Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Pleural Effusion

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A 70-year-old man with an 80-pack-year history of smoking and a history of congestive heart failure presents with increasing shortness of breath. He also has aching chest pain on the right side that worsens with deep inspiration. He is afebrile. The chest radiograph reveals bilateral pleural effusions, with more pleural fluid on the right than on the left. How should this patient be evaluated?

THE CLINICAL PROBLEM

Although many different diseases may cause a pleural effusion (Table 1), the most common causes in the United States are congestive heart failure, pneumonia, and cancer. The diagnostic workup of a patient with a pleural effusion will depend on the probable causes of the condition in that patient.

STRATEGIES AND EVIDENCE

Initial Evaluation

The history and the physical examination are critical in guiding the evaluation of pleural effusion. Several aspects of the physical examination should receive special attention. Chest examination typically reveals dullness to percussion, the absence of fremitus, and diminished breath sounds or their absence. Distended neck veins, an S_3 gallop, or peripheral edema suggests congestive heart failure, and a right ventricular heave or thrombophlebitis suggests pulmonary embolus. The presence of lymphadenopathy or hepatosplenomegaly suggests neoplastic disease, and ascites may suggest a hepatic cause.

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Table 1. Leading Causes of Pleural Effusion in the United States, According to Analysis of Patients Subjected to Thoracentesis.*

Cause	Annual Incidence	Transudate	Exudate
Congestive heart failure	500,000	Yes	No
Pneumonia	300,000	No	Yes
Cancer	200,000	No	Yes
Pulmonary embolus	150,000	Sometimes	Sometimes
Viral disease	100,000	No	Yes
Coronary-artery bypass surgery	60,000	No	Yes
Cirrhosis with ascites	50,000	Yes	No

*Adapted from Light.[1]

Since conditions other than pleural effusions may produce similar radiologic findings, alternative imaging studies are frequently necessary to verify that a pleural effusion is present. Ultrasonographic studies or lateral decubitus radiographs are used most commonly, but computed tomographic (CT) scans of the chest allow imaging of the underlying lung parenchyma or mediastinum.

Indications for Thoracentesis

The indication for diagnostic thoracentesis is the presence of a clinically significant pleural effusion (more than 10 mm thick on ultrasonography or lateral decubitus radiography) with no known cause (Fig. 1). If a patient presents with congestive heart failure and bilateral effusions of similar size, is afebrile, and has no chest pain, a trial of diuresis can be undertaken. Since more than 80 percent of patients with pleural effusions caused by congestive heart failure have bilateral pleural effusions,[2] thoracentesis is indicated if the effusion is unilateral. Approximately 75 percent of effusions due to congestive heart failure resolve within 48 hours after diuresis is begun.[2] If the effusions persist for more than three days, thoracentesis is indicated.

The initial thoracentesis is usually performed for purposes of diagnosis, unless the patient has shortness of breath when at rest, in which case therapeutic thoracentesis to remove up to 1500 ml of fluid is indicated. Thoracentesis can be performed at the bedside with the aid of diagnostic imaging. Ultrasonographic guidance is indicated if difficulty is encountered in obtaining pleural fluid or if the effusion is small.[3] It remains uncertain whether the use of ultrasonography

decreases the incidence of pneumothorax after thoracentesis; the extent of the operator's experience is probably more important than whether ultrasonography is used.[1] It is not necessary to perform chest radiography routinely after thoracentesis unless air is obtained during the thoracentesis; coughing, chest pain, or dyspnea develops; or tactile fremitus is lost over the superior part of the aspirated hemithorax.[3] In one series of 506 thoracenteses, pneumothorax was present in 13 of the 18 patients with one or more of these symptoms (72 percent) but in only 5 of 488 patients with none of these symptoms (1 percent).[4]

