Approach Considerations

Thoracentesis should be performed for new and unexplained pleural effusions when sufficient fluid is present to allow a safe procedure. Observation of pleural effusion is reasonable when benign etiologies are likely, as in the setting of overt congestive heart failure, viral pleurisy, or recent thoracic or abdominal surgery.

Laboratory testing helps to distinguish pleural fluid transudates from exudates; however, certain types of exudative pleural effusions might be suspected simply by observing the gross characteristics of the fluid obtained during thoracentesis. Note the following:

- Frankly purulent fluid indicates an empyema
- A putrid odor suggests an anaerobic empyema
- A milky, opalescent fluid suggests a chylothorax, resulting most often from lymphatic obstruction by malignancy or thoracic duct injury by trauma or surgical procedure
- Grossly bloody fluid may result from trauma, malignancy, postpericardiotomy syndrome, or asbestos-related effusion and indicates the need for a spun hematocrit test of the sample; a pleural fluid hematocrit level of more than 50% of the peripheral hematocrit level defines a hemothorax, which often requires tube thoracostomy

Normal pleural fluid

Normal pleural fluid has the following characteristics:

- Clear ultrafiltrate of plasma that originates from the parietal pleura
- A pH of 7.60-7.64
- Protein content of less than 2% (1-2 g/dL)
- Fewer than 1000 white blood cells (WBCs) per cubic millimeter
- Glucose content similar to that of plasma
- Lactate dehydrogenase (LDH) less than 50% of plasma

Distinguishing Transudates From Exudates

The initial diagnostic consideration is distinguishing transudates from exudates. Although a number of chemical tests have been proposed to differentiate pleural fluid transudates from exudates, the tests first proposed by Light et al have become the criterion standards.[21]

The fluid is considered an exudate if any of the following applies:

- Ratio of pleural fluid to serum protein greater than 0.5
- Ratio of pleural fluid to serum LDH greater than 0.6
- Pleural fluid LDH greater than two thirds of the upper limits of normal serum value

These criteria require simultaneous measurement of pleural fluid and serum protein and LDH. However, a meta-analysis of 1448 patients suggested that the following combined pleural fluid measurements might have sensitivity and specificity comparable to the criteria from Light et al for distinguishing transudates from exudates:

- Pleural fluid LDH value greater than 0.45 of the upper limit of normal serum values
- Pleural fluid cholesterol level greater than 45 mg/dL
- Pleural fluid protein level greater than 2.9 g/dL

Clinical judgment is required when pleural fluid test results fall near the cutoff points.

The criteria from Light et al and these alternative criteria identify nearly all exudates correctly, but they misclassify approximately 20-25% of transudates as exudates, usually in patients on long-term diuretic therapy for congestive heart failure (because of the concentration of protein and LDH within the pleural space due to diuresis).

Using the criterion of serum minus pleural protein concentration level of less than 3.1 g/dL, rather than a serum/pleural fluid ratio of greater than 0.5, more correctly identifies exudates in these patients.

Although pleural fluid albumin is not typically measured, a gradient of serum albumin to pleural fluid albumin of less than 1.2 g/dL also identifies an exudate in such patients.

In addition, studies suggest that pleural fluid levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are elevated in effusions due to congestive heart failure. Moreover, elevated pleural NT-proBNP was shown to out-perform pleural fluid BNP as a marker of heart failure–related effusion. Thus, at institutions where this test is available, high pleural levels of NT-proBNP (defined in different studies as >1300-4000 ng/L) may help to confirm heart failure as the cause of an otherwise idiopathic chronic effusion.

**Pleural Fluid LDH, Glucose, and pH**

**Pleural fluid LDH**

Pleural fluid LDH levels greater than 1000 IU/L suggest empyema, malignant effusion, rheumatoid effusion, or pleural paragonimiasis. Pleural fluid LDH levels are also increased in effusions from *Pneumocystis jiroveci* (formerly, *P carinii*) pneumonia; the diagnosis is suggested by a pleural fluid/serum LDH ratio of greater than 1, with a pleural fluid/serum protein ratio of less than 0.5.

**Pleural fluid glucose and pH**

In addition to the previously discussed tests, glucose and pleural fluid pH should be measured during the initial thoracentesis in most situations.

A low pleural glucose concentration (30-50 mg/dL) suggests malignant effusion, tuberculous pleuritis, esophageal rupture, or lupus pleuritis. A very low pleural glucose concentration (ie, < 30 mg/dL) further restricts diagnostic possibilities, to rheumatoid pleurisy or empyema.

