MANAGEMENT OF CARDIOPULMONARY COMPLICATIONS OF CIRRHOSIS

Prabha Sawant, Mukesh Nasa, Mumbai

End stage liver disease with the accompaniment of advanced portal hypertension results in an inadequate detoxification of blood from splanchnic circulation by the failing liver. Hepatic dysfunction resulting in an increased absorption and impaired neutralisation of the gastrointestinal bacteria and endotoxins and also associated with portosystemic shunts. Due to shunting of blood and decreased detoxification of bacteria cardiopulmonary complications occur which include hepatopulmonary syndrome, cirrhotic cardiomyopathy, portopulmonary hypertension and right sided hydrothorax

HEPATOPULMONARY SYNDROME

This terminology is defined by classical triad of presence of chronic liver disease or portal hypertension, alteration of arterial oxygenation, characterised by widened age corrected alveolar-arterial oxygen gradient with or without arterial hypoxemia and evidence of intrapulmonary vascular dilatations [IPVD]1

IPVD includes diffuse peripheral dilatation of pulmonary capillaries with resultant altered gas exchange. Cirrhotics evaluated for liver transplant the prevalence of HPS is approximately 10 to 20%. These patients should be evaluated for HPS irrespective of the stage of the liver injury. Without liver transplant the median survival for HPS is 2 years. The survival is worse if PO2 is less than 50 mm Hg; however death is more often due to the complications of liver disease or portal hypertension related events.2,3

Severe hypoxemia related to HPS is primarily due to IPVD. Nitric oxide (NO) is the major mediator of pulmonary vascular abnormality and acts as a vasodilator through guanylyl cyclase in vascular smooth muscle.4 Pulmonary vascular dilatation results in intrapulmonary shunting and impaired gas exchange. There is an alveolar capillary disequilibrium or diffusion-perfusion impairment due to dilatation of pulmonary precapillary and capillary vessels. The dilated capillary results in impairment of oxygen uptake by RBCs in the central stream of blood vessels.5 The transit time to the lung vasculature is shortened due to hyperdynamic circulation in the patients with liver disease.

Increased TNF-α due to bacterial translocation in cirrhosis leads to, increased macrophage adherence to pulmonary microvasculature which results in an increased inducible NO synthetase derived NO production.6 HPS should be considered independently of stage or etiology of liver disease. HPS has also been diagnosed in noncirrhotic portal hypertension and in chronic viral hepatitis without cirrhosis.

In patients who do not undergo liver transplantation, the 5 year survival rate is diminished in those who have HPS (20% vs 32-63% without HPS).7

Patients with HPS mostly present with exertional dyspnoea and subsequently at rest. Most patients will have signs and symptoms of chronic liver disease like gastrointestinal bleeding, esophageal varices, ascites, and splenomegaly. Digital clubbing, cyanosis, dyspnea, platypnea, orthodeoxia are the associated other pulmonary signs. In HPS nearly 20% or more of the cardiac output bypasses the functioning alveoli and with exercise this shunt fraction increases Dyspnea is the presenting symptom in 18% of patients.8 Five percent of patients of cirrhosis have platypnea and orthodeoxia.9,10 Platypnea is defined as dyspnea induced by the upright position and relieved by recumbency11 and orthodeoxia,
defined as arterial deoxygenation accentuated in the upright position and relieved by recumbency.12

DIAGNOSIS

Simple and useful approach to diagnose HPS is by using pulse oximetry. Oxygen saturation less than 96% is 100% sensitive with specificity of 88% to detect PaO2 less than 70 mm Hg.13

One should exclude other contributing cardiopulmonary causes such as pulmonary atelectasis, ascites, chronic obstructive pulmonary disease, and hepatic hydrothorax before labeling a patient to have HPS.

Chest radiography shows prominent pulmonary vascular markings in bilateral lower lobes but is not specific. However, a chest X-ray is mandatory to rule out reversible conditions. Pulmonary function test should be performed to rule out chronic obstructive pulmonary disease.

