Pleural Effusions

Richard W. Light, MD

KEYWORDS

• Pleura • Pleural effusion • Empyema • Parapneumonic effusion
• Malignant pleural effusion

Approximately 1.5 million people develop a pleural effusion in the United States each year.[1] There are many different causes of pleural effusions (**Box 1**). When a patient is seen who has a pleural effusion, efforts should be made to find the cause of the effusion so that appropriate treatment can be instituted. In this article an approach to the diagnosis of pleural effusions is suggested and the diagnosis and management of the most common causes of pleural effusion are discussed.

SEPARATION OF EXUDATES FROM TRANSUDATES

One of the main reasons to do a thoracentesis in a patient with an undiagnosed pleural effusion is to determine whether the patient has a transudative or an exudative pleural effusion. The reason to make this differentiation is that the existence of a transudative pleural effusion indicates that systemic factors such as heart failure or cirrhosis are responsible for the effusion, whereas the existence of an exudative effusion indicates that local factors are responsible for the effusion. If the patient has a transudative effusion, the systemic abnormality can be treated and no attention need be diverted to the pleura. Alternatively, if an exudative effusion is present investigations need to be directed toward the pleura to find out the cause of the local problem.

For the past several decades, the principal manner by which transudates and exudates are identified is with the Light criteria.[2] According to the Light criteria, an exudative effusion is present if one or more of the following conditions are met: (1) pleural fluid protein/serum protein level greater than 0.5, (2) pleural fluid lactic acid dehydrogenase (LDH)/serum LDH level greater than 0.6, or (3) pleural fluid LDH level greater than two-thirds the upper normal limit for serum LDH.

The primary problem with the Light criteria is that they identify 15% to 20% of transudative effusions as exudative effusions. This situation is particularly likely if the patient has been receiving diuretics before the thoracentesis.[3] If the patient has CHF or cirrhosis but the pleural fluid meets exudative criteria by a small amount, then the difference between the serum protein and the pleural fluid protein should

Financial Disclosures: I am a consultant and am on the speaking bureau for Care Fusion, which makes the PleurX catheter.
Division of Allergy/Pulmonary/Critical Care, Vanderbilty University Medical Center, 1161 21st Avenue South, Nashville, TN 37232, USA
E-mail address: rlight98@yahoo.com

Med Clin N Am 95 (2011) 1055–1070
doi:10.1016/j.mcna.2011.08.005 **medical.theclinics.com**
0025-7125/11/$ – see front matter

Box 1
Differential diagnoses of pleural effusion

1. Transudative pleural effusions
   a. Congestive heart failure (CHF)
   b. Cirrhosis
   c. Nephrotic syndrome
   d. Superior vena caval obstruction
   e. Fontan procedure
   f. Urinothorax
   g. Peritoneal dialysis
   h. Glomerulonephritis
   i. Myxedema
   j. Cerebrospinal fluid leak to pleura
   k. Hypoalbuminemia
2. Exudative pleural effusions
   a. Neoplastic diseases
      i. Metastatic disease
      ii. Mesothelioma
      iii. Body cavity lymphoma
      iv. Pyothorax-associated lymphoma
   b. Infectious diseases
      i. Bacterial infections
      ii. Tuberculosis
      iii. Fungal infections
      iv. Parasitic infections
      v. Viral infections
   c. Pulmonary embolization
   d. Gastrointestinal disease
      i. Pancreatic disease
      ii. Subphrenic abscess
      iii. Intrahepatic abscess
      iv. Intrasplenic abscess
      v. Esophageal perforation
      vi. Postabdominal surgery
      vii. Diaphragmatic hernia
      viii. Endoscopic variceal sclerosis
      ix. Postliver transplant
   e. Heart diseases
      i. Postcoronary artery bypass graft (post-CABG) surgery
      ii. Postcardiac injury (Dressler) syndrome

iii. Pericardial disease
iv. Pulmonary vein stenosis postcatheter ablation of atrial fibrillation