Pleural fluid pH is highly correlated with pleural fluid glucose levels. A pleural fluid pH of less than 7.30 with a normal arterial blood pH level is caused by the same diagnoses as listed above for low pleural fluid glucose. However, for parapneumonic effusions, a low pleural fluid pH level is more predictive of complicated effusions (that require drainage) than is a low pleural fluid glucose level. In such cases, a pleural fluid pH of less than 7.1-7.2 indicates the need for urgent drainage of the effusion, while a pleural fluid pH of more than 7.3 suggests that the effusion may be managed with systemic antibiotics alone.

In malignant effusions, a pleural fluid pH of less than 7.3 has been associated in some reports with more extensive pleural involvement, higher yield on cytology, decreased success of pleurodesis, and shorter survival times.

Handle pleural fluid samples as carefully as arterial samples for pH measurements, with fluid collected in
heparinized syringes and ideally transported on ice for measurement within 6 hours. However, studies have shown that when collected in heparinized syringes, pleural fluid pH does not change significantly even over several hours at room temperature. Consequently, if appropriately collected samples can be processed quickly, pH measurements should not be canceled simply because the sample was not transported on ice.

**Pleural Fluid Cell Count Differential**

If an exudate is suspected clinically or is confirmed by chemistry test results, send the pleural fluid for total and differential cell counts, Gram stain, culture, and cytology.

Pleural fluid lymphocytosis, with lymphocyte values greater than 85% of the total nucleated cells, suggests TB, lymphoma, sarcoidosis, chronic rheumatoid pleurisy, yellow nail syndrome, or chylothorax. Pleural lymphocyte values of 50-70% of the nucleated cells suggest malignancy.

Pleural fluid eosinophilia (PFE), with eosinophil values greater than 10% of nucleated cells, is seen in approximately 10% of pleural effusions and is not correlated with peripheral blood eosinophilia. PFE is most often caused by air or blood in the pleural space. Blood in the pleural space causing PFE may be the result of pulmonary embolism with infarction or benign asbestos pleural effusion. PFE may be associated with other nonmalignant diseases, including parasitic disease (especially paragonimiasis), fungal infection (coccidioidomycosis, cryptococcosis, histoplasmosis), and a variety of medications.

The presence of PFE does not exclude a malignant effusion, especially in patient populations with a high prevalence of malignancy. The presence of PFE makes tuberculous pleurisy unlikely and also makes the progression of a parapneumonic effusion to an empyema unlikely.

Mesothelial cells are found in variable numbers in most effusions, but their presence at greater than 5% of total nucleated cells makes a diagnosis of TB less likely. Markedly increased numbers of mesothelial cells, especially in bloody or eosinophilic effusions, suggests pulmonary embolism as the cause of effusion.

**Pleural Fluid Culture and Cytology**

Culture of infected pleural fluid yields positive results in approximately 60% of cases; this occurs even less often for anaerobic organisms. Diagnostic yields, particularly for anaerobic pathogens, may be increased by directly culturing pleural fluid into blood culture bottles.\[28]\n
Malignancy is suspected in patients with known cancer or with lymphocytic, exudative effusions, especially when bloody. Direct tumor involvement of the pleura is diagnosed most easily by performing pleural fluid cytology.

Heparinize samples (1 mL of 1:1000 heparin per 50 mL of pleural fluid) if bloody, and refrigerate if samples will not be processed within 1 hour.

The reported diagnostic yields in cytology vary from 60-90%, depending on the extent of pleural involvement and the type of primary malignancy. Cytology findings are positive in 58% of effusions related to mesothelioma.

The sensitivity of cytology is not highly related to the volume of pleural fluid tested; sending more than 50-60 mL of pleural fluid for cytology does not increase the yield of direct cytospin analysis,\[29, 30]\ and volumes of approximately 150 mL are sufficient when both cytospin and cell block preparations are analyzed.\[30]\n
Tumor markers, such as carcinoembryonic antigen, Leu-1, and mucin, are suggestive of malignant effusions (especially adenocarcinoma) when pleural fluid values are very high. However, because of low sensitivity, they are not helpful if the values are normal or only modestly increased.

