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Pleural Effusion: A Review of Pathophysiology, Diagnosis and Treatment.

Vidhyashree MD[1], Raveendran SR[2]*, Lakshmipriya R[3], Kanmani Sree SM[2], and Radhika B[2].

[1] Sree Balaji Medical College & Hospital, Chennai, Tamil Nadu, India.
[2] Madha Medical College & Research institute, Chennai, Tamil Nadu, India.
[3] ESIC Medical College & PGIMSR, Chennai, Tamil Nadu, India.

ABSTRACT

Pleural effusion is a respiratory disorder characterized by collection of excess fluid between the parietal and visceral pleura of lung. Pleural fluid is meant for lubrication between the parietal and visceral pleura for the easy movement of lungs in thoracic cavity. The movement of lungs are restricted during ventilation because of abnormal collection of fluid. Pleural effusion can be due to, increased formation of pleural fluid or decreased re-absorption of pleural fluid from pleural space which can be due to congestive heart failure, hepatic cirrhosis, nephrotic syndrome, pulmonary embolism, malignancy, infection, pulmonary infarction. Diagnosis can be done by physical examination, chest radiography and analysis of pleural fluid. Managing pleural effusion is by diuretic therapy, thoracentesis, tube thoracostomy, pleurodesis, tunnelled pleural catheters (TPCs).

Keywords: Pleural effusion, diagnosis, pathophysiology, treatment.

Corresponding author

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INTRODUCTION

Pleural effusion is a respiratory disorder characterized by collection of excess fluid between the parietal and visceral pleura of lung [1]. Around 20 ml of pleural fluid is secreted by the capillaries of parietal pleura and reabsorbed by lymphatics [2]. The pleural fluid is meant for lubrication between the parietal and visceral pleura for the easy movement of lungs in thoracic cavity. The major causes of pleural effusion are congestive heart failure, hepatic cirrhosis, nephrotic syndrome (systemic disease), pulmonary embolism, malignancy, infection, pulmonary infarction (Local disease). The fluid which is present in local and systemic disease can be transudate or exudates [3]. Depending upon their biochemical characteristics it can be differentiated as transudative and exudative. Transudative pleural effusions results due to the imbalances in hydrostatic and oncotic force and occurs in conditions like heart failure and cirrhosis whereas exudates occurs when the local factors influencing the accumulation of pleural fluids caused by infection, inflammation by pneumonia, malignancy and thromboembolism [4].

The movement of lungs are restricted during ventilation because of abnormal collection of fluid. Incidence of pleural effusion in a year was 5 lakhs in chronic heart disease, 3 lakhs in pneumonia, 2 lakhs in malignancy and the mortality of pleural effusion depend on the aetiology of pleural effusion [5].

Types of Pleural Effusion

Depending upon the types of fluid present in the pleural cavity, pleural effusion is classified as [6]

- Hydrothorax
- Hemothorax
- Chylothorax
- Pyothorax

Hydrothorax [7]

Hydrothorax is a type of pleural effusion which is characterised by the collection of serous fluid within the pleural cavity. The condition is often associated with ascites or cirrhosis of liver (quercus solaris)

Hemothorax [8]

Hemothorax is otherwise known as hemorrhagic pleural effusion characterised by the collection of blood within the pleural cavity. Hemothorax is caused by trauma.

Chylothorax [9]

Chylothorax is a type of pleural effusion characterised by the collection of lymph within the pleural cavity. The aetiology may be lymphoma or trauma which leads to the leakage of lymph from thoracic duct/ other main lymphatic vessels.

Pyothorax [10]

Pyothorax is otherwise known as pleural empyema characterised by the collection of pus within the pleural cavity.

