12 Preoperative Assessment and Optimization of Liver Transplant Patients: Pulmonary Issues

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12.1 Introduction

Chronic liver disease is one of the common causes of morbidity and mortality in adults. Liver transplant is the only management for end-stage liver disease (ESLD) and has evolved rapidly since the first successful transplant in 1967. The post-liver transplant survival rate has improved over last few decades, despite increasing donor and recipient age. For best possible outcomes, patients for liver transplant must be carefully evaluated and optimized.

Pulmonary disorders are the most commonly encountered comorbidities in liver transplant patients. Pulmonary disorders also have a significant impact on the prognosis of these patients. Respiratory symptoms may occur as a complication of chronic liver failure or may be seen in these patients due to coexisting respiratory illness. Smoking and chronic obstructive pulmonary diseases are very common in patients with liver failure. Moreover, certain liver diseases are associated with specific respiratory system abnormalities (like cystic fibrosis, sarcoidosis, α1 antitrypsin deficiency, primary biliary cirrhosis). Patients with end-stage liver disease with long-standing tense ascites may develop intercostal muscle wasting leading to restrictive respiration.

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Respiratory complications are very common after liver transplantation and are associated with increased morbidity and mortality. A thorough preoperative evaluation of the pulmonary system and a good understanding of the pathophysiology of the disorders are necessary to optimize them before the transplant surgery.

The MELD system of scoring liver disease is used for ranking the patients awaiting deceased donor transplant, but the score does not have any respiratory parameter. Certain pulmonary disorders associated with liver failure affect the survival of these patients, so "standard MELD exceptions" have been made to upgrade the MELD score which include hepatopulmonary syndrome and portopulmonary hypertension.

Pulmonary disorders associated with liver failure and their management are discussed under the four main headings—hepatopulmonary syndrome (HPS), portopulmonary hypertension (PoPH), hydrothorax, and others.

12.2 Hepatopulmonary Syndrome

Hepatopulmonary syndrome is seen in advanced liver disease and is a clinical triad of hepatic disease, abnormal gas exchange, and intrapulmonary vasodilatation (IPVD). HPS can also occur with noncirrhotic portal hypertension, acute and chronic hepatitis, acute liver failure, and

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congenital vascular abnormalities like cavopulmonary shunts.

There are no specific symptoms of HPS but dyspnea, which is progressive, is the commonest complaint. Platypnea (dyspnea on standing and improved by lying supine) and orthodeoxia (decrease in arterial PO_2 by 5% or ≥4 mmHg from supine to upright) are the hallmarks of HPS. Other features that are seen in HPS are spider naevi, digital clubbing, cyanosis, nailbed telangiectasia, and hypoxemia (not responding to 100% O_2).

The diagnosis of HPS in the setting of liver disease is done by gas exchange analysis and documentation of intrapulmonary vasodilatation.

Arterial blood gas analysis is done while breathing ambient air and alveoloarterial gradient ≥15 mmHg (>20 mmHg in age >64 years), or PaO_2 < 80 mmHg is diagnostic of oxygenation defect. Pulse oximetry may be used as a noninvasive screening test for hypoxemia in sitting position. HPS may be classified as mild, moderate, or severe according to alveoloarterial pressure gradient (Table 12.1).

Intrathoracic vasodilatation may be diagnosed by transthoracic contrast echocardiography, radionuclide lung perfusion scan, pulmonary angiography, or high-resolution CT scan. The preferred method is transthoracic contrast echocardiography. In this technique, agitated saline (that creates microbubbles ≤10 μm in diameter) is injected intravenously and transthoracic echocardiography is done. Normally the bubbles are not seen as they get absorbed in the lung, but if pulmonary vasodilatation or shunts are present they come to the left side of the heart. If bubbles appear within 3 heartbeats, it indicates intracardiac shunt and if it appears within 4–6 heartbeats it indicates intrapulmonary shunts (HPS).

Lung perfusion scanning using technetium-99-m labeled microaggregated albumin is another method of diagnosing HPS. Normally Tc^{99m} labeled albumin gets trapped in the lungs. In the presence of intrapulmonary shunts, it passes to systemic arteries and appears in the brain and kidneys. More than 6% uptake in the brain is significant. However, the scan cannot differentiate between intrapulmonary and intracardiac shunt.

Pulmonary angiography may also be done for diagnosis but is not routinely done because of its invasive nature.

High-resolution CT scan has been used for demonstrating dilatation of pulmonary arteries [1].

Table 12.1 Classification of disease severity in hepatopulmonary syndrome

Disease severity	Alveolar arterial gradient (mmHg)	PaO_2 (room air) (mmHg)	PaO_2 (100% O_2) (mmHg)
Mild	≥15 or >20 if age >64 years	≥80	
Moderate		60–79	
Severe		50–59	
Very severe		<50	<300

PaO_2 partial pressure of oxygen in arterial blood

12.3 Epidemiology and Pathophysiology

HPS is found in 5–30% of liver transplant patients [2]. HPS is not related to severity of liver disease or its etiology. History of smoking is more common in liver transplant patient with HPS than those without HPS [3]. Some studies have observed an association between HPS and abnormal genes [4]. Since neither the etiology nor the severity of liver disease affects development of HPS, it contributes to the hypothesis of a genetic predisposition.