**Tuberculous pleuritis**

Suspect tuberculous pleuritis in patients with a history of exposure or a positive PPD finding and in patients with lymphocytic exudative effusions, especially if less than 5% mesothelial cells are detected on differential blood cell counts.
Because most tuberculous pleural effusions probably result from a hypersensitivity reaction to the *Mycobacterium* rather than from microbial invasion of the pleura, acid-fast bacillus stains of pleural fluid are rarely diagnostic (<10% of cases), and pleural fluid cultures grow *M tuberculosis* in less than 65% of cases.

In contrast, the combination of histology and culture of pleural tissue obtained by pleural biopsy increases the diagnostic yield to 90%.

ADA activity of greater than 43 U/mL in pleural fluid supports the diagnosis of tuberculous pleuritis. However, the test has a sensitivity of only 78%; therefore, pleural ADA values of less than 43-50 U/mL do not exclude the diagnosis of TB pleuritis.[31]

Interferon-gamma concentrations of greater than 140 pg/mL in pleural fluid also support the diagnosis of tuberculous pleuritis, but this test is not routinely available.

**Additional Laboratory Tests**

Additional specialized tests are warranted when specific etiologies are suspected. Measure pleural fluid amylase levels if a pancreatic origin or ruptured esophagus is suspected or if a unilateral, left-sided pleural effusion remains undiagnosed after initial testing. Of note, increased pleural fluid amylase can also be seen with malignancy. An additional assay of amylase isoenzymes can help distinguish a pancreatic source (diagnosed by elevated pleural fluid pancreatic isoenzymes) from other etiologies.

Measure triglyceride and cholesterol levels in milky pleural fluids when chylothorax or pseudochylothorax is suspected.

Consider immunologic studies, including pleural fluid antinuclear antibody and rheumatoid factor, when collagen-vascular diseases are suspected.

**CT Scanning and Ultrasonography**

A study by Gurung et al involving 41 consecutive patients with hepatic hydrothorax indicated that hepatic hydrothorax virtually always presents with ascites that can be revealed by ultrasonography or computed tomography (CT) scanning.[32]

Chest CT scanning with contrast should be performed in all patients with an undiagnosed pleural effusion, if it has not previously been performed, to detect thickened pleura or signs of invasion of underlying or adjacent structures. The 2 diagnostic imperatives in this situation are pulmonary embolism and tuberculous pleuritis. In both cases, the pleural effusion is a harbinger of potential future morbidity. In contrast, a short delay in diagnosing metastatic malignancy to the pleural space has less impact on future clinical outcomes. CT angiography should be ordered if pulmonary embolism is strongly suggested.

**Chest Radiography**

Effusions of more than 175 mL are usually apparent as blunting of the costophrenic angle on upright posteroanterior chest radiographs. On supine chest radiographs, which are commonly used in the intensive care setting, moderate to large pleural effusions may appear as a homogenous increase in density spread over the lower lung fields. Apparent elevation of the hemidiaphragm, lateral displacement of the dome of the diaphragm, or increased distance between the apparent left hemidiaphragm and the gastric air bubble suggests subpulmonic effusions. (See the images below.)
Posteroanterior, upright chest radiograph shows isolated, left-sided pleural effusion and loss of left, lateral costophrenic angle. Image courtesy of Allen R. Thomas, MD.

Anteroposterior, upright chest radiograph shows bilateral pleural effusions and loss of bilateral costophrenic angles (meniscus sign). Image courtesy of Allen R. Thomas, MD.

Chest radiograph, lateral view, shows loss of bilateral, posterior costophrenic angles. Image courtesy of Allen R. Thomas, MD.

Lateral decubitus films more reliably detect smaller pleural effusions. Layering of an effusion on lateral decubitus films defines a freely flowing effusion and, if the layering fluid is 1 cm thick, indicates an effusion of greater than 200 mL that is amenable to thoracentesis. Failure of an effusion to layer on lateral decubitus films indicates the presence of loculated pleural fluid or some other etiology causing the increased pleural density. (See the image below.)
Left lateral decubitus film showing freely layering pleural effusion.

Diagnostic Thoracentesis

Perform diagnostic thoracentesis if the etiology of the effusion is unclear or if the presumed cause of the effusion does not respond to therapy as expected. Pleural effusions do not require thoracentesis if they are too small to safely aspirate or, in clinically stable patients, if their presence can be explained by underlying congestive heart failure (especially bilateral effusions) or by recent thoracic or abdominal surgery.

Depending on the clinician’s experience, a pulmonologist can be consulted for assistance with high-risk diagnostic thoracentesis.

