REVIEW

JOSÉ C. YATACO, MD
Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation

RAED A. DWEIK, MD
Director, Pulmonary Vascular Program, Department of Pulmonary, Allergy and Critical Care Medicine, The Cleveland Clinic Foundation

Pleural effusions: Evaluation and management

ABSTRACT

Pleural effusions are very common, and physicians of all specialties encounter them. A pleural effusion represents the disruption of the normal mechanisms of formation and drainage of fluid from the pleural space. A rational diagnostic workup, emphasizing the most common causes, will reveal the etiology in most cases.

KEY POINTS

Symptoms depend on the amount of fluid accumulated and the underlying cause of the effusion. Many patients have no symptoms at the time a pleural effusion is discovered. Possible symptoms include pleuritic chest pain, dyspnea, and dry nonproductive cough.

A key question in evaluating an effusion is whether the excess pleural fluid is transudative or exudative.

Treatment depends on the severity and the cause. Thoracentesis is done to relieve symptoms. Chest tubes provide continuous drainage in cases of pneumothorax, hemothorax, penetrating chest trauma, complicated parapneumonic effusion or empyema, or chylothorax. Pleural sclerosis (pleurodesis) is usually indicated for patients with uncontrolled symptomatic malignant effusions.

MANY CONDITIONS can cause pleural effusions, including diseases that are local (in the lungs or pleura), extrapulmonic, or systemic. In many cases the cause is a chronic condition for which the patient is already receiving treatment; therefore, a patient with pleural effusion may present to a pulmonologist—or to a general internist, other medical specialist, or surgeon. In up to 20% of cases the cause remains unknown despite a diagnostic workup.

AN IMBALANCE OF FLUID FORMATION AND DRAINAGE

A pleural effusion—an excessive accumulation of fluid in the pleural space—indicates an imbalance between pleural fluid formation and removal.

The normal pleural space contains a relatively small amount of fluid, 0.1 to 0.2 mL/kg of body weight on each side.[1,2]

Pleural fluid is formed and removed slowly, at an equivalent rate, and has a lower protein concentration than lung and peripheral lymph. It can accumulate by one or more of the following mechanisms[1–3]:

- Increased hydrostatic pressure in the microvascular circulation: clinical data suggest that an elevation in capillary wedge pressure is the most important determinant in the development of pleural effusion in congestive heart failure.
- Decreased oncotic pressure in the microvascular circulation due to hypoalbuminemia, which increases the tendency to form pleural interstitial fluid.
- Increased negative pressure in the pleural space, also increasing the tendency for

pleural fluid formation; this can happen with a large atelectasis.

- Separation of the pleural surfaces, which could decrease the movement of fluid in the pleural space and inhibit pleural lymphatic drainage; this can happen with a trapped lung.
- Increased permeability of the microvascular circulation due to inflammatory mediators, which would allow more fluid and protein to leak across the lung and visceral surface into pleural space; this has been documented with infections such as pneumonia.
- Impaired lymphatic drainage from the pleural surface due to blockage by tumor or fibrosis.
- Movement of ascitic fluid from the peritoneal space through either diaphragmatic lymphatics or diaphragmatic defects.

SIGNS AND SYMPTOMS

Accumulation of pleural fluid produces a restrictive ventilatory defect and decreases total lung capacity, functional capacity, and forced vital capacity.[4] It may cause ventilation-perfusion mismatches due to partially atelectatic lungs in dependent areas and, if large enough, may compromise cardiac output[5] by causing ventricular diastolic collapse.

The symptoms depend on the amount of fluid and the underlying cause. Many patients have no symptoms at the time a pleural effusion is discovered. Possible symptoms include pleuritic chest pain, dyspnea, and dry nonproductive cough.

Physical findings are reduced tactile fremitus, dullness on percussion, and diminished or absent breath sounds. A pleural rub may also be heard during late inspiration when the roughened pleural surfaces come together.

IMAGING STUDIES

The evaluation of a pleural effusion begins with imaging studies to assess the amount of pleural fluid, its distribution and accessibility, and possible associated intrathoracic abnormalities.

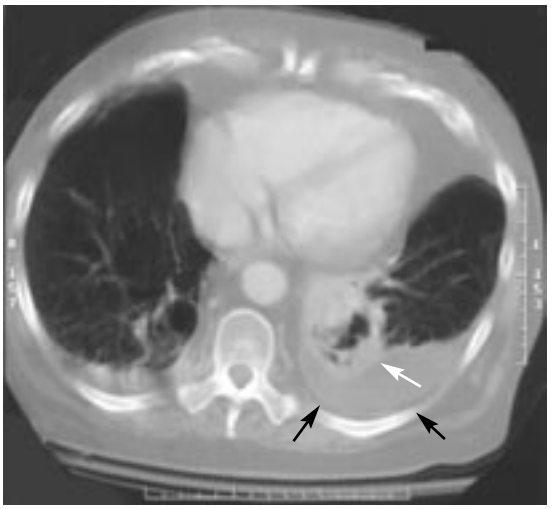

FIGURE 1. Computed tomographic scan showing cavitating retrocardiac infiltrate (white arrow) with adjacent pleural effusion (black arrows).

Chest radiography

Standard posteroanterior and lateral chest radiography remains the most important technique for the initial diagnosis of pleural effusion. Free pleural fluid flows to the most dependent part of the pleural space. In the upright position, this is the subpulmonic region, and accumulation of fluid causes apparent elevation of the hemithorax, lateral displacement of the dome of the diaphragm, and blunting of the costophrenic angle.[6] However, at least 250 mL of fluid must accumulate before it becomes visible in a posteroanterior radiograph.

