EVALUATION OF PLEURAL EFFUSION

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INTRODUCTION: Normal pleural space between visceral and parietal pleura is lined by thin film of fluid, but excess fluid accumulation in pleural space under certain pathological condition is termed pleural effusion.[1] Pleural effusions is common occurrence in both medical and surgical patients. The prevalence of pleural effusion is estimated to be slightly in excess of 400/100000 population.[2] Pleural effusion is an indicator of an underlying disease process that may be pulmonary or non-pulmonary in origin and may be acute or chronic. The most common types of fluid in pleural effusion include transudates and exudates, though there can be blood or pus also in pleural effusion. However, mechanisms leading to pleural effusion are different. (Box 1) These may differ in different etiologies, and include: increased hydrostatic pulmonary pressure in heart failure, increased capillary permeability in pneumonia, decreased oncotic pressure in hypoalbuminemia, decreased intrapleural pressure in atelectasis, obstructed lymph flow and increased pleural membrane permeability in pleural malignancy/infection, and diaphragmatic defects in hepatic hydrothorax. Rupture of thoracic duct is involved in chylothorax.[3]

Box 1. Mechanisms in Pleural effusion

- Increase in production or a decrease in removal of pleural fluid.
- Changes in hydrostatic capillary, intravascular or extravascular colloid osmotic pressure.
- Negative intrathoracic pressure.

DIAGNOSIS OF PLEURAL EFFUSION: Patients with pleural effusions should be studied systematically. Detailed history taking and physical examination can help to establish direction towards diagnosis even before any other investigations. Based on history and examination, with signs/symptoms indicating a suspected pleural effusion, the initial step in evaluation of such patients is to confirm the diagnosis with radioimaging techniques (Chest X ray, ultrasound, computed tomography (CT) scan, etc). Next, the distinction between transudative and exudative pleural effusions would give an idea about the nature of fluid and narrow down the diagnosis. However, in many cases, a definitive diagnosis may require thoracentesis which allows withdrawing the pleural fluid sample and undertaking its physical, chemical, and microbiological studies.[4]

INITIAL EVALUATION BASED ON POTENTIAL CAUSES: Although there are several causes of pleural effusion, most common cases in adults include congestive heart failure, malignancy, pneumonia, tuberculosis, and pulmonary embolism, whereas pneumonia is the leading etiology in children.[1,5] Based on causative pathology, history and physical examination are vital in evaluation of pleural effusion, as signs and symptoms vary depending upon underlying disease, and guide in the evaluation of pleural effusion (Table 1).[1,5] Salient features of pleural effusion are:

- Dyspnea, cough, and pleuritic chest pain are common symptoms.
- Chest examination often reveals dullness to percussion, decreased/absent tactile fremitus, and decreased breath sounds on the side of effusion.
- Rapid, shallow respiration is seen in large-volume effusions.
- Pleural friction rub, although infrequent, if present is the classic physical sign of pleural effusion.[1,2]

History/ Signs/Symptoms	Potential Causes
Abdominal surgery	Postoperative pleural effusion, subphrenic abscess, pulmonary embolism
Artificial pneumothorax therapy	Tuberculous empyema, pyothorax-associated lymphoma
Exposure to asbestos	Benign asbestos pleural effusion
Coronary artery bypass graft surgery (CABG)	Pleural effusion secondary to CABG
Chronic hemodialysis	Uremic pleuritis
Cirrhosis	Hepatic hydrothorax, bacterial empyema
Esophageal dilatation/endoscopy	Pleural effusion secondary to esophageal perforation
Human immunodeficiency virus (HIV) infection	Pneumonia, primary effusion lymphoma,
Superovulation with gonadotrophins	Pleural effusion secondary to ovarian hyperstimulation syndrome
Trauma	Hemothorax, chylothorax
Ascites	Hepatic hydrothorax
Fever	Pneumonia, empyema, tuberculosis
Hemoptysis	Lung cancer, tuberculosis
Weight loss	Malignancy, tuberculosis

