Diagnostic Approach to Pleural Effusion

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Pleural effusion affects more than 1.5 million people in the United States each year and often complicates the management of heart failure, pneumonia, and malignancy. Pleural effusion occurs when fluid collects between the parietal and visceral pleura. Processes causing a distortion in body fluid mechanics, such as in heart failure or nephrotic syndrome, tend to cause transudative effusions, whereas localized inflammatory or malignant processes are often associated with exudative effusions. Patients can be asymptomatic or can present with cough, dyspnea, and pleuritic chest pain. Dullness to percussion on physical examination suggests an effusion; chest radiography can confirm the diagnosis. Thoracentesis may be indicated to diagnose effusion and relieve symptoms. Ultrasound guidance is preferred when aspirating fluid. Routine assays for aspirated fluid include protein and lactate dehydrogenase levels, Gram staining, cytology, and pH measurement. Light's criteria should be used to differentiate exudative from transudative effusions. Additional laboratory assays, bronchoscopy, percutaneous pleural biopsy, or thoracoscopy may be required for diagnosis if the initial test results are inconclusive. (*Am Fam Physician*. 2014;90(2):99-104. Copyright © 2014 American Academy of Family Physicians.)

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 74.

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▶ **Patient information:** A handout on pleural effusion, written by the authors of this article, is available at http://www.aafp.org/afp/2014/0715/99-s1.html

More than 1.5 million persons develop pleural effusions each year in the United States.[1] Many of the disease processes commonly seen in primary care are associated with pleural effusion, which requires family physicians to be familiar with its causes, diagnosis, and management.

Etiology and Pathogenesis

The visceral and parietal pleural membranes border a potential space within the thoracic cavity. Normally, a small physiologic amount of pleural fluid (0.1 mL per kg) rests within this space. Oncotic and hydrostatic pressures regulate fluid movement between the pleura, which adapt to a range of pressures to maintain the amount of fluid within a preset range. Abnormally high capillary and interstitial hydrostatic pressures can cause an abnormal accumulation of pleural fluid (e.g., in heart failure), as can an abnormally decreased capillary oncotic pressure (e.g., in nephrotic syndrome). Fluid that accumulates as a result of an imbalance in these forces produces transudative effusions. Additionally, inflammatory and malignant processes can promote local capillary and pleural membrane permeability or lymphatic blockage, which allows for the accumulation of exudative pleural fluid (i.e., fluid that is higher in protein and lactate dehydrogenase than transudative fluid).[2] Furthermore, an interruption in diaphragmatic integrity can allow fluid to enter the pleural space.[3]

Pleural effusions can arise from a variety of disease states or medications *(Table 1*[1-14] *and Table 2*[15]*)*. Despite the variety of conditions associated with effusions, many are idiopathic; these effusions tend to follow a benign course.[16]

Clinical Presentation

Patients with pleural effusion can be asymptomatic or can present with dyspnea, cough, or pleuritic chest pain. The history and physical examination can narrow the diagnostic considerations *(Table 3*[1-10,13] *and Table 4*[17]*)*. The history should focus on differentiating pulmonary etiologies from cardiovascular and other causes of effusion. A thorough chest examination should be performed, with particular attention to dullness to percussion because it is sensitive and specific for diagnosing effusion.[17] *Figure 1* outlines an approach to evaluating and diagnosing the cause of pleural effusion.[10,17-20]

Imaging

When pleural effusion is suspected, chest radiography should be performed to confirm the diagnosis. Abnormal findings can be detected on posteroanterior radiography in the presence of 200 mL of fluid, and