Chest radiographs remain the most important technique for the initial diagnosis of pleural effusion

Lateral decubitus radiography is extremely valuable in the evaluation of a subpulmonic effusion. It is very sensitive, detecting effusions as small as 5 mL in experimental studies,[7,8] and should be a routine test.

On supine chest radiography, commonly used in intensive care, moderate to large pleural effusions may escape detection because the pleural fluid settles to the back, and no change in the diaphragm or lateral pleural edges may be noted. In these cases, a pleural effusion must be suspected when there is increased opacity of the hemithorax without obscuring of the vascular markings. If an effusion is suspected, lateral decubitus radiography or ultrasonography should be ordered, since both are more reliable for detecting small

TABLE 1

Causes of pleural effusions

FREQUENCY	TRANSUDATES	EXUDATES
Common	Congestive heart failure Nephrotic syndrome Cirrhosis with ascites	Parapneumonic effusion Malignancy Pulmonary embolism Collagen vascular disease Pancreatitis Tuberculosis Postcardiac injury syndrome
Less common	Peritoneal dialysis Urinothorax Atelectasis Pulmonary embolism Myxedema	Chylothorax Uremia Esophageal perforation Asbestos-related disease Drug-induced reactions Viral infection Yellow nail syndrome Sarcoidosis

pleural effusions in the intensive care setting.

Loculated effusions, defined as effusions that do not shift freely in the pleural space, occur when there are adhesions between the visceral and parietal pleura. The lateral decubitus view helps in differentiating free fluid from loculated fluid. The patient should be positioned with the affected side down on the x-ray table.

Even large effusions may be missed on supine chest radiographs because the pleural fluid settles to the back

Chest radiographs can also provide important clues to the cause of an effusion. Bilateral effusions accompanied by cardiomegaly are usually caused by congestive heart failure. Large unilateral effusions without contralateral mediastinal shift suggest a large atelectasis, infiltration of the lung with tumor, a mesothelioma, or a fixed mediastinum due to tumor or fibrosis.[6]

Ultrasonography

The major advantage of ultrasonography over radiography is its ability to differentiate between solid components (eg, tumor or thickened pleura) and liquid components of a pleural process. It is useful in detecting abnormalities that are subpulmonic (under the lung) or subphrenic (below the diaphragm) and in differentiating them.[9–11]

A major use of ultrasonography is to guide thoracentesis in small or loculated pleural effusions, thereby increasing the yield and safety of the procedure. However, it is not practical to recommend ultrasonography for all effusions. Portable ultrasound units can be brought to the bedside of extremely ill patients.[11]

Computed tomography

Computed tomography (CT), with its cross-sectional images, can be used to evaluate complex situations in which the anatomy cannot be fully assessed by plain radiography or ultrasonography (FIGURE 1). For instance, CT is helpful in distinguishing empyema from lung abscess, in detecting pleural masses (eg, mesothelioma, plaques), in detecting lung parenchymal abnormalities "hidden" by an effusion, and in outlining loculated fluid collections.[10]

THORACENTESIS AND LABORATORY STUDIES

Transudate vs exudate

Although the history, physical examination, and radiographic studies may provide important clues to the cause of a pleural effusion, almost all cases should be evaluated with diagnostic thoracentesis.[12,13]

Possible situations in which thoracentesis

TABLE 2

Light's criteria for distinguishing transudative from exudative pleural fluid

	PLEURAL/SERUM PROTEIN RATIO	PLEURAL/SERUM LACTATE DEHYDROGENASE RATIO	SERUM LACTATE DEHYDROGENASE
Transudate	≤ 0.5	≤ 0.6	≤ 200 U/L*
Exudate†	> 0.5	> 0.6	> 200 U/L*

*2/3 upper limit of normal serum level
†A single positive criterion is enough to classify the fluid as an exudate

TABLE 3

Sensitivity and specificity of tests to distinguish exudative from transudative effusions

	SENSITIVITY FOR EXUDATES (%)	SPECIFICITY FOR EXUDATES (%)
Light's criteria	98	83
Pleural-fluid cholesterol level > 60 mg/dL	54	92
Pleural-fluid cholesterol level > 43 mg/dL	75	80
Ratio pleural-fluid cholesterol/serum cholesterol > 0.3	89	81
Serum albumin level minus pleural fluid albumin level ≤ 1.2 g/dL	87	92

MODIFIED WITH PERMISSION FROM LIGHT RW. PLEURAL EFFUSION. N ENGL J MED 2002; 346:1971–1977.

Almost all effusions should be evaluated with a diagnostic thoracentesis

should not be done are when the effusion is too small to be safely aspirated (< 10 mm thick on ultrasonography or lateral decubitus radiography) or when it can be explained by underlying congestive heart failure (especially bilateral effusions that improve with diuresis), recent thoracic or abdominal surgery, or postpartum status. However, the procedure may still be indicated in these situations if the patient's clinical condition deteriorates.

After obtaining a sample of pleural fluid, the clinician should determine whether the effusion is transudative (ie, due to hydrostatic forces, and with a low protein content) or exudative (due to increased permeability of the pleural surfaces and blood vessels, with a relatively high protein content). If the fluid is a transudate, the possible causes are relatively few, and further diagnostic procedures are not necessary. In contrast, if the fluid is an exudate, there are many possible causes, and more diagnostic tests are required (TABLE 1).