Intrapulmonary shunting can be demonstrated by a sensitive test contrast echocardiography.14 Agitated saline or indocyanine green produces bubbles of at least 15 microns in diameter and is given intravenously. Normally pulmonary vasculature traps and absorbs these microbubbles. In intracardiac right to left shunts, these microbubbles are seen in the left heart within the first three cardiac cycles.15 In HPS due to intrapulmonary shunting the bubbles are seen in the left heart usually between the third and sixth heart beat. Esophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting.16

Indirect evidences of HPS on echocardiography include a left atrial volume more than 50 ml, a simple and reliable parameter to detect HPS.17 Right ventricular diastolic dysfunction is more common in cirrhotic patients with HPS.18

Contrast enhanced echocardiography cannot quantify the shunting and cannot differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication. Although contrast echocardiography is highly sensitive for HPS, it lacks specificity.19 Contrast echocardiography is a less useful to detect HPS in patients with concomitant intrinsic lung diseases.

99mTc-Technetium macroaggregated albumin (Tc-99m MAA) lung perfusion scan which uses albumin macroaggregates with more than 20 μm in diameter, normally get entrapped in the pulmonary vasculature. However in patients with intrapulmonary shunts, these albumin macroaggregates escape from the pulmonary vasculature and are taken up by other organs. Normally less than 5% of isotope reaches brain circulation compared to the lung. In HPS patients, the fraction is more than 6%.20

In cirrhotic patients with concomitant intrinsic pulmonary disorders, Tc-99m MAA scan can diagnose HPS and can overcome the disadvantages of low specificity of contrast echocardiography. However, the major disadvantage of Tc-99m MAA scan is its inability to differentiate intracardiac from intrapulmonary shunting. Pulmonary angiography is a potential useful diagnostic tool but it is an invasive procedure21 and is reserved for those patients who have a poor response to 100% oxygen.

Type 1 HPS is characterized by precapillary pulmonary artery dilatation without arteriovenous fistulas and Type 2 HPS there is localized pulmonary arteriovenous fistulous communications. Type 1 angiographic findings can vary from normal to diffuse ‘spider-like’ or spongy appearance. Type 1 HPS patients with diffuse pulmonary changes have more severe hypoxemia and respond poorly to 100% oxygen. Type 2 HPS is less common and do not respond to 100% oxygen. These patients should be considered for embolotherapy although there are case reports of coil embolization in patients with Type 1 HPS also.

Two newer diagnostic modalities for assessing HPS are evaluation of pulmonary blood transit time and high-resolution chest computerized tomography (CT). The degree of pulmonary microvascular dilation observed on chest CT shows good correlation with the severity of gas exchange abnormalities in patients with HPS.22

Pulmonary transit time of erythrocytes, by using echocardiographic analysis of human serum albumin air microbubble complexes, also correlates with gas exchange abnormalities in patients with HPS.23 These tests need further evaluation on a large scale.

THERAPY

Liver transplantation is the only established effective therapy for HPS. There is significant improvement in gas exchange post-operatively in more than 85% of reported patients and it may take more than one year for the gas exchange abnormalities to normalise.24

There is increased mortality after transplantation in patients who have HPS compared with subjects who do not have HPS. Those patients with marked hypoxemia (PaO2 < 50 mmHg) and intrapulmonary shunting (shunt fraction > 20%) have an increased mortality. Complications such as pulmonary hypertension, cerebral embolic hemorrhages, and prolonged mechanical ventilation may contribute to increased postoperative mortality and morbidity.25-28

MELD exceptions points have been given to patients with HPS and a resting PaO2 of <60 mmHg by the UNOS. Oxygen supplementation is commonly used when PaO2 < 60 mmHg or in conditions with exercise-induced oxygen desaturation. Its use has been demonstrated to enhance arterial oxygenation, improve exercise tolerance and quality of life. Thus oxygen supplementation is a treatment option with low risk.29