Table 1. Pleural Effusion: Causes, Types, and Clinical Clues

Condition	*Exudative or transudative*	*Clinical clues*
Most common (by decreasing frequency)		
Heart failure	Transudative	Hypoxia, pulmonary/peripheral edema
Bacterial pneumonia	Exudative	Chills, cough, fever, infiltrate
Pulmonary embolism	Exudative	Dyspnea, immobilization, pleuritic chest pain, recent travel
Malignancy	Exudative	History of cancer, lung mass
Viral disease	Exudative	Cough, fatigue, fever, muscle aches, rash
Post-cardiac surgery	Exudative	Recent surgery
Less common (alphabetical order by organ system)		
Cardiovascular		
Pericarditis	Exudative	Electrocardiographic findings, pericardial effusion on ultrasonography, sharp chest pain
Pulmonary vein stenosis	Exudative	Recent heart catheterization
Superior vena cava obstruction	Transudative	Facial swelling and ruddy complexion, upper extremity swelling
Gastrointestinal		
Abdominal abscess	Exudative	Abdominal pain, chills, fever, nausea, vomiting
Cirrhosis	Transudative	History of alcohol abuse or viral hepatitis; ascites, caput medusae, palmar erythema
Esophageal perforation	Exudative	History of esophageal tumor or reflux; chest or abdominal pain, fever
Pancreatitis	Exudative	Abdominal pain, anorexia, elevated amylase and lipase levels, nausea, vomiting
Post-abdominal surgery	Exudative	Recent surgery
Genitourinary		
Endometriosis	Exudative	Dysmenorrhea, infertility, pelvic pain
Meigs syndrome	Exudative	History of ovarian tumor
Ovarian hyperstimulation syndrome	Exudative	History of infertility treatment, abdominal pain
Postpartum effusion	Exudative	Recent childbirth
Urinothorax	Transudative	Recent urologic procedure, urinary obstruction
Pulmonary		
Mesothelioma	Exudative	History of asbestos exposure, pleural mass
Other		
Chylothorax	Exudative	Chest mass, lipids in pleural fluid, trauma
Pseudochylothorax	Exudative	History of tuberculosis or pleural disease, lipids in pleural fluid, rheumatoid disease
Medications (Table 2)	Exudative	Medication use
Nephrotic syndrome	Transudative	Edema, proteinuria
Rheumatoid arthritis	Exudative	Joint pain and swelling
Yellow nail syndrome	Exudative	Lymphedema, yellow nails

Information from references 1 through 14.

on lateral radiography with as little as 50 mL of fluid.[10] Lateral decubitus radiography may be obtained to help determine the size of the effusion and whether it is free-flowing or loculated.

If chest radiography is inconclusive, computed tomography and ultrasonography may be useful.[21,22] Computed tomography can detect effusions not apparent on plain radiography, distinguish between pleural fluid and pleural thickening, and provide clues to the underlying etiology.[22] Ultrasonography is more accurate than auscultation or chest radiography in detecting pleural effusion in the critical care setting, and is more sensitive than computed tomography in detecting pleural fluid septations.[10,21]

Thoracentesis

INDICATIONS AND PROCEDURE

Diagnostic small-volume aspiration of pleural fluid (50 to 60 mL) is indicated when the underlying cause of effusion is unknown. Large-volume aspiration is reserved for treatment of effusion-related symptoms, such as

dyspnea.[10,23] Emergent thoracentesis and/or chest tube placement is necessary in patients with pleural effusion and significant respiratory or cardiac decompensation.

Chest radiography can help guide patient selection. Aspiration is required in an undiagnosed patient with an effusion larger than 1 cm on a decubitus film.[18] Likewise, an effusion larger than 5 cm on a lateral radiograph in a patient with pneumonia warrants diagnostic aspiration, because parapneumonic effusions and empyema can cause nonresponse to treatment.[19] Patients with suspected transudative bilateral effusions should not undergo thoracentesis unless they have atypical features (e.g., fever, pleuritic chest pain, effusions of disparate size) or do not respond to treatment.[10,18] Guidelines recommend that, when possible, thoracentesis be performed with ultrasound guidance; this increases the likelihood of successful aspiration, decreases the risk of organ puncture (odds ratio for pneumothorax with ultrasonography = 0.3 to 0.8), and is associated with lower hospital costs.[10,20,24] A recent systematic review, however, indicates no benefit from skin marking or ultrasound-guided needle insertion.[25] Postprocedural chest radiography is not indicated unless symptoms develop.[20,26] A video depicting thoracentesis is available at http://www.nejm.org/doi/full/10.1056/NEJMvcm053812 (subscription required).

Table 2. Medications Associated with Pleural Effusion

Amiodarone	Methotrexate
Beta blockers	Nitrofurantoin (Furadantin)
Ergot alkaloids	Phenytoin (Dilantin)
L-tryptophan	

Information from reference 15.

Table 3. Signs and Symptoms that Suggest an Etiology of Pleural Effusion

Signs and symptoms	*Suggested etiology*
Ascites	Cirrhosis
Distended neck veins	Heart failure, pericarditis
Dyspnea on exertion	Heart failure
Fever	Abdominal abscess, empyema, malignancy, pneumonia, tuberculosis
Hemoptysis	Malignancy, pulmonary embolism, tuberculosis
Hepatosplenomegaly	Malignancy
Lymphadenopathy	Malignancy
Orthopnea	Heart failure, pericarditis
Peripheral edema	Heart failure
S3 gallop	Heart failure
Unilateral lower extremity swelling	Pulmonary embolism
Weight loss	Malignancy, tuberculosis

Information from references 1 through 10, and 13.

