenic signaling pathways including Akt and ERK in endothelial cells. $CX_3CL1/CX_3CR1$ signaling contributes to this monocyte accumulation and angiogenesis. Akt, protein kinase B; CBDL, common bile duct ligation; CO, carbon monoxide; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated protein kinase; ET-1, endothelin-1; $ET_B$, endothelin B receptor; HPS, hepatopulmonary syndrome; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TNF-$\alpha$, tumor necrosis factor alpha; VEGF-A, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor; $CX_3CL\text{-}1_B$, chemokine fractalkine membrane bound; $CX_3CL\text{-}1_S$, chemokine fractalkine soluble; $CX_3CR1$, Chemokine fractalkine receptor.

known about the pathophysiology of HPS is derived from this experimental animal model. In common bile duct ligated rats increased activity of both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) in the pulmonary microvasculature are found.[7] Increased hepatic production of endothelin-1 (ET-1) and tumor necrosis factor alpha and release of ET-1 are key mechanisms that drive NOS activation.[8] ET-1 enhances activation of eNOS and contributes to monocyte accumulation through endothelin B receptor overexpression in the pulmonary vascular endothelium, likely in response to shear stress.[9,10] Bacterial translocation and endotoxemia also contribute to the accumulation of macrophages in the pulmonary microvasculature.[11,12] Endothelial activation of the fractalkine ($CX_3CL1$) chemokine in the lung may be a common pathway for monocyte adherence in the pulmonary microcirculation.[11,13] Monocytes express iNOS and also produce heme oxygenase-1, leading to increased carbon monoxide production, further augmenting vasodilatation.[14]

More recently, pulmonary angiogenesis has been recognized as an important contributor to pulmonary vascular alterations in experimental HPS. Both vascular endothelial growth factor A, produced in part by activated intravascular monocytes, and increased $CX_3CL1$ production contribute to angiogenesis.[13,15] Moreover, single nucleotide polymorphisms in genes involved in the regulation of angiogenesis are associated with the risk of HPS in cirrhosis patients.[16] Figure 1 summarizes our current understanding of the pathophysiology of HPS.

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### *Epidemiology and Natural History*

IPVD is detected by echocardiography in 50%-60% of cirrhosis patients undergoing LT evaluation. The majority of these patients have normal gas exchange and do not meet diagnostic criteria of HPS, suggesting that mild IPVD, insufficient to alter gas exchange, is common in cirrhosis patients.[17] Moreover, it is not clear what drives a subset of patients with IPVD to develop HPS, since many patients with IPVD may have stable oxygenation over time.[18]

The prevalence of HPS reported in cirrhosis patients undergoing LT evaluation ranges from 5%-30%.[19-21] The natural history of HPS is not clear, although small cohort studies describe worsening oxygenation over time.[18,20] Most important, HPS is associated with a significant adverse effect on survival and impaired quality of life.[19-21] In a large prospective multicenter cohort study conducted in patients undergoing LT evaluation, mortality was doubled in cirrhosis patients with HPS compared to non-HPS cirrhosis patients, independent of age, model for endstage liver disease (MELD) score, hypoxemia, and comorbidities.[21] In retrospective series mortality in HPS has been associated with the degree of hypoxemia.[19,20,22]

### *Clinical Presentation*

HPS is more common in Caucasians than in Hispanics and African Americans, and less common in smokers.[21] Patients with HPS may present with the insidious onset of dyspnea or even be completely asymptomatic during the early stage. Dyspnea upon standing (platypnea) and hypoxemia exacerbated in the upright position (orthodeoxia) are present in almost 25% of HPS patients and are attributed the predominance of the IPVD in the lung bases, and the increase in the blood flow through these regions when upright. Significant sleep-time oxygen desaturation may occur in patients with HPS, even if daytime hypoxemia is moderate.[23] Patients with severe HPS may display digital clubbing and cyanosis.

Chest radiographs may be normal or show bibasilar nodular or reticulonodular opacities, reflecting diffuse vascular pulmonary dilation.[24] Pulmonary function tests typically demonstrate a reduced diffusion capacity for carbon monoxide (DLCO).[25]

### *Diagnosis*

Diagnosis of HPS requires both the demonstration of IPVD and abnormal arterial gas exchange in the absence of significant intrinsic pulmonary disease. In the presence of coexisting pulmonary disease, further testing is required to assess the contribution of HPS to gas exchange abnormalities.