Grading Of Pleural Effusion [11]

According to National Cancer Institute (NCI) pleural effusion has been graded (Table 1) Grading of pleural effusion

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Table 1: Grading Of Pleural Effusion

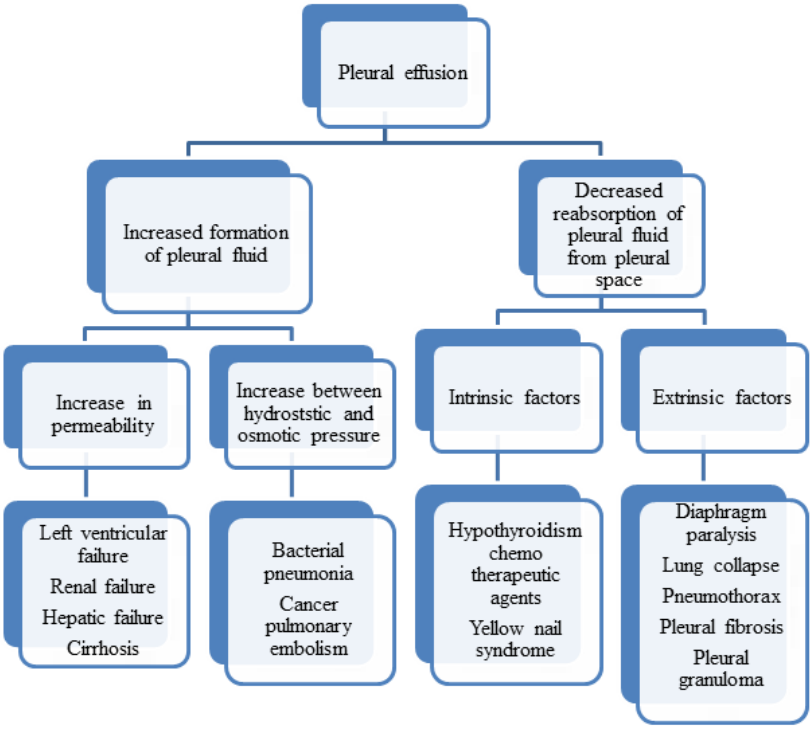
Grade 1	•Asymptomatic
Grade 2	•Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracentesis indicated
Grade 3	•Symptomatic and supplemental oxygen, >2 therapeutic thoracentesis, tube drainage, or pleurodesis indicated
Grade 4	•Threatening (e.g., causing hemodynamic instability or ventilatory support indicated)
Grade 5	•Death.

Pathophysiology [12,13]

The accumulation of pleural fluid in the pleural cavity is due to **(Flow Chart 1):**

- Increased formation of pleural fluid:
  - Increase in permeability.
  - Imbalance between hydrostatic and osmotic pressure.
- Decreased re-absorption of pleural fluid from pleural space.

Flow Chart 1: Pleural Fluid Accumulation



Increase in permeability

In case of any local disturbance such as infection /tumours, there is an increase in the permeability of vessels, which leads to accumulation of pleural fluid in pleural space. The fluid is exudative in nature.

Imbalance between hydrostatic and osmotic pressure

According to starling's equation. $j_v = k_f [p_c - p_i] - \sigma[\pi_c - \pi_i])$. Where p_c is the capillary hydrostatic pressure and π_c is the capillary osmotic pressure. Normally capillary hydrostatic pressure is responsible for the filtration of pleural fluid from vessel and this mechanism is balanced by capillary osmotic pressure which reabsorbs the pleural fluid back into the vessel [2]. In case of any systemic disease such as heart failure, increase in the hydrostatic pressure, increases the accumulation of fluid. In case of hypoproteinemia, decrease in plasma osmotic pressure leads to decrease in resorption of fluid. The fluid is transudative in nature [1].

Decreased reabsorption of pleural fluid from pleural space

Any abnormality in lymphatic vessels causes decreased resorption of pleural fluid. It may be due to intrinsic and extrinsic factors. These are all intrinsic factors which inhibit the lymphatic vessels to contract:

- Cytokines and products of inflammation
- Anatomical abnormalities
- Cancerous growth in lymphatic
- Injury by radiation/drugs

Extrinsic factors

Extrinsic compression of lymphatics (pleural fibrosis, pleural granulomas)
Blockage of lymphatics (fibrin deposition).

Table 2: Mechanism of Pleural Effusion

Production Of Pleural Effusion And Its Mechanism
• Systemic increase in hydrostatic pressur
• Increased permeability of the pleural microvascular circulation
• Decreased oncotic pressure in the microvascular circulation
• Increase in pulmonary interstitial fluid
• Impaired lymphatic drainage
• Movement of fluid from other cavities or sites such as the peritoneal, retroperitoneal, or subarachnoid spaces, or catheters
• Decrease in negative pressure within the pleural space
• Rupture of the thoracic duct
• Vascular rupture in the chest

Clinical Examination [15]

Inspection

Inspection is done to evaluate chest expansion, shape of the chest, respiratory rate and breathing position adopted by the patient. Bulging of intercostal spaces is seen in severe cases. Inspection is not very useful to detect the pleural effusion.