Appearance of the Pleural Fluid

The gross appearance of the pleural fluid provides useful information (Table 2). A bloody appearance of the pleural fluid narrows the differential diagnosis. In a series of 21 cases of pleural effusion with bloody fluid, 12 were due to cancer, 5 to pulmonary embolism, 2 to trauma, and 2 to pneumonia.[5] Turbidity of the pleural fluid can be caused either by cells and debris or by a high lipid level (Table 2).[1] The odor of the pleural fluid also provides useful information. A putrid odor indicates that the patient probably has an infection due to anaerobic bacteria, and an odor of urine indicates probable urinothorax.[1]

Differentiation of Exudates from Transudates

A transudative pleural effusion occurs when pleural fluid accumulates because of an imbalance between the hydrostatic and oncotic pressures. The leading causes of transudative pleural effusions are congestive heart failure, cirrhosis, and pulmonary embolism. In contrast, an exudative pleural effusion occurs when the local factors influencing the accumulation of pleural fluid are altered. The leading causes of exudative effusions are pneumonia, cancer, and pulmonary embolism.

The first step in the evaluation is to determine whether an effusion is transudative or exudative.[6] If it is exudative, more diagnostic tests are required in order to determine the cause of the local disease, whereas if it is transudative, the physician must establish or rule out a diagnosis of congestive heart failure, cirrhosis, or pulmonary embolism.

For the past several decades, transudates have been differentiated from exudates according to Light's criteria,[7] by measurement of the levels of protein and lactate dehydrogenase in the pleural fluid and in the serum (Table 3). Since these criteria were originally published, several alternative measurements have been proposed for making this distinction[8,9] (Table 3). Light's criteria are the most sensitive for identifying exudates but have lower specificity than other criteria — that is, on the basis of Light's criteria, some patients who actually have transudative pleural effusions will be thought to have exudative pleural effusions. If the clinical appearance suggests a transudative effusion but the pleural fluid is an exudate according to Light's criteria, the difference between the albumin levels in the serum and the pleural fluid should be measured. Almost all patients with a serum albumin level that is more than 1.2 g per deciliter higher than the pleural-fluid albumin level have a transudative effusion.[9] However, this albumin gradient alone should not be used to distinguish transudates from exudates because it will misidentify approximately 13 percent of exudates as transudates.[9]

For an effusion that is likely to be transudative, initial measurement should be limited to the pleural-fluid protein and lactate dehydrogenase levels.[10] In patients with such effusions, additional tests provide no additional information and sometimes produce misleading results.[10]

Evaluation of an Exudative Effusion

Additional tests are needed, however, on exudative pleural fluids. Depending on the clinical presentation, these may include total and differential cell counts, smears and cultures for organisms, measurement of glucose and lactate dehydrogenase levels, cytologic analysis, and testing for a pleural-fluid marker of tuberculosis.

Total and Differential Cell Counts

A predominance of neutrophils in the pleural fluid (more than 50 percent of the cells) indicates that an acute process is affecting the pleura. In one series, 21 of 26 parapneumonic effusions (81 percent), 4 of 5 effusions secondary to pulmonary embolus (80 percent), and 4 of 5 effusions secondary to pancreatitis (80 percent) contained more than 50 percent neutrophils, but only 7 of 43 malignant effusions (16 percent) and none of 14 tuberculous effusions contained more than 50 percent neutrophils.[5]

A predominance of mononuclear cells indicates a

Figure 1 (facing page). Algorithm for the Evaluation of Patients with Pleural Effusion.

Pulmonary embolism should be considered earlier in the evaluation if there are clinical symptoms or signs that suggest this diagnosis (for example, pleuritic chest pain, hemoptysis, or dyspnea out of proportion to the size of the effusion). LDH denotes lactate dehydrogenase.

