Hepatopulmonary syndrome in adults: Prevalence, causes, clinical manifestations, and diagnosis

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INTRODUCTION

Hepatopulmonary syndrome (HPS) is characterized by the triad of abnormal arterial oxygenation caused by intrapulmonary vascular dilatations (IPVDs) in the setting of liver disease, portal hypertension, or congenital portosystemic shunts [1].

The prevalence, causes, clinical manifestations, and diagnostic evaluation of HPS are reviewed here. The natural history, treatment, and outcomes of HPS are discussed separately. (See "Hepatopulmonary syndrome in adults: Natural history, treatment, and outcomes".)

PREVALENCE

Estimates of the prevalence of HPS among patients with chronic liver disease range from 4 to 47 percent (on average one quarter), depending upon the diagnostic criteria, methods used, and population studied [2-13]. As examples:

- In one prospective study of 111 patients with cirrhosis, HPS was reported in 24 percent when transthoracic contrast echocardiography, blood gas analysis, and pulmonary function testing were used for its detection [2].
- In another prospective study of patients with liver cirrhosis, 26 percent had HPS by similar criteria [7].

These data are derived primarily from liver transplantation centers (ie, from patients with severe liver disease). Although HPS can occur in patients with both mild and severe liver disease, observational studies have sometimes reported a correlation between the presence of HPS or degree of HPS-associated shunt and the Child-Pugh classification (table 1) or Model for End-stage Liver Disease (MELD) score (calculator 1) [7,13,14]. This correlation is not consistently identified among studies [15,16]. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Child-Pugh classification' and "Model for End-stage Liver Disease (MELD)".)

ETIOLOGIES AND PATHOGENESIS

Etiology — HPS is most commonly seen in patients with chronic liver disease, particularly those with portal hypertension; these and other causes are listed in the table (table 2) [17-19].

- **Chronic liver disease** – Chronic liver disease (CLD) of virtually any etiology including congenital liver disease that limit venous flow to the lung (eg, cavopulmonary shunt) and Abernethy malformation (congenital portosystemic shunt) [20,21] can be associated with HPS, particularly when CLD is complicated by portal hypertension.

- **Portal hypertension** – HPS is most commonly seen in patients with portal hypertension in association with chronic liver disease but can also occur in those who have portal hypertension without underlying liver disease [22].

Acute liver diseases are rarely associated with HPS. As examples, ischemic or hypoxic hepatitis [23-25] has been associated with HPS, and transient HPS has been reported in a patient with acute hepatitis A [26].

In patients with liver disease, no risk factors other than the presence of portal hypertension are known to predispose to the development of HPS.

HPS may coexist with other pulmonary disease (eg, chronic obstructive pulmonary disease) and, in particular, portopulmonary hypertension, which may aggravate hypoxemia [27].

Pathogenesis — The pathogenesis of HPS has not been clearly delineated. However, several factors have been implicated in the development of HPS (figure 1).

Pathogenic processes that have been proposed include:

- Increased bacterial translocation and toxin release (intestinal endotoxemia) from portal hypertension may stimulate the release of vasoactive mediators including nitric oxide

(NO), heme-oxygenase-derived carbon monoxide, and tumor necrosis factor alpha [28-32]. Such mediators may result in pulmonary vasodilation or angiogenesis [33].

- HPS has been associated with proangiogenic biomarkers (eg, angiopoietin 2, tenascin c, c-KIT, vascular cell adhesion molecule [VCAM] 1, and von Willebrand factor) [32].

- In an HPS model by common bile duct ligation in mice, hypoxemia and intrapulmonary shunting were shown to be mediated by placental growth factor (PIGF), and therapeutic antiplacental growth factor (anti-PIGF) impeded HPS development [34].

- Failure of the damaged liver to clear circulating pulmonary vasodilators, production of circulating vasodilators by the damaged liver, and inhibition of circulating vasoconstrictive substances by the damaged liver have also been proposed.

In support of these processes, preclinical and clinical studies suggest that increased NO and endothelin-1 (ET-1) levels may play a role in pulmonary vasodilatation [28,35-45]:

- In an experimental rat model of HPS (common bile duct ligation), proliferating cholangiocytes produce and secrete ET-1 that binds to an upregulated endothelin beta receptor (ETB) in the pulmonary vasculature, resulting in intrapulmonary vascular dilatations (IPVDs) by increasing the production of NO [34,35]. In a similar animal model, upregulation of endothelial nitric oxide synthase (eNOS) in the intralobar pulmonary arteries, and enhanced eNOS-derived NO production were associated with the development of HPS [39]. The enhanced eNOS-derived NO production may have resulted from pulmonary ETB receptor overexpression and increased circulating ET-1-induced vasodilation [40]. Depletion of pulmonary intravascular macrophages, which are known to generate angiogenic, proliferative, and vasodilatory growth factors, prevented or reversed HPS in a rat model [41]. Experimental models have also implicated the role of angiogenic factors like vascular endothelial growth factor (VEGF) A, platelet-derived growth factor (PDGR), and PIGF [34,46]. On this basis, human trials of a tyrosine kinase receptor inhibitor, sorafenib, which directly targets angiogenic factors, have been undertaken. Other potential beneficial effects of sorafenib include direct mitigation of liver injury and blockage of cholangiocyte proliferation and ET-1 production, thereby decreasing eNOS.

- In humans with HPS, serum NO is elevated and the administration of NO inhibitors (eg, methylene blue) can enhance oxygenation [42,47]. In a prospective cohort pilot study of 40 patients with liver disease undergoing transjugular liver biopsy, hepatic venous blood was assayed for endothelin-1 (ET-1) [36]. Hepatic venous ET-1 levels were significantly higher in patients with IPVDs and correlated positively with percent volume of cholangiocytes but not with other measures of liver dysfunction.

Although no single gene mutation has been identified, HPS is more commonly found in those with the monocyte chemoattractant protein-1 (MCP-1) 2518G gene and less commonly in those with eNOS 298 Asp allele [48,49].

Pathophysiology — Regardless of the exact mechanism, these pathogenetic processes are thought to induce pulmonary capillary dilation and occasionally direct arteriovenous connections. The resulting IPVDs range in diameter from 15 to 500 microns (normal is 8 to 15 microns) and are associated with HPS-related hypoxemia [50]. IPVDs cause hypoxemia mostly via ventilation-perfusion mismatch and oxygen diffusion limitation and rarely via shunt (figure 2 and figure 3) [16,17,51-54] (see "Measures of oxygenation and mechanisms of hypoxemia"):

- Ventilation-perfusion mismatch is a consequence of increased blood flow through the IPVDs in the setting of preserved alveolar ventilation, resulting in the passage of mixed venous blood into the pulmonary veins.

- The oxygen diffusion limitation is a consequence of diffusion-perfusion impairment (also called alveolar-capillary oxygen disequilibrium) [55,56]. At room air, the partial pressure (or driving pressure) of oxygen is insufficient for equilibration with blood moving near the center of the alveolar capillary because of the increased diameter of the IPVDs. Supplemental oxygen increases the driving pressure of oxygen and improves oxygenation, which distinguishes IPVDs as physiologic rather than anatomic shunts.

- Anatomic shunt due to direct communication between the pulmonary arterial capillary bed and pulmonary venous capillary bed is rare but when present can contribute to hypoxemia and is generally unresponsive to 100 percent oxygen.

Patients with mild to moderate HPS-related hypoxemia have modest intrapulmonary shunting, ventilation-perfusion mismatch, and oxygen diffusion limitation. Severely hypoxemic patients have diffuse dilatation of the pulmonary circulation, over-perfusion of poorly ventilated alveoli, and worsening of their ventilation-perfusion mismatch, diffusion limitation, and orthodeoxia [52].

