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Review Article

Lung Abnormalities in Liver Cirrhosis

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ABSTRACT

Regardless of preexisting lung illness, patients suffering from liver cirrhosis, especially decompensated liver cirrhosis can develop distinct pulmonary complications. Liver cirrhosis patients should be assessed for hepatopulmonary syndrome (HPS), portopulmonary hypertension (PoPH), hepatic hydrothorax (HH) and spontaneous bacterial empyema (SBEM) which are the most clinically significant pulmonary consequences, in particular when dyspnea develops in conjunction with hepatic cirrhosis. These entities differ in terms of pathophysiology, clinical characteristics, diagnosis and suitable treatment options. This emphasize the need of specific diagnostic algorithm in liver cirrhosis patients presenting with dyspnea or other pulmonary symptoms. These pulmonary complications might be rare in patients with liver cirrhosis and portal hypertension but these complications might carry significant morbidity and mortality risks and, therefore, strong clinical suspicion is required to make an early accurate diagnosis. There are several medical therapies available for each condition in the multiple studies but most of the treatments and proceures doesn't have significant benefit or have short lived benefit. The only treatment that changes the clinical prognosis of decompensated cirrhosis effectively in long term is liver transplantation. However liver transplantation also needs careful considerations as on some cases it might increase the risk of morbidity and mortality.

Keywords: Cirrhosis Hepatis, Hepatopulmonary Syndrome, Portopulmonary Hypertension, Hepatic Hydrothorax, Spontaneous Bacterial Empyema

INTRODUCTION

Chronic liver diseases might further developed into cirrhosis. According to studies, within developed countries, HCV, HBV, alcoholic liver disease, and NASH are the most prevalent etiologies. Other plau-sible etiologies includes alpha-1 anti-trypsin deficiency, Budd-Chiari syndrome, Wilson disease, cirrhosis included by autoimmune hepatitis, primary biliary and primary sclerosing cholangitis, hemo-chromatosis, drug-induced cirrhosis of the liver, and chronic right heart failure.(1)

It has been known for a while that chronic liver disease does coexist with changes in pulmonary function. It was already reported in 1977 on a post-mortem examination of the lungs showing extensive vasodilatation of the pulmonary vasculature in patient suffering with liver cirrhosis. It was then suspected that these changes are related to the pulmonary clinical changes in patients suffering from chronic liver disease.(2)

Patients with hepatic cirrhosis are at risk for developing respiratory problems. It is important to distinguish between these

specific problems and primary lung conditions such as COPD, which might also affect liver patients but isn't linked to hepatic cirrhosis. Hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax, and pulmonary empyema, are some of the most prevalent and clinically distinct pulmonary conse-quences.[3] Pulmonary complications increase the risk of further mortality and morbidity.[4,5]

Liver Cirrhosis: Causes and Pathophysiology

Cirrhosis can occur due to intoxication (alcoholism), infection (Hepatitis B, Hepatitis C), allergic reaction, immunopathological/autoimmune disorder (autoimmune hepatitis, autoimmune cholangiopathy), or congenital metabolism disorders (inherited metabolic liver disease such as hemochromatosis, wilson's disease, cystic fibrosis, or a_1 Antitrypsin deficiency). Worldwide, around 2 million deaths are contributed by liver disease, where 1 million of them are due to cirrhosis. In Indonesia, according to *Riskesdas* survey done in 2013, Hepatitis B prevalence reaches to 7,10% of the population. In Indonesia, the proportion of pregnant women with reactive HBsAg is 1.61% in 2021. In addition, there were around 820,000 deaths in 2019 due to Hepatitis B virus infection, mainly occurring through the development of cirrhosis and hepatocellular carcinoma.[6–8]

Regardless of the possible etiologies, pathological characteristics consist of fibrosis development resulting in architectural distortion with formations of regenerative nodules. This fibrosis process will then gradually decreases hepatocellular mass, function, and alter liver vascularization. Fibrosis induction started with hepatic stellate cells activations, increasing collagen and other extracellular matrix.[7]