f. Obstetric and gynecologic disease
i. Ovarian hyperstimulation syndrome
ii. Fetal pleural effusion
iii. Postpartum pleural effusion
iv. Meigs syndrome
v. Endometriosis

g. Collagen vascular diseases
i. Rheumatoid pleuritis
ii. Systemic lupus erythematosus
iii. Drug-induced lupus
iv. Immunoblastic lymphadenopathy
v. Sjögren syndrome
vi. Familial Mediterranean fever
vii. Churg-Strauss syndrome
viii. Wegener granulomatosis

h. Drug-induced pleural disease
i. Nitrofurantoin
ii. Dantrolene
iii. Methysergide
iv. Ergot drugs
v. Amiodarone
vi. Interleukin 2
vii. Procarbazine
viii. Methotrexate
ix. Clozapine

i. Miscellaneous diseases and conditions
i. Asbestos exposure
ii. Postlung transplant
iii. Postbone marrow transplant
iv. Yellow nail syndrome
v. Sarcoidosis
vi. Uremia
vii. Trapped lung
viii. Therapeutic radiation exposure
ix. Drowning
x. Amyloidosis
xi. Milk of calcium pleural effusion
xii. Electrical burns

xiii. Extramedullary hematopoiesis
xiv. Rupture of mediastinal cyst
xv. Acute respiratory distress syndrome
xvi. Whipple disease
xvii. Iatrogenic pleural effusions
j. Hemothorax
k. Chylothorax
l. Pseudochylothorax

be measured. If this difference is greater than 3.1 gm/dL, then the patient in all probability has a transudative pleural effusion.[4]

CHF is by far the leading cause of transudative pleural effusions. In recent years it has been shown that levels of N-terminal probrain natriuretic peptide (NT-proBNP) are increased in the pleural fluid and serum of patients with CHF.[5] Levels more than 1500 pg/mL in either the serum or the pleural fluid are virtually diagnostic of CHF.[5] The levels of NT-proBNP are virtually identical in the pleural fluid and the serum.[6] It has been shown that the pleural fluid BNP levels are less accurate than the pleural fluid NT-proBNP in identifying patients with CHF, although a BNP level of 115 pg/mL does identify most patients with CHF.[7]

Routine Tests on Pleural Fluid

In addition to measuring the protein and LDH levels in the pleural fluid to differentiate transudates and exudates, the following tests are recommended on the pleural fluid[8]: description of the fluid; cell count and differential; glucose; pH particularly if the patient has a parapneumonic effusion; cytology; smears and cultures for bacteria, mycobacteria, and fungi; and adenosine deaminase (ADA) if tuberculous pleuritis is in the differential.

The appearance of the pleural fluid should always be noted. If it is very cloudy or milky, then it should be centrifuged. A clear supernatant indicates that the cloudiness is caused by cells or debris and the patient probably has an empyema. If cloudiness persists after centrifugation, the cloudiness is caused by a high lipid level in the pleural fluid and the patient has a chylothorax or a pseudochylothorax. If the fluid looks very bloody, a hematocrit should be obtained on the pleural fluid. A hemothorax is present if the pleural hematocrit exceeds 50% of the peripheral hematocrit.

Most transudates have a nucleated cell count less than 1000/mm^3, whereas most exudates have a nucleated cell count more than 1000/mm^3. The cell count in empyemas is frequently low because the sediment is caused by debris and dead cells. The cells in the pleural space are classified as neutrophils, small lymphocytes, other mononuclear cells, and eosinophils.[1] The presence of predominantly neutrophils indicates that the pleural process is acute. If the presumptive diagnosis is a parapneumonic effusion and there are not predominantly neutrophils in the pleural fluid, an alternate diagnosis should be sought. The presence of predominantly small lymphocytes in the pleural fluid suggests pleural tuberculosis, malignancy, or a post-CABG surgery pleural effusion. Eosinophilic pleural effusions have more than 10% eosinophils and are most commonly idiopathic or caused by malignancy.[9,10]