Pathology — The unique pathological feature of hepatopulmonary syndrome (typically visualized by autopsy or on explanted lungs) is gross dilatation of the pulmonary precapillary and capillary vessels (15 to 500 microns), as well as an absolute increase in the number of dilated vessels. A few pleural and pulmonary arteriovenous shunts and portopulmonary anastomoses (rare) may also be seen. [17,57].

CLINICAL MANIFESTATIONS

The clinical features of HPS are those of the underlying liver disease and oxygenation impairment. More than 80 percent of patients present with dyspnea in the setting of established liver disease; the remainder experience progressive dyspnea as their initial symptom [15].

Features of chronic liver disease — Most patients with HPS have symptoms and signs of chronic liver disease, none of which is sensitive or specific for HPS. These may include weakness, fatigue, anorexia, ascites, a large or small liver, splenomegaly, spider angiomata, palmar erythema, jaundice, asterixis, anasarca, nail changes, digital clubbing, hypertrophic osteoarthropathy, caput medusae, gynecomastia, and testicular atrophy. Some patients will have a history of prior gastrointestinal bleeding due to esophageal or gastric varices, and many will have hemodynamic manifestations of liver dysfunction. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Spider nevi (also referred to as spider angiomas) in a patient with chronic liver disease or portal hypertension should raise the suspicion for the presence of possible HPS (picture 1). Spider nevi are cutaneous lesions most commonly found on the face, neck, upper trunk, and arms:

- In one study, patients with cutaneous spider nevi had more systemic and pulmonary vasodilation, more profound gas exchange abnormalities, and less hypoxic pulmonary vasoconstriction than patients without these lesions [58]. The alveolar-arterial (A-a) oxygen gradient was 20 mmHg in patients with spider nevi compared with 8 mmHg in patients without spider nevi. Similarly, the measured shunt fraction (Qs/Qt) was higher in patients with spider nevi (7 versus 2 percent).

- In another study, a higher prevalence of spider nevi was seen in HPS compared with patients who had liver disease without HPS (48 versus 17 percent) [7]. In the same study, spider nevi and digital clubbing were associated with the presence of HPS. Regardless, other studies have not shown a higher prevalence of spider angiomata in patients with HPS compared with those with liver disease without HPS [32]. (See "Measures of oxygenation and mechanisms of hypoxemia", section on 'Alveolar-arterial (A-a) oxygen gradient'.)

Features of intrapulmonary vascular dilatations

Dyspnea — Most patients with HPS eventually develop dyspnea on exertion, at rest, or both, usually after years of liver disease. However, dyspnea is a non-specific finding in patients with

liver disease because it may also be the consequence of other liver-related conditions (eg, hepatic hydrothorax and portopulmonary hypertension). (See 'Differential diagnosis' below.)

Platypnea and orthodeoxia — Platypnea and orthodeoxia are classic manifestations that are more specific for HPS, but not pathognomonic [7,17,59,60]:

- Platypnea – Platypnea is an increase in dyspnea that is induced by moving into an upright position and relieved by recumbency. In one series, the presence of platypnea was associated with HPS and a higher rate of platypnea was reported in patients with HPS compared with patients with liver disease who did not have HPS (66 versus 6 percent) [7].

- Orthodeoxia – Orthodeoxia refers to a decrease in the arterial oxygen tension (by more than 4 mmHg [0.5 kPa]) or arterial oxyhemoglobin desaturation (variably defined as a change by more than 3 or 5 percent [32]) when the patient moves from a supine to an upright position, which is improved by returning to the recumbent position. Orthodeoxia may be more commonly found than platypnea, affecting up to 88 percent of patients with HPS compared to 5 percent or fewer of patients with cirrhosis alone [15,60].

It is hypothesized that platypnea and orthodeoxia in HPS are caused by preferential perfusion of intrapulmonary vascular dilatations (IPVDs; which disproportionately occur in the lung bases) when the patient is upright [61]. Although these manifestations are suggestive of HPS, other conditions can present with similar symptoms. (See 'Differential diagnosis' below.)

Hypoxemia — HPS-related hypoxemia is due to ventilation-perfusion mismatch and reduced diffusion from IPVDs. Hypoxemia can be mild to severe, depending on the degree of intravascular shunting [62]. The evaluation for hypoxemia may be prompted by the presence of dyspnea or pulse oximetry and is discussed separately. (See 'Pathophysiology' above and 'Impaired oxygenation' below.)

Imaging — Chest imaging is usually not helpful diagnostically but can rule out other important etiologies in the differential.

Chest radiography — Chest radiographic abnormalities due to HPS are infrequent and subtle. Some patients have increased bibasilar interstitial markings that may be misinterpreted as interstitial lung disease. These markings are probably a manifestation of IPVDs.

Chest computed tomography — High resolution computed tomography (HRCT) of the chest may reveal two characteristic findings of IPVDs, dilated peripheral pulmonary vessels and increased pulmonary artery to bronchus ratios. In an observational study that included ten patients with HPS, these two findings successfully distinguished the patients with HPS from

healthy controls or patients with cirrhosis who were hypoxemic [63]. However, these finding are not universally present [64] with another study of 23 patients with HPS reporting no difference in the artery to bronchus ratio on CT [65]. Rarely, more direct communications similar to an arteriovenous malformation may be appreciated, presumably when IPVDs are large (image 1) [64,66].

A novel technique that fuses HRCT and single photon emission computed tomography (SPECT) images may demonstrate perfusion defects that may identify subpleural reticulonodular opacities and/or dilated vessels in the lung bases; while it holds promise for imaging IPVDs, it is not routine [67].

Contrast pulmonary angiography — Pulmonary angiography is an invasive test that is not routinely performed in patients with HPS but was performed in the past before the era of contrast echocardiography. Three angiographic patterns were described in a study of seven patients with HPS [15]:

- The type 1 minimal pattern was characterized by normal to finely diffuse, spidery abnormalities. It was associated with severe hypoxemia, orthodeoxia, and a good response to 100 percent inspired oxygen.
- The type 1 advanced pattern which evolves from the type 1 minimal pattern. It was characterized by a diffuse spongy or blotchy angiographic appearance. It was also associated with severe hypoxemia and orthodeoxia but may be less responsive to 100 percent oxygen.
- The type 2 discrete pattern was characterized by localized, visible arteriovenous communications (image 1) and was associated with a poor response to supplemental oxygen.

Pulmonary function tests — Pulmonary function testing is usually not helpful diagnostically but can rule out significant obstructive or restrictive impairment. Patients with HPS generally have normal spirometry (unless there is coexisting obstructive or restrictive lung disease) and normal lung volume measurements [32]. However, the diffusing capacity for carbon monoxide (DLCO) is typically mildly to severely impaired [68]. As an example, 15 of 18 patients with HPS had a DLCO less than 80 percent of predicted [15]. However, the absence of impaired diffusion does not completely rule out the diagnosis.

The finding of low DLCO is nonspecific and less useful when compared with measurements of impaired oxygenation. In one study, 80 percent of patients with severe cirrhosis who had low DLCO values did not fulfill the criteria for HPS [68]. In addition, an alveolar-arterial oxygen

gradient ≥20 mmHg had a higher diagnostic accuracy than did a DLCO of less than 80 percent predicted (91 versus 41 percent). (See 'Impaired oxygenation' below.)

DIAGNOSTIC EVALUATION

Overview — HPS should be suspected in patients with chronic liver disease who have dyspnea, platypnea/orthodeoxia, spider nevi, and/or evidence of impaired oxygenation, such as a peripheral arterial oxygen saturation <96 percent. All liver transplant candidates should also undergo diagnostic testing, regardless of symptoms (algorithm 1). (See 'Clinical manifestations' above.)

Chest imaging (ie, chest radiography and computed tomography) and a low diffusing capacity on pulmonary function testing are not diagnostically helpful but are typically performed since they help to exclude alternate causes of dyspnea and hypoxemia and narrow the differential. (See 'Imaging' above and 'Pulmonary function tests' above.)

