GUIDELINES FOR DIAGNOSIS OF UNILATERAL PLEURAL EFFUSION

Pakistan Chest Society

Message by chairman guideline committee

Guidelines for pleural disease working group

Expert review committee

INTRODUCTION

Pleural disease is common problem faced by family practitioners, general physicians and especially respiratory physicians. A pleural effusion is an abnormal collection of fluid in the pleural space. It is the most common manifestation of pleural disease. Pleural effusion is a common disease worldwide. Approximately 1.5 million pleural effusions are diagnosed in the United States each year. The estimated prevalence in developed countries is 320 cases per 100,000 population. The exact prevalence in under-developed countries has not been estimated, but tuberculosis (Tb) remains an important cause. Pleural disease results from a wide range of diseases, therefore, needs a systematic approach to investigation in order to reach to diagnosis and proper management. These guidelines attempt to help health care professionals to manage patients with pleural disease in a systematic way in the light of best clinical evidence taking into consideration the local context.

These pleural disease guidelines will consist of following sections

1. Approach to diagnosis of unilateral pleural effusion.
2. Diagnosis & management of pleural infection
3. Diagnosis & management of Malignant Pleural effusion
4. Diagnosis & Management of Pneumothorax.
5. Pleural Procedures.

Basics about pleura and pleural space

ANATOMY OF PLEURAL SPACE:

Pleural space is a potential closed space between the two pleural surfaces that covers the entire lungs. It contains 1-5ml of clear fluid. However in pathological states, it has the capacity to accommodate liters of pleural fluid.

The pleural cavity is lined by a thin semi-permeable membrane(3). The side of pleural membrane covering the lung is known as visceral pleura. The side covering the chest wall is called the parietal pleura. The normal anatomical structures surrounding the pleura are shown in figure 1 below:

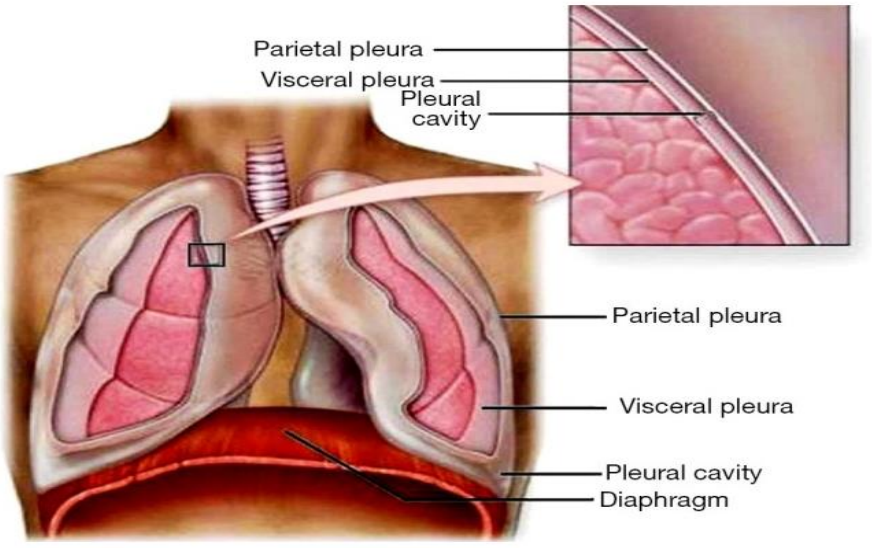


Figure 1: Anatomy of Pleural Space(3)

There is no anatomical connection between the two pleural cavities. The mediastinum is the partition between the lungs and includes the mediastinal pleura covering of the lung surface surrounding the mediastinum. The pleura dips into the fissures between its lobes and cause the partition of right lung into three (upper, middle and lower) lobes and left lung into two (upper and lower) lobes. The rest of the membrane lining covers the diaphragmatic side of the lung. The two layers are continuous with one another around and below the root of the lung. The visceral pleura receive blood supply from the bronchial circulation and the parietal pleura receive the blood supply from the intercostal arteries.

The pleura enhance functioning of the lungs during breathing. They transmit movements of the chest wall to the lungs, particularly during heavy breathing. The closely approved chest wall transmits pressures to the visceral pleural surface and hence to the lung(3).

Pleura plays a vital role in respiration. The potential space of the pleural cavity in healthy patients conjoins the natural outward movement of the chest wall to that of the natural inward movement of the lungs via two mechanisms.

1. The potential space's relative vacuum sustains the visceral and parietal pleurae's extreme adherence and is uninterrupted and not disrupted.
2. A minute volume of pleural fluid (calculated at 0.13 mL/kg of body weight under normal situations) serves as the lubricant to facilitate the normal physiologic sliding motion of both pleural surfaces against each other during inspiration and expiration. This small volume of lubricating fluid is maintained via a delicate balance of hydrostatic and oncotic pressure and lymphatic drainage; disturbances in any of these mechanisms may lead to pathology and, possibly, manifest as a pleural effusion(4).

PATHOPHYSIOLOGY OF PLEURAL EFFUSIONS:

Considering the anatomical arrangements, it appears that five compartments are involved in development of pleural effusion as given in figure 2 below; the parietal systemic capillaries; the parietal interstitial space; the pleural cavity; the lung interstitium; and the visceral microcirculation (either systemic from bronchial artery or pulmonary). The membranes separating such compartments are: the capillary endothelium (on parietal and visceral side); and the parietal and the visceral mesothelium. The lymphatics provide drainage of the interstitial spaces but also of the pleural cavity, as they open directly on the parietal pleura.