There are several cells contributing to the progression of liver fibrosis. The primary cell type implicated in this process is hepatic stellate cells (HSCs). Due to the response of constant liver injury, HSC decrease the expression of genes including glial fibrillar acidic protein, PPARγ (peroxisome proliferator-activated receptor gamma), lose lipid droplets and activate into myofibroblasts. The expression of fibrogenic genes such as collagen Type I and alpha-smooth muscle actin (-SMA) begins in myofibroblast. They multiply and go to the liver injury site, secreting ECM. Vascular endothelial growth factor (VEGF) which is directly associated with HSC proliferation is also released by myofibroblasts. Myofibroblasts and fibrogenic genes would then alters the contractile tone of smooth muscle cells, thus increasing the sinusoidal blood flow (around sinusoids and hepatic venules), which will lead to further vascular syndromes in liver cirrhosis.[5]

Another important component are hepatocytes. Osteopontin, Transcriptional coactivator with PDZ-binding motif (TAZ), NADPH oxidase 4 (NOX4), Notch and Indian Hedehog are just a few of the fibrogenic factors that hepatocytes begin to produce after liver injury. Furthermore, damaged hepatocytes may discharge exosomes containing micro RNAs (miRNAs) that contributes to HSCs activation. However, in the absence of persistent inflammation, hepatocyte-derived fibrogenic factors would not cause liver fibrosis.[9]

The next components are inflammatory cells and cytokines induced by chronic inflammation. Neutrophils, Kupffer cells (hepatic macrophages), Th17, and bone marrow-derived monocytes are promoting HSC initiation by inducing cytokines and growth factors productions. Liver macrophage, specifically Kupffer cells (KC) is a primary source of TGF-β. TGF-β binds to its receptor in HSCs, activating myofibroblast and collagen Type I and III synthesis inducing fibrogenesis. KC also mediates liver inflammation and is thought to exacerbate liver injury and fibrosis, particularly be-

cause KC is continuously activated by DAMP (Damage Associated Molecular Pattern) released by dead hepatocytes in the late stages of the disease. Other fibrogenic cytokine secreted during liver injury includes CCL2 promoting HSCs initiation by recruiting monocyte derived macrophage. There's also PDGF (Platelet-derived growth factor) signaling pathwaysa that is important to HSC initiation.[9,10]

Aside from that, reactive oxygen species (ROS) also promotes HSC activation. Kupffer cells, not only contribute to cytokines and chemokines production, also further contribute to the production of ROS. NADPH oxidase (NOX) promotes ROS production. ROS would then also contributes to the activation of HSCs and further contributes the progression of fibrosis.[9,11]

Liver Cirrhosis and Lung Complication

Cirrhosis might cause portal hypertension which further might cause esophageal and gastric varices. Further-more, decompensated cirrhosis might develops into several complications such as ascites, hepatic encephalopathy, variceal bleeding.[10,12]

Pulmonary complications can occur irrespective to the severity of the cirrhosis. There are several specific lung complication such as hepato-pulmonary syndrome (HPS), porto-pulmonary syndrome (PoPH), hepatic hydrothorax and sponataneous bacterial empyema.[3]

1. Hepatopulmonary Syndrome (HPS)

The definition of hepatopulmonary syndrome (HPS) is a decrease in arterial oxygen saturation due to dilated pulmonary vessels in portosystemic shunting or advanced to decompensated liver disease. HPS tends to develop on more severe liver disease. HPS on cirrhosis patient is also reported to double mortality rates.[2,3]

In HPS there are microvascular changes in the pulmonary arterial circulation, namely vasodilation and neoangiogenesis. Studies have shown that excessive production of pulmonary vasodilatory factors (nitrogen (NO), carbon monoxide (CO), and endothelin-1 (ET-1) contributes to pulmonary vasodilation Liver cirrhosis and portal hypertension increases ET-1 production by hepatic cells, inducing more eNOS activation and accumulation of monocytes. Activation of eNOS and iNOS elevates NO production inside pulmonary vasculature. Accumulating monocytes and monocyte-derived macrophages express iNOS and produce heme oxygenase-1, induce the production of CO and contributes to vasodilatation. The macrophages and monocytes may accumulate in the lungs due to translocation of intestinal bacteria and endotoxemia due to liver disease in the patient. These cells produce tumor necrosis factor-alpha (TNF-α) which will induce iNOS activation and progressively produce heme oxygenase which causes heme degeneration and CO release. Angiogenesis also plays an important role on the development of HPS and has been confirmed by studies showing that inhibition of angiogenesis enhances gas exchange abnormalities. Angiogenesis is initiated by circulating monocytes that produced and upregulates CX3CL1 and VEGF. Both vasodilatation and neoangio-genesis leads perfusion and unaltered alveolar ventilation mismatch. Thus limitting right-left shunt, alveolar-capillary diffusion, and resulting in hypoxia.