Although practice varies, additional diagnostic testing usually focuses on the objective demonstration of impaired oxygenation and the presence of shunt from intrapulmonary vascular abnormalities (IPVDs) using the following:

- Oximetry and arterial blood gas (ABG) analysis – When HPS is suspected (eg, clinical symptoms and pulse oximetry <96 percent on room air in patients with liver disease [6]), ABGs should be performed in the resting position on room air. Many clinicians additionally perform bedside oximetry and/or ABGs in the supine and standing position (evaluates orthodeoxia and suggests shunt) on room air. (See 'Impaired oxygenation' below and 'Platypnea and orthodeoxia' above.)

- Transthoracic contrast echocardiography (TTCE) – In those with evidence of impaired oxygenation (eg, alveolar-arterial [A-a] gradient ≥15 mmHg [2 kPa], arterial oxygen tension [PaO_2] <80 mmHg (9.7 kPa), orthodeoxia on lying, and standing oximetry or ABG analysis), TTCE should be performed. TTCE is usually sufficient to demonstrate the presence of an intrapulmonary shunt supportive of underlying IPVDs. The 100 percent oxygen method and technetium scanning are less sensitive and generally performed only when TTCE is unhelpful. However, they cannot distinguish intracardiac from intrapulmonary shunt. (See 'Shunt assessment' below.)

- Other – Other more invasive tests (eg, transesophageal or intracardiac echocardiography, contrast pulmonary angiography) are rarely required unless TTCE is equivocal, unavailable,

or the diagnosis is in doubt. (See 'Other' below and 'Contrast pulmonary angiography' below.)

In most patients, the diagnosis of liver disease is already established. The identification of liver disease is discussed separately in disease-specific topic reviews. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis" and "Portal hypertension in adults".)

Impaired oxygenation — To determine the presence of hypoxemia, ABGs should be drawn with the patient sitting upright at rest on room air (algorithm 1). While there is no clear consensus of what exactly constitutes hypoxemia, most experts agree on any one of the following criteria (at sea level):

- An elevated A-a oxygen gradient ≥15 mmHg (2 kPa) (calculator 2) [17]. In patients who are ≥65 years, an A-a gradient ≥20 mmHg (2.7 kPa) or ≥age-adjusted value is also acceptable.
- A PaO_2 of <80 mmHg (10.7 kPa); a PaO_2 <70 mmHg (9.3 kPa) is an alternative in those ≥65 years.

The A-a oxygen gradient is generally considered the more sensitive of the two measures because it compensates for hyperventilation, which is common in patients with chronic liver disease. (See "Measures of oxygenation and mechanisms of hypoxemia", section on 'Alveolar-arterial (A-a) oxygen gradient'.)

Obtaining two consecutive abnormal oxygenation results on different days may improve the accuracy of diagnosis since oxygenation may demonstrate variability at different times [69]. While this practice is not routine, it may be considered in those with borderline or equivocal results.

Pulse oximetry demonstrating a peripheral arterial saturation <96 percent may be used to prompt arterial blood gas analysis to identify those with a PaO_2 <70 mmHg (9.3 kPa) but is typically not sufficient for diagnosis [6,70,71]. Pulse oximetry has become a useful tool to evaluate patients with chronic liver disease, especially liver transplant candidates, for HPS, with a reported sensitivity and specificity of 100 and 88 percent respectively when a cut-off of <96 percent is used [6,71]. A value <94 percent detected patients with a PaO_2 <60 mmHg (8 kPa) with an improved specificity of 93 percent.

ABG analysis may also be indicated for the evaluation of platypnea/orthodeoxia as discussed above; if present, platypnea/orthodeoxia is supportive of HPS but not diagnostic. (See 'Platypnea and orthodeoxia' above and 'Differential diagnosis' below.)

Intrapulmonary vascular dilatations

Shunt assessment — IPVDs act as physiologic shunts that allow a higher than usual volume of pulmonary arterial blood to bypass the alveoli for oxygenation (typically >5 to 6 percent of the normal cardiac output); thus assessments of shunt are typically elevated in patients with HPS. TTCE is the test of first choice for the evaluation of a right-to-left shunt due to suspected IPVDs because it is more sensitive than other methods and less invasive than pulmonary arteriography (algorithm 1) [17,72]. The 100 percent oxygen method and radionuclide perfusion scanning can be used as alternatives for measuring of shunt when TTCE is not helpful, equivocal, or not available. Pulmonary arteriography is rarely, if ever, used (image 2). Patients with liver disease can have subclinical pulmonary vasodilatation and, therefore, positive shunt testing may occur even in the absence of hypoxemia [73]. However, the detection of intrapulmonary shunt alone in patients with liver disease is insufficient to diagnose HPS since impaired oxygenation is also required [74].

Transthoracic contrast echocardiography — In patients with liver disease, detection of an intrapulmonary right-to-left shunt by TTCE ("bubble study") is strongly suggestive of IPVDs. TTCE is performed by injecting contrast material (usually agitated saline) intravenously during echocardiography. Under normal resting circumstances, the contrast opacifies only the right heart chambers because it is filtered by the pulmonary capillary bed [19,75]. However, the contrast may opacify the left heart chambers if a right-to-left intracardiac or intrapulmonary shunt is present. The appearance of bubbles in the left heart varies with cardiac output, heart rate, and shunt size, in general [75]:

- Intracardiac shunt – contrast (microbubbles) generally appears in the left atrium within one cardiac cycle after its appearance in the right atrium.
- Intrapulmonary shunt – contrast generally appears in the left heart three to eight heart beats after its appearance in the right atrium, though even later appearance has been described [76].
- Indeterminate location – contrast appears in the left atrium within one to three cardiac cycles.

Contrast-enhanced echocardiography may be more sensitive when performed in the upright position than in the supine position, probably due to an increase in both the number and size of the shunts [77]. Further details regarding TTCE and shunt grading (0 through 3) are discussed separately. (See "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults", section on 'Transthoracic contrast echocardiography'.)

Left ventricle enlargement and higher systolic velocity, representative of increased flow through the shunt, may also be seen in patients with HPS who have IPVDs, although this feature is

nonspecific [3,78].

There is a paucity of high-quality data reporting the diagnostic sensitivity of TTCE in this population. However, based upon extrapolated data derived in other populations (eg, pulmonary arteriovenous malformation), most experts agree that TTCE is a sensitive tool for diagnosing shunt. However, it may detect shunt that is not clinically relevant or associated with hypoxemia. As an example, one study reported that intrapulmonary shunt was found in 38 percent of patients with cirrhosis by contrast echocardiography but only half had gas exchange abnormalities (18 percent) and one-fifth (8 percent) had associated hypoxemia [12]. Similarly, another prospective study of liver transplant candidates found shunt using TTCE in up to 82 percent, but only 8 percent had hypoxemia defined as partial pressure of arterial oxygen (PaO_2) <70 mmHg (9.3 kPa) [13]. In another study, 10 percent of normoxemic patients with severe cirrhosis had a positive TTCE [79].

Other

Transesophageal and intracardiac echocardiography — Rarely is transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) performed for shunt assessment [80]. Although TEE detects IPVDs with greater specificity due to direct visualization of microbubbles in the pulmonary veins as they enter the left atrium [81,82], it is more invasive and often avoided in this population due to the risk associated with sedation or bleeding from esophageal varices. ICE is more invasive than TEE or TTCE but may be an alternative to TTCE or TEE when the need to distinguish intracardiac from intrapulmonary shunt is necessary.

100 percent oxygen method — The shunt fraction can be measured by drawing an arterial blood gas while the patient is breathing 100 percent oxygen with a nose clip in place. It is usually performed in the laboratory setting and can confirm and quantify the degree of shunt by measuring the fraction of cardiac output that bypasses the pulmonary capillaries. The normal fraction is approximately 5 percent, and the shunt increases by 5 percent for every 100 mmHg drop in PaO_2 below 600 mmHg (80 kPa). A limitation of this formula is that it assumes that the cardiac output is normal rather than increased and may therefore introduce error in estimating the true shunt [83]. Further details are described separately. (See "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults", section on '100 percent oxygen'.)