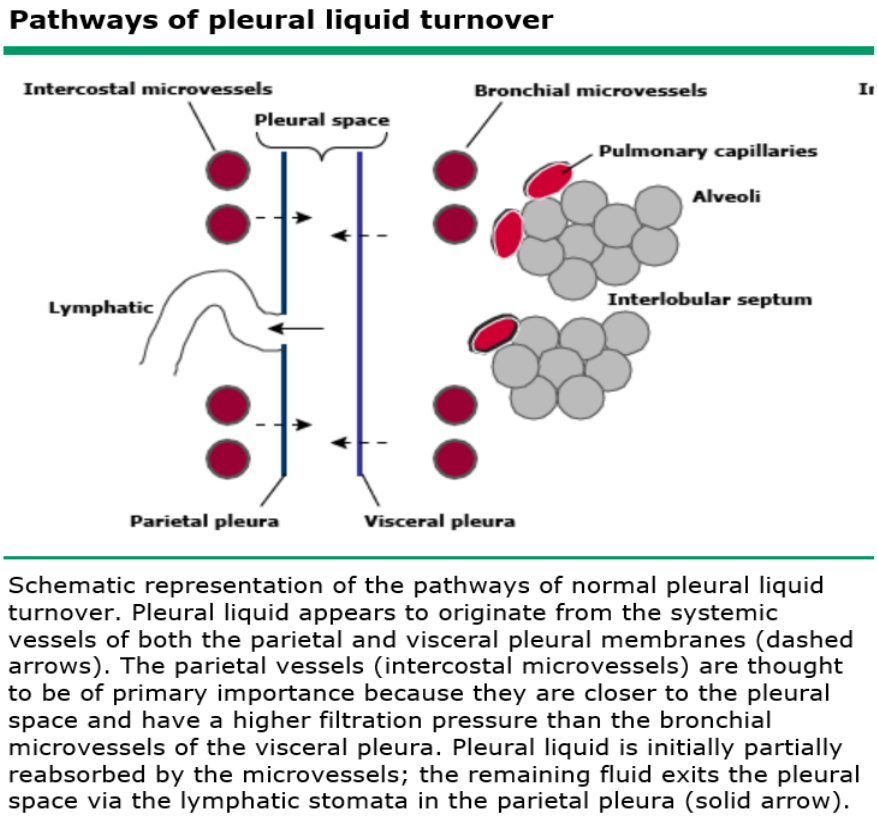


Fig 2: Pathophysiology of pleural effusion

The Normal Pleural fluid constituents are shown in table 1 below,

Normal Pleural fluid content

Color	Clear
pH	7.60-7.64
Protein content	<2% (1-2g/dL)
WBCs	<1000/m^3
Glucose	Same as that in plasma
LDH	<50% of plasma

Table1: Contents of normal pleural fluid.

Presence of a pleural effusion represents an underlying disease process that may be pulmonary or non-pulmonary in origin and may be acute or chronic. Although the etiologic spectrum of pleural effusion can be extensive, most pleural effusions are caused by congestive heart failure, pneumonia, malignancy, or pulmonary embolism(5). The following mechanisms may play a role in the formation of pleural effusion:

- Increased capillary hydrostatic pressure in the systemic and/or pulmonary circulation (e.g. congestive heart failure, superior vena cava syndrome).
- Reduction in intravascular oncotic pressure (e.g. hypo-albuminemia due to nephrotic syndrome or cirrhosis)
- Altered permeability of the pleural membranes (e.g., inflammation, malignancy, pulmonary embolism)
- Increased capillary permeability or vascular disruption (e.g., trauma, malignancy, inflammation, infection, pulmonary infarction, drug hypersensitivity, uremia, pancreatitis)
- Reduction of pressure in the pleural space (i.e. due to an inability of the lung to fully expand during inspiration); this is known as "trapped lung" (e.g. extensive atelectasis due to an obstructed bronchus or contraction from fibrosis leading to restrictive pulmonary physiology)
- Decreased lymphatic drainage or complete lymphatic vessel blockage, including thoracic duct obstruction or rupture (e.g. malignancy, trauma)
- Increased peritoneal fluid with micro-perforated extravasation across the diaphragm via lymphatic’s or microstructural diaphragmatic defects (e.g. hepatic hydrothorax, cirrhosis, peritoneal dialysis)
- Movement of fluid from pulmonary edema across the visceral pleura.
- Persistent increase in pleural fluid oncotic pressure from an existing pleural effusion, causing further fluid accumulation.

Approach to diagnosis of patient with unilateral pleural effusion

As with any other disease, the most important aspect of an approach to any patient is via taking appropriate history. One should suspect pleural effusion if the patient presents with:

1. Gradual worsening of shortness of breath
2. Pleuritic or dull chest pain on the effected side
3. Persistent fever
4. Cough

Once history suggest pleural effusion, focus should be on the cause of the effusion. Certain points in history can easily suggest the cause.

One of the most important tool in history is inquiring about past history. Past history may suggest chronic illnesses like CCF, CLD, CKD or malignancy which might be helpful in reaching for the cause of the effusion.

Other important factors to be taken care of in history are, the age of the patient (malignancy in old age and Tb in young), occupation (benign asbestos related pleural effusion or mesothelioma), and smoking history.

Examination

Clinical examination reveals reduced movements on the affected side, contralateral shifting of mediastinum (endobronchial obstruction leading to collapse results in ipsilateral shifting), reduced chest expansion, decreased tactile fremitus, and dull percussion, reduced or absent breath sounds, ego phony may be heard at the upper border of pleural effusion and pleural friction rub may be audible. Examination should be extended to find a cause of pleural effusion. Sign/symptoms suggestive of etiology is given in table 2.

Sign and symptoms suggestive of etiology	
Sign and symptoms	**Suggested etiology**
Ascites	Cirrhosis
Distended neck veins, Dyspnea on exertion, Orthopnea , peripheral edema, S3 gallop,	Heart failure
Fever	Para-pneumonic, empyema, tuberculosis, malignancy.
Hemoptysis	Malignancy, Tuberculosis, Pulmonary embolism
Lymphadenopathy, Hepatosplenomegaly	Malignancy
Unilateral lower limb swelling	Pulmonary embolism
Weight loss	Malignancy, Tuberculosis

Table 2: Sign/Symptoms suggestive of etiology.

Imaging

Chest X-Ray: Pleural effusion presents as blunting of the costophrenic angle on PA chest x ray (at least 200ml of fluid required to be detected at PA view) and as blunting of the posterior costophrenic sulcus on lateral radiographs (at least 50ml of fluid required to be detected by lateral X-Ray). Fig 2 shows a left sided pleural effusion on a CXR... Table 3 shows a list of other diagnosis which may mimic pleural effusion on CXR.