There are two types of HPS, defined by the location of the vasodilatation. Type 1st type of HPS have vasodilated vessels on precapillary levels, near the place where gas exchange is performed in the lungs. On this type of HPS, supplemental O2 can increase PaO2. However, on the 2nd type of HPS, where larger vasodilatation caused arteriovenous to shunts away from gas exchange units, supplemental O2 is not beneficial.[2,3]

In the early phase of HPS, patients are usually asymptomatic. Cirrhotic patients with new HPS may experience unspecified

dyspnea that worsens with exertion, tachypnea, orthopnea, platypnea, cyanosis, diffuse telangiectasis (spider naevi), and clubbing finger. Platypnoea is a form of dyspnoea that gets worsen when sitting or standing and relieved by lying down. Meanwhile, orthodeoxia is a decrease in PaO2 of more than (upright) 5% or more than 4 mmHg when moving from supine to standing or sitting. Orthodeoxia is a result of incresing V/Q mismatch and decreasing cardiac output due to a shift from supine to upright position. Platypnoea and orthodeoxia are common features associated with HPS patients, although their sensitivity is low, they increase with the severity of HPS.[2,3]

Pulse oximetry should be used as a first-line screening test. Mild hypoxemia have PaO2 of >80 mmHg, moderate hypoxaemia have >60 - <80 mmHg PaO2, severe hypoxaemia have >50 - <60 mmHg PaO2, while very severe hypoxemia have <50 mmHg PaO2. Pulse oxymetry result below 96% for detecting HPS in patient with PaO2 bellow 70 mmHg is highly sensitive (100%) and specific (88%). The next testing in patients with suspected HPS is BGA. It is carried out within room air, with the patient seated first. This procedure is repeated in standing position for around 15 to 20 minutes. Increase in AaDO2 (alveolar-arterial oxygen partial pressure difference) ≥15 mmHg (at the age younger than or equal to 64 years old) or ≥20 mmHg (at the age older than 64 years old). Orthodeoxiais characterized by an increase in PaO2 with 100% oxygen inhalation, which should be above 300 mmHg, and a reduction in PaO2 of 4 mmHg or 5% from supine to upright position.[2,3]

Although a chest X-ray may show strong pulmonary vascular signs in lower lobes, HPS is not always the cause of this finding. CT is also usually done only to exclude possible pulmonary pathologies. To rule out any other related intrinsic lung diseases, pulmonary function tests should be carried out. The test with the highest sensitivity for showing an intrapulmonary shunt is echocardiography with contrast. In order to create bubbles larger than 10-15 microns in diameter, agitated 0.9% saline or indocyanine green are intravenously inject-ed during echocardiography. This is now established as the gold-standard method on evaluating intrapulmonary vasodilation. The test is positive when left atrial opacification is found with microbubbles between 4th to 6th cardiac cycle. This can further be graded into stage 1 (less than 30 microbubbles), 2 (30 to 100 microbubbles) and 3 (more than 100 microbubbles). Pulmonary angiography can also be used to differentiate type I and type II HPS. Type I HPS have normal or "spongy" appearance, while type II have discrete arteriovenous communications.[2–4]

Oxygen therapy is recommended for patients with severe hypoxemia (PaO2 ≤55 mmHg or SaO2 ≤88%), and given until liver transplantation can be performed. Transjugular intrahepatic portosystemic shunt (TIPS) still can't be recommended since there are still limited data with variative outcome. It may exacerbate hyperkinetic circulatory state, increase intrapulmonary vasodilatation, shunting, exacerbate hypoxemia, risk of decompensation and encephalopathy. The only recommended effective definitive treatment available is liver transplant. This is the only method shown giving significant benefit to increase survival rate and increase quality of life.[2–4,8]