Arterial blood gas (ABG) measurement allows the calculation of the $P[A\text{-}a]O_2$ in HPS patients. Standard criteria for the diagnosis of HPS in adults <65 years include either a $P[A\text{-}a]O_2 \geq 15$ mmHg or a decreased partial pressure of oxygen ($PaO_2$) <80 mmHg, while breathing room air at sea level. For adults ≥65 years a $P[A\text{-}a]O_2 \geq 20$ mmHg cutoff is used.[1,26] Severity of HPS can be categorized by the degree of hypoxemia as mild ($PaO_2 \geq 80$ mmHg), moderate ($PaO_2$ 60-79 mmHg), severe ($PaO_2$ 50-59 mmHg), and very severe ($PaO_2 < 50$ mmHg).[1]

Pulse oximetry indirectly measures oxygen saturation ($SpO_2$) in a noninvasive fashion. A recent prospective study of patients undergoing LT evaluation found that $SpO_2$ <96% was highly sensitive (100%) and specific (88%) for detecting all HPS patients with a $PaO_2$ of <70 mmHg, limiting ABG testing to only 14% of the cohort.[27] Serial $SpO_2$ measurements may be a useful approach to monitor impaired oxygenation over time in patients with HPS.[18]

Contrast-enhanced transthoracic echocardiography (CTTE) is the most sensitive test for detecting IPVD in adults. CTTE is typically performed by injecting agitated saline intravenously during routine transthoracic echocardiography, producing sonographically visible microbubbles. These microbubbles are visualized in the right ventricle within seconds of administration, and in the absence of right to left shunt, the microbubbles are absorbed at the alveoli. IPVD is characterized by the delayed appearance of the microbubbles in the left cardiac chambers 3-6 cardiac cycles after injection.[17] Contrast-enhanced transesophageal echocardiography (CTEE) may increase the sensitivity of detecting IPVD by directly detecting microbubbles emanating from the pulmonary veins. However, CTEE is more invasive and expensive and is not routinely needed.[28]

Radionuclide lung perfusion scan using technetium-labeled macroaggregated albumin (MAA) particles is another method for detecting IPVD. During MAA scanning, particles of 20-50 $\mu$m in size of MAA are injected intravenously, lodging in the pulmonary microvasculature of healthy individuals.[29] In HPS patients, MAA particles escape through the abnormal pulmonary capillaries and stay in downstream capillary beds supplied by systemic arteries, such as the brain, kidneys, and spleen. Quantitative imaging of the MAA particles distribution in the brain and lung allows the calculation of the degree of shunting.[30] The MAA scan is less sensitive than CTTE, does not distinguish intracardiac from intrapulmonary shunting, and has not been properly standardized, making it a less useful screening test for IPVD.[17] The MAA scan may be a complementary tool to CTTE in two specific