480
A number of medical agents have been used in the treatment of HPS without any robust data showing their benefits. The agents that have been tried with variable success are sympathomimetic agents, somatostatin, almitrine, indomethacin, and plasma exchange.36 Methylene blue, a dye that inhibits NO production with transient improvement in oxygenation. Inhaled L-NAME which inhibits nitric oxide production has also been shown to improve oxygenation only transiently.31 Norfloxacin may be beneficial in improving oxygen saturation in HPS, it decreases the bacterial translocation and resultant decrease in TNF-α.32 A trial that used garlic has suggested a beneficial effect. In this trial, garlic powder was administered for a minimum of 6 months. Six out of 15 (40%) patients with HPS had improvements greater than 10 mmHg in the PaO2.33

Improvement in gas exchange using transjugular intrahepatic portosystemic shunts (TIPS) have been documented with variable success. In a more recent study that involved 3 patients with HPS the use of TIPS did not lead to any overall improvement and hence TIPS specifically to treat HPS is not recommended.34

Transcatheter coil embolization of the arteriovenous pulmonary fistulas in type 2 HPS before and after liver transplantation has been successfully evaluated.35 In type 2 HPS prior to transplantation, embolotherapy is used as a bridge to liver transplantation. With Type 1 HPS, coil embolization has also shown some benefit in reducing morbidity prior to transplantation.36

**CIRRHOTIC CARDIOMYOPATHY**

In cirrhotic patients several systemic hemodynamic changes occur. These patients have hyperdynamic circulatory state, decreased peripheral resistance, increased cardiac output and decreased arterial blood pressure.37 As the systemic vascular resistance is reduced due to increase arterial compliance, left ventricular failure may be latent in cirrhosis and become manifest under strain or treatment with vasoconstrictors. There is impaired beta adrenergic signalling pathways resulting in an impaired ventricular response to stress and exercise, NO overproduction, increased endocannabinoids and carbon mono-oxide and/or decreased sensitivity to vasoconstrictors (endothelin-1) with cardiomyocyte dysfunction. Increased NO production in cirrhosis decreases vascular responsiveness to vasoconstrictors. NO antagonism can lead to improved responsiveness to vasoconstrictors. Beta receptor dysfunctioning occurs due to increase cell membrane fluidity. There is an increase in endocannabinoids that act through CB1 receptors and result in arterial hypotension. CB1 receptor stimulation also enhances the apoptosis of hepatic stellate cells thus producing portal hypertension.38 There is impaired function of membrane L-type calcium channels. The intracellular storage and release of calcium is not affected. Cirrhotic patients have hyperdynamic circulation with low systemic arterial pressure and decreased arterio-venous oxygen difference, decreased peripheral vascular resistance, increased cardiac output and stroke volume, increased organ blood flow. The level of circulating vasoactive substances which are not inactivated by liver is increased such as vasoactive intestinal peptide, glucagon, tumour necrosis factor-α, prostacyclin, nitric oxide, endothelin-1 and endothelin-3.39

The ventricular systolic response to stress is decreased. On stress testing, cirrhotic patients have impaired increase in ejection fraction, chronotropic incompetence and decreased cardiac index. Cardiac response to exercise is blunted. Impaired cardiac performance depends on degree of hepatic failure.40 Systolic function of heart is related to heart rate, stroke volume and cardiac output. During exercise left ventricular dimensions increase because of impaired cardiac systolic function. The right ventricular and pulmonary artery pressure, as well as pulmonary capillary wedge pressure (PCWP) range around upper limit of normal.41 Patients primarily have diastolic dysfunction with left ventricular hypertrophy, left atrial enlargement, isovolumetric relaxation time prolongation and decreased early to late diastolic flow ratio (E/A ratio).

Pathologically, in cirrhotic patients heart weight is increased, dilatation of cardiac chambers, myocardial hypertrophy and structural changes such as myocardial cell edema, nuclear vacuolation, fibrosis, exudates and pigmentation occur. The ventricular contractility is regulated by beta adrenergic receptor signalling pathway. The activation of receptor acts through stimulatory G protein (Gαs) with increased cyclic AMP. The cyclic AMP promotes phosphorylation and activation of various cellular proteins by stimulation of protein kinase, with increased intracellular calcium and positive inotropic response.42

Cirrhotic cardiomyopathy [CCM] remains clinically undetectable but manifests under stressful stimuli. Cirrhotic patients have peripheral vasodilatation with reduced afterload that prevents the development of congestive heart failure. Clinical interventions in cirrhotic patients such as placement of TIPS may result in appearance of signs of frank congestive heart failure.