Palpation

Palpation is done to detect asymmetric chest expansion.

Chest expansion

Chest expansion is done by placing the hands in the back of the chest with thumb pointing towards spine.

Tactile fremitus

Tactile fremitus is the vibration felt by the clinician's hand which is placed on the chest wall of the patient and patient is asked to say words repeatedly e.g. one. Fermitus over an effusion will be decreased.

Percussion

Percussion is done with the middle finger of one hand (pleximeter) tapping on the middle finger of other hand using a wrist action (plexor) to detect resonance/dullness. A minimum of 500ml of fluid should be present to detect the pleural effusion. Shifting dullness in the lateral supine position indicate the movement of fluid.

Auscultation

In pleural effusion, breath sounds may be absent or diminished. Pleural rub may present.

Egophony

It is a pathognomonic sign associated with moderate pleural effusion. There will be change in pronounced sound of e to a. It is due to upward displacement and compression of lung at the top of effusion.

Diagnosis of Pleural Effusion

Diagnosis of pleural effusion begins with obtaining the patient‘s clinical history and by doing a physical examination which is then followed by chest radiography and analysis of pleural fluid in appropriate instances. The fluid analysis yields very important diagnostic information in many instances related to pleural effusions and in some instances fluid analysis alone is enough for the diagnosis. A history of hemoptysis is usually associated with malignant neoplasm, pulmonary embolism or severe tuberculosis [16].

Patient’s history should also contain a previous history of exposure to asbestos, medications taken by the individual and also the presence of medical conditions such as heart disease, tuberculosis, neoplastic disease and connective tissue disease. Diagnosis of Tuberculous pleural effusions depends upon the demonstration of *Mycobacterium tuberculosis* in sputum, pleural fluid or pleural biopsy specimens. A combined spectrum of medical history, physical examination and basic laboratory test results helps to establish a diagnosis before thoracentesis is done [18].

Unilateral and bilateral pleural effusions yield two different spectrum of diagnosis. Diagnostic thoracentesis is done only when the patient has bilateral effusion. If necessary, further investigation like Computer Tomography (CT) of the thorax, pleural biopsy, thoracoscopy and bronchoscopy are done [16].

Apart from physical examination and clinical history, radiography technique also plays an important role in ruling out diagnosis. An effusion of more than 75ml of fluids is often visible in chest radiograph. The pleural effusion either can be free flowing or loculated or either typically or atypically sited (subpulmonic, fissural or mediastinal) [18].

Thoracocentesis

Colour, gross appearance for example - turbidity of the pleural fluid can be caused either by the cells and debris in case of empyema or by a high lipid level in case of infections caused by anaerobic microorganisms and ammoniac in case of urinothorax [18].

Sometimes, the fluid aspirated may be blood stained, which occurs in conditions such as pneumonia, malignant neoplasm, pulmonary embolism with infarction, benign effusion related to asbestos exposure and trauma. In order to differentiate empyema from chylothorax, turbid or milky fluid, centrifugation is carried out [16].

In frankly bloody effusion, the hematocrit of the pleural fluid exceeds the simultaneous peripheral blood hematocrit which is indicative of hemothorax [17].

Lab Investigations Done With the Fluid

After the fluid is aspirated it is sent for biochemical, microbiological and cytological analysis (Table 2). Biochemical analysis includes determination of protein, pH, Lactate Dehydrogenase (LDH), glucose and albumin levels. These components enter the pleural space with water and protein, which is regarded as important criteria for the differentiation of exudates and transudates [16].