A low pleural fluid glucose (<60 mg/dL) indicates that the pleural effusion is probably caused by 1 of the following 4 entities: complicated parapneumonic effusion,

malignant pleural effusion, tuberculous pleural effusion, and rheumatoid pleural effusion. Other rare causes of low glucose effusions are hemothorax, paragonimiasis, Churg-Strauss syndrome, and occasionally lupus pleuritis. If a patient has a parapneumonic effusion, the pleural fluid pH should be measured because the lower the pH, the more likely the patient is to require surgery for the effusion.[11] To be clinically useful, the pH must be measured with a blood gas machine; pH meter and indicator strips are not sufficiently accurate.[12]

If there is any suspicion that the patient has a malignancy, a cytologic examination on the pleural fluid is indicated. If the patient has malignancy, the cytology is diagnostic in about 65%. The cytology is more likely to be positive with adenocarcinoma than with squamous cell carcinoma, Hodgkin disease, or lymphoma.

If bacterial infection is suspected as a cause of the pleural effusion, bacterial smears and cultures of the pleural fluid should be obtained. It has been shown that using blood culture bottles inoculated at the bedside increases the number of positive cultures by about 50%.[13] In like manner if tuberculous pleuritis is suspected, use of a BACTEC (BD Franklin Lakes, NJ, USA) system with bedside inoculation provides higher yields and faster results than do conventional methods.[1] If tuberculous pleuritis is suspected, a pleural fluid ADA level should be obtained. Pleural fluid ADA levels more than 40 U/L in a patient with predominantly lymphocytes in their pleural fluid are virtually diagnostic of tuberculous pleuritis.[14]

Approach to Patient with No Diagnosis After a Thoracentesis

When one considers the diseases most likely to cause pleural effusions (**Table 1**), this provides some guidance as to how to proceed. The first procedure that is recommended is a computed tomography (CT) angiogram. Not only does the CT angiogram show whether or not a pulmonary embolus (the fourth leading cause of a pleural effusion) is present, it also identifies the presence of pulmonary infiltrates, pleural masses, or mediastinal lymphadenopathy, providing clues to the cause of the pleural effusion.

Observation

If the CT angiogram is not diagnostic of pulmonary embolism and if there are no other abnormalities in the parenchyma, pleura, or mediastinum, observation is probably the

Table 1
Estimated annual incidence of various causes of pleural effusions in the United States

CHF	500,000
Parapneumonic effusion	300,000
Malignant pleural effusion	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	60,000
Pulmonary embolization	150,000
Viral disease	100,000
Cirrhosis with ascites	50,000
Post-CABG surgery	50,000
Gastrointestinal disease	25,000
Tuberculosis	2500

best course of action if the patient is improving. It is estimated (see **Table 1**) that 100,000 cases of pleural effusions each year are caused by viral illnesses. Pleural effusions caused by viral illnesses are self-limited, and invasive procedures such as bronchoscopy or thoracoscopy do not establish the diagnosis.

Needle Biopsy of Pleura

If the patient has a pleural mass or pleural thickening, consideration should be given to performing a CT-guided cutting needle biopsy of the abnormal area.[15] The CT-guided cutting needle biopsy provides a significantly higher diagnostic yield than does the blind needle biopsy of the pleura.[15] In the past blind needle biopsy of the pleural was frequently performed primarily to establish the diagnosis of tuberculous pleuritis or malignancy. However, for the following reasons needle biopsy is rarely indicated if thoracoscopy is readily available. The diagnosis of tuberculous pleuritis is more easily established by showing a pleural fluid ADA more than 40 U/L. Moreover, if the pleural fluid cytology is negative and the patient has malignancy, blind needle biopsy is diagnostic of malignancy in only about 20% of cases.[16]

Bronchoscopy

If the patient has a parenchymal lesion, a massive pleural effusion or hemoptysis, bronchoscopy should be performed. However, if none of these abnormalities is present, then bronchoscopy is not indicated because in this situation it is rarely diagnostic.[17] If the mediastinum is shifted toward the side of the effusion, bronchoscopy is also indicated because this finding is suggestive of an obstructed bronchus.