Macroaggregated albumin scanning — Technetium 99m (^{99m}Tc)-labeled macroaggregated albumin (MAA) scanning is an alternative, less-sensitive method of confirming and quantifying shunt from IPVDs in patients with liver disease and has been reported to be positive in up to one-third of patients with HPS (image 3). It involves

intravenously injecting ^{99m} Tc-labeled albumin macroaggregates that under normal circumstances should be trapped in the pulmonary capillary bed. Scans that identify uptake of the radionuclide by the kidneys and/or brain suggest that the macroaggregates passed through either an intrapulmonary or intracardiac shunt, although unlike TTCE, distinguishing intracardiac versus intrapulmonary shunts is not possible with MAA scanning [55,84].

This method is valuable in those with concomitant lung disease to determine the contribution of shunt versus lung disease to hypoxemia [85]. It may also be performed to quantify shunt prior to liver transplant as patients with a shunt fraction ≥20 percent may have a higher perioperative mortality. The proportion of radionuclide taken up by the kidneys and brain quantifies the shunt, which in HPS is typically >6 percent. Some advocate whole-body scanning to better estimate the percent shunt using MAA scanning [66,86]. Further details regarding radionuclide scanning are provided separately. (See "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults", section on 'Radionuclide perfusion scanning'.)

Contrast pulmonary angiography — Pulmonary angiography is invasive and, therefore, seldom performed in patients with suspected HPS. It is generally reserved for patients in whom there is a suspicion for pulmonary arteriovenous malformations, which can occur only rarely in HPS and may be amenable to embolization. (See 'Imaging' above and "Therapeutic approach to adult patients with pulmonary arteriovenous malformations".)

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of HPS are nonspecific and several other conditions should be considered during the evaluation:

- **Platypnea/orthodeoxia and shunt** – The presence of platypnea/orthodeoxia and a shunt in a patient with liver disease is strongly suggestive of HPS. However, these symptoms and the presence of a shunt can be seen in other situations including arteriovenous malformations (pulmonary and extra pulmonary), post-pneumonectomy, recurrent pulmonary emboli, atrial septal defects, and patent foramen ovale [87]. Similarly, dyspnea may be due to a hepatic hydrothorax, portopulmonary hypertension, anemia, ascites, fluid retention, muscle wasting, and chronic cardiopulmonary disease [17,88]. These disorders can be distinguished by clinical examination, chest computed tomography (CT), CT angiography, and/or contrast echocardiography, most of which are performed during the evaluation of suspected HPS.

- **Hypoxemia** – Hypoxemia is a common, but nonspecific, finding in patients with liver disease. Potential causes include atelectasis due to compression of the lung parenchyma by ascites or pleural fluid (hepatic hydrothorax), portopulmonary hypertension, coexistent underlying cardiopulmonary disease, and HPS [73]. Severe hypoxemia (arterial oxygen tension [PaO_2] <60 mmHg) in the absence of coexisting cardiopulmonary disease is strongly suggestive of HPS, since atelectasis and portopulmonary hypertension generally cause mild hypoxemia [75,89]. Most of these can be distinguished by pulmonary function testing, chest imaging, and echocardiography.

  Where originally HPS and portopulmonary hypertension were thought to be distinct entities on opposite ends of the spectrum, observational studies suggest that they can coexist in a small proportion of patients with liver disease, potentially worsening symptoms and hypoxemia [90-92]. The presence of portal hypertension and/or echocardiographic findings consistent with pulmonary hypertension (eg, elevated right ventricle pressures) may prompt additional investigations including right heart catheterization to distinguish the contributions of each entity so that appropriate therapy can be administered. (See "Portopulmonary hypertension".)

DIAGNOSIS

The diagnosis of HPS is a clinical one that can only be made when **all** of the following abnormalities have been confirmed and other etiologies have been excluded [17,57,72]:

- Evidence of the presence of liver disease (with or without concomitant portal hypertension) (see 'Features of chronic liver disease' above)
- Evidence of impaired oxygenation (see 'Impaired oxygenation' above)
- Intrapulmonary vascular abnormalities (see 'Intrapulmonary vascular dilatations' above)

Once the diagnosis is made, the HPS should be graded according to severity. (See 'Grading disease severity' below.)

Although the diagnosis can be made histologically at autopsy or on explanted lungs, lung tissue is not generally obtained due to the high risk nature of biopsy in this population and the high sensitivity of noninvasive testing. (See 'Pathology' above.)

GRADING DISEASE SEVERITY

Most experts use the following grading system in those with an alveolar-arterial (A-a) oxygen gradient ≥15 mmHg (2 kPa) (table 3) [17,57]:

- Mild – Arterial oxygen tension (PaO_2) ≥80 mmHg (10.7 kPa) while breathing room air
- Moderate – A PaO_2 ≥60 mmHg and <80 mmHg (≥8 kPa and <10.7 kPa) while breathing room air
- Severe – A PaO_2 ≥50 mmHg and <60 mmHg while breathing room air
- Very severe – A PaO_2 <50 mmHg (6.7 kPa) while breathing room air or a PaO_2 <300 mmHg (40 kPa) while breathing 100 percent oxygen.

In general, those with severe or very severe HPS are considered candidates for liver transplantation, while those with mild to moderate disease are more likely to be monitored, depending upon the severity of their underlying liver disease. (See "Hepatopulmonary syndrome in adults: Natural history, treatment, and outcomes", section on 'Treatment and prognosis' and "Model for End-stage Liver Disease (MELD)".)

SUMMARY AND RECOMMENDATIONS

- Hepatopulmonary syndrome (HPS) is characterized by the triad of abnormal arterial oxygenation from intrapulmonary vascular dilatations (IPVD) in the setting of liver disease, portal hypertension, or congenital portosystemic shunts. The prevalence of HPS ranges from 4 to 47 percent but on average affects one quarter of patients with severe chronic liver disease. (See 'Prevalence' above.)
- HPS is most commonly seen in patients with chronic liver disease, particularly those with portal hypertension; it can also be found in patients with portal hypertension in the absence of liver disease and rarely in acute liver disease (table 2). The pathogenesis of HPS is unknown but several vasoactive factors have been implicated, including increased levels of circulating nitric oxide and endothelin-1 (figure 1). The resulting IPVDs cause HPS-associated hypoxemia via ventilation-perfusion mismatch and oxygen diffusion limitation and rarely via shunt (figure 2 and figure 3). (See 'Etiologies and pathogenesis' above.)
- The clinical manifestations of HPS are nonspecific and largely comprise features of liver and pulmonary dysfunction. HPS should be suspected in patients with chronic liver disease who have dyspnea, platypnea/orthodeoxia, spider nevi, and/or evidence of impaired oxygenation (eg, peripheral arterial oxygen saturation <96 percent). Chest imaging is

frequently nonspecific and pulmonary function testing is often normal (in the absence of other contributors to abnormal pulmonary function) except for a reduction in diffusion capacity. (See 'Clinical manifestations' above.)

- Since in most patients the diagnosis of liver disease is already established, additional diagnostic testing usually focuses on the objective demonstration of impaired oxygenation and the presence of shunt from IPVDs (algorithm 1). Impaired oxygenation is confirmed when an arterial blood gas analysis demonstrates an alveolar-arterial (A-a) oxygen gradient ≥15 mmHg (2 kPa; ≥20 mmHg if ≥65 years) or an arterial oxygen tension (PaO_2) <80 mmHg (10.7 kPa) while breathing room air (≤70 mmHg [9.3 kPa] if ≥65 years). An intrapulmonary shunt is best evaluated on transthoracic contrast echocardiography (TTCE). Other methods of shunt assessment and invasive testing are rarely needed unless TTCE is equivocal, unavailable, or the diagnosis is in doubt. (See 'Diagnostic evaluation' above.)