Table 1: Initial Diagnosis Of Pleural Effusion Based On Causes

CHEST RADIOGRAPH: Chest x-ray is usually the first test done to confirm suspected pleural effusion, and may provide further diagnostic insight prior to thoracentesis. Smaller effusions can be more reliably detected in lateral decubitus films. Lateral upright chest radiograph can detect 75 mL and more of pleural fluid blunting posterior costophrenic angle. However, it usually requires at least 175 mL or more to appreciate blunting of lateral costophrenic angle. Moderate to

large pleural effusions may appear as a homogenous increase in density spread over lower lung fields. Larger pleural effusions (> 4 L) may cause complete opacification of hemithorax and may even cause mediastinal shift to opposite side. More than 50% of these massive pleural effusions are caused by malignancy; other causes are complicated parapneumonic effusion, empyema, and tuberculosis.[6] Smaller effusions undetected by chest radiograph can be detected by ultrasound or CT scans. If doubt exists in chest radiography, ultrasound or CT scans are definitive for detecting small effusions and for differentiating pleural fluid from pleural thickening.[7]

FREE FLUID VS LOCULATED EFFUSION:

Box 2: Transudative Vs Exudative Effusions in Chest X-ray
Consider transudative effusion in bilateral effusions:

- Congestive heart failure; bilateral effusion with cardiomegaly.
- Cirrhosis; bilateral effusion associated with ascites in an alcoholic.
- Nephrotic syndrome.
- Hypo-proteinemia.

Most of Unilateral effusions are exudative:

- Malignancy (primary, secondary, lymphoma etc); massive effusion with nodes or mass or bone lytic lesions.
- Infections (tuberculosis, empyemas etc); effusion with infiltrates.
- Auto immune disease (Rheumatoid arthritis etc).
- Trauma; hemothorax with blood in effusion.

Pleural effusions can be either free flowing or loculated. Loculated effusions occur mostly in conditions causing intense pleural inflammation, such as empyema, hemothorax, or tuberculosis. Layering on lateral decubitus films defines a freely flowing effusion and if >1 cm thick, it indicates an effusion of greater than 200 mL which is amenable to thoracentesis. Failure of an effusion to layer on lateral decubitus film indicates presence of loculated pleural fluid. Although CT is not routinely indicated, it helps in evaluating underlying lung parenchyma for infiltrates or masses when lung is obscured by the effusion. CT also helps when radiograph details are insufficient for distinguishing loculated fluid from a solid mass.[2,3]

SOLITARY VS BILATERAL EFFUSION ON CHEST RADIOGRAPH: While unilateral solitary effusions are mostly exudative, bilateral effusions are transudative (Box 2). In solitary pleural effusions, infectious causes, such as a tuberculous pleural effusion, viral pleurisy, or limited bacterial pneumonia may be considered. In massive effusion leading to opacification of entire hemithorax and mediastinal shift, likelihood is lung cancer leading to endobronchial obstruction;

however, massive effusion without contralateral mediastinal shift, malignant mesothelioma is more likely.[4] Bilateral effusions are most commonly transudates, as seen with congestive heart failure, nephrotic syndrome, hypoalbuminemia, and constrictive pericarditis. Bilateral pleural effusions with no cardiomegaly is most likely related to malignancy, or may occur in hepatic hydrothorax and hypoalbuminemia.[8]

ULTRASOUND IN PLEURAL EFFUSION: Ultrasound has advantages as it can be done at bedside and is ideal for detecting localized, loculated or small pleural effusions. It can detect pleural masses, and can detect debris or septations in hemothorax or empyema. Ultrasound is also advantageous for pre-evaluation before thoracentesis and guides thoracentesis avoiding tissue/organ injury. Overall ultrasound offers several important advantages in evaluation of pleural effusion. (Box 3) [9,10] However, ultrasound also has certain limitations as soft tissue edema, subcutaneous emphysema, or obesity can reduce quality of images and make it difficult to interpret.[4]

Box 3: Advantages of Ultrasound in the Evaluation of Pleural Effusion:

- Ultrasound allows distinction between effusion and lung consolidations not otherwise possible in radiograph many a times.
- Ultrasound has higher accuracy in detecting pleural effusion compared to chest X-rays.
- Ultrasound can detect effusions as small as 20 mL while chest X-rays need minimum of 75 ml or more.
- Ultrasound in sitting position allows a more precise quantification of pleural effusion.
- Ultrasound has a distinct advantage in guiding thoracentesis also in evaluation of pleural effusion.
- Use of ultrasound in thoracentesis reduces rate of complications (i.e., pneumothorax).
- Ultrasound allows identification of best site to perform puncture for thoracentesis.
- Ultrasound allows study of intercostal spaces prior to needle insertion in thoracentesis and avoid vascular injury by identifying any aberrantly positioned intercostal vessels.
- Appearance of pleural effusion on ultrasound can also provide clues to necessary intervention required.