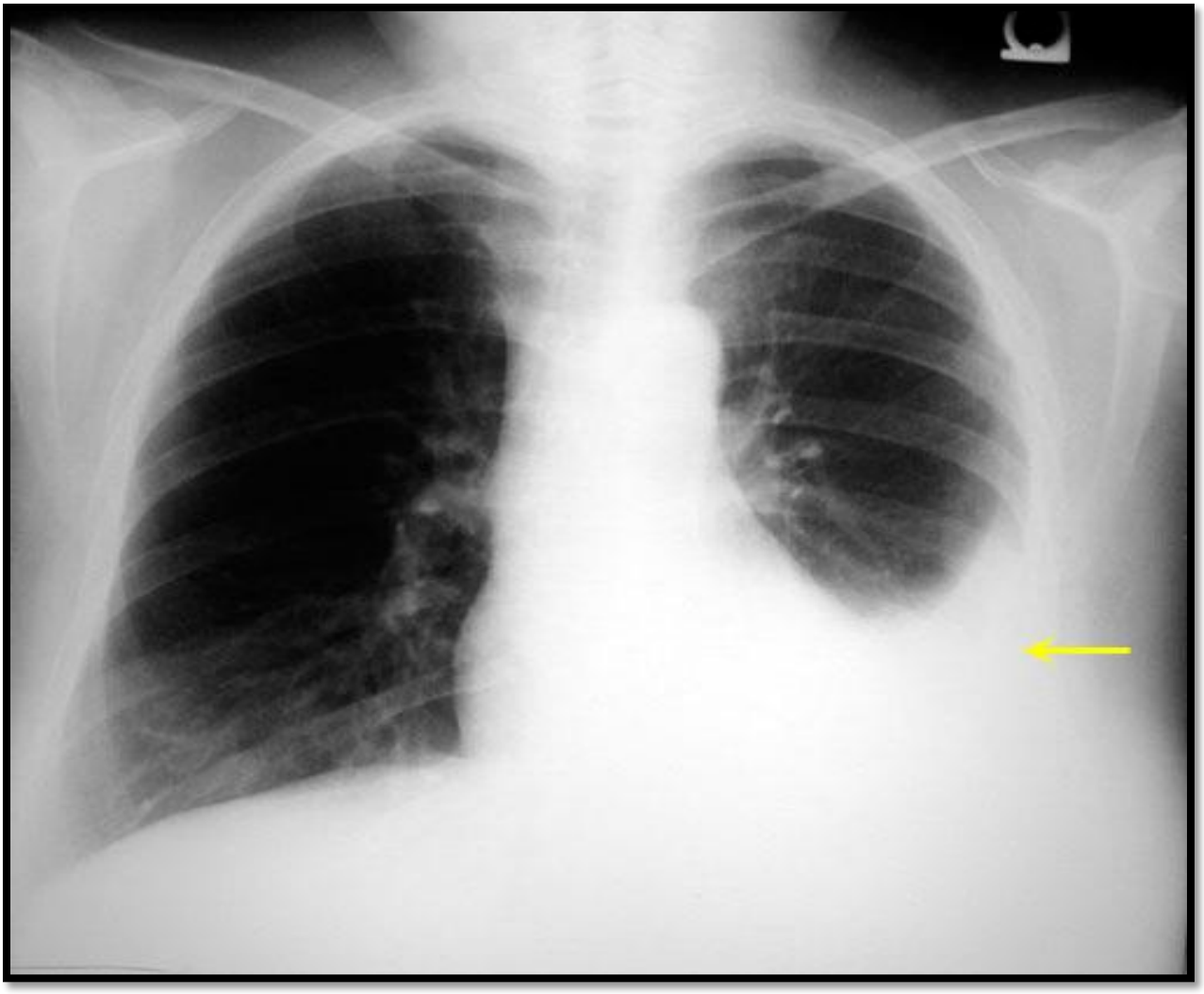


Fig 2: Left sided pleural effusion.

Ultrasonography: Various studies have shown that ultrasound has 100% sensitivity for detection of pleural effusion. It is also useful for loculated effusion for marking site of pleural tap, detection of septations. Ultrasound is more sensitive than CT-chest in detection of septations. It is also more accurate in detection of pleural effusion in ICU setting. Fig 3 shows pleural effusion as seen on ultrasound.

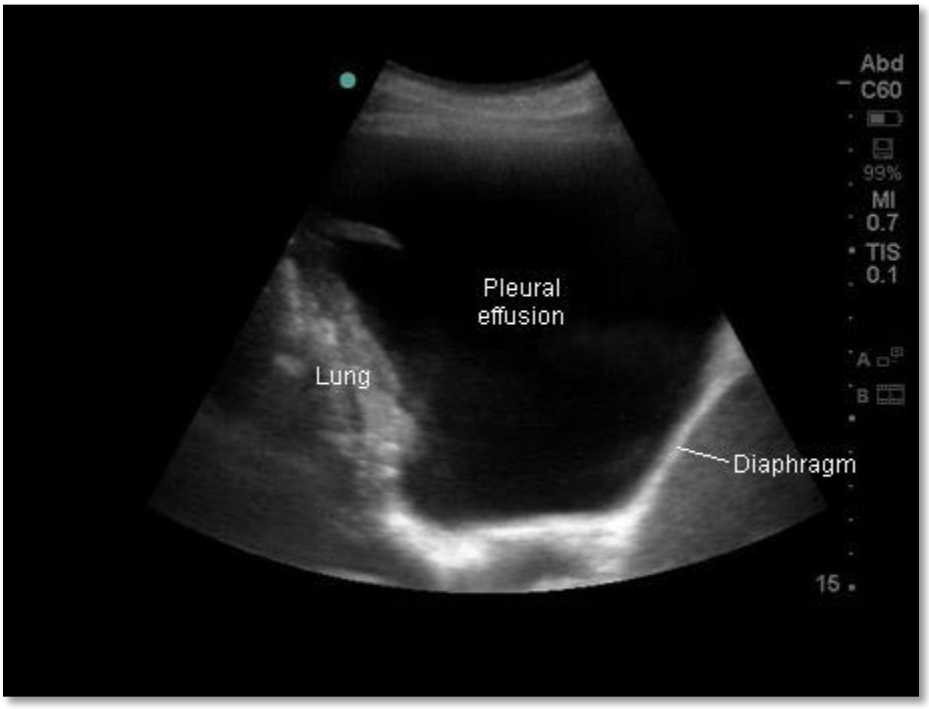


Fig 3: Ultrasound image showing pleural effusion.

CT-chest: CT scan of the chest is an alternate option to confirm pleural effusion and indicated if there is loculated pleural effusion or pleural thickening, underlying collapse/ consolidation, raised hemidiaghram, associated lymphadenopathy, pleural nodularity and underlying lung disease. Fig 4 shown bilateral pleural effusion on a CT-chest image.