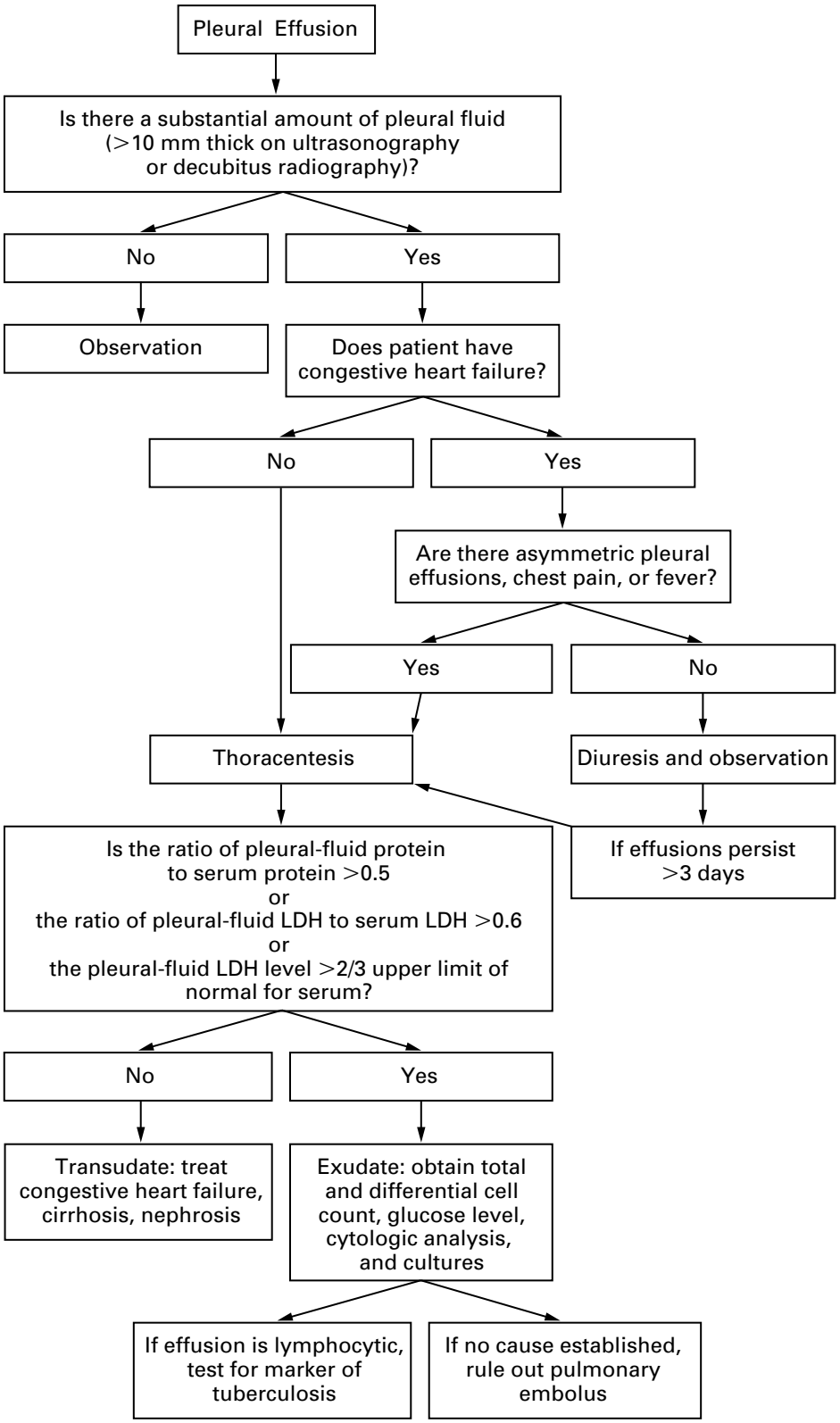

TABLE 2. TESTS INDICATED, ACCORDING TO THE APPEARANCE OF THE PLEURAL FLUID.