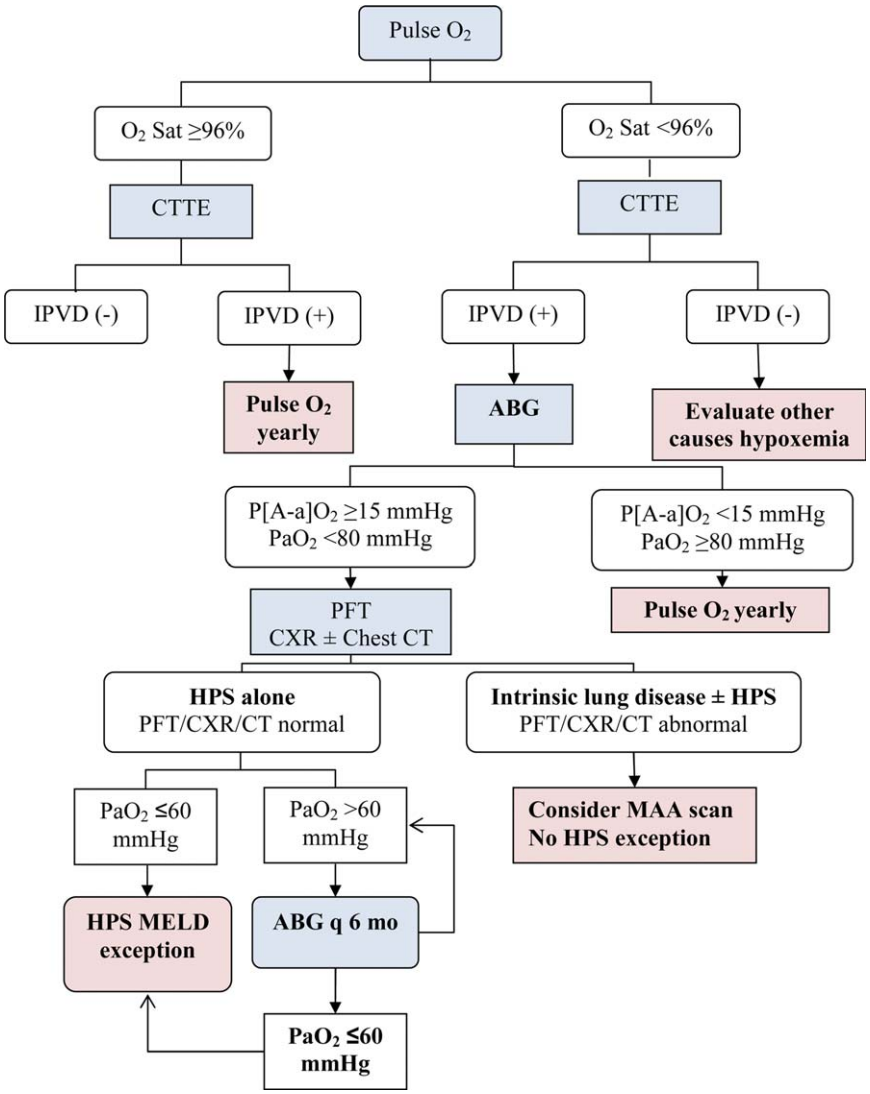


Fig. 2. Screening and treatment for HPS in LT candidates. Pulse $O_2$: pulse oximetry; $O_2$ Sat: oxygen saturation; CTTE: contrast-enhanced transthoracic echocardiography; IPVD: intrapulmonary vascular dilatation; ABG: arterial blood gas; P[A-a]$O_2$: alveolar-arterial oxygen gradient; $PaO_2$: partial pressure of oxygen; PFT: pulmonary function tests; CXR: Chest X Ray; CT: Computed tomography; HPS: hepatopulmonary syndrome; MAA: macroaggregated albumin; MELD: model for endstage liver disease; mo: months.

scenarios. First, in patients with coexistent HPS and intrinsic lung disease with severe hypoxemia ($PaO_2$ <60 mmHg), an elevated MAA shunting (>6%) supports that HPS is the major contributor to hypoxemia.[22] Second, a large MAA shunt (>20%) detected in patients with very severe HPS ($PaO_2$ <50 mmHg) has been associated with high mortality after LT.[31] Angiography is a more invasive test for the detection of IPVD, but is not clinically useful for diagnosing HPS.

Diagnosis of severe HPS ($PaO_2$ <60 mmHg) during LT evaluation is particularly important, given that HPS influences LT candidacy, listing priority and requires special management before and after LT. One study showed cost-effectiveness of pulse oximetry screening for HPS in LT candidates, followed by CTTE and ABG based on results.[32] Figure 2 illustrates a proposed algorithm employing pulse oximetry for HPS screening in LT candidates.

### *Medical Therapy*

There is no established medical therapy currently available for HPS. In patients with $PaO_2$ <60 mmHg at rest or with exertion, the administration of supplemental oxygen is appropriate, since chronic hypoxemia itself may contribute to the mortality in HPS.[19,20] Administration of garlic has resulted in improvement in the $PaO_2$ in two uncontrolled trials and a small randomized study.[33] No study has explored whether ET-1 receptor antagonist or angiogenesis inhibitors are clinically useful in HPS patients.

A number of case reports and series have evaluated the effect of transjugular intrahepatic portosystemic shunt (TIPS) in HPS. No recommendation for TIPS to treat HPS can be made based on the limited data available.[34]

### *Liver Transplantation*

LT is an effective therapy for HPS, resulting in complete resolution or significant improvement in gas

exchange in over 85% of patients with severe hypoxemia.[20,35,36] During the pre-MELD era, a prospective study found that the strongest predictor of mortality was a preoperative $PaO_2$ of $\leq$50 mmHg, particularly in combination with an MAA shunt fraction $\geq$20%, where mortality was increased 7.5-fold relative to patients with less severe HPS.[31]