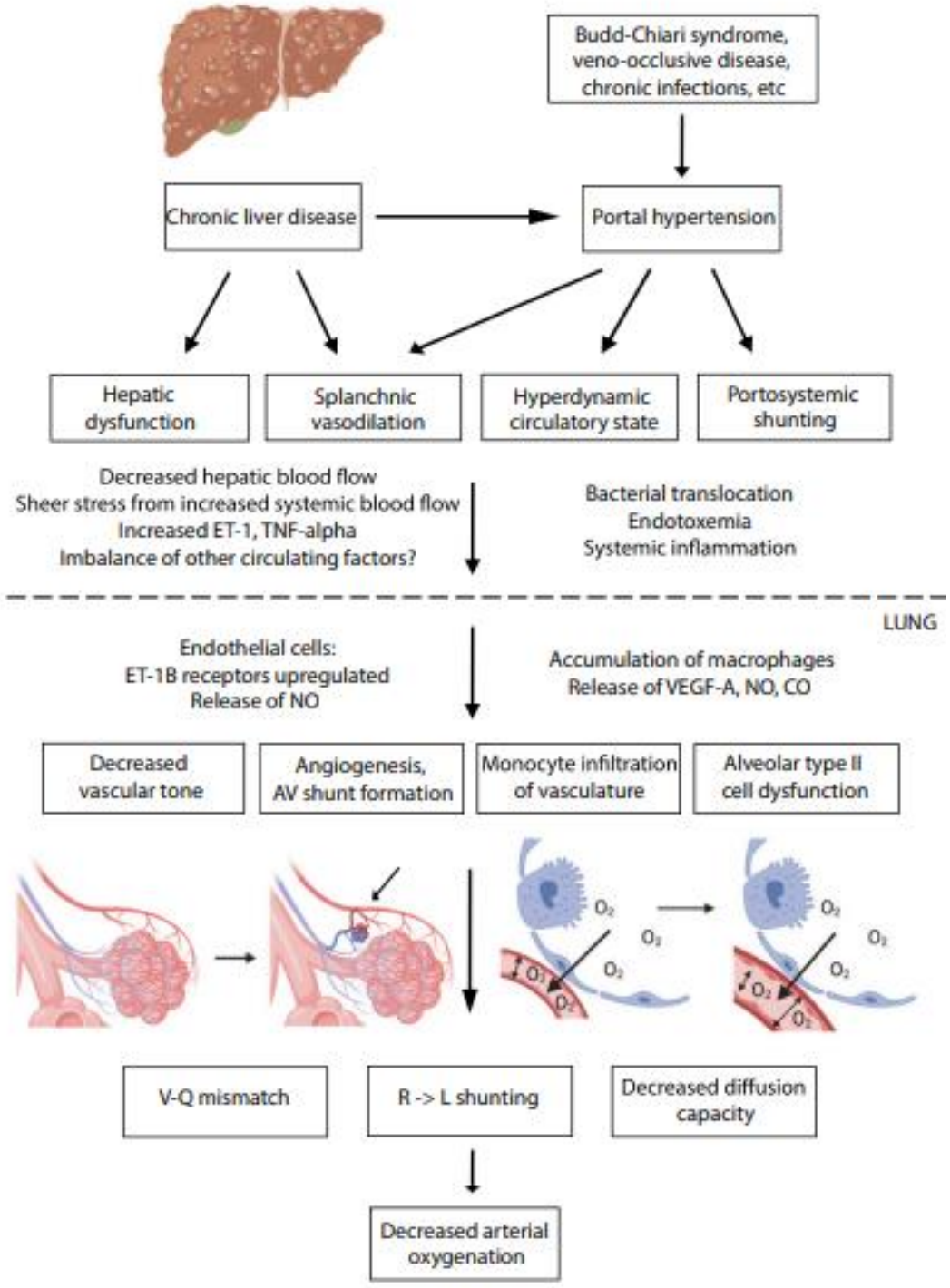

Figure 1. Pathogenesis of Hepatopulmonary Syndrome (HPS)[13]. Decrease in vascular tone, angiogenesis, and monocyte infiltration will contribute to V-Q mismatch, right to left shunting, and decrease in diffusion capacity. These will further decrease arterial oxygenation. Figure 1: Pathogenesis of Hepatopulmonary Syndrome (HPS).(13) Decrease in vascular tone, angiogenesis, and monocyte infiltration will contribute to V-Q mismatch, right to left shunting, and decrease in diffusion capacity. These will further decrease arterial oxygenation.

2. Portopulmonal Hypertension (PoPH)

Portopulmonary hypertension is defined as a disorder present with pulmonary artery hypertension (>25 mmHg) during resting coupled with the presence of portal hypertension and pulmonary capillary wedge pressure ≤15 mmHg with or without

significant liver disease. This condition has the same histo-logical characteristic of plexogenic arterio-pathy of idiopathic pulmonary hypertension. It also involves proliferation of endothelial and smooth muscle.[3,8]

Although its pathogenesis is still unknown due to lack of animal models, but some pathophysiological hypothesis were suggested. Firstly is the imbalance among vasoconstrictor and vasodilator mediators such as ET-1, thromboxane, IL-1, IL-6, and angiotensin. Hyperdinamic pulmonary circulation due to sphlanchnic vasodilation and increasing resistance to hepatic blood flow can also occur, resulting in portal venous hypertension. This will then increase sheer stress on pulmonary vascular wall as a result of increasing turbulence, leading to vascular remodelling. Permanent vascular remodelling due to this damage to pulmonary endothelium and the underlying smooth muscle then occur (mediated by E2, BMP9, and BMPR2). There's also a hypothesis suggesting there might be elevated local inflammation and oxidative and nitrative stress as a result of increasing cytokine associated with liver cirrhosis. At the same time, portosystemic shunts and inability of liver to filter blood adequately from digestive tract might result in bypass of bacteria endotoxins and increasing vasoactive substance into pulmonary circulation. Genetic polymer-phism also has some role in disease progression. Although all the hypothesis above might seems simmilar to HPS, but PoPH main pathophysiology is vasoconstriction, not vasodilatation.[3,4,14,15]