Several tests of the pleural fluid have been proposed to differentiate transudates from exudates. Light's criteria (TABLE 2), originally published in 1972 and still the gold standard, require simultaneous measurement of the levels of protein and lactate dehydrogenase in the pleural fluid and in the serum.[2,12,13] Newer proposed criteria are not much more sensitive or specific (TABLE 3).[14–16]

A particular use for some of the newer criteria is to differentiate between transudates and exudates in some patients with congestive heart failure who receive diuretics—which can cause a transient increase in protein concentration in the pleural fluid due to movement of water from the pleural fluid into the blood—and are found to have an exudative effusion by Lights's criteria. If the clinical appearance suggests an uncomplicated transudative effusion, the albumin levels in the

TABLE 4

Newer criteria for classification of exudates and transudates

	LACTATE DEHYDROGENASE	CHOLESTEROL	PROTEIN
Transudate	≤ 45%*	≤ 45 mg/dL	≤ 2.9 g/dL
Exudate	> 45%*	> 45 mg/dL	> 2.9 g/dL

*Of serum upper limit of normal

TABLE 5

Definitive diagnosis based on pleural fluid analysis

DIAGNOSIS	CRITERIA
Urinothorax	pH < 7, transudate, pleural fluid-to-serum creatinine ratio > 1
Empyema	Pus, positive Gram stains or cultures
Malignancy	Positive cytologic testing
Chylothorax	Triglycerides > 110 mg/dL, chylomicrons
Tuberculosis, fungal infection	Positive stains or cultures
Hemothorax	Hematocrit > 50% of blood
Esophageal rupture	pH < 7, high amylase (salivary)

Each of these tests should be ordered based on clinical suspicion

serum and the pleural fluid should be measured. A difference of 1.2 g/dL or less indicates an exudate, while a difference greater than 1.2 g/dL indicates a transudate.[17] A low concentration of cholesterol in the pleural fluid may also be more accurate in classifying this fluid as a transudate.

If a pleural effusion is likely to be a transudate, initial laboratory tests can be limited to levels of protein, cholesterol, and lactate dehydrogenase in the pleural fluid (TABLE 4).[14,15] These tests could be an alternative to all the measurements required by Light's criteria.

If the effusion is exudative, further studies should be undertaken to establish a diagnosis (TABLE 5, TABLE 6). FIGURE 2 provides an initial diagnostic algorithm for pleural effusions.

Specific tests of pleural fluid

The glucose level in transudates and most exudates is similar to that of serum. Few conditions can cause very low pleural fluid glucose levels (< 25 mg/dL), eg, rheumatoid arthritis, tuberculosis, empyema, and malignancies with extensive pleural involvement. The clinical presentation usually is helpful in identifying the most likely cause.

The pH of the normal pleural fluid is around 7.64, owing to active transport of HCO_3 into the pleural space. Depending on the clinical setting, a low pleural fluid pH can be useful in establishing a diagnosis, guiding therapy, and determining prognosis. In general, a lower pH is seen in inflammatory and infiltrative processes such as infected parapneumonic effusions, empyema, malignancies, collagen vascular disease, tuberculosis, and esophageal rupture. Urinothorax is the only transudative effusion that can present with a low pleural fluid pH.

Measurement of pleural fluid pH is especially important if one suspects that the effusion is parapneumonic, ie, due to pneumonia. A pleural fluid pH below 7.2 in this situation indicates the patient is at increased risk for poor outcome and indicates the need for drainage (TABLE 7).[18]

In the case of malignancy, patients with extensive tumor burden of the pleura have a pleural fluid with a low pH (< 7.28) and low glucose. In general, these patients have a poor short-term survival rate, but pleural pH alone has insufficient accuracy for clinical use in identifying patients who should not undergo pleural sclerosis, in view of poor procedure success (see **Pleural sclerosis**, below).[19,20]

Amylase. A high pleural amylase level (> 200 U/dL) usually indicates pancreatitis, malignancy, or esophageal rupture. The clinical setting usually separates these entities, but if needed, additional assay of isoenzymes can be ordered (salivary vs pancreatic source).[21,22] In esophageal rupture and up to 10% of nonpancreatic malignancies, the amylase is of the salivary type. Esophageal rupture presents with an amylase level approximately five times higher than the serum level, while in pancreatitis and pancreatic cancer the amylase level in the pleural fluid is much higher (10–30 times the serum level).[22]

OTHER DIAGNOSTIC TESTS

Pleural biopsy

The main conditions that can be established with needle biopsy of the pleura are tuberculous pleuritis and malignancy of the pleura. Needle biopsy is currently recommended when tuberculous pleuritis is suspected and the pleural fluid adenosine deaminase or interferon-gamma levels are not definitive (see **Tuberculosis**, below). A parietal pleural biopsy specimen is positive for granulomas in up to 80% of cases of tuberculous pleurisy, acid-fast staining is positive in 26%, and culture is positive in 56%. At least one of these three tests is positive in 91% of cases.[23]

The incidence of granuloma on pleural biopsy is comparable in patients with and without human immunodeficiency virus (HIV) infection (CD4+ counts below 200/mm^3). The pleural fluid in HIV patients is more likely to be smear-positive and culture-positive for acid-fast bacilli.

Pleural biopsy is also recommended when malignancy is suspected but cytologic study of the pleural fluid is negative and thoracoscopy is not readily available.

Thoracoscopy

Thoracoscopy (or pleuroscopy) involves passing an endoscope through the chest wall to directly view and collect samples from the pleura.