Abnormal functioning of these L-type calcium channels with resultant abnormal release of calcium may explain the abnormality of myocardial contraction in cirrhotic patients.43 The myocardial contractility is regulated by intracellular calcium availability. ATP pumps transfer calcium from cytoplasm into the sarcoplasmic reticulum (SR), the release of calcium from sarcoplasmic reticulum is regulated by calcium channels. Influx of calcium through L-type calcium channels of cell membrane stimulates further release of calcium from the SR.
The myocardial performance improves in cirrhotic patients after administration of NO-synthetase inhibitor. Due to altered lipid metabolism in cirrhosis, the cholesterol content of membrane is increased with increased membrane fluidity resulting in desensitization of beta adrenergic receptors. There are decreased Gsα levels in the membrane and increased catecholamines levels in cirrhotic patients.

Nitric oxide has inhibitory effect on myocardial contractility through increased cyclic GMP which impairs beta adrenergic receptor signalling and calcium release from sarcoplasmic reticulum. Transient bacteremia and endotoxin release occurs in cirrhotic patients with concomitant overproduction of cytokines. Carbon monoxide levels are increased in cirrhotic patients. CO induces guanylyl cyclase activity with increased cyclic GMP. Inhibition of heme oxygenase activity can result in improved myocardial contractility.

There is increased in corrected QT interval, the pathogenesis is unclear. The increased interval correlates with a higher incidence of sudden cardiac death. Membrane fluidity due to structural changes in cardiomyocyte membrane compromises the calcium and potassium pumps. In cirrhotics increased plasma levels of estrogens and portal hypertension induced portosystemic shunting may lead to an increased incidence of QT interval prolongation. This interval is increased in 30 to 60% of patients and level of increase relates to degree of hepatic dysfunction. Increased interval improves with liver transplantation.

Post transplant patient must have careful fluid replacement because of reduced cardiac reserve. Another complication seen in these post transplant patients is post perfusion syndrome, characterised by decrease of mean arterial pressure of at least 30% for 1 minute within 5 minutes after reperfusion with decrease of heart rate. Likely etiology of which is hyperkalemia, acidosis and increased tumour necrosis factor-α.

No clinical imaging or biochemical findings predict development of CCM so no precise diagnostic criteria have been put forward. Treatment guidelines for management have not been clear as there are no definite diagnostic criteria for CCM.

Measures include bed rest, supplemental oxygen and careful use of diuretics in patients with clinically evident heart failure.

The cirrhotic patients have decreased afterload and so tolerability to drugs that decrease preload/afterload is reduced. There is beta receptor signalling defect because of reduced density of receptors in cardiomyocyte membrane. Use of beta agonists such as dobutamine and isoproterenol is less beneficial. There is increased sympathetic catecholamine stimulation in non-cirrhotic heart failure. The use of beta adrenoreceptor antagonists is preferred over beta agonists in treating non-cirrhotic patients with heart failure.

Use of aldosterone antagonists such as spironolactone results in ventricular remodelling with reduced left ventricular chamber size and thickness and an improvement in diastolic function. Over a period of 6 to 12 months orthotopic liver transplantation has been associated with the gradual improvement of the cardiac function. Liver transplantation can reverse cirrhotic cardiomyopathy one of the complications of cirrhosis.

**PORTOPULMONARY HYPERTENSION**

Portopulmonary hypertension [POPH] defined as pulmonary arterial hypertension, with or without associated liver disease, was first described by Mantz and Craige in 1951. The criteria for diagnosis is

1. The presence of portal hypertension,
2. Mean pulmonary arterial pressure more than 25 mm Hg at rest
3. A pulmonary capillary wedge pressure less than 15 mm Hg and
4. With the pulmonary vascular resistance greater than 240 dynes.sec.cm⁻²

Most patients of POPH have underlying cirrhosis but it can also develop in non-cirrhotic portal hypertension. There is no direct correlation between severity of POPH and etiology or severity of liver disease. POPH is found in 2 to 10% of cirrhotic patients. In patients of refractory ascites evaluated for TIPS an unusual high prevalence of POPH of 16% has been reported.