PoPH are usually asymptomatic at first. History of risk factors must be asessed during history taking, including diseases associated with PH. Manifestations might occur from underlying liver disease or other complications, thus can be confused with PoPH manifestations itself, such as fatigue, weakness, orthopnea, or hemoptysis. History that msut be assessed on patients suspected with PoPH are dyspnea both at rest or on exertion, weakness, fatigue, orthopnea, palpitations, syncope, and chest pain. Cyanosis is rarely present. Physical examination might show protrussion of pulmonary component from P2 (second heart sound), right sided S3 and a right sided S4 on the right side. Tricuspid regurgitation murmur might also present. Distended jugular venous, ascites, or edema on both lower extremity can also be found. Definitive diagnosis should be made by right heart catheterization (measuring MPAP, PAOP, CO, and PVR).[3,4,14]

Portopulmonary hypertension staging is measured made based on mean pulmonary arterial pressure either by right heart cathetherization (the gold standard method) or estimated cardiographically (a front line non-invasive alternative). MPAP of 25-35 mmHg is considered mild, 35-45 mmHg is moderate, and lastly >45 mmHg is considered severe. Pulmonary arterial wedge pressure (PAWP) should be ≤15 mmHg, peripheral vascular resistance (PVR) should be >240 dyn.sec.cm^{-5} and transpulmonary gradient (TPG) of >12 mmHg coupled with PH clinical evidence. Meanwhile echocardiograph can predict RVSP by measuring peak TRV using the modified version of Benoulli equation. TRV >3.4 m/sec or 2.9 to 3.4 m/sec along with echocardiographic findings of PoPH confirms high possibility of PoPH. Using echocardiographic, estimated RVSP ≥35 mmHg usually imply PAP >24 mmHg, while RSVP <30 mmHg can exclude PoPH. Electrocardiography might also show right atrial enlargement, right ventricular hyper-trophy, RBBB, and deviated axis to the right.[4,14]