Contraindications

Relative contraindications to diagnostic thoracentesis include a small volume of fluid (< 1 cm thickness on a lateral decubitus film), bleeding diathesis or systemic anticoagulation, mechanical ventilation, and cutaneous disease over the proposed puncture site. Mechanical ventilation with positive end-expiratory pressure does not increase the risk of pneumothorax after thoracentesis, but it increases the likelihood of severe complications (tension pneumothorax or persistent bronchopleural fistula) if the lung is punctured.

Complications

Complications of diagnostic thoracentesis include pain at the puncture site, cutaneous or internal bleeding, pneumothorax, empyema, and spleen/liver puncture. Pneumothorax complicates approximately 12-30% of thoracenteses but requires treatment with a chest tube in less than 5% of cases. Use of needles larger than 20 gauge increases the risk of a pneumothorax complicating the thoracentesis. In addition, significant chronic obstructive or fibrotic lung disease increases the risk of a symptomatic pneumothorax complicating the thoracentesis.

Procedure

In patients with large, freely flowing effusions and no relative contraindications to thoracentesis, diagnostic thoracentesis can usually be performed safely, with the puncture site initially chosen based on the chest radiograph and located 1-2 rib interspaces below the level of dullness to percussion on physical examination. In other situations, ultrasonography or chest CT scanning should be used to guide thoracentesis.

After the site is disinfected with chlorhexidine (preferred) or povidone/iodine (no longer recommended) solution and sterile drapes are placed, anesthetize the skin, periosteum, and parietal pleura with 1% lidocaine through a 25-gauge needle. If pleural fluid is not obtained with the shorter 25-gauge needle, continue anesthetizing with a 1.5-inch, 22-gauge needle. For patients with larger amounts of subcutaneous tissue, a 3.5-inch, 22-gauge spinal needle with inner stylet removed can be used to anesthetize the deeper tissues and find the effusion.

Confirm the correct location for thoracentesis by aspirating pleural fluid through the 25- or 22-gauge needle before introducing larger-bore thoracentesis needles or catheters. If pleural fluid is not easily aspirated, stop the procedure and use ultrasonography or chest CT scanning to guide thoracentesis.

When possible, patients should sit upright for thoracentesis. Patients should not lean forward, because this causes pleural fluid to move to the anterior costophrenic space and increases the risk of puncture of the liver or spleen. For debilitated and ventilated patients who cannot sit upright, obtain pleural fluid by puncturing over the eighth rib at the midaxillar to posterior axillary line. In such patients, imaging may be required to guide thoracentesis.

Supplemental oxygen is often administered during thoracentesis to offset hypoxemia produced by changes in ventilation-perfusion relationships as fluid is removed and to facilitate reabsorption of pleural air if pneumothorax complicates the procedure.

The frequency of complications from thoracentesis is lower when a more experienced clinician performs the procedure and when ultrasonographic guidance is used.[33] Consequently, a skilled and experienced clinician
should perform thoracentesis in patients who have a higher risk of complications or relative contraindications for thoracentesis and in patients who cannot sit upright.

Postprocedure expiratory chest radiographs to exclude pneumothorax are not needed in asymptomatic patients after uncomplicated procedures (single needle pass without aspiration of air). However, postprocedure inspiratory chest radiographs are recommended to establish a new baseline for patients likely to have recurrent symptomatic effusions.

**Idiopathic Exudative Effusions**

Despite primary evaluation with repeated diagnostic thoracenteses, approximately 20% of exudative effusions remain undiagnosed. Clues to the diagnosis that may have been overlooked include (1) occupational exposure to asbestos 10-20 years earlier, which may suggest benign asbestos effusion; (2) medication exposure to nitrofurantoin, amiodarone, or medications associated with a drug-induced lupus syndrome; and (3) hepatic hydrothorax unrecognized in a patient with minimal or undetectable ascites.