Table 4. Accuracy of Common Clinical Findings for Diagnosing Pleural Effusion

Finding	*Sensitivity (%)*	*Specificity (%)*
Pleural friction rub	5.3	99
Asymmetric chest expansion	74	91
Reduced vocal resonance	76	88
Reduced vocal fremitus	82	86
Auscultatory percussion	30 to 96	84 to 95
Diminished breath sounds	42 to 88	83 to 90
Dullness to percussion	30 to 90	81 to 98
Crackles	56	62

Information from reference 17.

FLUID ANALYSIS

Gross appearance of the pleural fluid can provide diagnostic clues *(Table 5)*.[10,11] Milky fluid may indicate a chylothorax or pseudochylothorax, whereas food particles suggest an esophageal perforation. Routine testing includes protein and lactate dehydrogenase levels, Gram staining and culture, cytology (malignant effusions can be diagnosed by cytology in 60% of cases), and pH level. Glucose levels may also be obtained.[10,18]

Protein and lactate dehydrogenase levels help determine whether collected pleural fluid represents a transudative or exudative effusion and are used to assess for Light's criteria *(Figure 1)*.[10,17-20] Light's criteria are 99.5% sensitive for diagnosing exudative effusion[27] and differentiate exudative from transudative effusions in 93% to 96% of cases.[10,28] In the absence of serum testing, pleural fluid protein and lactate hydrogenase levels have a