The hallmark of HPS is microvascular dilatation of pulmonary vasculature. This results in passage of mixed venous blood into systemic circulation and results in hypoxemia, ventilation–perfusion mismatch, shunting, and diffusion limitation. The exact cause of this vasodilatation is not clear and is multifactorial. Liver injury or portal hypertension triggers the release of vasoactive mediators like nitric oxide (NO), heme oxygenase-derived carbon monoxide, and tumor necrosis factor alpha which result in pulmonary vasodilatation or angiogenesis. Other mechanisms include failure of damaged liver to clear vasodilators (like vasoactive intestinal peptides and other substances synthesized by

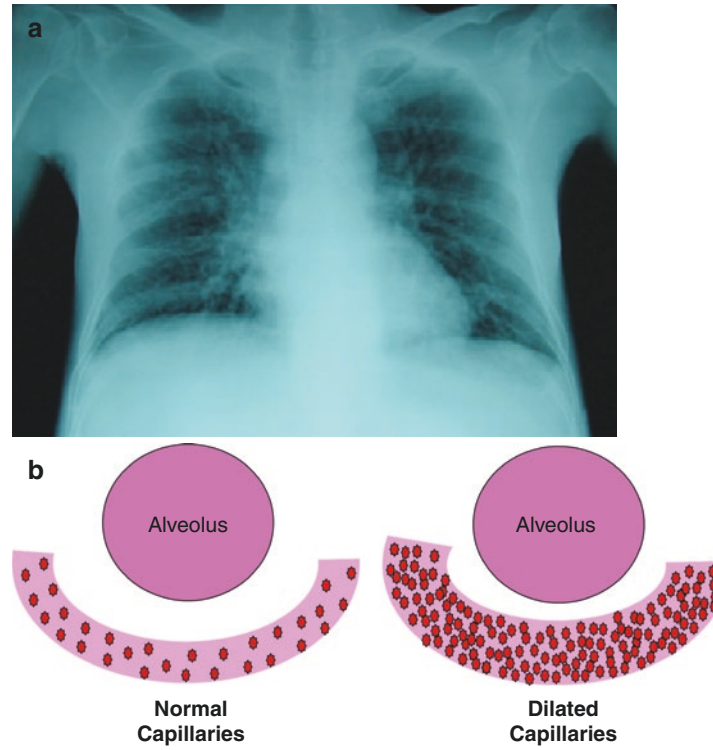

Fig. 12.1 (**a**) Chest PA view showing increased vascularity in the lung parenchyma. (**b**) Dilated pulmonary capillaries in hepatopulmonary syndrome

intestinal bacteria) or inhibition of circulating vasoconstrictors. Portal hypertension may decrease gut perfusion allowing translocation of bacteria and presence of endotoxin in portal blood. The key vasodilator involved in HPS is nitric oxide (NO). In a study on 45 patients with cirrhosis, those who met the diagnosis of HPS had high value of exhaled NO and there was correlation between exhaled NO and alveoloarterial oxygen difference [5, 6].

Regardless of the exact mechanism, these pathophysiological processes induce pulmonary capillary vasodilatation and direct arteriovenous connections. Increased blood flow through IPVDs with preserved alveolar ventilation results in ventilation–perfusion mismatch. At room air, partial pressure of oxygen is not sufficient for equilibrium with blood moving in the center of dilated capillary (because of increased diameter) resulting in hypoxia (Fig. 12.1a).

HPS-related hypoxemia is because of intrapulmonary shunting, ventilation–perfusion mismatch, impaired hypoxic pulmonary vasoconstriction (HPV), oxygen diffusion limitation, and atelectasis. Platypnea and orthodeoxia is caused by preferential perfusion of IPVDs, which occur disproportionately in lung bases (Fig. 12.1b) [6].

12.4 Portopulmonary Hypertension

Portopulmonary hypertension (PoPH) is characterized by pulmonary hypertension in a patient with coexisting portal hypertension and no alternative cause of pulmonary hypertension (like idiopathic heritable pulmonary hypertension, collagen vesicular disease, congenital heart disease, human immunodeficiency virus or drugs). The criteria for diagnosing this hemodynamic condition are [7]:

- Mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest
- Pulmonary vascular resistance (PVR) >3 Wood units (240 dynes/s/cm^5)
- Pulmonary arterial wedge pressure (PAWP) <15 mmHg

The gold standard for diagnosing POPH is right heart catheterization. Excluding other causes of pulmonary arterial hypertension (PAH) like chronic thromboembolic pulmonary hypertension, sleep-disordered breathing, diastolic dysfunction, and significant obstructive and restrictive lung diseases is also important to make the diagnosis. An elevated PVR is important in making the diagnosis and to distinguish patients with precapillary disease from those who have passive elevation in mPAP due to hyperdynamic circulatory changes associated with chronic liver disease. It can be explained by the simple formula [8]:

$$\text{mPAP} = (\text{CO} \times \text{PVR}) + \text{PAWP}$$

PoPH always occurs in chronic liver disease with portal hypertension. A few cases have been reported in patients in absence of portal hypertension [9] and in patients without hepatitis [10]. Diagnosis of portal hypertension is usually clinical but it can be confirmed by hepatic venous catheterization, if necessary.