Male to female ratio is 1.1:1. POPH can occur at any age but commonly presents in fifth decade of life. Diagnosis of portal hypertension precedes the diagnosis of POPH by more than 4 years. The natural history of POPH has not been fully ascertained. Spontaneous resolution of POPH does not occur. In pre-transplant era median survival as low as 6 months was noted. The overall 3 to 5 year survival ranges from 30 to 50%.

Death occurs due to complications of liver disease and POPH in equal proportions. In those with low cardiac index the probability of death due to cardiopulmonary complications is high. An increase in plasma brain natriuretic peptide (BNP) indicates stress on the right ventricle. The differential diagnosis of dyspnea in a patient of liver disease includes intrinsic cardiopulmonary conditions such as COPD, pneumonia, pulmonary embolism, congestive heart failure, valvular heart disease; and conditions related to underlying liver disease and portal hypertension such as ascites and hepatic hydrothorax.

The X-ray chest may show cardiomegaly and prominent main pulmonary artery. Arterial blood gas analysis shows hypocapnia, an increased alveolar-arterial oxygen gradient.
and mild hypoxemia. POPH is graded according to the degree of elevation of mean pulmonary arterial pressure. Mild POPH (mPAP=25-35 mm Hg) does not have an increased operative risk for liver transplantation and may not require medical therapy. Moderate POPH (mPAP=35-50 mm Hg) has increased operative risk for liver transplantation and require medical therapy. Severe POPH (mPAP > 50 mm Hg) has high operative mortality and is managed with medical therapy. Histologically POPH has medial proliferation and vascular thrombosis of pulmonary vasculature. Cirrhosis is associated with hyperdynamic circulation with increased shearing stress on pulmonary vasculature with resultant progressive pulmonary vascular remodelling and thrombosis. There is an imbalance between vasodilators and vasoconstrictors. The associated bowel wall congestion due to splanchnic vasodilatation leads to the release of endotoxins such as endothelin-1 and thromboxane.57-59

The most common symptom is exertional dyspnœa, other symptoms include chest discomfort, fatigue, syncope and light headedness. The signs are elevated jugular venous pressure, loud second pulmonic heart sound, murmur of tricuspid regurgitation and lower extremity edema, peripheral edema out of proportion to degree of ascites.60,61

Transthoracic echocardiography is used as a screening test to exclude valvular heart disease and other causes of elevated mPAP. The correlation of right ventricular pressure measured during echocardiography and that from right heart catheterization is not good. Pulmonary vascular resistance cannot be estimated on echocardiography in approximately 30-40% of patients.62

Echocardiography may reveal changes due to raised resistance to pulmonary flow such as pulmonary valvular insufficiency, interventricular septal thickening, paradoxical movement of septum right atrial dilatation, right ventricular hypertrophy and dilatation. During echocardiography evaluation another parameter measured is pulmonary acceleration time. The pulmonary acceleration time greater than 100 m sec indicates POPH. Echocardiography is also helpful in follow-up of patients with POPH.

Estimation of mPAP, pulmonary capillary wedge pressure and cardiac output; calculation of pulmonary and systemic vascular resistance is done by right heart catheterization. Cirrhotic patients have volume overload and hyperdynamic circulation. The diagnosis of POPH may be missed in those with pulmonary capillary wedge pressure greater than15 mm Hg. The use of transpulmonary pressure gradient helps in identification of patients with obstruction to flow, independent of pulmonary capillary wedge pressure. It is calculated by subtracting pulmonary wedge pressure from mean pulmonary arterial pressure.63

Presence of right ventricular abnormalities or right ventricular systolic pressure greater than 40 mm Hg support further evaluation for POPH. Pulmonary artery catheterization is performed to establish diagnosis and assess severity of POPH in all patients with echocardiographic abnormalities suggestive of POPH.