Among patients with undiagnosed pleural effusions after the primary evaluation, those who meet all 6 of the following clinical parameters are predicted to have a benign course, and no further evaluation is necessary:

- Patients are clinically stable
- Patients do not have weight loss
- The results of the purified protein derivative (PPD) test, used in detecting tuberculous pleural effusion, are negative and the pleural adenosine deaminase (ADA) value, also used in diagnosing tuberculous pleural effusion, is less than 43 U/mL
- The patient does not have a fever
- The pleural fluid differential blood cell count has less than 95% lymphocytes
- The effusion occupies less than 50% of the hemithorax

For other patients with undiagnosed exudative effusions, approximately 20% have a specific etiology determined, including malignancy. For such patients, weigh the benefits and risks of pursuing a diagnostic strategy that will involve using progressively more invasive procedures, given the low likelihood of finding a curable etiology. Note the following:

- Bronchoscopy - Consider only if a patient has parenchymal abnormalities or hemoptysis
- Surgical approaches to the diagnosis of pleural effusions - Include thoracoscopy (pleuroscopy) and open thoracotomy, which reveal an etiology in 92% of effusions that remain undiagnosed after a medical evaluation
- Medical thoracoscopy - Where available, may be diagnostic and therapeutic; complete drainage of the effusion and talc sclerosis can be performed at the time of the procedure

Note that in most medical centers, surgical exploration using thoracoscopy or thoracotomy entails the risks of general anesthesia and is probably warranted only in patients who are symptomatic and anxious for a (potentially incurable) diagnosis.

**Biopsy**

Pleural biopsy should be considered, especially if TB or malignancy is suggested. Medical thoracoscopy with the patient under conscious sedation and local anesthesia has emerged as a diagnostic tool to directly visualize and take a biopsy specimen from the parietal pleura in cases of undiagnosed exudative effusions. As an alternative, closed-needle pleural biopsy is a blind technique that can be performed at the patient's bedside.

Medical thoracoscopy has a higher diagnostic yield for malignancy; closed-needle pleural biopsy findings aid in diagnosis of only 7-12% of malignant effusions when cytology findings alone are negative. However, the yield of closed-needle pleural biopsy (histology plus culture) is as high as thoracoscopy for tuberculous pleuritis and is a useful alternative procedure for this diagnosis when available.

In a randomized comparison of medical thoracoscopy with CT scan–guided cutting-needle pleural biopsy (CT-CNPB), Metintas et al found no statistically significant difference in diagnostic sensitivity. The study included 124
patients with exudative pleural effusion who could not be diagnosed by cytologic analysis. These researchers recommended using CT-ANPB as the primary diagnostic procedure in patients with pleural thickening or lesions observed on CT scans, and using medical thoracoscopy in patients whose CT scans show only pleural fluid, as well as in those who may have benign pleural pathologies other than TB.[34]

**Contributor Information and Disclosures**

**Author**

Jeffrey Rubins, MD  Professor of Medicine, University of Minnesota Medical School; Director, Palliative Medicine, Hennepin County Medical Center

Jeffrey Rubins, MD is a member of the following medical societies: American Academy of Hospice and Palliative Medicine, American College of Chest Physicians, and American Thoracic Society

Disclosure: Nothing to disclose.

**Chief Editor**

Zab Mosenifar, MD  Director, Division of Pulmonary and Critical Care Medicine, Director, Women's Guild Pulmonary Disease Institute, Professor and Executive Vice Chair, Department of Medicine, Cedars Sinai Medical Center, University of California, Los Angeles, David Geffen School of Medicine

Zab Mosenifar, MD is a member of the following medical societies: American College of Chest Physicians, American College of Physicians, American Federation for Medical Research, and American Thoracic Society

Disclosure: Nothing to disclose.

**Additional Contributors**

Harold L Manning, MD  Professor, Departments of Medicine, Anesthesiology and Physiology, Section of Pulmonary and Critical Care Medicine, Dartmouth Medical School

Harold L Manning, MD is a member of the following medical societies: American College of Chest Physicians, American College of Physicians, and American Thoracic Society

Disclosure: Nothing to disclose.

Stephen P Peters, MD, PhD, FACP, FAAAAI, FCCP, FCPP  Professor of Genomics and Personalized Medicine Research, Internal Medicine, and Pediatrics, Associate Director, Center for Genomics and Personalized Medicine Research, Director of Research, Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Wake Forest University School of Medicine

Stephen P Peters, MD, PhD, FACP, FAAAAI, FCCP, FCPP is a member of the following medical societies: American Academy of Allergy Asthma and Immunology, American Association of Immunologists, American College of Chest Physicians, American College of Physicians, American Federation for Medical Research, American Thoracic Society, and Sigma Xi

Disclosure: See below for list of all activities None None

Francisco Talavera, PharmD, PhD  Adjunct Assistant Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference

Disclosure: Medscape Salary Employment

**References**


43. Tan C, Sedrakyan A, Browne J, Swift S, Treasure T. The evidence on the effectiveness of management for