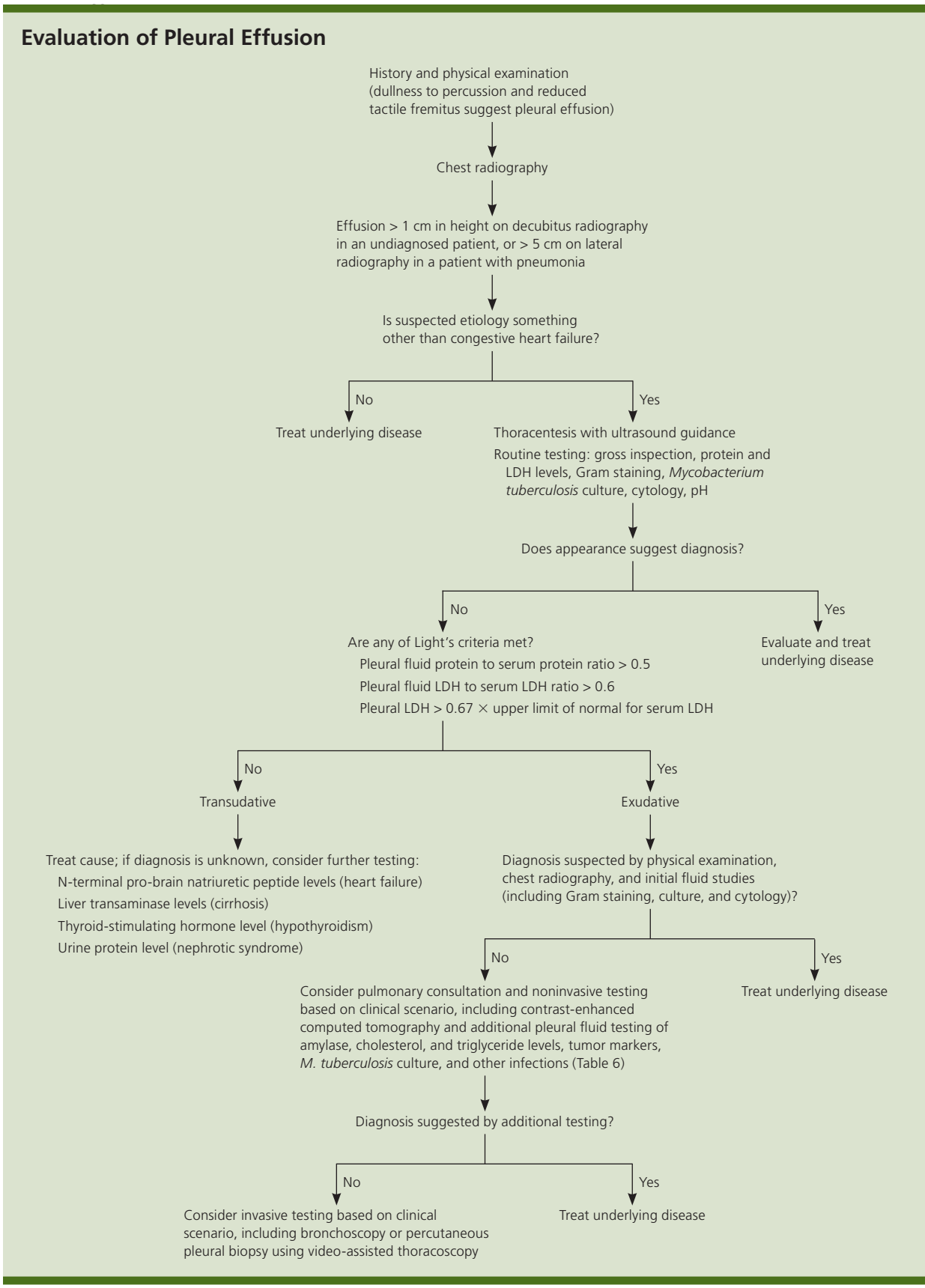

Figure 1. Algorithm for evaluating pleural effusion. (LDH = lactate dehydrogenase.)

Information from references 10, and 17 through 20.

Table 5. Gross Pleural Fluid Findings and Potential Etiologies

Finding	*Potential etiology*
Anchovy brown fluid	Ruptured amoebic abscess
Bile staining	Cholothorax (i.e., biliary fistula)
Black fluid	*Aspergillus* infection
Food particles	Esophageal perforation
Milky fluid	Chylothorax or pseudochylothorax
Putrid odor	Anaerobic empyema
Urine	Urinothorax

Adapted with permission from Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. *2010;65(suppl 2):ii7, with additional information from reference 11.*

92% concordance with Light's criteria for differentiating between transudative and exudative effusions.[29] A recent systematic review revealed that a pleural cholesterol level greater than 55 mg per dL (1.42 mmol per L), a pleural to serum cholesterol ratio greater than 0.3, and a pleural lactate dehydrogenase level greater than 200 units per L (3.3 μkat per L) were among the most specific findings for diagnosing an exudate.[25]

Gram staining may help identify a causative pathogen. A cell count may also reveal an underlying etiology. Neutrophil predominance tends to indicate an acute process, such as a parapneumonic effusion or pulmonary embolism, whereas lymphocyte predominance may be noted in longstanding effusions, heart failure, malignancy, tuberculosis, and thoracic duct injury.[10,30] Pleural fluid pH less than 7.30 may indicate a malignant effusion, connective tissue disease, or esophageal perforation; a value less than 7.20 indicates the need for tube drainage in patients with parapneumonic effusions, especially in the setting of an elevated lactate dehydrogenase level and a glucose level less than 60 mg per dL (3.3 mmol per L).[10] Further tests are guided by clinical suspicion and may include acid-fast bacillus testing (including adenosine deaminase) for tuberculosis and measurement of triglyceride, cholesterol, amylase, hematocrit, and N-terminal pro-brain natriuretic peptide levels *(Table 6)*.[6,10,11,18,30,31] Tumor markers are not routinely obtained.

If thoracentesis is unsuccessful or the results of fluid analysis are unclear, pulmonary consultation and additional testing can be helpful. Percutaneous pleural biopsy or thoracoscopy may be indicated if malignancy is suspected. Bronchoscopy may be warranted if hemoptysis or bronchial obstruction is present.[10]

Data Sources: A PubMed search was completed using the keyword and medical subject headings pleural effusion and thoracentesis. The search included randomized controlled trials, meta-analyses, clinical trials, systematic reviews, clinical practice guidelines, and review articles. Also searched were Essential Evidence Plus, the National Guideline Clearinghouse, and the Cochrane Database of Systematic Reviews. Search dates: January 2012 through April 2014.

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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.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Thoracentesis should be performed with ultrasound guidance.	A	10, 20, 24	Ultrasonography increases the likelihood of successful aspiration, decreases the risk of organ puncture (odds ratio for pneumothorax with ultrasonography = 0.3 to 0.8), and is associated with lower hospital costs.
Light's criteria should be used to differentiate transudative from exudative effusions.	C	10, 27, 28	Light's criteria have a diagnostic accuracy of 93% to 96%.
In patients with a pleural effusion classified as exudative by Light's criteria in which a cardiac etiology is suspected, N-terminal pro-brain natriuretic peptide can help differentiate cardiac from noncardiac conditions.	C	10, 11	—

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

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