APPEARANCE OF FLUID	TEST INDICATED	INTERPRETATION OF RESULT
Bloody	Hematocrit	<1% → nonsignificant 1–20% → cancer, pulmonary embolus, or trauma >50% of peripheral hematocrit → hemothorax
Cloudy or turbid†	Centrifugation	Turbid supernatant → high lipid levels
Turbid supernatant	Triglyceride level	>110 mg/dl → chylothorax >50 mg/dl, but ≤110 mg/dl → obtain lipoprotein analysis Presence of chylomicrons → chylothorax ≤50 mg/dl and cholesterol >250 mg/dl → pseudochylothorax
Putrid odor	Stain and culture	Putrid odor → possible anaerobic infection

*To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

†This appearance is consistent with the presence of either cells and debris or high lipid levels.

TABLE 3. SENSITIVITY OF TESTS TO DISTINGUISH EXUDATIVE FROM TRANSUDATIVE EFFUSIONS.*

TEST	SENSITIVITY FOR EXUDATE	SPECIFICITY FOR EXUDATE
	%	
Light's criteria (one or more of the following three)	98	83
Ratio of pleural-fluid protein level to serum protein level >0.5	86	84
Ratio of pleural-fluid LDH level to serum LDH level >0.6	90	82
Pleural-fluid LDH level >two thirds the upper limit of normal for serum LDH level	82	89
Pleural-fluid cholesterol level >60 mg/dl (1.55 mmol/liter)	54	92
Pleural-fluid cholesterol level >43 mg/dl (1.10 mmol/liter)	75	80
Ratio of pleural-fluid cholesterol level to serum cholesterol level >0.3	89	81
Serum albumin level − pleural-fluid albumin level ≤1.2 g/dl	87	92

*LDH denotes lactate dehydrogenase.

chronic process. A preponderance of small lymphocytes indicates that the patient most likely has cancer or tuberculous pleuritis, although such a preponderance is also seen in pleural effusions after coronary-artery bypass surgery.[5,11,12] The combined data from two series[5,11] show that 90 of 96 exudative pleural effusions consisting of more than 50 percent lymphocytes (94 percent) were due to cancer or tuberculosis. In these series, 90 of 116 tuberculous pleural effusions (78 percent) contained more than 50 percent lymphocytes.[5,11]

Pleural-fluid eosinophilia (more than 10 percent eosinophils) is caused in about two thirds of cases by blood or air in the pleural space.[13] Pleural-fluid eosinophilia is uncommon in patients with cancer or tuberculosis, unless the patient has undergone repeated thoracenteses.[13-15] Unusual causes of eosinophilic pleural effusions include reactions to drugs (dantrolene, bromocriptine, or nitrofurantoin), exposure to asbestos, paragonimiasis, and the Churg–Strauss syndrome.[1]

Smears and Cultures

Gram's staining and culture for both aerobic and anaerobic bacteria will identify infected pleural fluids. The yield with culture is increased if blood-culture bottles are inoculated at the bedside with the pleural fluid.[16] If there is a reasonable likelihood that the pa-

tient has mycobacterial or fungal infection — for example, as indicated by a pleural fluid with more than 50 percent lymphocytes or a chronic febrile illness — cultures for these organisms are indicated. Smears of the pleural fluid may reveal fungi, but smears for mycobacteria are rarely positive unless the patient has a tuberculous empyema or the acquired immunodeficiency syndrome.[14,17]

Pleural-Fluid Glucose Level

The presence of a low pleural-fluid glucose concentration (less than 60 mg per deciliter) indicates that the patient probably has a complicated parapneumonic[18] or a malignant effusion.[19,20] Less common causes of low-glucose pleural effusions are hemothorax, tuberculosis, rheumatoid pleuritis, and more rarely, the Churg–Strauss syndrome, paragonimiasis, and lupus pleuritis.[1]

Pleural-Fluid Lactate Dehydrogenase Level

The level of lactate dehydrogenase in the pleural fluid correlates with the degree of pleural inflammation and should be measured each time pleural fluid is sampled from a pleural effusion whose cause has not been determined. A lactate dehydrogenase level that increases with repeated thoracentesis suggests that the degree of inflammation is increasing, and a diagnosis should be aggressively pursued.[1] Conversely, if the lactate dehydrogenase level in the pleural fluid decreases with repeated thoracentesis, a less aggressive diagnostic approach may be considered.