The goal of medical thoracoscopy (performed by a pulmonologist with the patient under conscious sedation) is to visualize the entire lung and, when needed, to perform biopsies of the parietal or visceral pleural surfaces. The main indications include pleural effusions of unknown cause, particularly if mesothelioma, lung cancer, or tuberculosis is suspected. It can also be done to introduce sclerosing agents.

Video-assisted thoracoscopic surgery takes place in an operating room with the patient under general anesthesia and with single lung ventilation. Several procedures can be performed in this way: stapled lung biopsy, lobectomy, pneumonectomy, resection of pulmonary nodules, repair of a bronchopleural fistula, and evaluation of mediastinal tumors or adenopathy.

TABLE 6

Pleural fluid tests

On all effusions
- Protein
- Lactate dehydrogenase
- Cholesterol
- Cell count and differential

On exudates*
- Cytologic analysis
- pH†
- Gram stain and culture
- Fungal stain/culture
- Acid-fast bacteria stain/culture

Other tests
- Glucose
- Amylase
- Adenosine deaminase or gamma-interferon level
- Antinuclear antibody titer
- Hematocrit
- Triglycerides
- Creatinine
- Albumin

*Fluid can be saved for further analysis based on initial results, although for practical reasons many clinicians order all tests at the same time
†pH need be measured in transudates only when urinothorax is suspected

The major contraindication to medical or surgical thoracoscopy is lack of a pleural space due to pleural adhesions. Relative contraindications include uncontrolled cough, hypoxemia, coagulopathy, and severe cardiac disease.

Complications from medical thoracoscopy (eg, persistent air leak, subcutaneous emphysema) are minor and infrequent. Death is extremely rare.[24,25]

PLEURAL EFFUSIONS IN SPECIFIC DISEASES

It is important to initially evaluate the patient for cardiac, renal, intra-abdominal, systemic, and inflammatory conditions that could elicit a pleural effusion.

Collagen vascular diseases

Pleural effusions develop in up to 75% of patients with systemic lupus erythematosus (SLE) and 5% of patients with rheumatoid

Pleural effusions are seen in up to 75% of patients with lupus

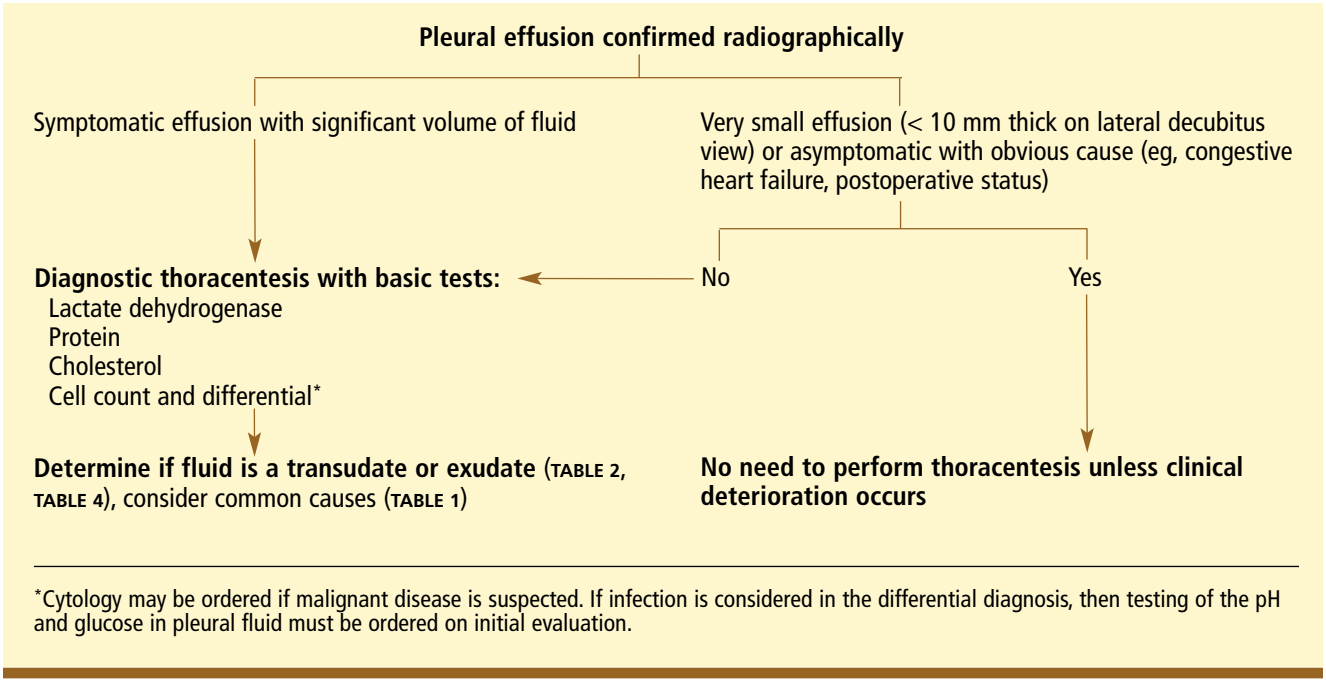

FIGURE 2. Approach to pleural effusions

arthritis during the course of the disease.

SLE. The pleural fluid antinuclear antibody (ANA) titer may help in separating SLE effusions from effusions due to other causes, even in patients with known SLE. A pleural fluid ANA titer greater than 1:160 or a pleural fluid-to-serum ANA ratio greater than 1.0 suggests lupus pleuritis.[26] Although these criteria appear to be highly specific, they are not highly sensitive.