Therapy for PoPH patients aims to reduce portal hypertension and prevent further complications (*e.g.*, thromboembolism or right heart failure). Routine anticoagulants administrations are not reccomended, as it increases the possibility of coagulopathy or esophageal varices, throm-

bocytopenia, increased bleeding risk. Some of the available medications commonly used includes endothelin receptor antagonists, prostacyclin pathway agonists, and NO-cyclic guanosine monophosphate enhancers (PDE5 inhibitors, such as sildenafil and tadalafil). CCB (calcium canal blockers) are not beneficial and BB (beta blocker) should also be avoided due to its side effect on increasing pulmonary resistance (PVR) and reducing right ventricle cardiac output.[3]

Liver transplantation in PoPH patients are complex as not all patient with would benefit from LT. Post-LT outcome in PoPH patient can be unpredictable and worsening pulmonary hypertension might occur, increasing mortality rate.[3,16]

In conclusion LT might improves PH and effective to treat PoPH, but it still need PAH-specific therapy, otherwise poor prognosis post-LT might still be found.[19,17]

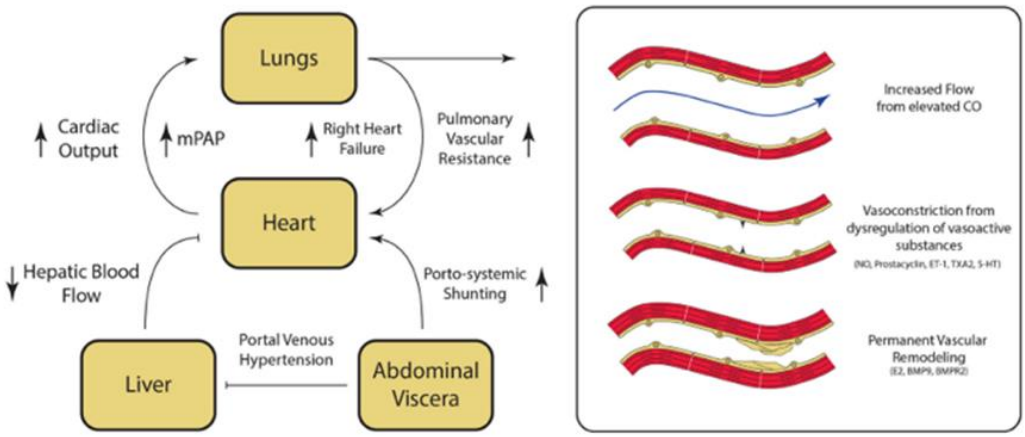

Figure 2: Pathogenesis of Portopulmonary Hypertension (PoPH)[14]. Fibrosis on the liver induce PH, followed by splanchnic vasodilatation and haptic blood flow resistance to increase. Overal circulating volume will then increase and blood flow diversion from liver to heart through porto-systemic shunting will lead to hyperdinamic state. At the same time remodelling on the vasculature mediated by inflammatory factors and cytokines will contribute to PH development.

3. Hepatic Hydrothorax (HH)

Pleural effusion, typically >500 mL in liver cirrhosis patients who has no coexisting cardiac or pulmonary disorders is referred to as hepatic hydrothorax (HH). This condition is thought to affect 5-10% patients with cirrhosis. The exact pathophysiology is not completely understood yet, but ther are some proposed hypothesis. Currently, transdia-phragmatic fluid shift to the pleural cavity through pleuroperitoneal communications from the peritoneal is the favored hypothesis. These might be observed in patients present with diaphragmatic lesions, frequently on right hemidiaphragm. This is because, compared to the left side, right side is less muscular and thinner.[3,4,18]

Even with a tiny amount of pleural effusion, patient with restrictive pattern of pulmonary function can nevertheless experience severe clinical symptoms. Patient may experience dizziness, fatigue, dyspnea at rest, dyspnea with exertion, pleuritic chest pain, chest discomfort, or non-productive cough. However clinical manifestation will not be specific, since usually HH coexist with ascites or other features of PH. Symptoms vary further according to effusion volume, rapidity of accumulation and associated cardiopulmonary disease presence.[3,18]