In 2007, the United Network for Organ Sharing (UNOS) recommended assigning a MELD score of 22 for the initial application of patients with severe HPS ($PaO_2$ <60 mmHg), with further increases every 3 months, to balance pre- and post-LT outcomes between HPS and non-HPS candidates. In the largest retrospective single-center series encompassing MELD implementation, patients with HPS had a 5-year survival rate of 67% after LT during the pre-MELD era, which improved to 88% in the post-MELD era, a rate comparable to cirrhosis patients without HPS undergoing LT during the post-MELD era.[37] Moreover, analysis of the UNOS database and a second recent single-center retrospective post-MELD era series found that selected patients with very severe HPS did not have worse survival after LT.[36,38] These findings may reflect recent improvements in the perioperative management of HPS patients and suggest that carefully selected patients with very severe HPS may be LT candidates. However, the early detection of HPS in potential LT candidates and the regular assessment of the severity of hypoxemia in those with HPS listed for LT are critical to facilitate LT prior to the occurrence of very severe hypoxemia.

## Portopulmonary Hypertension

Portopulmonary hypertension (POPH) is characterized by pulmonary arterial hypertension (PAH) that occurs in the setting of portal hypertension, with or without advanced liver disease.[26] POPH was defined by the European Respiratory Society/US Consensus Group in 2004 based on hemodynamic parameters measured during right heart catheterization (RHC), which include mean pulmonary artery pressure (mPAP) of >25 mmHg, pulmonary artery occlusion pressure (PAOP) of <15 mmHg, and pulmonary vascular resistance (PVR) of >240 dyn/s/cm$^{-5}$ in patients with documented portal hypertension.[1,26]

The two largest series of POPH patients in LT candidates published in the U.S. found an estimated prevalence of 5.3%-8.5%.[39,40] Female sex and a diagnosis of autoimmune hepatitis are risk factors for POPH.[41] The severity of POPH does not correlate with the degree of liver dysfunction or the severity of portal hypertension.[39,41]

### *Pathophysiology*

The pathophysiology of POPH is not fully understood, partly due to the absence of an animal model of POPH and the low prevalence of the condition. Most of the knowledge about pathogenesis is derived from the study of PAH. The histopathology of POPH is similar to idiopathic PAH, and is triggered by vascular injury reflected by the development of plexiform arteriopathy, concentric intimal fibrosis, and proliferation and muscularization of the pulmonary arterioles.[42] However, germline mutations in the bone morphogenetic protein receptor type 2, a member of the transforming growth factor $\beta$ signaling family, and genetic alterations in serotonin transport, which have been implicated in familial and idiopathic PAH, are not found in POPH.[43,44]

In a recent case-control study POPH was associated with female sex, single nucleotide polymorphisms in genes involved in estrogen metabolism (estrogen receptor-1, aromatase), and elevated circulating estrogen levels, supporting a potential role for sex hormones in POPH pathogenesis.[43] Deficiency in endothelial prostacyclin synthase, causing platelet dysfunction and elevated ET-1 levels, has also been described in PAH patients.[45] The favorable effect of prostacyclin inhibitors has been linked to this mechanism.

Finally, the development of POPH several years after surgically created portocaval shunts described decades ago may also contribute to the development of POPH.[46] Animal models of PAH have shown an additive effect of increased pulmonary blood flow to the underlying vascular injury of PAH, similar to that caused by portocaval shunts in POPH, inducing severe pulmonary vascular remodeling.[42] More recently, the presence of large portosystemic shunts (>10 mm diameter) in cirrhosis patients has been linked to the diagnosis of moderate to severe POPH.[47] These observations have led to the hypothesis that significant portal shunting exposes the pulmonary vascular bed to additional shear stress and vasoactive mediators that contribute to pulmonary arterial vasoconstriction and remodeling.

Medical therapies in POPH and PAH are broadly targeted towards the defect in endothelial production of vasodilators or to the changes in tone and remodeling in the vascular wall.

### *Diagnosis and Screening in Cirrhosis*

Initial symptoms of POPH are subtle and patients may remain asymptomatic at the time of diagnosis despite advanced disease.[48] Dyspnea on exertion is the most common initial symptom of POPH and fatigue,

orthopnea, chest pain, peripheral edema, syncope, and dyspnea at rest may develop as the disease progresses.[49,50]

Radiologically, a prominent main pulmonary artery or cardiomegaly may be appreciated in severe cases. Electrocardiographic abnormalities present in POPH include right atrial enlargement, right ventricular hypertrophy, right axis deviation, and/or right bundle branch block.[49] Pulmonary function tests commonly show reduced lung volumes, forced vital capacity, and DLCO. Accentuation of respiratory alkalosis and an increased $P[A\text{-}a]O_2$ with mild hypoxemia may be seen on ABG testing in POPH.[50]