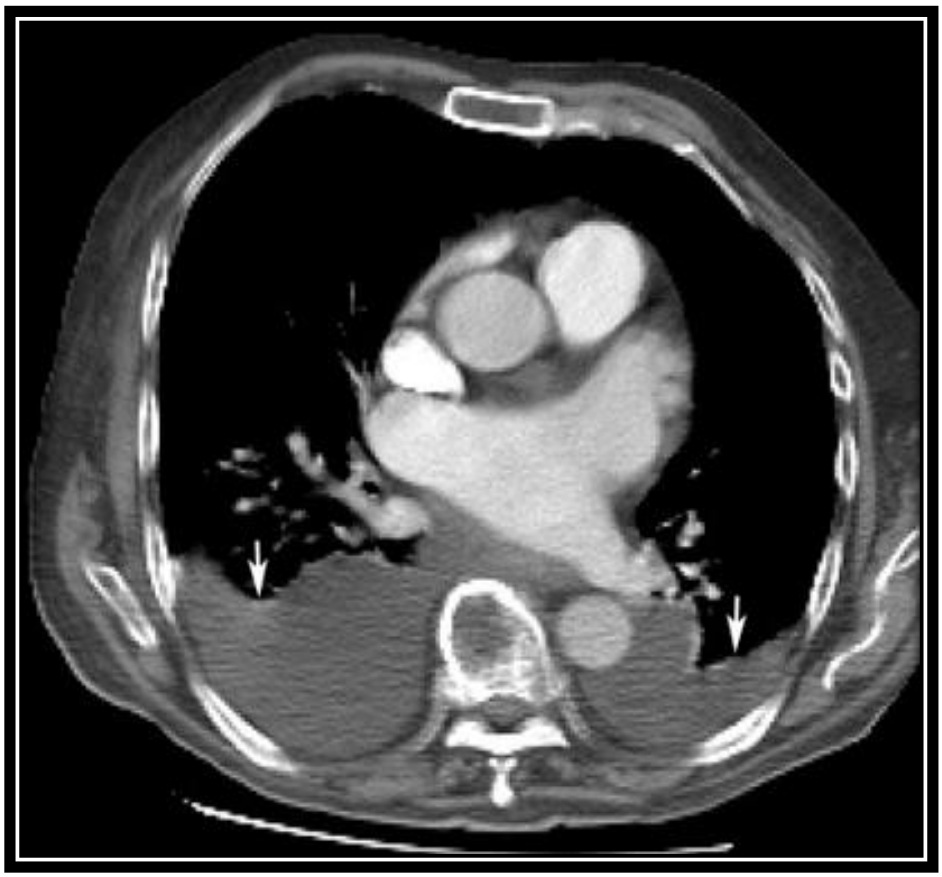


Fig 4: CT-chest showing bilateral pleural effusion,

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Pleural thickening	• Patient has a history of prior pleural disease such as TB or empyema, or exposure to environmental agents.	• Thickened pleura from pleural fibrosis resulting from previous pleural inflammation or prior environmental exposures, such as asbestos, beryllium, and silica, can appear similar to a pleural effusion on CXR. Ultrasound and CT distinguish fluid from thickening alone.
Pulmonary collapse and consolidation	• History to support a possible underlying cause, such as haemoptysis and weight loss in lung cancer.	• Can occur in conjunction with the pleural effusion from compression or can be mistaken for a pleural effusion on CXR. CT scan or ultrasound can more clearly define the difference between lung collapse, consolidation, and mass lesions from effusions.
Elevated hemidiaphragm	• Can result from paralysis of the phrenic nerve. • Paradoxical chest movement during the respiratory cycle can be a clue to diagnosis.	• A fluoroscopic test or ultrasound to analyse diaphragmatic movement with rapid breathing (often called a 'sniff test') can evaluate diaphragm paralysis.
Pleural tumours/ extrapleural fat	• Extrapleural fat is asymptomatic.	• The density of fat is much lower than that of fluid on CT scan and should be readily differentiated. • Pleural tumours can also be easily demonstrated on CT. • The presence of nodularity is often key to a malignant process.

Table 3: List of differential diagnosis on a CXR.

TYPES AND CAUSES OF PLEURAL EFFUSIONS:

Pleural effusions pose an important diagnostic challenge faced by a pulmonologist. Around 20% of cases remain undiagnosed despite utilizing multiple modalities of diagnosis. There are numerous causes of this illness, and important differentiating parameter is the protein content. Pleural effusions are generally classified as transudates or exudates, based on the mechanism of fluid formation and pleural fluid chemistry. Transudates result from an imbalance of oncotic and hydrostatic pressures, whereas exudates are the result of inflammatory processes of the pleura and/or decreased lymphatic drainage. In some cases, it is not rare for pleural fluid to exhibit mixed characteristics of transudate and exudate.

Four most common causes of pleural effusion in order of incidence in USA are congestive heart failure, malignancy, pneumonia and pulmonary embolism, however, Tuberculosis is main cause of unilateral pleural effusion in TB endemic areas like Pakistan. Two main causes of transudative pleural effusion are congestive heart failure and cirrhosis whereas Tuberculosis, malignancy and pneumonia are three main causes of exudative pleural effusion. Viral infections, pulmonary embolism and effusion after coronary artery bypass graft surgery are other common causes of exudative pleural effusion.

Data from studies conducted in Pakistan have shown that around 60%-65% of patients presenting with unilateral pleural effusion have tuberculous pleural effusion, around 15% have malignancy, and 10%-12% have cirrhosis/CCF, while 10%-15% remain undiagnosed. However these studies have small sample size therefore necessitating a study with a considerably large sample size in order to have a representative figures.

Transudative pleural effusion can be differentiated from exudative by its protein content, i.e. protein of <2.5g/dL is transudative while >3,0g/dL is exudative, however in cases where it is between 2.5-3.0g/dL we apply the lights criteria, which is as follow:

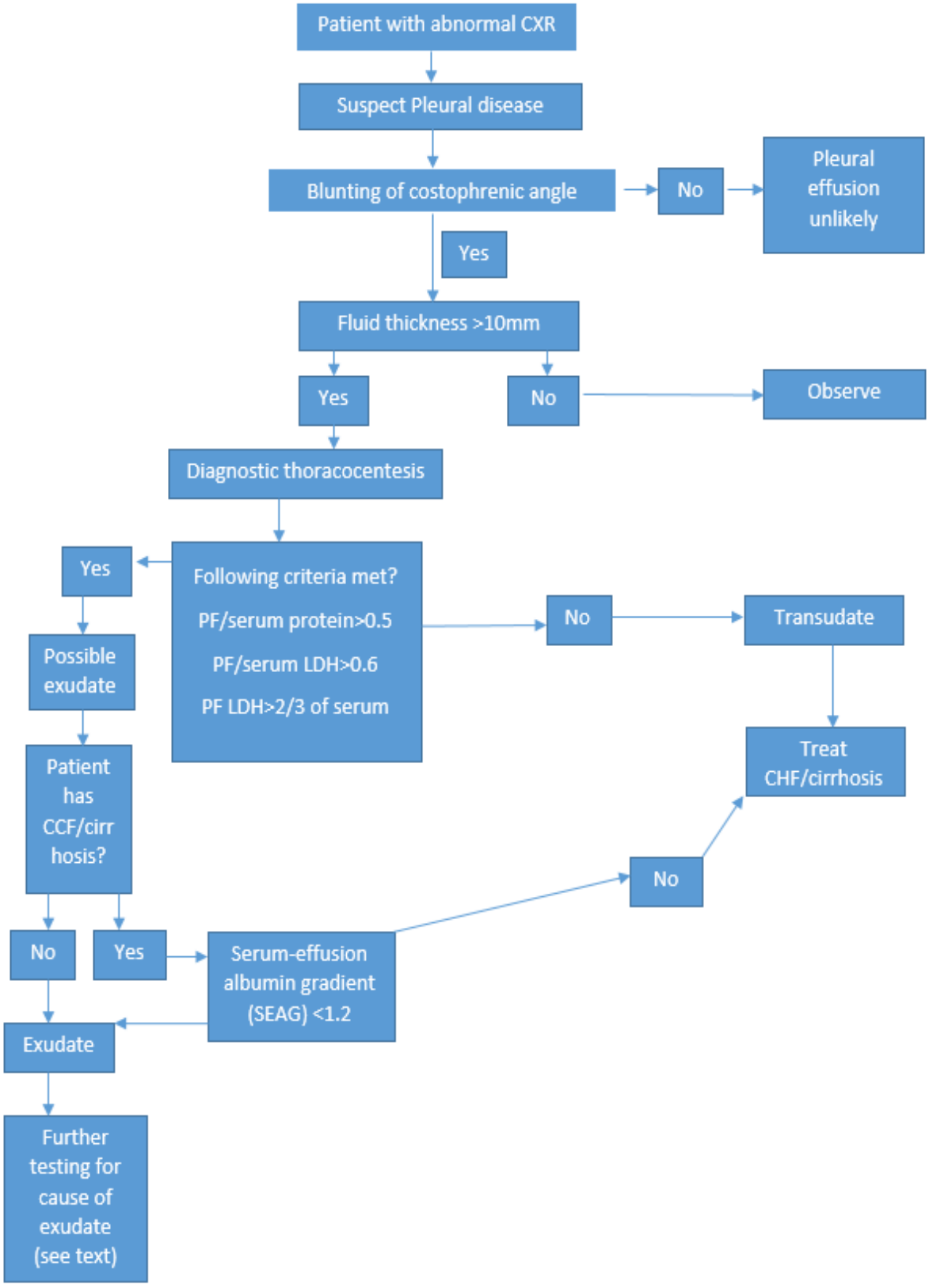
Criteria	Transudative	Exudative
Pleural fluid protein to serum protein ratio	≤0.5	**>0.5**
Pleural fluid LDH to serum LDH ratio	≤0.6	**>0.6**
Pleural fluid LDH	<2/3 of serum LDH	>2/3 of serum LDH

Table 4: Lights criteria

Certain additional parameters for differentiating exudative effusion from transudative have also been proposed e.g.

1. Pleural fluid LDH value more than 0.45 of the upper limit of normal serum value.
2. Pleural fluid cholesterol more than 45 mg/dl.
3. In CCF patients on diuretic therapy up to 25% of patients with transudative effusion can be misdiagnosed as exudative pleural effusion. In such cases a gradient of pleural fluid albumin to serum albumin (SEAG) of >1.2 gm/dl indicates transudate. The difference between serum proteins and pleural fluid can also be measured. If this difference is more than 3.1 g/dl then effusion is transudative and no further tests should be conducted
4. NTpro-BNP of more than 1300-4000ng/l of in pleural fluid diagnoses CCF as the cause of pleural fluid.

A general approach towards assessment of patient with pleural effusion is given in the following algorithm.


Patient with abnormal CXR
Suspect Pleural disease
Blunting of costophrenic angle
No
Pleural effusion unlikely
Yes
Fluid thickness >10mm
Yes
No
Observe
Diagnostic thoracocentesis
Yes
Following criteria met?
PF/serum protein>0.5
PF/serum LDH>0.6
PF LDH>2/3 of serum
No
Transudate
Possible exudate
Patient has CCF/cirr hosis?
Treat CHF/cirrhosis
No
Yes
Serum-effusion albumin gradient (SEAG) <1.2
No
Exudate
Further testing for cause of exudate (see text)

Transudative Pleural effusion

Common causes
Left Ventricular failure
Liver Cirrhosis
Nephrotic syndrome
Hypoalbomenimia
Peritoneal dialysis

Less common causes
Hypothyroidism
Pulmonary Embolism
Constrictive pericarditis
Malignancy (5%)
Mitral stenosis
Superior Venacaval Obstruction
Miegs Syndrome

Exudative Pleural effusion

Common Causes	Less common causes	Rare Causes
Para-pneumonic effusion/Empyema	Pulmonary Infarction	Yellow nail Syndrome
Tuberculous Pleural effusion	Systemic lupus erythematosus	Chylothorax
Malignancy	Dressler syndrome	Drugs
Rheumatoid pleural disease	Benign Asbestos related Pleural effusion	Sarcoidosis
	Post CABG	Ovarian Hyper stimulation
	Pancreatitis	

Drugs Causing Pleural effusion

Hydralazine
Nitrofurantion
Sulphonamide
Methotrexate
Parctolol
Methysergide
Isoniazid
Amiodarone

PLEURAL FLUID ANALYSIS

Collection of Pleural fluid sample

It should be collected in 2-5ml syringe/plain container, however for microscopy and C/S it should be sent a blood culture bottle. Pleural fluid should be collected in heparinized syringe for pH, fluoride oxalate bottle for glucose and EDTA bottle for hematocrit measurement.

Appearance of Pleural Fluid

Based on naked eye look, pleural fluid can be broadly classified into

- Clear
- Cloudy
- Bloody

If the fluid appears bloody then hematocrit should be advised. If Hct is < 1% it is not significant and if it is > 1 %, three main differential diagnoses should be kept in mind.

- Malignancy
- Pulmonary Embolism
- Trauma

Hct > 50% of blood indicates hemothorax If RBC count in pleural fluid is obtained accurately, it is possible to estimate hematocrit by dividing the RBC count by 100,000. An RBC count of

1000,000 in Pleural fluid corresponds to Hct of 10%.

Frank pus suggests empyema. Fouling smelling fluid indicates anaerobic infection.

Black-colored pleural fluid is seen in fungal infections with Aspergillus Niger and Rhizopus, malignant mesothelioma and ruptured pancreatic pseudo cyst.

Milky or cloudy fluid suggests chylothorax or pseudochylothorax. These two entities can be differentiated by the patient's history, examination of the sediment for cholesterol crystals, and lipid analysis of the supernatant. Pseudochylothoraces usually occurs in long standing effusions. Cholesterol crystals are present in the sediment, and levels of triglycerides are not usually high. In contrast, chylothoraces are more acute, do not contain cholesterol crystals, and are characterized by high levels of triglycerides.