- Several other conditions should be considered during the evaluation of suspected HPS, including conditions that present with shunt (eg, arteriovenous malformations, post-pneumonectomy syndrome, recurrent pulmonary emboli, atrial septal defects, and patent foramen ovale) and conditions that present with hypoxemia (eg, atelectasis, hepatic hydrothorax, portopulmonary hypertension, and coexistent underlying cardiopulmonary disease). Most of these can be excluded on chest imaging, echocardiography, and pulmonary function testing. (See 'Differential diagnosis' above.)

- The diagnosis of HPS is a clinical one that can only be made in a patient who has evidence of liver disease, impaired oxygenation, and intrapulmonary shunt when other etiologies have been sufficiently excluded. (See 'Diagnosis' above.)

- A system that uses the A-a oxygen gradient and the PaO_2 is used by many experts to define the severity of HPS, which in turn may determine treatment strategies (table 3). (See 'Grading disease severity' above.)

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Topic 8248 Version 31.0

GRAPHICS

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Liver diseases associated with the hepatopulmonary syndrome

Cryptogenic cirrhosis
Postnecrotic cirrhosis
Alcoholic cirrhosis
Autoimmune cirrhosis
Primary biliary cholangitis
Chronic active hepatitis
Primary sclerosing cholangitis
Alpha-1 antitrypsin deficiency (associated with Z and M-malton, and Siiyama alleles)
Wilson's disease
Sarcoidosis[1]
Hemochromatosis
Biliary atresia
Non-cirrhotic portal hypertension
Tyrosinemia
Gaucher disease
Schistosomiasis
Nodular regenerative hyperplasia of the liver
Hepatic allograft rejection
Langerhans-cell histiocytosis
Hepatic graft-versus-host disease following hematopoietic stem cell transplantation
Short telomere syndrome
Budd Chiari Syndrome
Chronic granulomatous hepatitis
Some acute liver diseases
Congenital vascular disease (eg, cavopulmonary shunt, Abernethy malformation)

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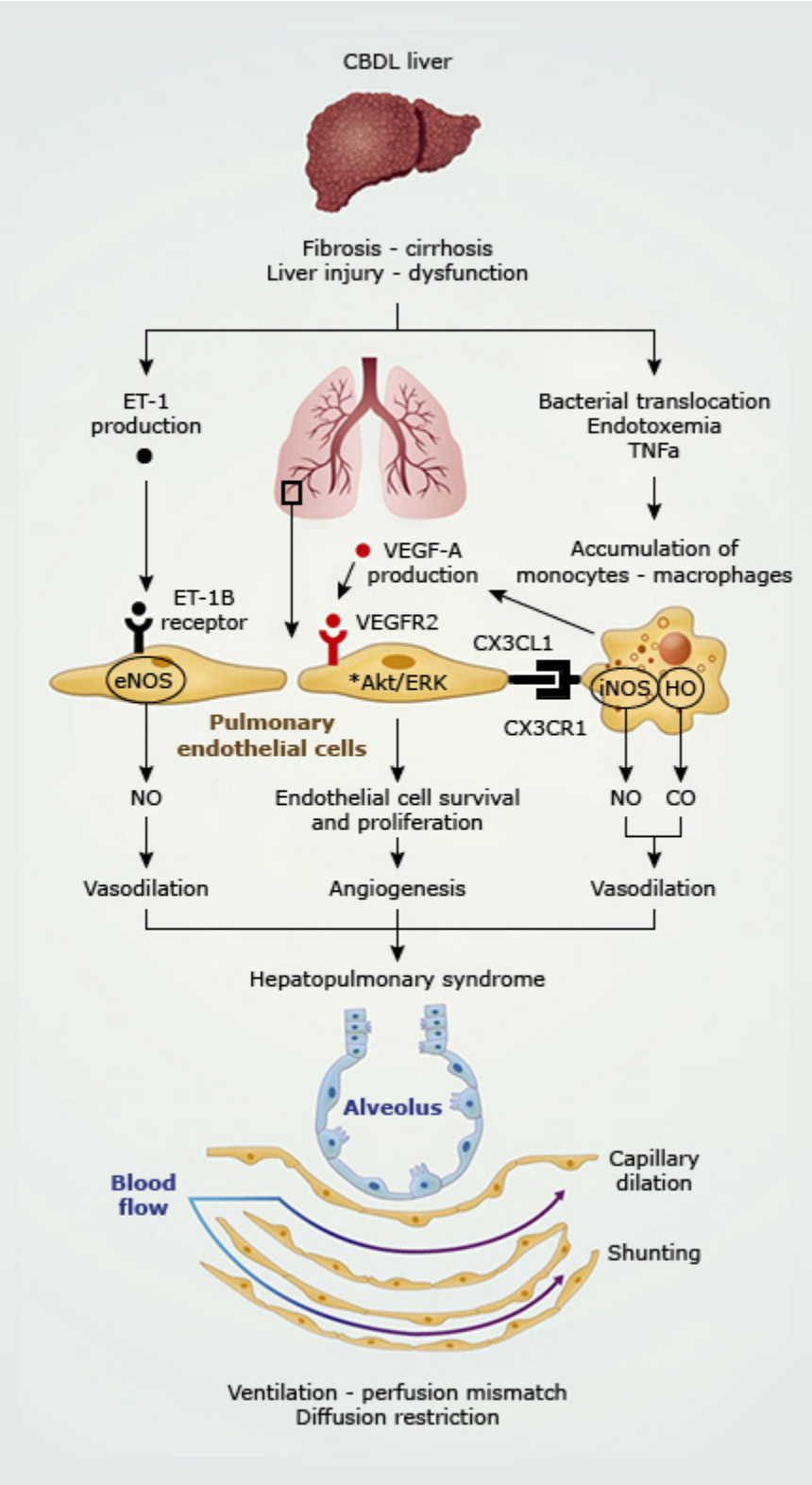
Adapted from: Krowka MJ. Clinical management of hepatopulmonary syndrome. Semin Liver Dis 1993; 13:414.

Graphic 66479 Version 6.0

Pathogenesis and pathophysiology of hepatopulmonary syndrome



Pathogenesis and pathophysiology of hepatopulmonary syndrome. Experimental HPS is induced by the technique of CBDL cirrhosis, which leads to pulmonary vasodilation, intravascular accumulation of activated macrophages and monocytes and angiogenesis.

Pulmonary vasodilation is caused by NO production, following eNOS and iNOS activation[1-5] and CO production[6,7]. In CBDL lungs, ET-1 binding to its ET-1B receptor induces eNOS activation[2,3] while iNOS and HO activation occurs in intravascular monocytes/macrophages[4-7]. Activated monocytes and macrophages are recruited to the lungs because of bacterial translocation and endotoxaemia after CBDL[4], in which CX3CL1/CX3CR1 signalling is responsible for correct monocyte/macrophage adherence to the pulmonary endothelium[8]. In addition, increased production of VEGF-A leads to endothelial cell survival and proliferation through angiogenic Akt/ERK signalling, when it binds to its VEGFR2 on pulmonary endothelial cells[9,10]. This combination of pulmonary vasodilation, angiogenesis, pulmonary capillary proliferation and formation of intrapulmonary arteriovenous shunts results in ventilation-diffusion mismatch, right-to-left shunting and diffusion restriction[11], finally contributing to gas exchange disturbances with arterial hypoxaemia, which characterizes HPS.

CBDL: common bile duct ligation; ET-1: endothelin-1; VEGF-A: vascular endothelial growth factor A; ET-1B receptor: endothelin-1 B receptor; VEGFR2: VEGF receptor 2; CX3CL1: chemokine fractalkine; TNFa: tumor necrosis factor a; eNOS: endothelial nitric oxide synthase; Akt: protein kinase B; ERK: extracellular signal-regulated kinase; iNOS: inducible nitric oxide synthase; HO: haem oxygenase; CX3CR1: chemokine fractalkine receptor; NO: nitric monoxide; CO: carbon monoxide; HPS: hepatopulmonary syndrome.