Diagnosis is performed based on thoracocentesis, distinguishing transudate and exudate. Pleural fluid analysis of HH will show the nature of transudative effu-

sion with simmilar feature to ascetic fluid. Total PMN (Polymorphonuclear) cell count should be <250/µL, total protein concentration <2.5 g/dL, a serum-to-pleural-albumin gradient >1.1 mg/dL, or an albumin quotient (pleural fluid/serum) <0.6. LDH gradient <0.6 (serum-pleural fluid), protein quotient <0.5 (pleural fluid /serum), pH value of 7.40 to 7.55, and pleural glucose level similar to serum level. Further imaging diagnosis such as USG and chest X-ray are valid to rule out other pulmonary diseases and malignancies. In some cases 99mTc-human serum albumin might also confirms HH when radioisotopes migrate into pleural space from peritoneal cavity.[3,4,18]

Liver transplantation remains the best choice for decompensated cirrhosis. It is also shown to provide best long-term survival and should be considered in all patients. On patients not eligible to perform LT, other procedures can be considered. Thoracocentesis is effective to relief symptoms, although benefits are short lived thus procedure needs to be repeated. TIPS can also be performed especially on refractory HH. TIPS is also superior compared to other modalities on rebleeding from varices prevention, however it doesn't improve end-stage liver disease prognosis. Medical management involves eliminating and preventing acites recurency. This includes sodium-restricted diet (70-90 mmol/day), weight loss 0.5 kg/day on non-edematous patient and 1 kg/day on edematous patient. Spironolactone 100 mg/day and loop diuretic such as furosemide 40 mg/day are used as initial regiment to excrete renal sodium >120 mEq/day. Medication dose may be increased every 3-5 days up to 160 mg/day for Furosemide and 400 mg/day for Spironolactone.[18]

4. Spontaneous Bacterial Empyema (SBEM)

Spontaneous bacterial empyema is a spontaneous infection from a pre-existing HH. This rarely occurs, but need to be considered. Diagnosis is based on total PMN (Polymorphonuclear) cell count <250/mm^3 with positive culture or PMN >500 cells/mm^3 with negative cultures. Therapy consist of IV 3rd generation of Cephalosporins (2g Ceftriaxone every 24 hous for 7-10 days). Piperacillin/ Tazobactam or Carbapenem should be considered on countries with high antibiotic resistance.[3]

It would be beneficial to consult patient with suspected liver cirrhosis as soon as possible with a hepatologist, especially to perform a thorough examination and evaluate unspecific symptoms such as dyspnea which can lead to suspicion of pulmonary involvement. Pulmonary complications increase the risk of further mortality and morbidity.[4,5] Thus, it is important to distinguish whether the symptoms arise from cirrhosis related pulmonary conditions or primary lung conditions such as COPD.

Early detection of the complication might lead to earlier treatment initiation. Patients with chronic liver cirrhosis would benefit from liver transplant, and most of the pulmonary complications such as HPS and HH would benefit from LT. However it should be noted that on patients with PoPH are more complex, as not every patient would benefit from LT.[13,17,19] This is where pulmonologist, cardiologist, and hepatologist might need to collaborate and determine the risk and benefit of the patient to determine whether the procedure should be admitted. Newer studies shows PoPH survival outcomes after LT were modest (higher PVR before LT was associated with worse survival, as was monotherapy use) and may reflect the need for more aggressive therapy.[19,20]