Thoracoscopy

Thoracoscopy establishes the diagnosis of either malignancy or tuberculosis in nearly 100% of cases.[18] Thoracoscopy should be performed only when less invasive procedures are nondiagnostic. In patients with undiagnosed pleural effusions, 4 characteristics are suggestive that the patient has a malignant pleural effusion, namely, (1) a symptomatic period of more than a month, (2) absence of fever, (3) blood-tinged or bloody pleural fluid, or (4) CT findings suggestive of malignancy (pulmonary or pleural masses, pulmonary atelectasis, or lymphadenopathy).[19] In 1 study of 93 patients with negative cytology who were referred for thoracoscopy, 28 had all 4 criteria and all had malignancy, whereas 21 had at most 1 criterion and none had malignancy.[19] If thoracoscopy is performed for an undiagnosed pleural effusion, a procedure should be performed to create a pleurodesis at the time of the thoracoscopy.

DISEASES THAT MOST COMMONLY CAUSE PLEURAL EFFUSION

In the sections that follow, the diseases that most commonly cause pleural effusions are discussed.

CHF

CHF is responsible for more pleural effusions than any other disease entity. In most cases the origin of the pleural fluid is fluid in the interstitial spaces of the lung resulting from an increased wedge pressure.[20] However, patients with right heart failure may also develop a pleural effusion.[21] The pleural effusion is usually bilateral, but if unilateral it is more commonly on the right.[22]

The diagnosis is usually suggested by the clinical picture of CHF. Initially a thoracentesis is indicated only if the patient has pleuritic chest pain, is febrile, or if the

effusions are greatly disparate in size. If the effusion persists after treatment of the CHF is initiated, a thoracentesis can be performed. The pleural fluid is a transudate by definition, but if diuretics have been administered to the patient, the pleural fluid may meet the Light exudative criteria, as discussed earlier. That the fluid is caused by CHF may be established by showing an NT-proBNP level more than 1500 pg/mL or a serum-pleural fluid protein gradient more than 3.1 g/dL. If the effusion is large and the patient is dyspneic, a therapeutic thoracentesis frequently relieves the dyspnea.

Cirrhosis

The other main cause of a transudative pleural effusion is cirrhosis with ascites. The predominant mechanism leading to a pleural effusion in a patient with cirrhosis and ascites is the movement of ascitic fluid through a diaphragmatic defect into the pleural space.[23] At times, the ascites may not be apparent clinically. The initial management of the pleural effusion associated with cirrhosis and ascites should be directed toward treatment of the ascites with a low-salt diet and diuretics. If this strategy is ineffective, then liver transplantation is the best option. If liver transplantation is not feasible, the next best treatment is implantation of a transjugular intrahepatic portosystemic shunt (TIPS).[24] If neither TIPS nor liver transplantation is feasible, the best alternative is probably videothoracoscopy with closure of the diaphragmatic defects and pleurodesis, but this approach is associated with significant morbidity and mortality.[25]

Parapneumonic Effusions and Empyema

A parapneumonic effusion is any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis. Approximately 1 million individuals are hospitalized each year with pneumonia and because approximately 40% have a pleural effusion, parapneumonic effusion is one of the most common pleural effusions. Parapneumonic effusions that require tube thoracostomy or that are culture positive are designated complicated parapneumonic effusions. If the pleural fluid is pus, an empyema is present.