A PVR of 3 Wood units is used for diagnosing PoPH but in presence of hyperdynamic circulation, PVR between 2 and 3 Wood units is considered abnormal and has poor outcomes [11].

PoPH has been classified as mild, moderate, and severe based on the severity of pulmonary artery hypertension (Table 12.2).

Table 12.2 Classification of PoPH according to severity

Severity	mPAP (mmHg)	PVR (Wood unit)
Mild	25–34	>3
Moderate	35–44	
Severe	≥45	

12.5 Epidemiology

PoPH is seen in 5–6% of liver transplant patients [12]. Usually it is seen equally in males and females; some studies have shown higher incidence in females [13]. Autoimmune hepatitis is a clinical risk factor for PoPH [13]. Because of the infrequent or sporadic occurrence of this hemodynamic entity in patients with portal hypertension, genetic predisposition has been proposed. It has been found that mutations in the pathway involving estrogen signaling, cell growth, apoptosis, and oxidative stress play a role [14]. The prevalence of PoPH is not influenced by the severity of liver disease.

12.6 Pathophysiology

The exact cause of development of PoPH is not known although many theories have been proposed like:

1. A humoral substance with vasoactive property (which is normally metabolized in the liver) reaches pulmonary circulation through portosystemic circulation and causes pulmonary hypertension. These mediators are serotonin, interleukin 1, endothelin 1, glucagon, secretin, thromboxane β2, and vasoactive intestinal peptide [15].
2. Thromboembolism from portal venous system: according to this theory, blood clots pass from the portal system to pulmonary circulation through shunts [16].
3. The hyperdynamic circulation in chronic liver disease may cause PoPH. High cardiac output and increased blood flow through pulmonary vasculature cause sheer stress with vasoconstriction, hypertrophy, and proliferation of endothelial cells, resulting in pulmonary arterial hypertension [17]. However, this theory is not supported by studies that show increased blood flow is readily accommodated by pulmonary vasculature [18].

4. Certain inflammatory mediators like IL1 β, IL-6, and TNF-alpha are increased in cirrhotic patients [19].
5. For hereditary pulmonary hypertension, a specific gene has been identified. For PoPH, specific genetic defect has not been found but several pathways have been proposed that may cause vascular pathology in these cases.

Histopathological findings of PoPH are indistinguishable from pulmonary hypertension and include medial hypertrophy, remodeling of pulmonary arterial walls, and in situ thrombosis.

12.7 Diagnosis

These patients are asymptomatic at early stage of the disease. The most common symptoms are progressive dyspnea and worsening fatigue. They may have peripheral edema, chest pain, syncope, or near syncope. On physical examination they have raised jugular venous pressure, loud pulmonic component of second heart sound, a systolic murmur on left sternal border (because of tricuspid regurgitation), right ventricular heave, and right-sided fourth heart sound. They may have ascites and peripheral edema. In PoPH patients, presence of peripheral edema and ascites is not indicative of its severity whereas in patients with idiopathic PH, these features reflect the severity of the disease.

The electrocardiogram reveals right axis deviation and right ventricular hypertrophy and may reveal right bundle branch block. Chest X-ray may demonstrate enlarged pulmonary arteries and cardiomegaly.

Patients with PoPH usually have mild hypoxia even when they have moderate to severe disease in contrast to HPS [20].

Transthoracic echocardiography is a specific test and is most commonly used in the diagnosis of PoPH and to rule out other causes of pulmonary hypertension. To exclude other causes of pulmonary hypertension like venous or arterial thromboembolism, ventilation–perfusion scan or computed tomography pulmonary angiography may be done. Right heart catheterization is the gold standard in the diagnosis and evaluation of PoPH.

Clinical features of HPS and PoPH are enumerated in Table 12.3.

Table 12.3 HPS versus PoPH

	HPS	PoPH
Diagnosis	Triad of	Pulmonary and portal hypertension
	Liver disease	mPAP > 25 mmHg
	Hypoxemia: P(A-a) > 15 mmHg	PVR > 3 Wood units
	IPVD	PAWP < 15 mmHg
Symptoms	Dyspnea, platypnea, orthodeoxia	Fatigue, dyspnea on exertion, orthopnea
	Clubbing, cyanosis, spider angiomas	Right heart failure (raised JVP, prominent P2, tricuspid regurgitation murmur, lower extremity edema)
Chest X-ray	Usually normal	Cardiomegaly
		Hilar enlargement
Diagnostic tools	Contrast echocardiography	Right heart catheterization
	Technetium-99 labeled macroaggregated albumin scan	Echocardiography
	Pulmonary angiography	
PFT	Decreased DLCO	Decreased DLCO
Treatment	Oxygen supplementation	Vasodilators (epoprostenol, iloprost, sildenafil)
	Liver transplant	Liver transplant (for mild to moderate)