CT-SCAN AND OTHER IMAGING TECHNIQUES: Chest CT scan with contrast is needed in an undiagnosed pleural effusion to detect thickened pleura or signs of invasion of underlying/ adjacent structures, in imperative pulmonary embolism or tuberculous pleuritis. CT angiography is mandatory if pulmonary embolism is suspected. Helical CT has become first-line modality for imaging in patients suspected with pulmonary embolism. Helical CT also can distinguish malignant from benign pleural disease. CT findings suggestive of malignant disease are the presence of pleural nodules or nodular pleural thickening, circumferential or mediastinal pleural thickening, or infiltration of chest wall or diaphragm. Positron emission tomography is also seems

promising for differentiating benign and malignant pleural diseases, showing good sensitivity and specificity.[11,12]

DIAGNOSTIC THORACENTESIS: Thoracentesis is a simple procedure with imaging guidance that permits fluid to be rapidly sampled, visualized, examined microscopically, and quantified for chemical and cellular content. In conjunction with clinical presentation, it almost helps diagnose cause of effusion in about 75% patients at first clinical evaluation.[1,13]

Box 3. Indications of Thoracentesis in Heart Failure patients

- Patient is febrile or has pleuritic chest pain
- Patient has unilateral effusion or effusions of markedly disparate size
- Effusion not associated with cardiomegaly
- Effusion fails to respond to management of heart failure.

Box 4. Diagnostic Possibilities: Gross haracteristics of Pleural Fluid

- Frankly purulent fluid indicates an empyema.
- Putrid odor suggests an anaerobic empyema.
- Milky, opalescent fluid suggests a chylothorax.
- Bloody fluid may result from trauma, malignancy, etc or may indicate hemothorax.
- Black pleural fluid may suggest infection with Aspergillus niger, or malignant melanoma/non-small cell lung cancer.

A diagnostic, interventional thoracentesis needs to be performed in unexplained pleural effusions or if patient does not responds to therapy. However, sufficient fluid needs to be present (>1 cm on lateral decubitus radiograph, ultrasound, or CT) for thoracentesis to be done safely, and should not be done if effusion is too small to safely aspirate. If the effusion is explained by underlying congestive heart failure or by recent thoracic/ abdominal surgery, thoracentesis is not required, and observation is more reasonable in such benign cases. However, thoracentesis in heart failure may be done in certain circumstances. (Box 3).[1,13]

Thoracentesis becomes urgent in suspected hemothorax or empyema as it needs immediate tube thoracostomy in these situations. In small effusion or loculated effusion, ultrasound-guided thoracentesis minimizes risk of pneumothorax.[14]

Pleural fluid analysis in Thoracentesis

Pleural fluid analysis is often useful in excluding various causes, and helps in clinical decision-making in majority of patients. Laboratory testing helps to distinguish pleural fluid transudates from exudates. Analysis of pleural fluid by thoracentesis yields valuable diagnostic information and even definitively establishes cause of the pleural effusion, more so if malignant cells, microorganisms, chyle are found. Gross characteristics of pleural fluid help indicate several exudative pathologies. (Box 4) 14

DISTINGUISHING EXUDATE AND TRANSUDATES: Pleural Fluid Biochemical Characteristics.

Based on biochemical characteristics of the fluid, which usually reflect physiologic mechanisms behind, pleural effusions are either transudates or exudates. (Table 2) A transudate can usually be treated without extensive evaluation, whereas cause of an exudate requires investigation. Although number of chemical tests has been proposed, tests proposed by Light et al[15] have become criterion standards in differentiating exduative and transudative effusions. (Box 5) Further, increased sensitivity to Light's criteria has been suggested to distinguish transudates from exudates (Box 5)[15,16] Nearly all exudates can be identified clearly by these criteria but approx 20-25% transudates are still classified as exudates, especially those with heart failure and receiving diuretics. In such cases, if difference between protein levels in serum and pleural fluid is > 3.1 g per dL and serum-effusion albumin gradient is > 1.2 g per dL, it indicates patient to most likely have true transudative effusion. Pleural fluid cholesterol > 55 mg/dL and pleural LDH >200 U/L each showed better positive and negative likelihood ratio for distinguishing exudates from transudates.[17,18,19]

OTHER TESTS FOR EXUDATIVE PLEURAL EFFUSION:

Causative Pathology	Transudate	Exudate
Congestive heart failure	Yes	No
Pneumonia	No	Yes
Cancer	No	Yes
Pulmonary embolism	Sometimes	Sometimes
Viral respiratory infection	No	Yes
Coronary-artery bypass surgery/ Other cardiac surgery	No	Yes
Cirrhosis	Yes	No