Table 3: Lab Investigations Done With the Fluid

Microbiology	Biochemistry	Pathology
• Gram stain • Culture of aerobic and anaerobic bacteria • Fungal cultures • Mycobacterium tuberculosis culture and smear test	• Glucose • Proteins • LDH • Cholesterol • Triglycerides • Amylase • Cells: WBC count and differential • Hematocrit	• Cytological studies • Tissue for histology

A pleural effusion with a protein level less than 30 g/l indicates a transudate whereas one with the level greater than 30g/L indicates exudates, provided the serum protein level within the normal reference range. When the protein level greater than 30g/L is used as the only reference criteria for the determination of type effusion, usually 10% of exudates and 15% of transudates are misclassified. The usage of light's criteria is usually recommended when the protein level is between 25 and 35g\L [16]. In clinical practice exudative effusions are well differentiated from the transudative effusions using light's criteria (Table 3). However neither protein nor albumin gradients are the primary tests used to distinguish transudative effusions from exudative effusions as they result in the misclassification of number of exudates [17].

Table 4: Light's Criteria

Effusion as exudates if	Effusion as transudate if
• The ratio of pleural fluid protein to serum protein is greater than 0.5 • The ratio of pleural fluid LDH to serum LDH is greater than 0.6. • The pleural fluid LDH level is greater than two third of the upper limit of normal serum LDH[5]	• The difference between serum and pleural levels of protein is greater than 3g/l • A difference of more than 12g/l between serum and fluid albumin level indicates transudate[1]

Further test for exudates

In patients with exudative effusions various tests should be performed with the fluid obtained during the initial thoracentesis. They are cell counts, differential count, glucose, Adenosine Deaminase (ADA) and cytological analysis. Bacterial cultures and pH can also be done if infection is a concern [17]. The fluid for White Blood Cell (WBC) count and differential cell count should be sent in an anticoagulant tube. Generally, white

blood cell count has no diagnostic value and can even rise to 10,000 cells/mm^3 in case of pneumonia, pancreatic disease, pulmonary embolism, pericardiotomy and SLE. Some of the cases in which neutrophilic pleural effusions occurs are pneumonia, pancreatitis, subphrenic abscess, pulmonary embolism and the early stages of pleural tuberculosis. Eosinophilia is also found in asbestos related effusions and in drug treatement [18].

Results obtained from pH values [17,18]

Pleural fluid for the pH evaluation is collected in a heparinised syringe and it is measured in a blood – gas machine. The pH value is generally between 7.45 and 7.55 for transudates and between 7.30 and 7.45 for exudates. Low pH value is artificially obtained by the use of local anaesthetics. A combined spectrum of low pH and low glucose values are seen in cases like hemothorax, pulmonary embolism, pancreatic pleural effusion, effusions secondary to malignancy, tuberculosis and often occur in Systemic Lupus Erythematosus (SLE).

Cultures and cytology [17,18]

Pleural fluids are sent to cultures in case of bacterial and fungal infection. Aerobic and anaerobic bacterial cultures will reveal the causative microorganism. Both sputum and pleural fluid are suspected to culture in case of tuberculous pleuritis. Because of delayed hypersensitivity in case of tuberculous pleural effusions it is not possible to isolate mycobacterium tuberculosis from pleural fluid in more than 60 to 70 percent of patient. Apart from the conventional methods, the usage of broth medium along with bedside inoculation leads to higher and faster results. Smears of mycobacterium tuberculosis are rarely positive unless and until the patient has a Tuberculous empyema.

Cytology [17,18]

Pleural fluid cytology is one among the tools which offers the highest yield for the diagnosis of malignancy. This technique is highly positive in approximately 60 percent of malignant pleural effusions and the sensitivity of this test ranges from 40% to 50% depending upon the cytologist experience.

Other diagnostic procedures [17].

Bronchoscopy

Bronchoscopy is useful in case of endobronchial malignancy which is suggested by one or more of the following characteristics: a pulmonary infiltrate or a mass on the chest radiograph or CT scan, haemoptysis, a massive pleural effusions, or shift of the mediastinum towards the side of the effusions.

Thoracoscopy

It is one of main diagnostic procedure done in more than 90% of patients with pleural malignancy and negative cytology. Moreover thoracoscopy offers the possibility of effective pleurodesis during the procedure.

Management of Pleural Effusion

There are three main categories in the treatment of pleural effusion. They are[19]

- Systemic therapy
- Local therapy
- Combination of both systemic and local therapy

Systemic therapy [19,20]

Transudative pleural effusions are more common in systemic disorders. Treatment of underlying cause helps to resolve pleural effusion. Congestive cardiac failure related pleural effusions usually resolves by diuretic therapy. In hepatic hydrothorax, diuresis and sodium restriction are required. In pancreatitis related pleural effusions somatostatin and octreotide are required for closure of fistula.