All patients with parapneumonic effusion should be treated with antibiotics. For patients with severe community-acquired pneumonia in whom *Pseudomonas* is not suspected, the recommended agents are a β-lactam plus either an advance macrolide or a respiratory fluoroquinolone. If a *Pseudomonas* infection is suspect, an anti-*Pseudomonas* antibiotic such as piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime should be included.[26] Because anaerobic bacteria cause many parapneumonic effusions, anaerobic coverage with either clindamycin or metronidazole is recommended.[27] If the patient has a health care-associated pneumonia, vancomycin should be administered because many of these are caused by methicillin-resistant *Staphylococcus aureus*.[28]

When a patient with pneumonia is evaluated, the possibility of a parapneumonic effusion should be considered. If the diaphragms are not visible throughout their lengths on both the posteroanterior and lateral chest radiograph, the possibility of a parapneumonic effusion should be evaluated with ultrasound, chest CT scan, or lateral decubitus chest radiographs. If the thickness of the fluid is greater than 20 mm, a thoracentesis should be performed.[29] Initially it was recommended that all effusions more than 10 mm thick be sampled,[30] but it now seems that only effusions more than 20 mm thick need be sampled because almost all effusions smaller than this resolve with only antibiotics.[29]

It is recommended that the initial thoracentesis be a therapeutic thoracentesis.[1] The reasoning behind this recommendation is that if a patient has a needle in their chest, it

is prudent to take all the fluid out. If the fluid does not return, one need not worry about the pleural effusion. Alternative approaches are to insert a small chest tube or perform a diagnostic thoracentesis. There are no controlled studies comparing the efficacy of these 3 approaches. The purpose of the thoracentesis is to determine whether the pleural fluid has those characteristics associated with a bad prognosis, namely a positive Gram stain or culture, a pH level less than 7.20, a glucose level less than 60 mg/dL, an LDH level greater than 3 times the upper limit of normal or the presence of pus. The yield with bacterial cultures is increased if the pleural fluid is inoculated directly into blood culture bottles at the bedside.[13] If the differential cell count does not show predominantly neutrophils, an alternative diagnosis should be sought.[1]

If the pleural fluid cannot be completely removed with the therapeutic thoracentesis or there are bad prognostic factors present, a chest tube should be inserted. Small chest tubes (<14 F) seem to be as effective as large chest tubes and are recommended because they are less painful.[31] If the pleural fluid is not completely removed by the small chest tube, the pleural fluid is probably loculated. The loculations are created by fibrin bands that result from the intense pleural inflammation. Many papers have been written attesting to the effectiveness of fibrinolytics such as streptokinase, urokinase, or tissue plasminogen activator (tPA) in facilitating drainage of loculated pleural effusions. However, these positive studies were mostly uncontrolled. In the largest study ever performed, 454 patients in a multicenter, double-blind randomized study received streptokinase 250,000 IU or saline, both in a total volume of 30 mL, twice a day for a total of 3 days.[32] There was no difference in the number of patients requiring additional therapy or the length of hospitalization in the 2 groups. Moreover, subgroup analysis was unable to show any group that appeared to benefit from the streptokinase.[32]

The same group conducted a second study in which they compared the efficacy of 10 mg tPA, 4 mg DNase (Pulmozyme), saline, and the combination of 10 mg tPA and 4 mg DNase[33] in a double-blind, randomized multicenter study of 210 patients. The primary end point for this study was the reduction in the percentage of the hemithorax occupied by the pleural fluid. The results were as follows: tPA 15.1%, saline 17%, DNase 17.1%, and tPA plus DNase 29.7%. The results with the combination were significantly better than the results with the other 3 regimens.[33] It is recommended that to treat a patient with a loculated parapneumonic effusion with fibrinolytics, the combination of 10 mg tPA plus 4 mg DNase be used.

The primary alternative approach to fibrinolytics for loculated parapneumonic effusions is video-assisted thoracic surgery (VATS) with the breakdown of adhesions, the optimal placement of chest tubes, and possibly decortication. Most patients who undergo VATS need no additional therapy. When 4 studies in the late 1990s are combined, VATS was the definitive procedure in 77% of the patients. After VATS, the median time for chest tube drainage was 5.3 to 12.3 days, the median hospital stay ranged from 5.3 to 12.3 days, and the overall mortality was 3%.[34–37] There have been no randomized studies comparing VATS with the combination of tPA and DNase in the treatment of loculated parapneumonic effusion. If VATS is available and the patient is a surgical candidate, then VATS is the preferred procedure.