12.8 Hepatic Hydrothorax

Hepatic hydrothorax (HH) is a manifestation of advanced liver disease and occurs in 5–12% of patients [21]. It is defined as accumulation of fluid in pleural space (usually >500 mL) in the absence of cardiac, pulmonary, or pleural diseases. It usually occurs in conjunction with ascites; however it may occur in the absence of ascites [22]. In the presence of ascites, the peritoneal fluid enters the thoracic cavity through microscopic openings in the tendinous part of the diaphragm. Cyclic negative intrathoracic pressure along with openings in diaphragm allows unidirectional passage of fluid from peritoneal to pleural cavity. HH becomes apparent when the absorptive capacity of pleural space is exceeded. It is usually right sided because congenital diaphragmatic fenestrations are more common in right hemidiaphragm, and left hemidiaphragm is thicker and muscular.

In the absence of ascites, the mechanism of fluid collection in the thoracic cavity is the same. In these cases, the reabsorption capacity of pleura is same as the accumulation of ascitic fluid, so ascites collection does not occur [23]. The mechanism of collection of fluid has been confirmed by demonstration of unidirectional passage of markers like 99mTc-human albumin or 99mTc-sulfur colloid from the peritoneal cavity to the pleural cavity [24, 25].

The fluid collected in HH is transudative in nature. Patients with HH may develop spontaneous bacterial empyema (SBE), similar to subacute bacterial peritonitis.

The symptoms of HH are nonspecific—dyspnea, nonproductive cough, and pleuritic chest pain and fatigue.

Thoracocentesis is done to establish the diagnosis and to exclude the other causes of pleural effusion, like infection, thromboembolic diseases, or metastatic carcinoma. Thoracocentesis also helps to relieve symptoms. Computed tomography is done to rule out lung or pleural lesion. Doppler ultrasonography may be done to evaluate portal and hepatic vessels patency.

Management of hepatic hydrothorax is similar to ascites. Diuretics and salt restriction are the first line of management. The aim of management is to relieve symptoms and to prevent infection and complications. Therapeutic thoracocentesis and paracentesis may be required before liver transplant surgery.

Refractory hydrothorax refers to persistent pleural effusion despite salt restriction <2 g/day and high-dose diuretic therapy and repeated thoracocentesis [26]. In these cases, transjugular intrahepatic portosystemic shunt (TIPS) may be considered to control pleural effusion.

Although hepatic hydrothorax is not an indication for liver transplant, it improves after the transplant surgery [26].

12.9 COPD and Smoking

Chronic obstructive pulmonary disease (COPD) is very common in patients undergoing liver transplantation. Old age and smoking are significant risk factors of COPD and have adverse consequences on the functional status and quality of life in these patients. Smoking is also commonly seen in patients undergoing liver transplant. According to a multicenter study, 60% of liver transplant candidates had a history of past or present smoking [27]. It is very important to optimize COPD and smoking in patients undergoing transplant because perioperative outcomes may be compromised. Moreover, smoking has been shown to increase the risk of malignancy [28].

COPD is characterized by progressive airflow limitation that is not fully reversible. These patients have dyspnea, exercise limitation, susceptibility to infections, and exacerbations. They have abnormal blood gases and pulmonary function tests. Patients with advanced liver disease also have abnormal pulmonary functions. Their lung volumes are decreased because of hepatomegaly, ascites, pleural effusion, and basal atelectasis. It is important to have prebronchodilator and postbronchodilator spirometry in patients suspected to have COPD to confirm the diagnosis. Postbronchodilator FEV1/FVC ratio less than 0.7 indicates airflow limitation.

The BODE index is a multidimensional system for the assessment of COPD severity and

prognosis. This is calculated based on weight (BMI), airway obstruction (FEV1), dyspnea score (mMRC), and exercise capacity (6 min walk distance) and has been used to assess an individual's risk of death.

12.10 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive nocturnal breathing cessation due to upper airway collapse. Recent studies have demonstrated that OSA is associated with the development and evolution of nonalcoholic fatty liver disease (NAFLD), independent of obesity or other shared risk factors [29]. It is very important to properly diagnose and manage OSA before taking up these patients for surgery. Untreated OSA leading to hypoxia and hypercapnia may present challenges to postoperative weaning from ventilator.

Preoperative screening using STOP-BANG questionnaire and sleep study must be done in patients at risk for OSA. CPAP should be initiated from the preoperative period in patients with severe OSA, and sedative medications including opioids must be used carefully.

12.11 Interstitial Lung Disease

Interstitial lung disease (ILD) is a group of disorders that causes fibrosis of the lungs. ILD is characterized by four manifestations: (1) respiratory symptoms such as shortness of breath and cough, (2) specific chest radiographic abnormalities, (3) decreased lung capacity and restrictive PFT, (4) characteristic inflammation and fibrosis of interstitium.

ILD is associated with primary biliary cirrhosis and autoimmune hepatitis [26]. In telomerase mutations, ILD and cryptogenic CLD may occur concomitantly. Liver transplant does not improve ILD, rather it continues to progress after transplant. Antifibrotic drugs may improve ILD, but does not cure it completely. Liver transplant is contraindicated in moderate to severe ILD.