In case of any connective tissue disorder such as rheumatoid arthritis and Systemic Lupus Erythematosus (SLE) pleural effusions are treated with steroids. Amoebic pleural effusions are treated with anti-amoebic drugs such as metronidazole 800mg three times a day for 5-10 days and diloxanide furoate 500mg three times a day for 10 days. Tuberculous pleural effusions are treated with anti-tuberculous drugs such as rifampicin, pyrazinamide, ethambutol and isoniazid. Regimen of systemic therapy also includes hormonal therapy and cytotoxic chemotherapy. Hormonal therapy includes estrogen, prednisone, androgen, tamoxifen. Cytotoxic chemotherapy includes cyclophosphamide, 5-fluorouracil, adriamycin, vinblastine, vincristine.

Local therapy

Local therapy of pleural effusion includes thoracocentesis, tube thoracostomy and pleurodesis.

Thoracocentesis [21]

Thoracocentesis is also known as pleural tap/ thoracocentesis. It is an invasive procedure done to remove the excess fluid or air from pleural space. It can be done for both diagnostic and therapeutic purposes. A hollow needle/cannula is introduced in the midaxillary line in eighth, ninth/tenth intercostal space. The procedure is done under local anaesthesia. It is contraindicated in patients with coagulation disorder, emphysema and only one functioning lung. This procedure is replaced by tube thoracostomy when cardiopulmonary status is compromised. Complications are pneumothorax, hemorrhage, and hypertension. When the aspiration exceeds one liter, pulmonary oedema may develop.

Tube thoracostomy [22]

Tube thoracostomy is otherwise known as Bulau drain/intercostal catheter. Chest tube is a flexible plastic tube inserted through the chest wall into the pleural space/mediastinum.

Chest tubes are commonly made up of Poly Vinyl Chloride (PVC) and soft silicone. Chest tubes are measured in French Catheter Scale. For children 6 Fr to 26 Fr are employed. For adults, 20 Fr to 40Fr are used. Some tubes are coated with heparin to prevent thrombus formation.

The procedure is done under local anaesthesia. The skin over the area of insertion is cleaned with antiseptic solution & local anaesthetic is injected into the skin. The insertion is commonly made in the 5^{th} intercostal space slightly anterior to midaxillary line. The tube is placed in the chest & it is sutured into skin. The free end of the tube is attached to the underwater seal. Tube thoracostomy is contraindicated in patients with refractory coagulopathy. Complications are hemorrhage, infection, re-expression pulmonary oedema. The most common complication is chest tube clogging. It is a thrombus formation inside the chest tube.

Pleurodesis [20,23]

Pleurodesis is a medical procedure done to prevent recurrent pneumothorax & recurrent pleural effusion where the pleural space is artificially obliterated. It is done by 2 methods:

- Chemical
- Surgical

Chemicals such as bleomycin, tetracycline, and slurry of talc are used. It is introduced through the chest drain. It causes irritation between parietal & visceral pleural. It closes off the pleural space. Surgical pleurodesis can be done via thoracostomy / thoracoscopy where the parietal pleura are mechanically irritated by a rough pad. Tunnelled Pleural Catheters (TPCs) are used in an outpatient setting. It results in an auto-pleurodesis. In chylothorax, medical treatment is decompression of pleural space with tube thoracostomy/repeated thoracentesis, chemo radiation, somatostatin/octreotide supplementation & nutrition support with a diet rich in low-fat, medium chain triglycerides. Surgical treatment includes thoracic duct ligation (done between -12 thoracic vertebrae just above aortic hiatus).It is a common procedure. The approach should be from right chest.

For refractory chylothorax, pleuroperitoneal shunt is the treatment of choice. Pleurodesis & surgical pleurectomy can be done. In hemothorax, tube thoracostomy is done. Surgical treatment is required when there is excessive bleeding. The management of emphysema includes antibiotic supplementation drainage of pus & restoration of lung expansion.

Combination of local and system therapy

Combination of both local and systemic therapy is required in some cases such as chronic Heart failure, pneumonia, breast cancer & some other neoplasms.

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