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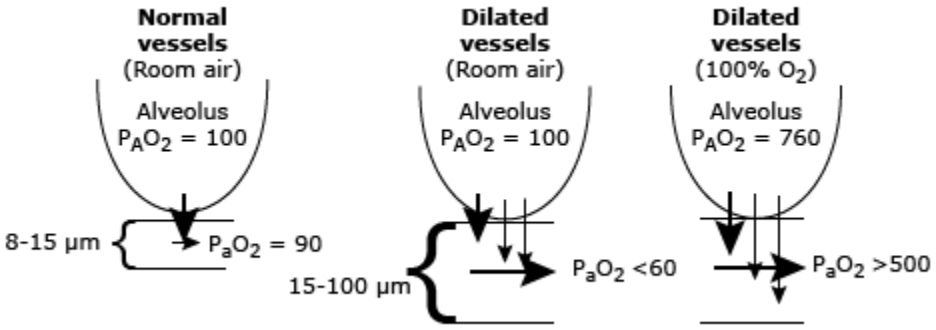
Graphic 110094 Version 1.0

Proposed mechanism for partial response to oxygen in the hepatopulmonary syndrome

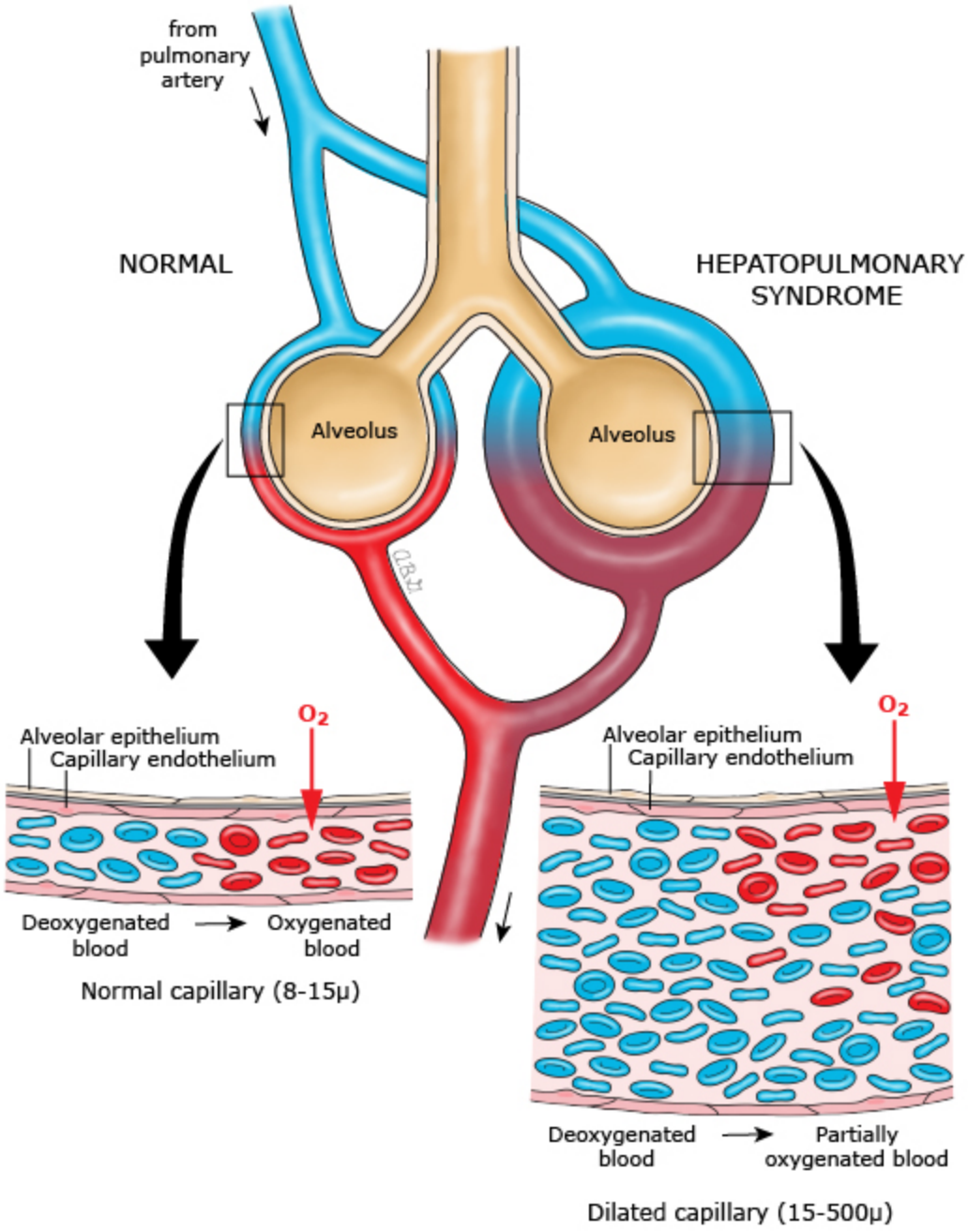


Diffusion-perfusion impairment (also called alveolar-capillary oxygen disequlibrium) occurs in the setting of vasodilation of alveolar capillaries; the partial pressure (or driving pressure) of oxygen in the alveolus is insufficient to achieve equilibration with blood moving near the center of the vessel. When alveolar oxygen is increased, the gradient for diffusion increases and oxygenation improves.

P_AO_2: partial pressure of alveolar oxygen; P_aO_2: partial pressure of arterial oxygen; %: percent.