Algorithm for evaluating the appearance of pleural fluid is givem below:

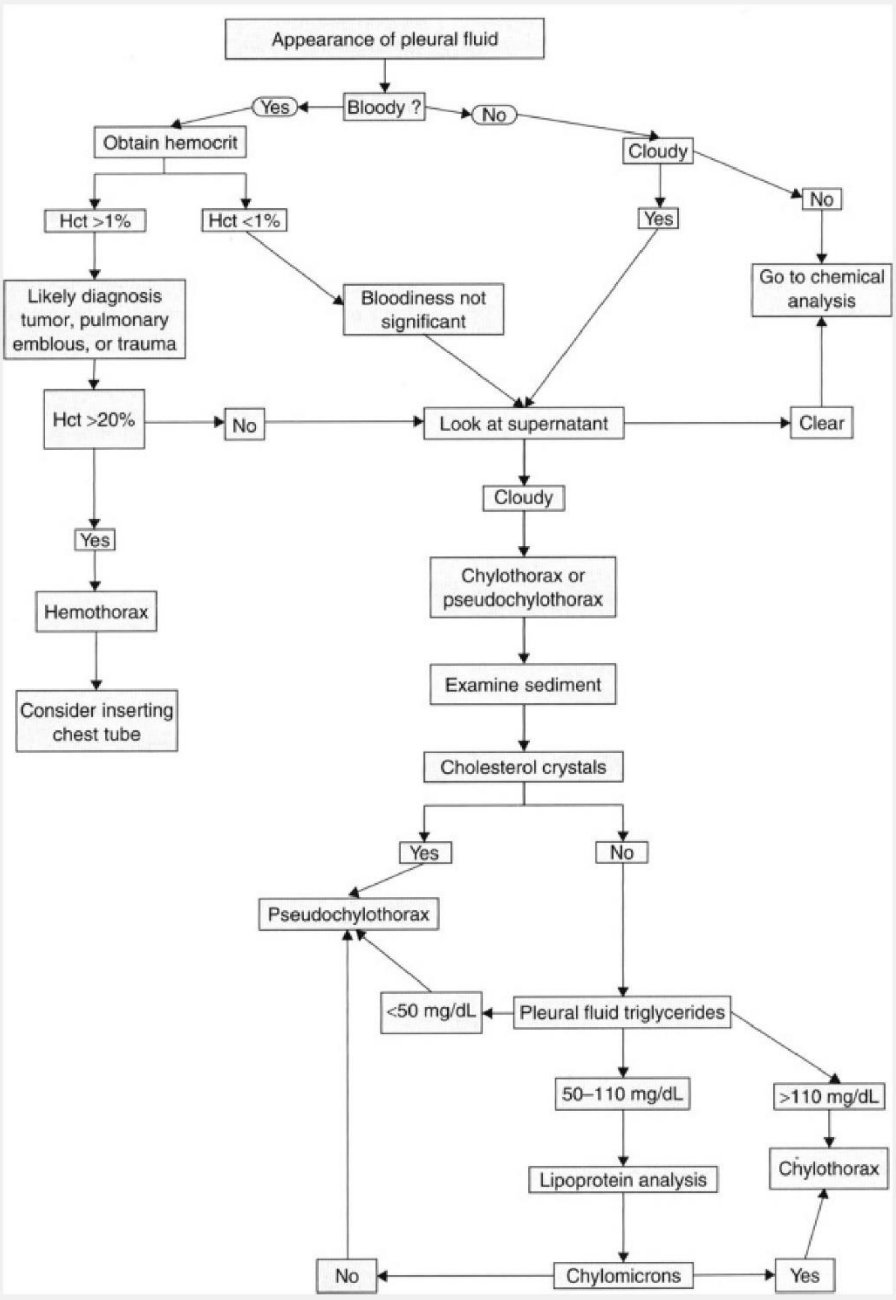


FIGURE 2 • Algorithm for evaluating the appearance of pleural fluid. Hct, hematocrit.

Routine Measurements on Exudative Pleural Fluids

Several tests are conducted to diagnose an exudative pleural effusion. A pleural fluid cell count and differential, pleural fluid glucose and LDH levels, cytology and markers for Tuberculosis should be obtained. A good starting point for the diagnostic assessment of an unknown exudate is the pleural fluid cytology.

Pleural fluid amylase should be obtained if acute pancreatitis, esophageal rupture, or chronic pancreatic pleural effusion is suspected.

Pleural Fluid Differential Cell Count

Cell count and the differential provide information about the etiology of the exudative pleural effusion. Neutrophillic predominant effusions are usually a result of an acute process and chest radiograph should be obtained to look for parenchymal infiltrates. The presence of an infiltrate indicates that the patient probably has a para-pneumonic effusion. Parenchymal infiltrates along with pleural effusion are also present in pulmonary embolism and lung cancer. Purulent sputum also points towards the para-pneumonic effusion. When sputum is not purulent and total leukocyte count is also normal then CT angiogram (CTPA) should be advised to rule out pulmonary embolus. If CTPA is also normal then bronchoscopy should be done with Tran's bronchial biopsy to determine the cause of the parenchymal infiltrate. If after all these studies the diagnosis is still not clear, video-assisted thoracoscopy should be performed if the infiltrate is worsening or the effusion is increasing in size.

If patient has neutrophillic exudative effusion without parenchymal infiltrates then possibility of

pulmonary embolus, viral infection, gastrointestinal disease, asbestos pleural effusion, malignant pleural disease, or acute tuberculous pleuritic should be kept in mind. CT pulmonary angiogram scan or lung scans for evaluation of pulmonary embolus should be advised. A gastrointestinal etiology of the pleural effusion can be evaluated with an abdominal CT scan or ultrasound. A careful history should be taken for asbestos exposure. The marker for tuberculosis (adenosine deaminase (ADA) or interferon-gamma) will indicate whether the patient has tuberculosis, and the cytology will provide the first evaluation for pleural malignancy.

Lymphocytic exudative pleural effusions are due to malignant disease, pulmonary embolization, pleural effusions following CABG, and tuberculosis and indicate a more chronic process. Detailed history, cytology, and elevated levels of ADA or interferon-gamma in pleural fluid will help in differentiating these possibilities. If none of the above diagnosis is made, CTPA should be advised to rule in/rule out pulmonary embolism.