**MEDICAL THERAPY**

Supplemental oxygen is given if patient is hypoxemic. For volume overload diuretics are used. Bosentan endothelin receptor antagonist, is dual ETA and ETB receptor antagonist given orally. Starting dose is 62.5 mg twice daily and then the dose can be increased to 125 to 250 mg twice daily.64 Treatment with low to medium dose bosentan improves exercise capacity and pulmonary hemodynamics. Bosentan inhibits bile salt export protein with dose dependant increase of liver enzymes. If patients are on β blockers, drugs are to be withdrawn and if varices are present band ligation of varices are done. Sildenafil inhibits the enzyme phosphodiesterase-5. NO promotes vasodilatation, but may exacerbate portal hypertension and hyperdynamic circulation.65

Prostacyclin analogue, Esoprostol acts as potent systemic and pulmonary vasodilator with antiplatelet aggregating properties. It requires long term continuous intravenous infusion as its half life of 3 to 5 minutes so.66 Common side effects include headache, flushing, diarrhoea, hypotension.67 In patients with severe POPH it may improve patient’s status so that liver transplantation can be safely done, morbidity and mortality rates are higher in patients with moderate to severe portopulmonary hypertension.68 Normalization, no change and worsening of POPH have been reported in patients undergoing liver transplantation [LT]. All candidates for liver transplantation should undergo screening for portopulmonary hypertension by echocardiography. If the echocardiography shows elevated pulmonary arterial pressures, right heart catheterization is performed to confirm the diagnosis. The ideal medical regimen remains to be determined. Although drug treatment may lower pulmonary artery pressures in selected patients so that liver transplantation can be safely done, morbidity and mortality rates are higher in patients with moderate to severe portopulmonary hypertension.70 Moderate to severe POPH with mPAP >50 mm Hg is contraindication to LT. Liver transplantation is not the treatment of choice for portopulmonary hypertension. Denovo POPH, transition from HPS to POPH and recurrences of POPH in cases of graft failure have been noted after LT.

**HEPATIC HYDROTHORAX**

Hepatic hydrothorax is defined as the presence of pleural fluid (usually greater than 500 cc) in a patient with cirrhosis after ruling out primary cardiac or pulmonary disease.71 85% have been right sided hydrothorax, 13% left-sided and 2 %
bilateral.\textsuperscript{72} It is more common with alcohol induced liver disease and with the concomitant presence of ascites. It occurs in 6-10\% of patients with advanced cirrhosis

**PATHOGENESIS**

For the development of hepatic hydrothorax several mechanisms have been postulated. The most acceptable explanation is the direct passage of peritoneal fluid via diaphragmatic defects. Scintigraphy using intraperitoneal instillation of \(99mTc\)-human serum albumin or \(99mTc\)-sulphur-colloid within minutes to hours after administration demonstrates radioactivity in the pleural cavity.\textsuperscript{73,74} Intraperitoneal injection of methylene blue can be used intraoperatively to localize the defect.

Negative intrathoracic pressure compared to increased intra-abdominal pressure causes the movement of radioisotope towards the pleural cavity. In patients of ascites, a rise in the intraperitoneal pressure stretches the diaphragm; thereby, creating or enlarging these defects. \(\text{...}\) The increase in abdominal pressure results in herniation of peritoneum through these gaps in the pleural cavity leads to the formation of peritoneo-pleural blebs which later may rupture and create free communication between the peritoneal and pleural cavities. The left hemidiaphragm is more muscular and relatively resistant to bleb formation.

There are several causes of pleural effusion in general and patients of cirrhosis can have any of those. In a study on patients with end-stage liver disease patients with pleural effusions 30\% of patients upon thoracentesis yielded a diagnosis other than hepatic hydrothorax including, Spontaneous bacterial empyema (SBEM), tuberculosis, adenocarcinoma, (other than hepatic hydrothorax including, Spontaneous bacterial empyema (SBEM), and undiagnosed exudates.\textsuperscript{75} Hence both thoracentesis and paracentesis should be performed to ascertain that both fluids are similar in character.\textsuperscript{76}

The composition of pleural fluid from hepatic hydrothorax is similar to that of ascitic fluid. However, ascitic and pleural fluid analysis may not be completely identical, perhaps due to the greater efficacy of water absorption by the pleural surface. Spontaneous bacterial empyema (SBEM) is the infection of a pre-existing pleural effusion (hydrothorax) in a patient with cirrhosis. Its incidence is around 15\% (similar to the incidence reported for spontaneous bacterial peritonitis; SBP) in cirrhotic patients with ascites.\textsuperscript{77} Its pathogenesis is also similar to that of SBP.