Graphic 58856 Version 6.0

Mechanisms of hypoxemia in hepatopulmonary syndrome

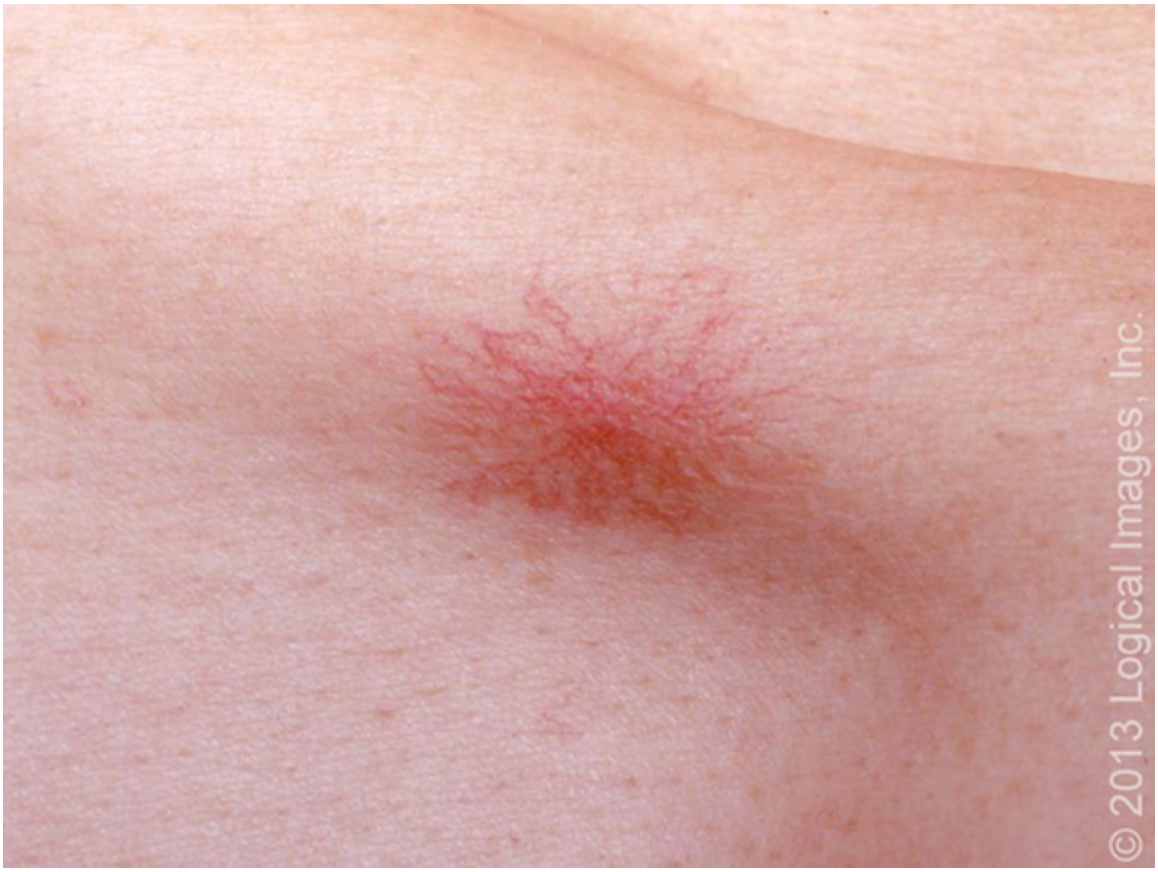


Modified from:

1. *Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. N Engl J Med 2008; 358:2378.*
2. *Tumgor G. Cirrhosis and hepatopulmonary syndrome. World J Gastroenterol 2014; 20:2586.*

Graphic 109638 Version 1.0

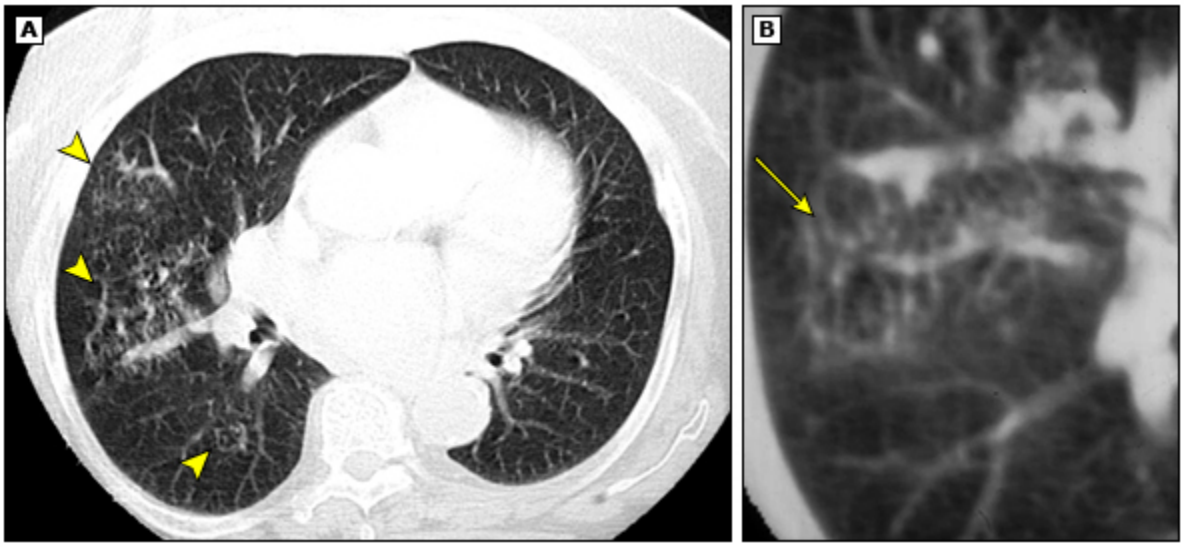
Cutaneous spider angioma



Spider nevus in a patient with liver cirrhosis.

Graphic 90356 Version 2.0

Hepatopulmonary syndrome with arteriovenous malformation on CT scan

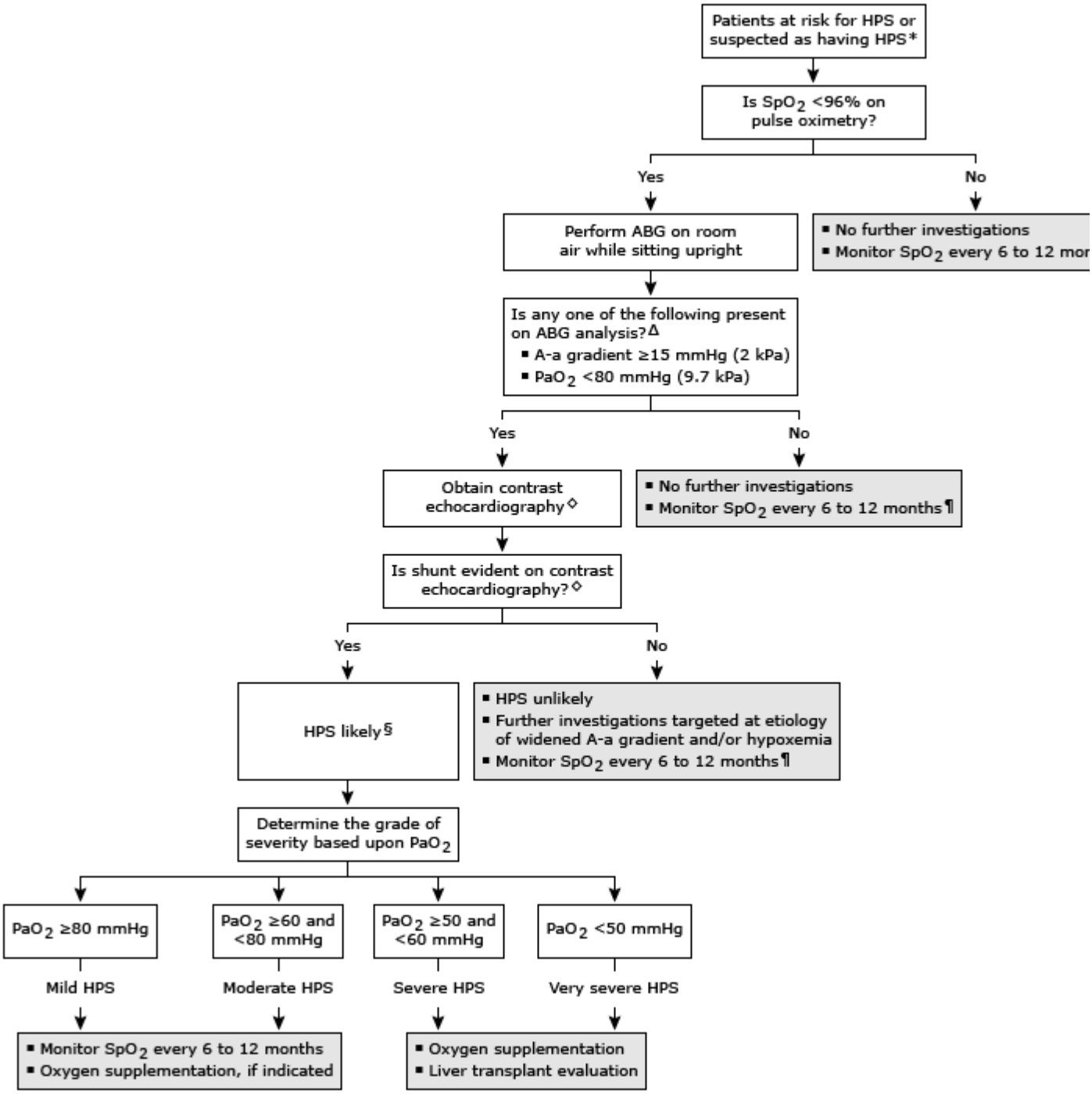


An axial CT scan through the chest (A) shows multicentric AVMs (arrowheads). A magnified view (B) highlights the largest AVM (arrow).