Rheumatoid arthritis. Pleural effusions in rheumatoid arthritis are often asymptomatic. They may be quite large and often persist for many months without change. Rheumatoid effusions usually occur in patients with high serum rheumatoid factor titers and rheumatoid nodules. The fluid typically has a very low glucose level. Pleural rheumatoid factor titers are not helpful in diagnosis because they may be elevated in pneumonia, tuberculosis, malignancy, and SLE.

In patients with rheumatoid arthritis being treated with anti-tumor-necrosis factor therapy, special concern is warranted to exclude tuberculosis.

Tuberculosis

In tuberculous pleuritis, pleural effusion can mimic acute bacterial pneumonia

In many areas of the world, tuberculosis continues to be the most common cause of pleural effusions in the absence of demonstrable pulmonary disease. Rupture of a subpleural caseous focus into the pleural space allows tuberculous protein to enter the pleural space and to generate a hypersensitivity reaction responsible for most of the clinical manifestations.

Pleural effusion in tuberculous pleuritis manifests as an acute illness that can mimic acute bacterial pneumonia. It is usually unilateral and can be of any size. Coexistence of parenchymal disease is visible on standard radiographs in 19% of patients.[23]

The pleural fluid in tuberculosis is invariably an exudate with more than 50% lymphocytes in the white cell differential count. It rarely contains more than 5% mesothelial cells, which is explained by the extensive involvement of the pleural surface by the inflammatory process.[2] A definitive diagnosis may be difficult and depends on the demonstration of acid-fast bacilli in sputum, pleural fluid, or pleural biopsy specimen, or the demonstration of granulomas in the pleura. Pleural fluid analysis and cultures for acid-fast bacilli are positive in less than 25% of cases. Pleural biopsy culture can increase the yield to 55%.[2,23]

Additional measurements that suggest the

TABLE 7

Suggested approach to classification and management of parapneumonic effusions*

RISK OF POOR OUTCOME	PLEURAL SPACE ANATOMY		pH		BACTERIOLOGY (GRAM STAIN OR CULTURE)	DRAINAGE INDICATED†
Very low	Minimal free-flowing effusion (< 10 mm on lateral decubitus)	AND	> 7.2	AND	Negative or unknown	No
Low	Small to moderate free-flowing effusion (> 10 mm and < 1/2 hemithorax)	AND	≥ 7.2	AND	Negative	No‡
Moderate	Large free-flowing or loculated effusion (≥ 1/2 hemithorax)	OR	< 7.2	OR	Positive	Yes
High			Pus	Yes		

*It is not necessary to have a proven bacterial pneumonia: clinical diagnosis is enough
†pH and bacteriologic study results have priority over amount of fluid
‡If clinical condition deteriorates, repeating thoracentesis and drainage should be considered

ADAPTED FROM COLICE GL, CURTIS A, DESLAURIERS J, ET AL; FOR THE AMERICAN COLLEGE OF CHEST PHYSICIANS PARAPNEUMONIC EFFUSIONS PANEL. ACCP CONSENSUS STATEMENT. MEDICAL AND SURGICAL TREATMENT OF PARAPNEUMONIC EFFUSIONS: AN EVIDENCE-BASED GUIDELINE. CHEST 2000; 118:1158–1171.

diagnosis include pleural fluid adenosine deaminase, interferon-gamma, and polymerase chain reaction for mycobacterial DNA. Elevations of pleural adenosine deaminase levels have been observed in tuberculous pleurisy, rheumatoid arthritis, and empyema. Adenosine deaminase levels above 40 U/L distinguish tuberculous effusions from other lymphocytic pleural effusions (ie, malignancies, lymphoma, collagen vascular diseases),[27,28] as do interferon-gamma levels above 140 pg/mL.[29]

Urinothorax

Urinothorax, a rare cause of pleural effusion, is believed to occur when urine moves retroperitoneally into the pleural space owing to urinary obstruction, trauma, a retroperitoneal inflammatory or malignant process, failed nephrostomy, or kidney biopsy.[2,30] The pleural fluid is a transudate with the unique feature of having a pleural fluid-to-serum creatinine ratio greater than 1.0. It also can have a low pH (< 7.3) or low glucose level, both of which are uncommon in transudative effusions.[31]

After coronary artery bypass grafting

Pleural effusions are common immediately after coronary artery bypass grafting (CABG).[32] The reported prevalence 1 week after surgery has ranged from 40% to 75%.

Pleural effusions are common immediately after CABG

Most of these effusions are small, unilateral, left-sided, and asymptomatic. In general, they gradually resolve over several weeks. Large pleural effusions (> 25% of hemithorax) not explained by any other cause occur in a small proportion of patients.

The fluid is invariably an exudate and can be classified according to its gross description.[32] Bloody effusions tend to occur earlier (< 4 weeks after surgery) and are easy to control with one to three therapeutic thoracenteses. Nonbloody effusions tend to occur later (> 4 weeks after surgery) and have a relatively low lactate dehydrogenase level and a high percentage of lymphocytes. Nonbloody effusions are more difficult to control despite repeat thoracentesis and may require anti-inflammatory agents or chemical pleurodesis.

Chylous effusion

A true chylous pleural effusion develops when chyle enters the pleural space owing to disrup-

tion of the thoracic duct by trauma (surgical or nonsurgical) or by malignancy. Continuous drainage of a chylous effusion may result in malnutrition and immunosuppression due to significant loss of protein, fats, electrolytes, and lymphocytes.