12.12 Alpha1 Antitrypsin Deficiency

Alpha1 antitrypsin deficiency (AAT) is a genetic disorder caused by the deficiency of alpha1 antitrypsin, a serine protease inhibitor. Individuals with this disorder develop obstructive pulmonary disease, liver disease (cirrhosis and hepatocellular carcinoma), and rarely skin lesions (panniculitis).

Individuals having 2 M alleles have normal AAT structure and function, whereas Z and S alleles have abnormal AAT [30]. The liver disease in this disorder occurs due to accumulation of abnormal AAT in the hepatocytes [31]. Emphysema results from an imbalance between neutrophil elastase in the lung that destroys elastin and the elastase inhibitor AAT that protects against proteolytic degradation of elastin [32].

Cigarette smoking and lung infections increase the elastase load in lungs further leading to lung degradation. The clinical features of AAT deficiency are similar to usual COPD except that its onset is at younger age and emphysema is panlobular or basilar and family history of emphysema may be present.

Liver transplant in these patients results in the normalization of AAT levels and function. However despite normal levels of AAT after liver transplant, FEV1 continues to decline unexpectedly in some ZZ or SZ patients [30].

12.13 Arteriovenous Malformations (AVM)

Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome) is an autosomal dominant disorder characterized by arteriovenous malformations in organs like liver, lung, brain, and gastrointestinal tract. It has a variety of clinical manifestations like epistaxis, gastrointestinal bleeding, iron deficiency anemia, and mucocutaneous telangiectasia.

Pulmonary AVM allow systemic venous blood to bypass pulmonary circulation and result in embolic stroke, brain abscess, and migraines. Cerebral AVMs can cause hemorrhagic stroke.

Hepatic AVMs can result in high output heart failure, portal hypertension, and biliary necrosis and require liver transplant. In patients with high output failure associated with hepatic AVM, **bevacizumab** has been shown to reduce cardiac output and quality of life [33]. Embolization of hepatic AVMs can also be done but may cause ischemic biliary necrosis.

12.14 Pulmonary Nodules

Pulmonary nodules may be detected during routine preoperative evaluation of liver transplant patients. A biopsy of the nodule is mandatory for diagnosis and further management. It can be primary lung malignancy or metastatic liver malignancy (HCC) or may represent granulomatous infection. In case it is granulomatous infection, it must be treated before transplant. However there is a possibility that the infection may be reactivated after transplant (immunosuppressive medication).

In metastatic HCC, liver transplant is contraindicated. In case nodules are >10 mm in diameter FDG-PET can be helpful in evaluation. If nodules are <10 mm in diameter, CT scan is preferable.

If pulmonary nodules are detected after the transplant surgery in HCC patients, they are managed with surgical excision of the nodules [26].

12.15 Preoperative Assessment

12.15.1 History

A carefully obtained detailed history from the patients scheduled for liver transplant is a must and helps in the diagnosis of diseases unrelated to liver failure. The most common pulmonary symptom in these patients is dyspnea, which can be multifactorial [8] (Table 12.4). It is important to ask the patient about the duration of symptoms and relieving or aggravating factors. Other associated symptoms like orthopnea, platypnea, cough, wheezing, chest pain, and edema should be asked for and should be characterized.

Table 12.4 Causes of dyspnea in patients with liver disease

Due to liver disease per se
1. Hepatopulmonary syndrome
2. Portopulmonary syndrome
3. Hepatic hydrothorax
4. Interstitial lung disease (associated with primary biliary cirrhosis)
5. Alpha1 antitrypsin deficiency (panlobular emphysema)
6. Arteriovenous malformations
7. Pulmonary nodules (metastatic)
8. Ascites (causes atelectasis and muscle wasting)
9. Cardiomyopathy (cirrhotic)
10. Severe anemia
Not related to liver disease
1. Chronic obstructive pulmonary disease
2. Restrictive pulmonary disease
3. Obstructive sleep apnea (OSA)
4. Cardiac disease

Dyspnea associated with cough with expectoration and wheezing indicates presence of COPD, bronchial asthma, or ILD. Dyspnea relieved with paracentesis is due to ascites. Dyspnea associated with platypnea suggests HPS. History of smoking should be elicited and if present, patient should be advised to quit before surgery.

Occupational hazards like exposure to asbestos may be present and can lead to ILD. These patients present with progressive dyspnea.

Symptoms like snoring, disturbed sleep, and daytime sleepiness suggest OSA, and appropriate measures should be taken to optimize the disorder. These patients may have difficulty in extubation during the postoperative period.

A positive family history helps in diagnosing α1 antitrypsin deficiency and hereditary hemorrhagic telangiectasia.

12.15.2 Physical Examination

A thorough physical examination of the patient provides clue to the diagnosis of pulmonary disorders. On general examination, patient's weight and BMI must be checked and recorded as it is important to screen for OSA [34]. If history of snoring and sleep breathing disorder is there,

STOP-BANG questionnaire helps in screening for OSA.