CT: computed tomography; AVM: arteriovenous malformation.

Graphic 89202 Version 1.0

Diagnostic algorithm for hepatopulmonary syndrome



HPS: hepatopulmonary syndrome; SpO_2: peripheral arterial oxygen saturation; ABG: arterial blood gas analy A-a gradient: Alveolar-arterial gradient; PaO_2: partial arterial pressure of oxygen.

* Suspected HPS – HPS should be suspected in patients with chronic liver disease and/or portal hypertensio HPS is rare in patients with acute liver disease. All patients who undergo evaluation for liver transplant shou be evaluated for HPS. Common manifestations include dyspnea, platypnea, orthodeoxia, and spider nevi.

¶ Some patients may have low grade shunt in the absence of hypoxemia which warrants continued monitor in the event of progression to HPS.

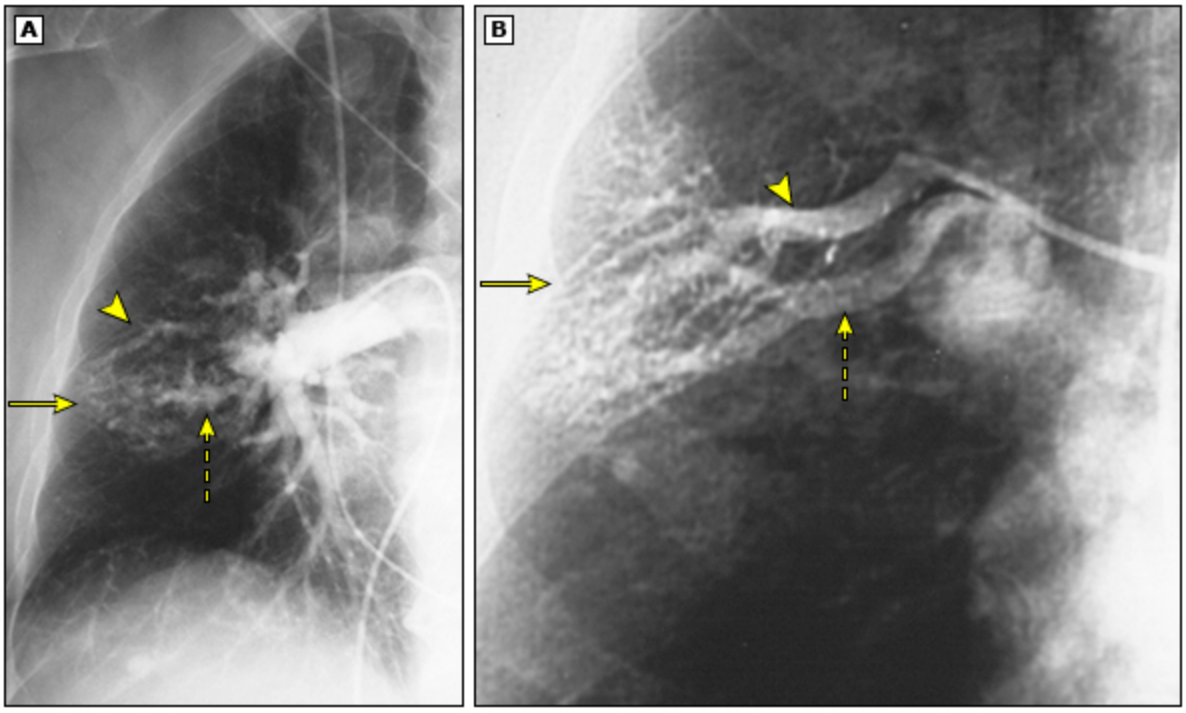
Δ Some clinicians additionally perform lying and standing oximetry and ABGs which, when positive, can indi the presence of a shunt.

◇ Contrast echocardiography typically involves the intravenous administration of agitated saline, followed b imaging with transthoracic echocardiography. Visualization of microbubbles in the left atrium within three t cardiac cycles after their appearance in the right atrium usually indicates an intrapulmonary shunt and prov strong evidence in favor of the presence of intrapulmonary vascular shunts consistent with HPS. Other form shunt assessment are rarely needed (refer to UTD text for details).

§ It is prudent to exclude contributing etiologies (eg, cardiac failure, intrinsic lung disease, pulmonary arteriovenous malformations; refer to UTD text for details).

Graphic 109726 Version 1.0

Hepatopulmonary syndrome with arteriovenous malformation on angiography

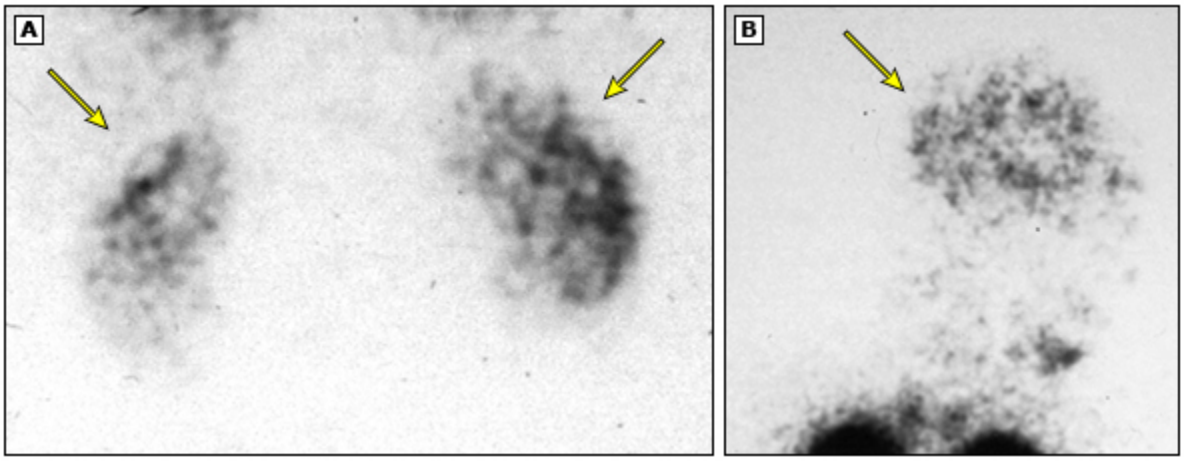


A right pulmonary angiogram (A) shows a cluster of abnormal vessels in the right mid lung field (arrow) supplied by an artery (arrowhead) and an early draining vein (dashed arrow). Selective angiography of the artery (arrowhead in panel B) confirms the presence of an AVM (arrow) and an early draining vein (dashed arrow).

AVM: arteriovenous malformation.

Graphic 89200 Version 1.0

Hepatopulmonary syndrome with arteriovenous malformation on 99mTc-MAA scan



An image of the upper abdomen (A) and head (B) following injection of technetium 99mTc albumin aggregate shows abnormal accumulation of the radioisotope in the kidneys (arrows in panel A) and the brain (arrow in panel B) indicating an arteriovenous shunt.

99mTc-MAA: technetium 99mTc albumin aggregated; AVM: arteriovenous malformation.

Graphic 89201 Version 1.0

Severity of hepatopulmonary syndrome

A-a gradient	PaO_2 (on room air)	Graded severity
≥15 mmHg (≥2 kPa)	≥80 mmHg (≥10.7 kPa)	Mild
≥15 mmHg (≥2 kPa)	≥60 mmHg and <80 mmHg (≥8 kPa and <10.7 kPa)	Moderate
≥15 mmHg (≥2 kPa)	≥50 mmHg and <60 mmHg (≥6.7 kPa and <8 kPa)	Severe
≥15 mmHg (≥2 kPa)	<50 mmHg (<6.7 kPa)*	Very severe

A-a gradient: Alveolar-arterial oxygen gradient; PaO_2: arterial oxygen tension.

* Patients with a PaO_2 <300 mmHg (40 kPa) while breathing 100% oxygen also have very severe hepatopulmonary syndrome.

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