Classification based on Cells

Lymphocytes (>85%)	Neutrophils	Eosinophils (>10%)
Tuberculous pleural effusion	Para-pneumonic effusion	Pneumothorax
Malignancy	Pulmonary embolism	Hemothorax
Sarcoidosis	Acute pleural injury	Drugs
Rheumatoid pleural effusion		Eosinophilic polyangitis with granulomatosis
Yellow nail syndrome		Malignancy
Chylothorax		Early post-CABG
		Benign asbestos related pleural effusion

Pleural Fluid Glucose

If patient has reduced glucose levels (<60 mg/dL) then the differential diagnosis are as following:

Common causes	Rare causes
Para-pneumonic effusion	**Paragonimiasis**
Malignant effusion	**Hemothorax**
Tuberculous effusion	**Churgh-Strauss syndrome**
Rheumatoid effusion	**Urinothorax**
	SLE

pH

Low pH is found in the cases with low glucose levels. In para-pneumonic effusions pH<7.20 necessitates drainage via chest tube. In malignant effusions low pH is associated with high malignant cell turnover, failure of pleurodesis, and poor prognosis. pH can be measured via ABG analyzer, provided pleural fluid is not grossly pus.

Pleural Fluid Lactate Dehydrogenase

Pleural fluid LDH should be obtained in every pleural fluid as it is a reliable indicator of the degree of pleural inflammation. Serial Pleural fluid LDH levels can be a guide to the worsening of disease and treatment response. LDH more than 1000 suggests empyema, malignancy, rheumatoid, paragonimiasis and PCP.

Pleural Fluid Cytology

Pleural fluid cytology is an effective way of diagnosing malignant pleural effusion. The percentage of malignant pleural effusions that are diagnosed with cytology has been reported to be anywhere between 40% and 87%. Diagnostic yield is highest with adenocarcinoma and less with squamous cell carcinoma, Hodgkin's disease, and sarcomas.

Obviously, the yield will also depend on the skill of the cytologist. It also depends on the extent of the tumor — the greater the tumor burden in the pleural space, the more likely the cytology is to be positive.

For adequate cytology report at least 50-150ml is should be sent malignant cells cytology.

How to differentiate mesothelioma from adenocarcinoma;

- Mesothelioma has true papillary aggregates, multinucleation with atypia, cell to cell apposition. Whereas adenocarcinoma has acinus-like structures, balloon like vaculation and large balls or clumps of cells. In immunohistochemical analysis, adenocarcinoma cells stain positive with PAS-D, and mesothelioma cells stain with Acian blue.
- Malignant mesothelial cells stain positive with calretinin and cytokeratin 5/6, whereas adenocarcinoma markers are CEA, MOC-31. But benign mesothelial cells also stain with calretinin and cyokeratin. So further staining is required. Benign mesothelial cells react to desmin and malignant mesothelial cells to Epithelial Membrane Antigen (EMA).
- Electron microscopy shows that unlike adenocarcinoma cells, malignant mesothelial cells have numerous long and thin microvilli.
- Hyaluronate level in pleural fluid of >75 mg/ml is 100% specific but 50% sensitive for mesothelioma.
- In metastatic breast carcinoma, malignant cells stain with Lactoferrin. In ovarian carcinoma, malignant cells from pleural effusion stain with CA-125.
- Thyroid Transcription Factor-1 stains only metastatic lung carcinoma cells.
- The utility of tumor markers is that if the patient has higher level of tumor markers like CEA, CA-125, CA 15-3 and cytokeratin 9 fragment in pleural effusion, he can be subjected to further diagnostic invasive investigations.

Algorithm for evaluating exudative effusion with unknown etiology.

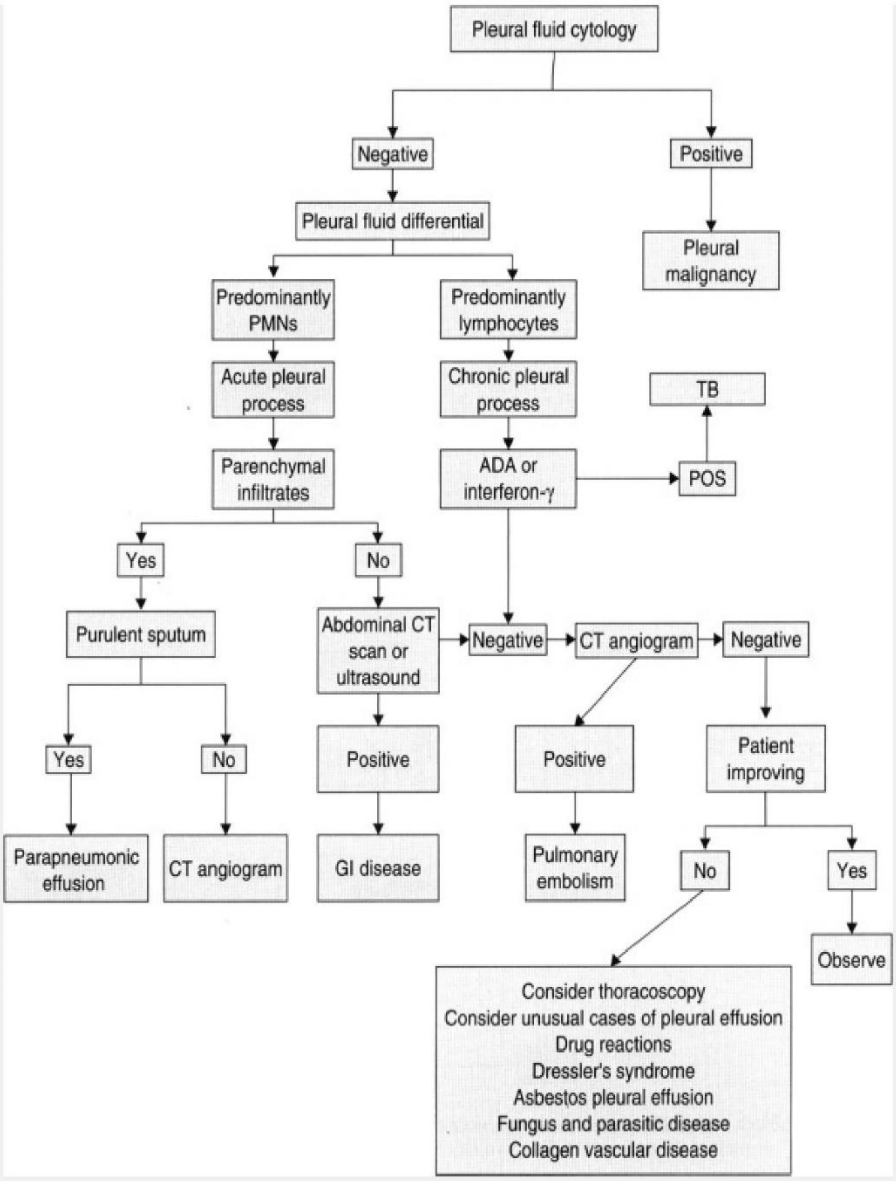


FIGURE 3 • Algorithm for evaluating exudates with an unknown etiology. PMN, polymorphonuclear neutrophil; TB, tuberculosis; ADA, adenosine deaminase; CT, computed tomography; GI, gastrointestinal; POS, positive.