Table 1. Comparison between Pulmonary Complications

	Hepatopulmonary Syndrome (HPS)	Portopulmonal Hypertension (PoPH)	Hepatic Hydrothorax (HH)	Spontaneous Bacterial Empyema (SBEM)
Underlying Pathogenesis	Decreasing arterial oxygen saturation due to dilated pulmonary vessels on precapillary level (type I) or larger vasodilatation causing arteriovenous to shunt away from gas exchange (type II)	Pathogenesis is still unknown due to lack of animal models, but some hypothesis such as imbalance of vasoconstrictor and vasodilator is suggested	Exact pathogenesis is not completely understood, but hypothesis such as transdiaphragmatic fluid shift has been suggested.	Spontaneous bacterial empyema due to spontaneous infection from pre-existing HH
Specific Symptoms	Platypnoea (a form of dyspnoea that worsen when sitting or standing, relieved by lying down)	- Physical examination showing protrusion of pulmonary component from P2, right sided S3 and right sided S4 - Tricuspid regurgitation murmur - Distended jugular venous, ascites, edema		
Other Symptoms	- Unspecified dyspnea worsenes with exertion - Tachypnea - Cyanosis - Diffuse telangiectasis (spider naevi) - Clubbing finger	Usually asymptomatic, or present with unspecific symptoms: - Dyspnea both at rest or on exertion - Weakness - Fatigue - Orthopnea - Palpitation - Syncope - Chest pain	Unspecific symptoms because usually coexist with other conditions: - Dizziness - Fatigue - Dyspnea both at rest or on exertion - Pleuritic chest pain or chest discomfort - Non-productive cough	Unspecific signs of infection
Specific Diagnostic Findings	- Echocardiography with contrast to evaluate intrapulmonary vasodilatation - Pulmonary angiography to differentiate normal or 'spongy' type I HPS to discrete AV communication on type II HPS - Detecting orthodeoxia (decrease of PaO2 >5% or >4 mmHg when moving from supine to standing or sitting)) using pulse oximetry and BGA - Increase in PaO2 with 100% O2 inhalation, which should be above 300 mmHg	Right heart catheterization to measure: - MPAP: 25-35 mmHg mild, 35-45 moderate, >45 severe - PAWP: ≤15 mmHg - PVR: >240 dyn.sec.cm^{-5} - TPG: >12 mmHg Echocardiograph to predict RVSP (≥35 mmHg implying PAP >24 mmHg or <30 mmHg with other findings) by measuring TRV >3.4 m/sec or 2.9-3.4 m/sec with echocardiographic findings of PoPH	Thoracocentesis to find: - Transudative effusion similar to ascetic fluid - PMN <250/μL - Total protein concentration <2,5 g/dL - Serum-to-pleural-albumin gradient >1.1 mg/dL or albumin quotient (pleural fluid/serum) <0.6 - LDH gradient <0.6 (serum-pleural fluid) - Protein quotient <0.5 (pleural fluid/serum) - pH value 7.4 – 7.55 - Pleural glucose level similar to serum level	Thoracocentesis to find: - PMN <250/mm^3 with positive culture or PMN >500 cells/mm^3 with negative cultures
Less specific diagnostic finding	- Chest x-ray showing strong pulmonary vascular signs in		- USG and chest ray might be used to rule out other pul-	

	lower lobes - Rule out other intrinsic lung diseases with pulmonary function test		monary disease and malignancy - 99mTc-human serum albumin to confirm HH when radioisotopes migrate into pleural space from peritoneal cavity	
Suggested therapy	Oxygen therapy for severe hypoxemia until liver transplantation is performed	Reduce hypertension with medications: endothelin receptor antagonists, prostacyclin pathway agonist, & NO-cyclic guanosine mono-phosphate enhancer	Liver transplantation remains the best choice for decompensated cirrhosis. Other medical managements: Na restricted diet, weight loss, and diuretic	- IV 3rd generation of Cephalosporins. - Piperacilin/ Tazobactam or Carbapenem should be considered on countries with high antibiotic resistance

CONCLUSION

Liver cirrhosis may rarely develop into several pulmonary complications. These complications may result in significant morbidity and mortality if not treated early on. Pulmonary complications might be suspected when dyspnea occurs on patient with cirrhosis. Several diseases that should be suspected includes hepatopulmonary syndrome (HPS), portopulmonary hypertension (PoPH), hepatic hydrothorax and spontaneous bacterial empyema which represent the most clinically relevant pulmonary complications of cirrhosis of the liver. Different diagnostic procedures should be performed personalized based on each manifestation. Patients with these illness should be examined and evaluated for liver transplantation eligibility since it is the only effective treatment that improves the clinical prognosis significantly.

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