On general examination, finger clubbing, peripheral cyanosis, nail telangiectasia, and spider angiomatosis may be present and point towards presence of HPS. The presence of peripheral edema may be because of right heart failure.

Airway assessment and neck examination must be done to screen for difficult intubation. These patients have deranged coagulation, so intubation should be smooth and atraumatic.

In cardiovascular examination, the presence of systolic murmur at left sternal border, loud pulmonic component of second heart sound, right ventricular heave, and raised JVP suggests the presence of pulmonary hypertension.

In respiratory system examination, we should look for adventitious breath sounds like rhonchi, crepts, and crackles. These may suggest the presence of COPD and ILD.

Pulse oximetry shows decreased saturation in patients with liver failure and indicates hypoxemia. Fall in oxygen saturation with change in position from supine to upright is seen in HPS and requires further evaluation.

12.15.3 Laboratory Investigations

Laboratory investigations help us in the evaluation of disease and establishing the diagnosis. Although not directly affecting pulmonary assessment, MELD scoring helps us in staging the liver failure and urgency of liver transplantation. In patients with high MELD score requiring urgent liver transplantation, any concomitant pulmonary disease must be identified and optimized early for better outcome.

α1 antitrypsin levels and genotypic analysis (for M, S, Z alleles) must be done in patients with suspected α1 antitrypsin deficiency.

Patients with suspected OSA must undergo **overnight pulse oximetry**, which is a simple screening method [35]. It is important to identify this disorder, as this may delay extubation and will add to the pulmonary complications. These patients may have to undergo sleep study or polysomnography and may be advised noninvasive BiPAP/CPAP till they undergo transplantation.

ABG is done in patients with end-stage liver disease as a part of evaluation to look for hypoxia and hypercapnia, which may be due to hypoventilation. In case of HPS, orthodeoxia is present in which PaO_2 decreases by more than 5% or 4 mmHg in upright position. Although this is seen in only 25% of the patients, it is a significant finding [36]. ABG is also done to assess the severity of HPS.

NT-pro brain natriuretic peptide is a useful prognostic indicator in patients with PoPH [37].

Chest X-ray is done as a routine investigation in patients undergoing transplant. Hepatic hydrothorax, COPD, or any lung lesion may be diagnosed with chest X-ray. In a country like India where pulmonary tuberculosis is so common, chest X-ray may reveal old tubercular infection. Any active infection needs to be treated. In case any parenchymal lesion is found on chest X-ray, **computed tomogram** (CT) may be done to define the lesion.

Electrocardiogram (ECG) is another routine investigation done in all patients to assess cardiac rate, rhythm, and any ischemic changes. Any chamber enlargement or bundle branch block may be seen in ECG.

Pulmonary function test (PFT) is done in all the patients undergoing liver transplant as a part of pulmonary assessment. Interstitial fluid collection, pleural fluid, and liver cirrhosis all lead to abnormalities in PFT. All the parameters like FEV1, FVC, and FEV1/FVC and FEF 25–75% may be affected in these patients.

In case the patient has any respiratory symptom, PFT helps in evaluating whether it is restrictive or obstructive lesion. Moreover, it tells about bronchodilator responsiveness in obstructive lesion. Patients with ILD have restrictive defects and must undergo PFT to assess functional capacity of the lungs. These patients also have reduced diffusion capacity of CO.

Echocardiography is done in all patients undergoing transplant [38]. As regards pulmonary system evaluation, transthoracic echocardiography (TTE) is a screening test in PoPH for assessing right ventricular size and function and to evaluate right ventricular systolic pressure. Patients awaiting transplant with normal echocardiography must repeat TTE once a year. Various studies have given different threshold values of right ventricular systolic pressure (RVSP) which should prompt further investigation like right heart catheterization. A value of 38–50 mmHg in presence of right ventricular dilatation or dysfunction has been suggested as a cutoff value for further evaluation [39]. Recent guidelines by American Association for the study of Liver Diseases (AASLD) recommend right heart catheterization in patients with RVSP ≥ 45 mmHg [38].

Right heart catheterization is an invasive procedure that is done, when indicated, to confirm the diagnosis of PoPH. The prerequisite for this invasive procedure involves platelet counts ≥50,000 and INR < 1.5. It may be done as a day-care procedure. Swan-Ganz catheter is inserted into central vein and placed in pulmonary artery and is used to measure mPAP and PACW. Cardiac output is measured using thermodilution or Fick method, and pulmonary vascular resistance is measured using the formula:

$$\mathrm{PVR} = \left(\mathrm{mPAP} - \mathrm{PAWP}\right) / \mathrm{CO}$$

It is very important to calculate PVR in patients suspected to have PoPH. PVR reflects right heart afterload and if it is increased it means right heart failure is present and this will cause increased central venous pressure. This will be transmitted backward and will cause hepatic venous congestion and graft failure.

When PAP is >25 mmHg, PAWP is <15 mmHg, and PVR is >3 Wood units, diagnosis of PoPH is made.