Estimation of right ventricular systolic pressure (RVSP) using the tricuspid regurgitant jet during Doppler echocardiography correlates well with the mPAP measured by RHC.[51] A single-center study found an estimated RVSP >30 mmHg in 10.3% of LT candidates, 59% of whom had documented POPH by RHC (sensitivity 100%, specificity 96%).[48] Additional studies using an estimated RVSP ≥50 mmHg as a threshold for RHC in LT candidates identified elevated values in 8.2% of patients, of whom 65% met the criteria for POPH on RHC (sensitivity 97%, specificity 77%) for detection of moderate POPH.[39,51] However, different techniques are used for RVSP estimation and the optimal cutoff for estimated RVSP in LT candidates to warrant RHC has not been agreed upon. Nonetheless, POPH screening is recommended in all cirrhosis patients undergoing LT evaluation, since POPH may influence LT candidacy.[52] Figure 3 depicts a proposed algorithm for the screening and management of POPH for cirrhosis patients undergoing LT evaluation.

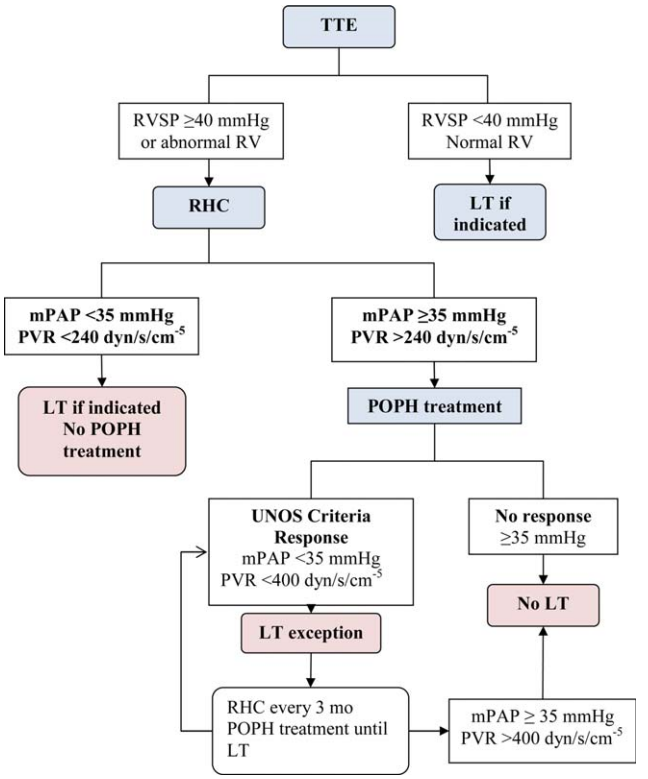


Fig. 3. Screening and treatment for POPH in LT candidates. TTE: transthoracic Doppler echocardiography; RVSP: right ventricular systolic pressure; RV: right ventricle; RHC: right heart catheterization; LT: liver transplantation; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; POPH: portopulmonary hypertension; UNOS: United Network for Organ Sharing; mo: months.

### *Pulmonary Hemodynamics in Liver Disease*

Two specific hemodynamic patterns distinct from the found on RHC in patients with POPH are also seen in a subset of cirrhosis patients with elevated estimated RVSP and elevated mPAP. First, up to 35% of such patients have changes reflecting the hyperdynamic circulation of cirrhosis with both elevated cardiac output and mPAP, but with normal PVR. However, these patients do not appear to be at risk for adverse outcomes with LT.[39,48] A second group of up to 15% of cirrhosis patients with high estimated RVSP has evidence of volume overload (elevated mPAP and PAOP, normal or mild increase in PVR) which has been associated with cirrhotic cardiomyopathy and chronic renal insufficiency.[39]

Calculation of the transpulmonary pressure gradient (TPG), equivalent to mPAP minus PAOP, is useful to identify patients with POPH when the PAOP is elevated (TPG >12 mmHg).[53] Table 1 illustrates these common hemodynamic patterns seen during RHC among patients with elevated RVSP.

### *Survival and Medical Treatment*

Long-term survival is poor among patients with POPH without pharmacological therapy, with an estimated 14% 5-year survival.[54] Mortality in POPH may be related to either complications of cirrhosis or to right-sided heart failure. Medical treatment has been increasingly used in POPH, although no randomized controlled studies are available in this setting. Three different classes of vasomodulators, which specifically target the aberrant structural and regulatory changes in the pulmonary vascular wall, have been used in the management of POPH, based mainly on clinical experience in PAH.