When a pleural infection is present, the pleural space must be eradicated before the infection can be cured. At times a rind of fibrous tissue forms on the visceral pleura that prevents the underlying lung from expanding and eliminating the pleural space. In such a situation, the fibrous tissue must be removed from the visceral pleura through a process called decortication. Decortication can frequently be performed at the time of VATS, but on occasion an open thoracotomy must be performed to remove all the fibrous tissue and allow the underlying lung to expand. If the patient does not have

uncontrolled pleural sepsis and there is fibrous tissue covering the visceral pleura, the patient need not go to surgery because the fibrous tissue usually resolves with time.

MALIGNANT PLEURAL EFFUSION

Malignant pleural effusions are the second most common exudative pleural effusion (see **Table 1**). Pleural effusions associated with neoplasms arise through at least 5 different mechanisms: (1) the pleural surfaces may be involved by the tumor, which leads to increased permeability of the pleural membranes, possibly because of vascular endothelial growth factor[38]; (2) the neoplasm may obstruct the lymphatics or veins draining the pleural space, leading to the accumulation of pleural fluid; (3) an endobronchial tumor may completely obstruct a bronchus, leading to atelectasis and a pleural effusion from the decreased pleural pressure; (4) a pneumonia distal to a partially obstructed bronchus may lead to a parapneumonic effusion; and (5) the malignancy may disrupt the thoracic duct, leading to a chylothorax.

When a pleural effusion is present in a patient with malignancy, one should attempt to determine the cause of pleural effusion with these 5 causes in mind. The pleural effusion may be caused by a different disease such as CHF, pulmonary embolism, or pneumonia.

The possibility of a malignant pleural effusion should be considered in all patients with undiagnosed exudative pleural effusions. The diagnosis is established by showing malignant cells in the pleural space. The easiest way to establish the diagnosis of a malignant pleural effusion is via cytology of the pleural fluid, as described earlier. If the cause remains undiagnosed after a cytologic examination, the most efficient way to make the diagnosis is with thoracoscopy or with a cutting needle biopsy of the pleura, as described earlier.

The initial step in the management of a malignant pleural effusion is to attempt to identify the site of the primary tumor to decide whether to administer systemic chemotherapy. Approximately 75% of pleural malignancies are caused by lung cancer, breast cancer, or leukemia. To identify the site of the primary, the following studies are indicated: CT scan of the chest looking for a lung primary, mediastinal lymphadenopathy suggestive of a lymphoma, and mammography looking for a breast primary. If these studies are not informative, additional studies should be based on the patient's symptoms and the results of the physical examination.

The prognosis of patients with malignant pleural effusions is grave, with a median life expectancy of 4 to 5 months. The presence of the malignant pleural effusion indicates that the malignancy is disseminated and is not curable with surgery. The aim of therapy for the pleural effusion is to provide the patient with the highest possible quality of life with a minimal amount of hospitalization.

The primary symptom caused by the pleural effusion is dyspnea. Maneuvers designed to remove or prevent the accumulation of pleural fluid are indicated only if the patient's quality of life is reduced by dyspnea and the dyspnea is relieved with a therapeutic thoracentesis. The 2 main treatments for the fluid accumulation with malignant effusions are the implantation of an indwelling catheter and the intrapleural injection of a sclerosing agent to produce a pleurodesis.