Table 2: Common Causes of Pleural Effusion: Transudate vs Exudate[1]

Other tests used for evaluation of exudative or transudative pleural effusion include levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), glucose levels and pH in different settings of pleural effusion. Differential cell counts, total WBC count, Gram stain, and pleural fluid culture (in infective cases) also help in narrowing the differential diagnosis and evaluate cases of pleural effusion. Direct tumor involvement of pleura is diagnosed most easily by performing

pleural fluid cytology. Pleural fluid cytology offers highest yield for diagnosing malignancy, with cytology positive in approximately 60% of malignant pleural effusions. Tumor markers are also helpful. Adenosine deaminase (ADA) is also a biochemical parameter and ADA activity of >43 U/mL in pleural fluid supports tuberculous pleuritis, though its sensitivity is not 100%.[20,21,22]

THORACENTESIS: CONTRAINDICATIONS AND COMPLICATIONS:

Relative contraindications to thoracentesis include a small pleural fluid volume, bleeding diathesis or systemic anticoagulation, mechanical ventilation, and cutaneous disease on puncture site. Ultrasound guidance helps in thoracentesis in difficult cases, apart from experienced hands. Some of the common complications of thoracentesis include pain at puncture site, cutaneous or internal bleeding from laceration of an intercostal artery or spleen/liver puncture, pneumothorax, empyema, and adverse reactions to anesthetics used in the procedure. Pneumothorax is seen in approximately 6% cases and requires drainage in some cases.[23]

Box 5. Differentiating Effusion based on Biochemical Characteristics

Normal Pleural Fluid:

- Clear ultrafiltrate of plasma thinly spread over visceral and parietal pleurae
- pH of 7.60-7.64
- Protein content < 2% (1-2 g/dL)
- < 1000 white blood cells (WBCs)/ cubic mm
- Glucose content similar to that of plasma
- Lactate dehydrogenase (LDH) < 50% of plasma

Exudate Pleural Effusion: Light's criteria

- Ratio of pleural fluid to serum protein > 0.5
- Ratio of pleural fluid to serum LDH > 0.6
- Pleural fluid lactic dehydrogenase (LDH) > two thirds (or > 0.45) of upper limits of normal serum value
- Fluid considered transudate if all of above are absent.

Increased sensitivity to Light's criteria if following present

- Pleural fluid cholesterol level > 45 mg/dL
- Pleural fluid protein level > 2.9 g/dL

OTHER PROCEDURES: BIOPSY, THORACOSCOPY/BRONCHOSCOPY: Pleural biopsy is considered only if TB or malignancy is suggested. Medical thoracoscopy has emerged as a diagnostic tool to take biopsy specimen in cases of undiagnosed exudative effusions, with

suspected malignancy or TB. Alternatively, closed-needle pleural biopsy with histology can also be performed and is recommended. Medical thoracoscopy/bronchoscopy has a higher diagnostic yield for malignancy, and closed needle pleural biopsy is as good as thoracoscopy in tuberculous pleuritis. Closed-needle biopsy with histologic examination has classically been recommended for undiagnosed exudative effusions when tuberculosis or malignancy is suspected. Combination of histology and culture of pleural biopsy tissue establishes diagnosis in up to 90% TB patients. The diagnostic yield from pleural biopsy is higher when it is used with some form of image guidance to identify areas of particular thickening or nodularity. As thoracoscopy is diagnostic in >90% patients with pleural malignancy and negative cytology, it is the preferred procedure in patients with cytology-negative patients suspected to have pleural malignancy.[24]

CONCLUSION: Evaluation of pleural effusion begins with history and physical examination. Chest X-ray is one of the first diagnostic modalities used for evaluating cases of pleural effusion. Ultrasound is effective in cases which have limitations being diagnosed by radiography. Ultrasound has several advantages and is also used to perform ultrasound-guided thoracentesis to reduce organ injury. CT-scan is useful in settings where ultrasound is not able to diagnose definitively. However, pleural fluid examination by thoracentesis is one of the most reliable techniques in differentiating various cases of pleural effusion. It also helps to distinguish exudative from transudative pleural fluid which narrows down the diagnosis. Various biochemical parameters are used, which include LDH levels, protein levels, glucose and cholesterol levels, apart from ADA, NT-proBNP, and pH of pleural fluid. Other procedures involved in evaluating undiagnosed cases of pleural effusion include pleural biopsy and bronchoscopy/thoracoscopy.

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REVIEW ARTICLE

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