Countercurrent immunoelectrophoresis(CIE):

It is used to detect bacterial antigens especially for streptococcus, staphylococcus aureus and hemophilus influenza over hours thereby obviating the need for bacterial cultures which take several days.

Direct Gas-Liquid Chromatography:

This test is employed to detect anaerobic infections.

Pleural Fluid Markers for Tuberculosis

1. **Pleural Fluid Adenosine Deaminase Level**

If a pleural fluid is lymphocytic exudative and high ADA levels (> 40 U/L) then tuberculosis should be the first possibility. High ADA levels are also present in are empyema and rheumatoid pleuritis, and both these conditions are easily distinguished from pleural tuberculosis by the clinical picture.

2. **Pleural Fluid Interferon-Gamma Levels**

Pleural fluid interferon-gamma levels are also elevated with tuberculous pleuritis. Pleural fluid interferon-gamma levels are more efficient than ADA levels at differentiating tuberculous from non-tuberculous pleural effusion. Pleural fluid Interferon gamma levels up to 3.7 U/ml has a sensitivity of 98% and a specificity of 97% in detecting tuberculous effusion.

Table 6. Selected Pleural Fluid Tests

Test	*Comments*
Acid-fast bacillus, adenosine deaminase level, *Mycobacterium tuberculosis* culture	Indicated if tuberculosis is a concern; measurement of adenosine deaminase may also be useful in determining the presence of tuberculosis (sensitivity and specificity > 90%, although it may also be elevated in patients with empyema or malignancy)
Amylase level	Elevated in patients with pancreatitis; may also be elevated in those with malignancy, esophageal perforation, or tuberculosis
Hematocrit level	Hematocrit > 1% indicates possible pneumonia, pulmonary embolism, malignancy, or trauma; pleural fluid hematocrit > 0.5 × peripheral blood hematocrit indicates hemothorax
N-terminal pro-brain natriuretic peptide level	Elevated in patients with heart failure; useful in diagnosing heart failure when effusion is classified as exudative by Light's criteria
pH and glucose levels	pH < 7.20 and glucose < 60 mg per dL (3.3 mmol per L) may indicate a complicated parapneumonic effusion or empyema; chest tube draining may be indicated
Triglyceride and cholesterol levels	Helpful in diagnosing and differentiating chylothorax and pseudochylothorax (patients with pseudochylothorax have increased cholesterol and decreased triglyceride levels)
Tumor markers	May be ordered based on clinical suspicion; includes carcinoembryonic antigen, cancer antigen 125, cancer antigen 15-3, cytokeratin 19 fragment, and mesothelin testing

Information from references 6, 10, 11, 18, 30, and 31.

Options when no Diagnosis is obtained after Initial Thoracentesis

When pleural fluid marker for tuberculosis and cytology are not helpful in diagnosing pleural effusion, then CTPA should be done for pulmonary embolus. Pleural masses or mediastinal lymphadenopathy should also be evaluated. If the CTPA is also inconclusive, then there are five options available to the physician:

- Observation
- Needle biopsy of the pleura
- Bronchoscopy
- Thoracoscopy
- Thoracotomy with open biopsy.

Observation

If the patient is improving and there are no parenchymal infiltrates then observation is probably the best option. Almost 15% of patients with exudative pleural effusion remain undiagnosed. Malignant effusions are less likely to improve spontaneously. Pulmonary embolism is diagnosed with CTPA and tuberculous pleuritic is diagnosed with the help of markers discussed above.

Bronchoscopy

Bronchoscopy is useful in one or more of the following four conditions are present.

a. A pulmonary infiltrate is present on the chest radiograph or the chest CT scan. In this situation, particular attention should be paid to the area that contains the infiltrate.
b. Hemoptysis is present in the presence of a pleural effusion. It suggests an endobronchial lesion (or pulmonary embolism).
c. The pleural effusion occupies more than three fourths of the hemithorax.
d. The mediastinum is shifted toward the side of the effusion. In this situation, an endobronchial lesion is probable.

In patients with pleural effusions with positive cytology but no hemoptysis or parenchymal infiltrates, bronchoscopy will not identify the primary tumor.

Thoracoscopy

If pleural fluid cytology and markers for tuberculosis have not yielded any diagnosis then more invasive methods like thoracoscopy should be done. If Malignancy is the clinical diagnosis then thoracoscopy will establish definitive diagnosis in more than 90% of the cases. The diagnosis of mesothelioma is probably best made with thoracoscopy. Thoracoscopy can also establish the diagnosis of tuberculosis. Thoracoscopy has also an advantage of pIeurodesis. It rarely establishes the diagnosis of benign disease. Thoracoscopy is helpful in case of an undiagnosed pleural effusion, malignancy or tuberculosis is present.

Needle Biopsy of the Pleura

Needle biopsy of pleura is helpful in obtaining tissue for cultures for drug resistant mycobacterium and guides treatment. However, yield of the pleural tissue culture is only 33% for tuberculosis. Pleural effusion due to disseminated multidrug-resistant tuberculosis is rare without parenchymal infiltrates. This is the reason; pleural biopsy is usually not indicated for the diagnosis of tuberculous pleuritis.

Pleural biopsy can also establish the diagnosis of malignant pleural disease. Cytology of pleural fluid is more sensitive in diagnosing malignant effusion that is why pleural biopsy is usually not indicated in cytology positive effusion. When cytology is negative then yield of pleural biopsy in malignant effusion is only 17%. In such cases, thoracoscopy is the best option. It can diagnose almost 90% of the effusions. If still there is diagnostic ambiguity, then biopsy should be carried either Needle biopsy of the pleura or thoracoscopically. Thoracoscopy is the preferred option for pleural biopsy. It is also indicated when pleural fluid markers are equivocal or unavailable and tuberculosis is the diagnosis under consideration.

Open Pleural Biopsy

Open pleural biopsy or thoracoscopy should be done in case of progressive undiagnosed pleural disease. Thoracoscopy is preferred over open pleural biopsy as it is associated with decreased morbidity.

Open pleural biopsy does not always provide a diagnosis in a patient with an undiagnosed pleural effusion.