Pleural-Fluid Tests for Cancer

Cytologic examination of the pleural fluid is a fast, efficient, and minimally invasive means for establishing a diagnosis of cancer. Yields on cytologic examination are increased if both cell blocks and smears are examined. If a patient has metastatic adenocarcinoma, cytologic analysis will establish the diagnosis in more than 70 percent of cases.[5,21] Cytologic analysis is less efficient at establishing the diagnosis of cancer if the patient has a mesothelioma (sensitivity, 10 percent), squamous-cell carcinoma (20 percent), lymphoma (25 to 50 percent), or a sarcoma (25 percent) involving the pleura.[1] Since a blind needle biopsy of the pleura adds little to cytologic analysis in terms of diagnosing pleural cancer,[21] thoracoscopy is the procedure of choice for patients with suspected cancer and negative results on cytologic examination. Cytologic testing is not routinely warranted in young patients with evidence of acute illness.

If lymphoma is suspected, flow cytometry can establish the diagnosis by demonstrating the presence of a clonal cell population in the pleural fluid.[22] Measurement of the levels of tumor markers in the pleural fluid has proved disappointing in establishing the diagnosis of pleural cancer.[23] If the cutoff level is set sufficiently high so that there are no false positives, the sensitivity of the test is less than 50 percent.

Pleural-Fluid Markers of Tuberculosis

If tuberculous pleuritis is not treated, the effusion will resolve, but pulmonary or extrapulmonary tuberculosis subsequently develops in more than 50 percent of patients.[24] Evaluation for tuberculosis is warranted if there is pleural-fluid lymphocytosis. Since less than 40 percent of patients with tuberculous pleuritis have positive pleural-fluid cultures,[12] alternative means, such as the measurement of adenosine deaminase or interferon-γ or the polymerase chain reaction (PCR) for mycobacterial DNA, are used to establish the diagnosis. In one study, the pleural-fluid adenosine deaminase level was above 40 U per liter in 253 of 254 patients with tuberculous pleuritis (99.6 percent) and below this cutoff point in 102 of 105 patients with lymphocytic pleural effusions from other causes (97.1 percent).[25] A pleural-fluid interferon-γ level of 140 pg per milliliter is comparable to an adenosine deaminase level of 40 U per liter in terms of diagnosing tuberculous pleuritis.[26] If DNA from *Mycobacterium tuberculosis* is detected in the pleural fluid by PCR, the diagnosis of tuberculous pleuritis is established.[27]

Other Tests on the Pleural Fluid

Other diagnostic tests on the pleural fluid are indicated in specific situations. Measurement of the pleural-fluid pH (with the use of a blood-gas machine) is warranted if a parapneumonic or malignant pleural effusion is suspected. A pleural-fluid pH below 7.20 in a patient with a parapneumonic effusion indicates the need for drainage of the fluid.[28] A pleural-fluid pH in this range in a patient with a malignant pleural effusion suggests that the patient's life expectancy is only about 30 days and that chemical pleurodesis is likely to be ineffective.[1]

An elevated pleural-fluid amylase level is seen in patients with pancreatic disease and esophageal rupture.[29] Amylase should therefore be measured if there are clinical symptoms or if the history suggests one of these diagnoses. In the absence of these indications, routine pleural-fluid amylase determinations are not useful.[29]

Immunologic tests on the pleural fluid, such as the determination of antinuclear antibody titers[30] or rheumatoid factor levels, add little diagnostic information; the diagnosis of lupus pleuritis or rheumatoid pleuritis is established by the clinical picture and the antinuclear antibody and rheumatoid factor levels in the serum. In addition, antinuclear antibody measurements were falsely positive at a high titer in 13 of