***Prostacyclin Analogs (Prostanoids).*** Epoprostenol, a potent pulmonary and systemic vasodilator and platelet aggregation inhibitor, causes clinical improvement and is the only therapy that improves survival in PAH. Several studies support that epoprostenol infusion in

**Table 1. Hemodynamic Patterns on Right Heart Catheterization in Cirrhosis Patients With Elevated RVSP on Echocardiogram**

| Hemodynamic pattern | Mean Pulmonary Artery Pressure (mPAP) | Pulmonary Vascular Resistance (PVR) | Pulmonary Artery Occlusion Pressure (PAOP) | Cardiac Output (CO) |
|---|---|---|---|---|
| Hyperdynamic circulation | ↑ | ↑ | ↑ | ↑ |
| Pulmonary venous hypertension | ↑ | ↔ ↑ | ↑ | ↑ |
| Portopulmonary hypertension | ↑ | ↑ | ↑ | ↑ Mild ↓ Severe |

Adapted from reference 79.

POPH improves mPAP, PVR, and exercise capacity.[39,55] A number of complications of intravenous epoprostenol including central venous catheter thrombosis, infection, infusion, and pump failure limit widespread use. Two newer prostacyclin analogs, subcutaneous treprostinil and inhaled iloprost, are easier to administer and are potential alternatives to intravenous epoprostenol.[56]

***Endothelin Receptor Antagonist (ERA).*** Orally administered ERAs are the most commonly used drugs in POPH. Bosentan is a dual ERA showing 20:1 ET-A/ET-B receptor selectivity, which improves pulmonary hemodynamics and exercise tolerance.[56] However, concerns regarding the risk of hepatotoxicity in advanced cirrhosis have been raised. Ambrisentan, a selective ERA with a 100:1 ET-A/ET-B selectivity, improves mPAP and PVR in POPH without documented hepatotoxicity.[57] The ambrisentan side effect profile includes nasal congestion, peripheral edema, and headaches. Both drugs have been approved by the U.S. Food and Drug Administration for the management of PAH.

***Phosphodiesterase-5 Inhibitors.*** Sildenafil has been used in POPH with improvement in the 6-minute walk test, cardiac output, and decreased mPAP and PVR without serious adverse effects.[58] Longer-acting agents such as tadalafil and vardenafil have also been used in POPH, based on favorable long-term safety data in PAH and convenient oral dosing.[59]

Orally administered ERA such as ambrisentan and long-acting phosphodiesterase-5 inhibitors such as vardenafil or tadalafil are the agents of choice in patients with moderate PAH and POPH due to ease of administration and a benign side effect profile. These agents could be used in combination. Epoprostenol, the most potent agent, is often reserved as initial therapy for those with more severe POPH due to the challenges associated with administration and the potential for more serious side effects. Medical therapy is generally assessed by measuring exercise tolerance using the 6-minute walk test and serial echocardiography with repeat RHC done at intervals to confirm the response in pulmonary hemodynamics before consideration of MELD exception in selected cases.

A single short-term study in patients with moderate to severe POPH found that the use of $\beta$-blockers was associated with worsening exercise capacity.[60] Discontinuation of $\beta$-blockers improved cardiac output with no effect on mPAP, resulting in a net decrease in PVR. Based on these findings, the use of $\beta$-blockers for management of varices in patients with moderate to severe POPH should be approached with caution.

### *Liver Transplantation*

Retrospective studies have found that the presence of moderate to severe POPH (mPAP >35 mmHg) is associated with increased mortality following LT. In those with an mPAP >50 mmHg, LT is contraindicated, as perioperative mortality approaches 100%.[52] Recent case series using newer medical regimens have reported favorable short-term LT outcomes in patients with moderate POPH who respond to medical therapy by achieving mPAP <35 mm Hg as long as the PVR becomes <400 dyn/sec/cm$^{-5}$ prior to surgery.[35,61] A small subset of these patients has been able to discontinue therapy for POPH following LT. Current UNOS policy allows MELD exception for POPH granting a MELD score of 22 for POPH patients whose baseline mPAP $\geq$35 mmHg, provided there is documentation of post-vasodilator treatment response by RHC with mPAP <35 mmHg and PVR <400 dyn/sec/cm$^{-5}$ and normal right ventricular function. MELD score may increase every 3 months only if RHC shows both mPAP and PVR remaining within the target range.[39,53]

## Hepatic Hydrothorax

Hepatic hydrothorax (HH) is a complication of portal hypertension, characterized by a transudative pleural effusion in the absence of underlying cardiac or pulmonary disease. Its prevalence has been estimated to be 5%-10% in cirrhosis patients, based on

retrospective observational data.[62] In the largest published series, HH was identified in 15.3% of patients with cirrhosis,[63] but only 6.5% of these patients required thoracentesis.