Contrast echocardiography is a technique used to evaluate intracardiac or intrapulmonary shunting. Agitated saline is the most commonly used contrast. The gas microbubbles are short lived and diffuse into the lungs while traversing the pulmonary circulation. Whenever gas bubbles appear on the left side of the heart (visualized as opacification), it means either there is intracardiac shunt or intrapulmonary arteriovenous malformation leading to shunting. For detection of intrapulmonary shunt, the gas bubbles must be smaller in size (<10 μm diameter) [40]. The agitated saline is administered intravenously, and the appearance of bubbles on the left side within one or two cardiac cycles means presence of intracardiac shunt. If the bubbles are visualized after three or more cardiac cycles, it indicates intrapulmonary shunting [2]. According to American Society of Echocardiography guidelines, an alternative name for echocardiographic contrast agents as Ultrasound enhancing agents (UEAs) has been given [41].

Macroaggregated Albumin Technetium-99m-labeled macroaggregated albumin (99mTc MAA) lung perfusion scanning is an alternative method of confirming intrapulmonary shunt in HPS. 99mTcMAA is injected intravenously and in normal conditions it gets trapped in pulmonary circulation. The normal diameter of lung capillary vessel is less than 8–15 μm. Agitated saline creates bubbles greater than 10 μm in diameter that do not normally pass the lung capillaries. Scans showing radionuclide uptake by the brain or kidney indicate shunting and if the uptake is >6%, it is consistent with HPS. Unlike contrast echocardiograph, it does not differentiate between intracardiac and intrapulmonary shunts. However, concomitant transesophageal echocardiography may be used to visualize the source of microbubbles in the left heart [2]. 99mTc MAA may be used to quantify the shunt fraction in patients with HPS. Patients with shunt fraction more than 20% have higher perioperative mortality. This method is also useful to differentiate hypoxemia due to concomitant liver disease and due to intrapulmonary shunting (HPS) [42].

Another test used to assess pulmonary status in patients with liver disease is **6-min walk test**.

Although nonspecific, it indicates physical function and may be used for therapeutic response in patients with pulmonary dysfunction. During the 6-min walk test, a healthy individual can walk up to 400–700 m [43]. In patients undergoing transplant, the walk distance <250 m is associated with poor outcome [44].

12.16 Management

12.16.1 HPS

This life-threatening complication of advanced liver disease usually develops insidiously. However, this insidious progression with stable nature of CLD often leads to delay in diagnosis and listing for LT.

The definitive treatment of HPS is liver transplantation. For mild to moderate HPS, oxygen support to maintain saturation >89% is the most effective therapy. Otherwise once the diagnosis is made and till the patient undergoes transplantation supportive management is initiated.

Other therapies that have been tried with variable effect on improvement of gas exchange in HPS are spring coil embolization (to physically occlude shunts), octreotide, nitric oxide synthase inhibitors, indomethacin, almitrine bismesylate, methylene blue (inhibits NO stimulated guanylate cyclase), alum sativum (garlic), propranolol, plasma exchange, and pentoxifylline [7].

In patients with mild HPS with resting PaO_2 > 55 mmHg or SpO_2 > 88%, oxygen support is not required unless they have exercise-induced or nocturnal hypoxemia. In these patients, 6-min walk test or nocturnal saturation monitoring may be done.

The prognosis of patients with HPS is poor with increased mortality, regardless of oxygenation status [3]. Due to poor quality of life and increased mortality, they should be considered for early liver transplantation, preferably before they have severe hypoxemia. Because of these reasons, HPS patients are eligible for "MELD exception policy." In case of PaO_2 < 60 mmHg on room air without clinical evidence of underlying pulmonary disease, presence of portal hypertension, and evidence of intrapulmonary vasodilatation by TTE, a score of 22 is assigned. The score increases by 10% mortality equivalent points if repeat ABG shows PaO_2 < 60 mmHg.

There is no lower cutoff limit of PaO_2 that would preclude liver transplant. However some studies have reported that severe hypoxemia (PaO_2 < 50 mmHg) and shunt fraction >20% are associated with increased mortality [45, 46].

The oxygenation usually improves after liver transplant, but the time course is variable. Some may improve within days after transplant; some may take 2–14 months. It may be related to the severity of pretransplant hypoxemia [45].

12.17 Portopulmonary Hypertension

Preoperative management of PoPH is complex and treatment should target portal hypertension as well as pulmonary hypertension. It should be done at experienced center with the goals to improve quality of life, exercise capacity, and survival of the patient. In liver transplant candidates, additional goals are improvement in pulmonary hemodynamics and right ventricular function to improve the outcomes of liver transplant.

General measures—like all patients with PAH, patients with PoPH should receive supportive measures like oxygen and diuretics. Oxygen is supplemented to maintain saturation >89%. They are counseled against smoking if positive history is there. They are encouraged to exercise as possible and receive vaccinations. Anticoagulants are generally not given to PoPH patients as they have coagulopathy, thrombocytopenia, and varices.

Patients with PoPH should receive treatment for portal hypertension. β blockers and TIPS are not indicated in these patients (management modality of portal hypertension). β blockers should be avoided as they can worsen right heart failure due to reduction in right ventricular output and increase in PVR [47]. TIPS can increase preload to right ventricle and worsen heart failure. In moderate PoPH, TIPS should be avoided.