**CLINICAL FEATURES**

In a patient of cirrhosis, chest radiograph performed may incidentally show hydrothorax. A small subset of cirrhotic patients may present primarily with pulmonary complaints such as dyspnea, non-productive cough, pleuritic chest pain or fatigue related to hypoxemia following hydrothorax.\textsuperscript{78} With large pleural effusions severe dyspnea and potential respiratory compromise can occur.

Patient with SBEM can present with local symptoms such as dyspnea or pleuritic chest pain, or with systemic symptoms such as fever, shock or encephalopathy. Up to 40\% of SBEM cases may not be associated with SBP.

**DIAGNOSIS**

This entity is usually suspected in a patient of cirrhosis if patients presents with pulmonary symptoms or features suggestive of pleural effusion on examination or on routine chest radiographs.

The cell count is usually low, and the total protein, albumin, cholesterol and total lipid levels may be marginally higher in the pleural fluid compared to ascitic fluid.\textsuperscript{79}

However, serum-to-pleural fluid albumin gradient is usually greater than 1.1 g/dL although, this has not been studied extensively.

The diagnosis of SBEM is made if the pleural fluid (PF) cultures are positive and a polymorphonuclear (PMN) count is \(>250\text{ cells/\mu L}\). If culture is negative (and compatible clinical course) the diagnosis is made with a pleural fluid PMN count \(>500\text{ cells/\mu L}\) and by excluding a parapneumonic infection.\textsuperscript{80}

The microorganisms responsible for SBEM appear similar to that of SBP.

A computerized tomographic (CT) scan of the chest should be obtained to exclude any mediastinal, pulmonary, or pleural pathology. Moreover, detailed information of the diaphragm may be obtained with a CT scan or a magnetic resonance imaging, permitting recognition of the small diaphragmatic defects.\textsuperscript{81}

Thoracoscopy may also reveal the defects, but this procedure is invasive and carries significant morbidity in patients with advanced liver disease and therefore is rarely performed. Echocardiography may be indicated if there is a suspicion of pericardial or a cardiac pathology. In difficult cases, specifically when ascites is not detected or the hydrothorax is present on the left side; an intraperitoneal injection of \([99Tcm]\)-sulphur colloid or \([99Tcm]\)-human serum albumin may be helpful.

Migration of the radioisotopes from the peritoneal cavity into the pleural space establishes a communication between both spaces and confirms that the ascites is the source of the effusion.\textsuperscript{82,83}

Conversely, failure of the marker to show up in the pleural space indicates an alternate diagnosis for the pleural effusion. This test has been considered the gold standard for identification of hepatic hydrothorax due to its very high specificity (up to 100\%). However, its sensitivity remains modest (approximately 71\%). Fortunately, the sensitivity of
the test can be greatly improved (up to 100%) by performing a thoracentesis prior to administration of radioisotopes in order to reduce pleural pressure.84

TREATMENT
Patients of hepatic hydrothorax can be managed by dietary, pharmacologic and radiological interventions. In selective patients with refractory hydrothorax, surgical approaches aimed at repairing the diaphragmatic defects responsible for pleural fluid accumulation can be considered.

DIET AND PHARMACOLOGICAL MANAGEMENT
Dietary restriction of sodium intake to 2 g/d (88mEq/d) is the simplest manner by which achieve a negative sodium balance can be achieved.85

Almost all patients with hepatic hydrothorax require diuretics (spironolactone and/or furosemide) along with salt restriction. These diuretics are maintained at a ratio of 10:4 (spironolactone 100 mg: furosemide 40 mg) to avoid electrolytic imbalance and dosages are increased as needed to attain a goal of producing renal excretion of at least 120mEq of sodium per day.86

Patients not responding despite fluid and sodium restriction and use of maximal tolerable doses of diuretics are considered to have refractory hydrothorax. These patients should be considered for orthotopic liver transplantation. Other agents such as terlipressin, octreotide and midodrine have been used in small studies with moderate benefit.87

These agents will reduce splanchic blood flow and hence decrease peritoneal and pleural fluid accumulation. However, presently there is not enough evidence to recommend routine use of these agents.