145 patients with effusions that were not caused by lupus (9 percent).[30]

Evaluation for Pulmonary Embolism

The possibility of pulmonary embolus should be considered if a patient has pleuritic chest pain, hemoptysis, or dyspnea out of proportion to the size of the effusion. The best screening test is measurement of the level of D-dimer in the peripheral blood.[31] There are many different D-dimer tests available with varying sensitivities and cutoff levels[31]; if a sensitive D-dimer test is used and it is negative, the diagnosis of pulmonary embolism is essentially ruled out. If the D-dimer test is positive, then additional specific diagnostic testing — such as duplex ultrasonography of the legs, spiral CT, perfusion scanning of the lungs, or pulmonary arteriography — is necessary to establish the diagnosis.

Pleural Effusion of Unknown Cause

The cause of the effusion remains unclear in the cases of a substantial percentage of patients with exudative effusions after the history, physical examination, and analysis of pleural fluid.[32] If the effusion persists despite conservative treatment, thoracoscopy should be considered, since it has a high yield for cancer or tuberculosis. If thoracoscopy is unavailable, alternative invasive approaches are needle biopsy and open biopsy of the pleura. No diagnosis is ever established for approximately 15 percent of patients despite invasive procedures such as thoracoscopy or open pleural biopsy.

AREAS OF UNCERTAINTY

It is uncertain whether the use of ultrasonography as an aid in performing thoracentesis decreases the likelihood of pneumothorax.[33,34] The best approach to diagnosing pulmonary embolus in patients with pleural effusion is not clear. There is controversy about whether patients with a lymphocytic pleural effusion should be treated for pleural tuberculosis solely on the basis of an elevated level of adenosine deaminase in the pleural fluid. Although I would recommend performing a battery of tests in patients with exudative pleural effusions of which the cause remains undiagnosed, no prospective study has been performed to evaluate the cost effectiveness of such an approach.

GUIDELINES

There are no formal guidelines dealing directly with the evaluation of pleural effusion of unknown cause.

CONCLUSIONS AND RECOMMENDATIONS

A thoracentesis should be performed in patients with a pleural effusion of unknown cause unless the effusion is small (less than 10 mm on ultrasonography) or the patient has congestive heart failure and bilateral pleural effusions. Ultrasonographic guidance for the thoracentesis is indicated if the effusion is small or if difficulty is encountered in obtaining fluid. If it is likely that the patient has a transudative pleural effusion, the only laboratory tests indicated are measurements of the lactate dehydrogenase and protein levels in the pleural fluid. If a patient has an exudative effusion, as indicated by a ratio of the pleural-fluid protein level to the serum protein level of more than 0.5, a ratio of the pleural-fluid lactate dehydrogenase level to the serum lactate dehydrogenase level of more than 0.6, or a pleural-fluid lactate dehydrogenase level that is more than two thirds the upper limit of normal for the serum lactate dehydrogenase level, the pleural fluid should be stained with Gram's stain and cultured for bacteria. In addition, the following tests should usually be performed on exudative pleural fluid: total and differential cell counts, measurement of the glucose level, an assay for a pleural-fluid marker of tuberculosis (if the effusion is predominantly lymphocytic), and cytologic analysis.

If no diagnosis is evident after this initial evaluation, the possibility of pulmonary embolus should be evaluated; this diagnosis should be pursued earlier if the clinical presentation is suggestive of this condition. If the diagnosis remains unclear, consideration should be given to performing more invasive tests, such as thoracoscopy, needle biopsy of the pleura, or open pleural biopsy.

In the case described in the vignette, congestive heart failure is a possibility, since the patient had a history of this condition. However, given the fact that the effusions are of unequal size and that chest pain is present, thoracentesis is indicated. An exudative effusion is an indication for cytologic testing, since cancer is a particular concern given the patient's age and history of heavy smoking. If the cytologic examination is nondiagnostic, thoracoscopy or another invasive evaluation should be considered.

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