Esophageal varices should be managed with banding. Balloon-occluded retrograde transvenous obliteration (BRTO) is a newer therapy in the management of acute bleeding from gastric varices.

12.18 Specific Therapy

12.18.1 PAH-Specific Therapy Includes

1. Prostacyclin pathway agonist—Epoprostenol, Iloprost, Treprostinil, and Beraprost are used for pretransplant management of PoPH. Epoprostenol is a potent vasodilator and is given as continuous intravenous infusion (short half-life 3–5 min). Some common side effects of epoprostenol are diarrhea, nausea, flushing, headache, jaw ache, and leg pain. The infusion should not be stopped abruptly as it may cause sudden rebound vasoconstriction and elevation of PAP. Treprostinil can be given intravenously or by subcutaneous route. Iloprost can be given intravenously, orally, or by inhalation route. **Selexipag**, an, oral prostacyclin agonist used in the treatment of pulmonary hypertension has not been tested in patients with PoPH.
2. Endothelin receptor antagonist—Bosentan, Macitentan, and Ambrisentan target endothelin-1 pathway. Bosentan has been shown to be effective in the management of PoPH [48]. However, it can cause liver injury, so monthly liver function tests are mandatory. Ambrisentan and Macitentan do not require frequent monitoring but baseline liver function tests must be done.
3. Phosphodiesterase—5 inhibitors—the drugs in this group act through cAMP and nitric oxide pathway and cause vasodilatation. Sildenafil, Tadalafil, and Vardenafil are some of the agents. Sildenafil is a selective lung tissue phosphodiesterase-5 inhibitor and is effective in reducing PAP in liver transplant patients. Combination therapy with two or three drugs may be given in severe PoPH.
4. Guanylate cyclase stimulant—Riociguat is a guanylate cyclase stimulant.
5. Calcium channel blockers—they are used in idiopathic PAH but avoided in PoPH. Calcium channel blockers may cause hypotension and splanchnic vasodilatation resulting in an increase in hepatic venous pressure gradient.

In the past, liver transplant was considered a contraindication for patients with PoPH but now transplant has been done successfully in patients with mild to moderate PoPH. Although liver transplant is not a treatment for PoPH, but it can be done in these patients provided their PAH is treatment responsive. In some studies, improvements in pulmonary dynamics have been reported after liver transplant in patients with treated PoPH [49].

In patients with mPAP > 50 mmHg, liver transplant is absolutely contraindicated. Guidelines [2] recommend treatment of PoPH with PAH-specific therapy in patients with mPAP > 35 mmHg with the aim to reduce mPAP < 35 mmHg, PVR to <2 Wood units, and improve right ventricular function.

MELD SCORE: As with HPS, patients with PoPH also receive MELD exception score of 22. Every 3 months, they undergo right heart catheterization and get their score upgraded by 10% while they are on liver transplant wait list.

12.19 Hepatic Hydrothorax

Management of hepatic hydrothorax is similar to ascites. Diuretics and salt restriction are the first line of management. The aim of management is to relieve symptoms and to prevent infection and complications. Therapeutic thoracocentesis and paracentesis are done in symptomatic patients and may be required before liver transplant surgery. Refractory hydrothorax refers to persistent pleural effusion despite salt restriction <2 g/day and high-dose diuretic therapy and repeated thoracocentesis [26]. In these cases, transjugular intrahepatic portosystemic shunt (TIPS) may be considered to control pleural effusion.

Chest tube should not be inserted for HH only because it can result in massive protein and electrolyte depletion, infection, renal failure, and bleeding [50]. Once inserted, it is very difficult to remove chest tube in these patients and also it has been associated with increased mortality and longer hospital stay [51]. Chest tube insertion is done in patients with SBE.

Pleurodesis is challenging in these HH, although it has been tried in patients with refractory HH. It is difficult to keep the two surfaces of pleura apposed for long time for inflammation to occur, as there is rapid filling of fluid in pleural cavity. Moreover this technique is associated with multiple complications [52].

Thoracoscopic mesh repair of diaphragmatic defects may be done for refractory HH [53].

12.20 Summary

In patients undergoing liver transplantation, pulmonary diseases are common and invariably affect prognosis. A thorough preoperative evaluation and management of pulmonary issues is mandatory in these patients to improve outcome.

Key Points

- A careful pulmonary evaluation and optimization of liver transplant patients improve the outcome.
- Hepatopulmonary syndrome is a clinical trial of abnormal arterial oxygenation caused by intrapulmonary vasodilatation in the setting of liver disease.
- Portopulmonary hypertension is pulmonary hypertension (>25 mmHg) associated with portal hypertension and the gold standard for diagnosing portopulmonary hypertension is right heart catheterization.
- Hepatic hydrothorax is collection of fluid (>500 mL) in patients with chronic liver disease in the absence of cardiac, pulmonary, or pleural disease.
- Patients with HPS have severe hypoxia and improve with liver transplant, whereas patients with portopulmonary hypertension have mild hypoxia and have variable outcome after liver transplant.

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