THORACOCENTESIS
It is a simple and relatively safe procedure performed in patients with dyspnea for immediate relief of symptoms. In patients with dyspnea and both hepatic hydrothorax and massive ascites, it is recommended to drain the ascites prior to performing a thoracentesis. It is recommended that no more than 2 liters of fluid should be removed during the first therapeutic thoracentesis, in order to minimize the risk of unilateral pulmonary edema and/or hypotension.88 However, given the relatively small volume of fluid removed at thoracentesis, intravenous albumin to avoid circulatory dysfunction unlike its routine use with large volume paracentesis seems unnecessary. The major risk of thoracentesis is development of pneumothorax. Usually diagnostic thoracentesis carries a low risk (1%) of pneumothorax, compared to therapeutic thoracentesis where the incidence is nearly 9%.89

However, when thoracentesis is required too frequently (< every 2-3 weeks) in patients on maximal sodium restriction and optimal diuretics, alternative treatment options must be considered. The treatment of SBEM is similar to that of SBP.90

Despite treatment, mortality remains high at approximately 20%. Albumin therapy at 1.5 g/kg on day 1 and 1.0 g/kg on day 3 in the setting of SBEM may be considered although albumin infusion has not been specifically studied in the setting of hepatic hydrothorax and SBEM.

RADIOLOGIC INTERVENTIONS: TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS (TIPS)
It is a nonselective side-to-side porto-systemic shunt which decreases the sinusoidal hypertension that leads to ascites formation- an essential step for pleural fluid accumulation. A recent study has shown that severity of liver dysfunction is directly related to non responsiveness and higher one year mortality after TIPS placement for refractory HH.91

Thus, it should be considered in selected patients who re-accumulate their effusions rapidly (despite medical treatment) with a Child-Pugh score of less than 10, are younger than 60, and do not have hepatic encephalopathy or severe pulmonary hypertension.

SURGERY
Pleurodesis
Chemical pleurodesis with tetracycline is not always successful and has a modest risk of complications such as fever, chest pain, empyema, incomplete re-expansion, pneumonia, and wound infection. Hence pleurodesis by itself is rarely performed and is reserved for patients in whom no other options exist. Interestingly, the use of continuous positive airway pressure (CPAP) appears effective in keeping the pleural cavity dry after chemical pleurodesis. The underlying mechanism postulated is that CPAP will decrease the negative pleural pressure and thus prevent the shift of fluid form the peritoneal to the pleural space.92

Further studies are needed before this can be routinely recommended.

Chest tube placement:
Chest tube insertion leads to massive fluid shifts, protein and electrolyte depletion and is considered a relative contraindication for the treatment of hepatic hydrothorax.93 Thoracoscopy to repair diaphragmatic defects with/without sclerosing the pleural membranes is a good alternative in patients with refractory hepatic hydrothorax who are not candidates for TIPS. Thoracoscopy appears to be more likely to be effective if diaphragmatic defects can be identified.

Two studies (15 and 41 patients each) showed almost 75% success rate with Video-assisted thoracoscopy with talc pleurodesis may be considered a palliative alternative not only to patients requiring frequent thoracentesis, but also an alternative to TIPS.94,95

Peritoneo-venous shunts: A peritoneo-venous shunt (Le
Liver transplantation: It is the only option available when all other therapies fail and is curative for most patients with this complication. The short- and long-term prognosis in patients undergoing liver transplantation for refractory hepatic hydrothorax appears similar to patients undergoing liver transplant for other indications.97

REFERENCES


70. Karen L. Swanson DO, Krowka MJ. Screen for portopulmonary
hypertension, especially in liver transplant candidates. Cleveland Clinic Journal of Medicine February 2008, 75 (2) 121-136