Initial conservative treatment consists of limiting dietary fat to medium-chain triglycerides that are absorbed through the portal venous system and not carried by lymph, in an attempt to decrease the lymph flow rate. If necessary, lymph flow can be further reduced by using total parenteral nutrition and avoiding oral intake.[33,34]

Surgical therapy for chylothorax, with thoracic duct ligation or pleuroperitoneal shunt implantation, may be necessary before the patient becomes too cachectic to tolerate the intervention.[33,34]

Pleural effusions due to pulmonary embolism

Pleural effusions occur in 30% to 50% of patients with pulmonary emboli. It is possible that a significant number of undiagnosed effusions are due to pulmonary embolism.

The cause of 15% to 20% of all pleural effusions will remain unknown

The fluid may be transudative (24%) or exudative, depending on the mechanism. A transudate occurs when there is right-sided heart failure and increased capillary pressure in the parietal pleura. An exudate occurs due to increased permeability of the capillaries in the lung (caused by ischemia or inflammatory mediators from the platelet-rich thrombi).

Standard anticoagulation is the treatment of choice.

Pleural effusions in the intensive care unit

The incidence of pleural effusions in the intensive care unit (ICU) varies according to the screening method. One study, using routine ultrasonography, found pleural effusions in 62% of medical ICU patients, with a predominance of transudates.[35] On the other hand, pleural effusions were detected by physical examination and opacification of at least one third of the lung field on radiography in only 8.4% of ICU patients. With the latter method, exudates related to infection were more common.[36]

Thoracentesis is not contraindicated in ICU patients receiving mechanical ventilation. In one study of clinically documented effusions, routine thoracentesis was complicated by pneumothorax in only 7% of patients.[36] The same study showed that thoracentesis altered the diagnosis in 45% of patients and changed the treatment in 33%. Use of ultrasound guidance has been shown to improve the safety of thoracentesis in mechanically ventilated patients.[37]

UNEXPLAINED EFFUSIONS

The cause of 15% to 20% of all pleural effusions will remain unknown despite intensive diagnostic efforts.[38] An unexplained pleural effusion has been defined as one without an apparent cause despite repeat thoracentesis. The clinician should ensure that all the unusual causes of pleural effusion are considered and requisite studies are obtained.

Roughly 50% of these effusions resolve spontaneously, and no disease is apparent on long-term follow-up. Many unresolved pleural effusions will turn out to be caused by malignant disease, which is obvious clinically or is incurable in any event. The most common treatable cause of an unexplained effusion is tuberculosis.[39]

Thus, invasive procedures such as video-assisted thoracoscopy or thoracotomy with direct sampling of the pleura are frequently recommended for these patients.

THERAPY

Therapeutic thoracentesis

Any pleural effusion large enough to cause severe respiratory symptoms should be drained regardless of the cause and regardless of concomitant disease-specific treatment. Relief of symptoms is the main goal of therapeutic drainage in these patients.

The only absolute contraindication to thoracentesis is active cutaneous infection at the puncture site. Some relative contraindications include severe bleeding diathesis, systemic anticoagulation, and a small volume of fluid.

Possible complications of the procedure include bleeding (due to accidental puncture of a vessel or lung parenchyma), pneumothorax, infections (soft-tissue infection or empye-

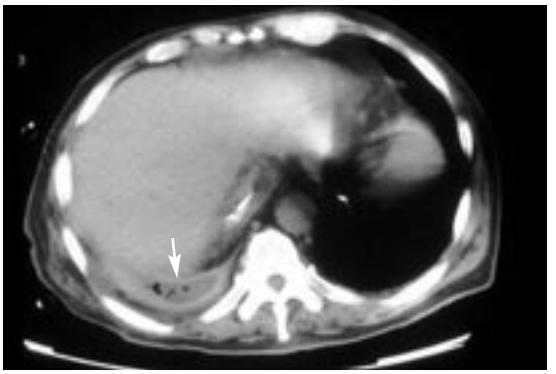

FIGURE 3. Chest computed tomographic scan with a "split pleural sign" (arrow), seen in empyema. This patient needed drainage with tube thoracostomy.

ma), laceration of intra-abdominal organs, hypotension, and pulmonary edema.[2]

In general, no more than 1,000 to 1,500 mL of fluid should be removed at one time. Rapid drainage of fluid may predispose patients to the rare complication of re-expansion pulmonary edema in the underlying lung or rapid fluid shift from the intravascular space to the pleural space (post-thoracentesis shock). These complications appear to be related to the creation of excessive negative pressure in the pleural cavity during thoracentesis. Large-volume thoracentesis can be undertaken with monitoring of the intrapleural pressure.[40,41]

Any pleural effusion large enough to cause severe respiratory symptoms should be drained

Tube thoracostomy (chest tube)

Tube thoracostomy allows continuous, large-volume drainage of air or liquid from the pleural space.

Specific indications for placement of a chest tube include spontaneous or iatrogenic pneumothorax (especially if large and symptomatic), hemothorax, penetrating chest trauma, complicated parapneumonic effusion or empyema, chylothorax, and pleurodesis of symptomatic pleural effusions.

In symptomatic or clinically unstable patients, there is no absolute contraindication to chest tube placement. In patients with complicated pleural spaces due to multiple loculations or previous pleurodesis, a contrast chest CT scan should be obtained to guide the placement of the chest tube.