### *Pathophysiology*

The presence of portal hypertension is the key factor in the development of ascites and HH in cirrhosis. A subset of patients with ascites develops preferential passage of ascitic fluid from the peritoneal into the pleural cavity resulting in HH. The most important mechanism leading to the passage of ascitic fluid from the peritoneal into the pleural cavity is the presence of diaphragmatic defects. These defects were corroborated by showing the passage of $^{99m}$Tc-human albumin from the abdomen into the pleural cavity, even in the absence of underlying ascites.[64] Most diaphragmatic defects, also referred to as pleuroperitoneal communications or blebs, are <1 cm in size and are predominantly located on the right hemidiaphragm.[65] Malnutrition in cirrhosis is thought to contribute to thinning of the diaphragmatic muscle and to the development of these defects. In addition, negative intrathoracic pressure is believed to contribute to the one-way directional flow of ascitic fluid from the abdominal cavity.

### *Clinical Presentation and Diagnosis*

HH is the most common cause of pleural effusions in cirrhosis. HH is right-sided in 70% of cases, left-sided in 18%, and bilateral in 12%.[62] The pleural cavity is a restricted space and symptoms often develop with smaller volumes of fluid (~500 mL) than what are found in the peritoneal space.

HH usually presents with respiratory symptoms including cough, dyspnea, chest discomfort, hypoxia, and in the most severe cases respiratory failure. Ascites is detectable in over 80% of those with HH, but is not required for diagnosis.[64,66] Chest radiography is used to confirm the presence of a pleural effusion and thoracentesis is typically required for the initial diagnosis of HH. Imaging studies to document that fluid is passing from the peritoneal space into the pleural space are rarely used in clinical practice.[64]

One retrospective series found that 70% of pleural effusions in a cohort of cirrhosis patients were due to uncomplicated HH, 15% were due to infected HH, and 15% were due to causes other than liver disease. In addition, 80% of right-sided pleural effusions were found to be uncomplicated HH, while only 35% of left-sided pleural effusions were uncomplicated HH.[67] Thoracentesis is indicated to identify the underlying cause of pleural fluid accumulation, to ascertain the presence of infection in the fluid, and to provide symptomatic relief.

**Table 2. Diagnostic Criteria for Hepatic Hydrothorax**

| |
|---|
| Uncomplicated Hepatic Hydrothorax |
| • Pleural Fluid Analysis |
| • Serum-to-pleural fluid albumin gradient (SPAG) >1.1 |
| • Pleural fluid total protein <2.5 g/dL or Pleural fluid/serum total protein ratio <0.5 |
| • Pleural fluid/serum lactate dehydrogenase ratio<0.6 |
| • Polymorphonuclear (PMN) cell count <250 cells/mm$^3$ |
| Spontaneous Bacterial Pleuritis - Diagnostic Criteria |
| • PMN >250 cells/mm$^3$ and positive pleural fluid culture OR |
| • PMN >500 cells/mm$^3$ and negative pleural fluid culture AND |
| • Absence of pneumonia or contiguous infection on chest imaging |

Adapted from reference 80.

In uncomplicated HH the serum-to-pleural fluid albumin gradient (SPAG) is >1.1, the pleural fluid total protein is <2.5 g/dL, and the polymorphonuclear cell count (PMN) is <250 cells/mm$^3$ as depicted in Table 2.[66]

### *Spontaneous Bacterial Pleuritis*

Spontaneous bacterial pleuritis (SBPL) results when HH becomes infected in the absence of pneumonia. SBPL is a more appropriate term than the commonly used "spontaneous bacterial empyema," since the presence of pus in the pleural space is not required for its diagnosis. Symptoms in SBPL vary from fever and pleuritic chest pain to subtle worsening of encephalopathy or deteriorating renal function, necessitating a high index of suspicion. A PMN >500 cells/mm$^3$ is diagnostic for SBPL in a pleural effusion, although SBPL with PMN between 250-500 cells/mm$^3$ is documented by positive pleural fluid culture.[68]