For drainage and pleurodesis of malignant pleural effusions, a silicone polymer (Silastic) chest tube 20 to 24 F is usually adequate, although small-bore catheters (8–14 F) placed under fluoroscopic, ultrasound, or CT guidance have also been successful.[42,43]

Complicated parapneumonic effusions and frank empyema (FIGURE 3) require drainage with a large-bore chest tube (28–36 F) to control the local pleural inflammatory reaction, which may not otherwise respond to intravenous antibiotics.

In multiloculated complicated effusions, image-guided placement of small-bore catheters (10–14 F) should be considered.[44–46]

If appropriate drainage is not obtained despite correct positioning of the tubes (verified with chest CT), fibrinolytic therapy can be used.[47,48] Agents such as streptokinase, urokinase, and alteplase can lyse fibrin and improve drainage.

Pleural sclerosis

Pleural sclerosis (pleurodesis) is considered for patients with uncontrolled and recurrent symptomatic malignant effusions, and rarely, in cases of benign effusions after failure of medical treatment. A sclerosing agent is instilled into the pleural cavity via a tube thoracostomy to produce a chemical serositis and subsequent fibrosis of the pleura.

Pleural sclerosis should be attempted only if the lung expands fully after fluid removal. The visceral and parietal pleura need to be approximated closely, obliterating the pleural cavity so that fibrotic healing achieves pleural symphysis.

The overall success rate with fibrosing agents (ie, talc, doxycycline, and tetracycline) is 75%, compared with a complete success rate of only 44% for antineoplastic agents (ie, bleomycin).[49] Talc is the most effective agent, with a complete success rate of 93%.[49,50] Pleurodesis failure is usually the result of suboptimal technique or inability to approximate the pleural surfaces.

Surgical therapy

Video-assisted thoracoscopic surgery is very useful in managing incompletely drained parapneumonic effusions. With thoracoscopy, the loculi in the pleura can be disrupted, the pleural space can be completely drained, and the chest tube can be optimally placed.[51]

In cases of empyema with uncontrolled sepsis or progression to the fibroproliferative phase, a full thoracotomy with decortication is performed with removal of all the fibrous tissue and evacuation of all the pus from the pleural space. Decortication in this situation will eliminate the septic source and allow the lung to expand.

REFERENCES

1. **Sahn SA.** State of the art. The pleura. Am Rev Respir Dis 1988; 138:184–234.
2. **Light RW.** Pleural diseases. Baltimore: Williams & Wilkins, 1995.
3. **Sy BAC, Dweik RA.** Pleural disease. The Cleveland Clinic Disease Management Project, 2002. http://www.clevelandclinicmeded.com/diseasemanagement/pulmonary/pleuraldisease/pleuraldisease.htm. Accessed 5/9/05.
4. **Gilmartin JJ, Wright AJ, Gibson GJ.** Effects of pneumothorax or pleural effusion on pulmonary function. Thorax 1985; 40:60–65.
5. **Agusti AG, Cardus J, Roca J, Grau JM, Xaubet A, Rodriguez-Roisin R.** Ventilation-perfusion mismatch in patients with pleural effusion: effects of thoracentesis. Am J Respir Crit Care Med 1997; 156:1205–1209.
6. **Pugatch RD, Spirn PW.** Radiology of the pleura. Clin Chest Med 1985; 6:17–32.
7. **Gallardo X, Castaner E, Mata JM.** Benign pleural diseases. Eur J Radiol 2000; 34:87–97.
8. **Moskowitz H, Platt RT, Schachar R, Mellins H.** Roentgen visualization of minute pleural effusion. An experimental study to determine the minimum amount of pleural fluid visible on a radiograph. Radiology 1973; 109:33–35.
9. **O'Moore PV, Mueller PR, Simeone JF, et al.** Sonographic guidance in diagnostic and therapeutic interventions in the pleural space. AJR Am J Roentgenol 1987; 149:1–5.
10. **McLoud TC, Flower CD.** Imaging the pleura: sonography, CT, and MR imaging. AJR Am J Roentgenol 1991; 156:1145–1153.
11. **McGahan JP.** Aspiration and drainage procedures in the intensive care unit: percutaneous sonographic guidance. Radiology 1985; 154:531–532.
12. **Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr.** Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77:507–513.
13. **Light RW.** Clinical practice. Pleural effusion. N Engl J Med 2002; 346:1971–1977.
14. **Peterman TA, Speicher CE.** Evaluating pleural effusions. A two-stage laboratory approach. JAMA 1984; 252:1051–1053.
15. **Costa M, Quiroga T, Cruz E.** Measurement of pleural fluid cholesterol and lactate dehydrogenase. A simple and accurate set of indicators for separating exudates from transudates. Chest 1995; 108:1260–1263.
16. **Burgess LJ, Maritz FJ, Taljaard JJ.** Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates. Chest 1995; 107:1604–1609.
17. **Roth BJ, O'Meara TF, Cragun WH.** The serum-effusion albumin gradient in the evaluation of pleural effusions. Chest 1990; 98:546–549.
18. **Colice GL, Curtis A, Deslauriers J, et al; for the American College of Chest Physicians Parapneumonic Effusions Panel.** AACP consensus statement. Medical and surgical treatment of parapneumonic effusions. An evidence-based guideline. Chest 2000; 118:1158–1171.
19. **Heffner JE, Nietert PJ, Barbieri C.** Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. Chest 2000; 117:79–86.
20. **Sahn SA, Good JT Jr.** Pleural fluid pH in malignant effusions. Diagnostic, prognostic, and therapeutic implications. Ann Intern Med 1988; 108:345–349.
21. **Kramer MR, Saldana MJ, Cepero RJ, Pitchenik AE.** High amylase levels in neoplasm-related pleural effusion. Ann Intern Med 1989; 110:567–569.
22. **Sherr HP, Light RW, Merson MH, Wolf RO, Taylor LL, Hendrix TR.** Origin of pleural fluid amylase in esophageal rupture. Ann Intern Med 1972; 76:985–986.
23. **Valdes L, Alvarez D, San Jose E, et al.** Tuberculous pleurisy: a study of 254 patients. Arch Intern Med 1998; 158:2017–2021.
24. **Boutin C, Viallat JR, Cargnino P, Farisse P.** Thoracoscopy in malignant pleural effusions. Am Rev Respir Dis 1981; 124:588–592.
25. **Menzies R, Charbonneau M.** Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med 1991; 114:271–276.
26. **Good JT Jr, King TE, Antony VB, Sahn SA.** Lupus pleuritis. Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. Chest 1983; 84:714–818.
27. **Lee YC, Rogers JT, Rodriguez RM, Miller KD, Light RW.** Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. Chest 2001; 120:356–361.
28. **Ocana I, Martinez-Vazquez JM, Segura RM, Fernandez-De-Sevilla T, Capdevila JA.** Adenosine deaminase in pleural fluids. Test for diagnosis of tuberculous pleural effusion. Chest 1983; 84:51–53.
29. **Villena V, Lopez-Encuentra A, Echave-Sustaeta J, Martin-Escribano P, Ortuno-de-Solo B, Estenoz-Alfaro J.** Interferon-gamma in 388 immunocompromised and immunocompetent patients for diagnosing pleural tuberculosis. Eur Respir J 1996; 9:2635–2639.
30. **Miller KS, Wooten S, Sahn SA.** Urinothorax: a cause of low pH transudative pleural effusions. Am J Med 1988; 85:448–449.
31. **Stark DD, Shanes JG, Baron RL, Koch DD.** Biochemical features of urinothorax. Arch Intern Med 1982; 142:1509–1511.
32. **Light RW, Rogers JT, Cheng D, Rodriguez RM.** Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular Surgery Associates, PC. Ann Intern Med 1999; 130:891–896.
33. **Sassoon CS, Light RW.** Chylothorax and pseudochylothorax. Clin Chest Med 1985; 6:163–171.
34. **Teba L, Dedhia HV, Bowen R, Alexander JC.** Chylothorax review. Crit Care Med 1985; 13:49–52.
35. **Mattison LE, Coppage L, Alderman DF, Herlong JO, Sahn SA.** Pleural effusions in the medical ICU: prevalence, causes, and clinical implications. Chest 1997; 111:1018–1023.
36. **Fartoukh M, Azoulay E, Galliot R, et al.** Clinically documented pleural effusions in medical ICU patients: how useful is routine thoracentesis? Chest 2002; 121:178–184.
37. **Lichtenstein D, Hulot JS, Rabiller A, Tostivint I, Meziere G.** Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. Intensive Care Med 1999; 25:955–958.
38. **Ansari T, Idell S.** Management of undiagnosed persistent pleural effusions. Clin Chest Med 1998; 19:407–417.