SBPL develops in 10%-16% of cirrhosis patients with HH, and is more common in those with low total protein (<1.5 g/dL), low $C_3$ complement levels in pleural fluid, and worse liver disease.[63,69] Over 40% of patients with ascites who develop SBPL do not have concomitant spontaneous bacterial peritonitis (SBP), emphasizing the importance of thoracentesis in such patients when infection is suspected and paracentesis is negative.[68] The microorganisms commonly involved in SBPL are similar to those involved in SBP, as is antibiotic therapy.[63,69] The use of albumin infusion to prevent hepatorenal syndrome has not been studied in SBPL patients. Chest tube placement is contraindicated in SBPL, in the absence of empyema, due to the risk of protein loss, prolonged drainage, secondary infection, and hepatorenal syndrome.[70] Antibiotic prophylaxis after an episode of SBPL is commonly used,

although no study has evaluated its role. Mortality associated with an episode of SBPL is ~20%.[68]

### *Treatment of HH*

The development of HH signals decompensating cirrhosis and should prompt consideration for LT.[71] Medical management of HH is similar to management of ascites. Restriction of sodium intake with the administration of diuretics is effective in controlling HH, although fluid mobilization from the pleural cavity may be slower than from the peritoneal cavity and ~20% of patients develop refractory HH.[72]

***Percutaneous Drainage.*** In patients with concomitant large volume ascites, paracentesis may improve respiratory symptoms and is often performed prior to consideration of thoracentesis.[73] Thoracentesis is used in the management of refractory HH, but is associated with an increased risk of infection, bleeding, and protein loss.[67] Limiting pleural fluid removal to 1-2 L has been recommended to decrease the risk of reexpansion pulmonary edema, although recent data support that larger volumes can be safely removed if no symptoms develop during the procedure and end-expiratory pleural pressure remains below 20 $cmH_2O$.[74] There are no data on whether albumin replacement is beneficial after thoracentesis.

Chest tube placement should be avoided in uncomplicated HH and SBPL due to the association with serious complications including empyema, hemothorax, pneumothorax, and hepatorenal syndrome.[70] In a single-center series of cirrhosis patients undergoing chest tube placement for pleural effusions (41% uncomplicated HH), 80% developed complications and 33% died.[75]

***Invasive Procedures.*** The standard of care treatment for refractory HH is TIPS placement with response rates of 70%- 80%.[72,76] Contraindications for TIPS in HH are similar to those for other indications including severe liver dysfunction, poorly controlled hepatic encephalopathy, right-sided heart failure, pulmonary hypertension, and complete portal vein thrombosis. Risk factors for increased mortality in patients receiving TIPS for HH include elevated baseline creatinine, MELD score >15, and poor response to TIPS.

Video-assisted thoracoscopy (VATS) with pleurodesis is a potential treatment alternative for patients with refractory HH who are not eligible for or who have failed TIPS. One single-center experience found an overall success of 48% in controlling HH, which increased to 60% with surgical closure of the diaphragmatic defect during VATS.[77] A second small series of VATS with talc pleurodesis found resolution of HH in 53% of patients after a single session and 73% after two sessions.[78] However, fluid control with VATS with pleurodesis appears to be inferior to TIPS and has not been evaluated in controlled trials. In addition, significant complications including pleurocutaneous fistula, empyema, and death have been reported following VATS. Therefore, VATS with pleurodesis is best reserved for situations where medical therapy and TIPS are not viable treatment options.

## Summary

Portal hypertension is critical in the appearance of pulmonary complications of chronic liver disease. HPS is the most common one, characterized by IPVD causing impaired oxygenation. Angiogenesis and circulating vasodilators are important pathogenetic mechanisms in HPS. Pulse oximetry and CTTE are complementary screening tests for HPS. HPS is associated with worse survival, which improves dramatically after LT. Pulmonary arterial vasoconstriction and remodeling are the main pathophysiologic events in POPH. Doppler echocardiography is a useful screening modality for POPH detection in LT candidates. Elevated RVSP should prompt RHC to ascertain POPH severity, since LT is contraindicated in severe POPH. Patients with moderate POPH who respond adequately to medical therapy may benefit from LT, although sufficient controlled data are lacking. HH should be suspected in any cirrhosis patient with pleural effusion, and is a valid indication for LT evaluation. SBPL is a serious infection of cirrhosis patients with HH and requires rapid initiation of antibiotic therapy. Diagnostic thoracentesis is mandated if pleural infection is suspected in a cirrhosis patient.

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