39. **Ferrer JS, Munoz XG, Orriols RM, Light RW, Morell FB.** Evolution of idiopathic pleural effusion: a prospective, long-term follow-up study. Chest 1996; 109:1508–1513.
40. **Light RW, Jenkinson SG, Minh VD, George RB.** Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis 1980; 121:799–804.
41. **Villena V, Lopez-Encuentra A, Pozo F, De-Pablo A, Martin-Escribano P.** Measurement of pleural pressure during therapeutic thoracentesis. Am J Respir Crit Care Med 2000; 162:1534–1538.
42. **Morrison MC, Mueller PR, Lee MJ, et al.** Sclerotherapy of malignant pleural effusion through sonographically placed small-bore catheters. AJR Am J Roentgenol 1992; 158:41–43.
43. **Parker LA, Charnock GC, Delany DJ.** Small bore catheter drainage and sclerotherapy for malignant pleural effusions. Cancer 1989; 64:1218–1221.
44. **Moulton JS.** Image-guided drainage techniques. Semin Respir Infect 1999; 14:59–72.
45. **Reinhold C, Illescas FF, Atri M, Bret PM.** Treatment of pleural effusions and pneumothorax with catheters placed percutaneously under imaging guidance. AJR Am J Roentgenol 1989; 152:1189–1191.
46. **Silverman SG, Mueller PR, Saini S, et al.** Thoracic empyema: management with image-guided catheter drainage. Radiology 1988; 169:5–9.
47. **Bouros D, Schiza S, Siafakas N.** Utility of fibrinolytic agents for draining intrapleural infections. Semin Respir Infect 1999; 14:39–47.
48. **Sahn SA.** Use of fibrinolytic agents in the management of complicated parapneumonic effusions and empyemas. Thorax 1998; 53(suppl 2):S65–S72.
49. **Walker-Renard PB, Vaughan LM, Sahn SA.** Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994; 120:56–64.
50. **Management of malignant pleural effusions.** Am J Respir Crit Care Med 2000; 162:1987–2001.
51. **Cassina PC, Hauser M, Hillejan L, Greschuchna D, Stamatis G.** Video-assisted thoracoscopy in the treatment of pleural empyema: stage-based management and outcome. J Thorac Cardiovasc Surg 1999; 117:234–238.

ADDRESS: *Raed A. Dweik, MD, Department of Pulmonary, Allergy and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5038; e-mail dweikr@ccf.org.*