The indwelling pleural catheter most commonly used is a 15.5-Fr silicone rubber catheter (PleurX catheter, CareFusion, Waukegan, IL, USA) that can be inserted on an outpatient basis[39,40] by pulmonologists, interventional radiologists, or surgeons. The catheter is tunneled and has a valve on the distal end that prevents fluid or air from passing in either direction through the catheter unless the catheter is accessed with a matching drainage line. The pleural fluid is drained at 24-hour to 48-hour

intervals by inserting the access tip of the drainage line into the valve of the catheter and then draining the fluid via an external tube into vacuum bottles.[39]

The indwelling pleural catheter is effective in managing malignant pleural effusions.[41] In 1 retrospective analysis of 250 tunneled pleural catheter insertions in 223 patients at a single center, symptom control was compete in 39% and partial in another 50%.[42] No additional procedure was necessary in 90%.[42] A spontaneous pleurodesis occurs in about 50% of patients who receive the indwelling catheter. In 1 study 173 of 295 catheters (58.6%) were removed because the fluid drainage had become less than 50 mL/d at a mean of 29.4 days after catheter insertion.[43] Reaccumulation of fluid that produced dyspnea occurred in only 5 of the 173 patients (2.9%). The biggest advantage of the indwelling pleural catheter is that it can be inserted as an outpatient. Adverse effects events associated with the indwelling catheter include pleural infection (2.8%) (which can be managed with intravenous antibiotics, leaving the catheter in place), catheter blockage (which can be managed with the instillation of a fibrinolytic into the catheter or replacement of the catheter), and chest pain with the removal of fluid (which can be minimized by draining the fluid more slowly).[44]

The primary alternative to insertion of an indwelling pleural catheter is to inject an irritant into the pleural space, which can create an intense inflammatory response, leading to fusion of the visceral and parietal pleural.[1] Many different agents have been used as pleurodesing agents, but doxycycline 500 mg is the agent I recommend. The only 2 agents approved by the US Food and Drug Administration are talc and bleomycin. Talc is the agent most commonly used,[45] but it is not recommended because it causes fatal acute respiratory distress syndrome (ARDS) in more than 1% of patients.[46] ARDS seems to be related to talc with small particle size, and talc should never be used if the size of the talc particles is not known.[1] Another reason that talc is not recommended is that in the biggest randomized controlled study ever performed for pleurodesis, talc administered either as a slurry or insufflated at thoracoscopy was not particularly effective.[46]

The following is the procedure recommended for pleurodesis. A chest tube (9–14 Fr) is inserted and the pleurodesing agent is injected as soon as the lung is completely expanded. Before the agent is injected, the patient should undergo conscious sedation with systemic medications such as lorazepam or midazolam, because the procedure can be painful. Doxycycline 500 mg in 50 mL saline is injected through the chest tube into the pleural space and then the tube is clamped for the next 1 to 2 hours. The chest tube is then unclamped and negative pressure is applied until the drainage becomes less than 150 mL/d. The chest tube is then removed. Pleurodesis performed in this manner is effective in obliterating the pleural space and controlling the effusion about 80% of the time. The disadvantage of this procedure is that the patient has to remain hospitalized for a median of about 5 days. If patients remain dyspneic after either insertion of the indwelling catheter or pleurodesis, the dyspnea can be treated with opiates, which are titrated just as they are for pain.

PLEURAL EFFUSION CAUSED BY PULMONARY EMBOLISM

Pulmonary embolism is the fourth leading cause of pleural effusions. Approximately 20% to 40% of patients with pulmonary embolism have a pleural effusion.[47] The presence of pleuritic chest pain in a patient with a pleural effusion is suggestive of pulmonary embolus. More than 75% of patients with pleural effusions secondary to pulmonary emboli have pleuritic chest pain.[47]

The pleural effusions secondary to pulmonary emboli are usually unilateral and occupy less than one-third of the hemithorax.[48] Approximately 20% of pleural

effusions secondary to pulmonary emboli are loculated, and loculation is more common if the diagnosis is delayed more than 10 days after symptoms develop.[48] There is not a good correlation between the side of the embolus and the side of the effusion.[48] The pleural fluid with pulmonary embolism is almost always exudative.[48,49]

The diagnosis of pulmonary embolism should be considered in every patient with an undiagnosed exudative pleural effusion. If the patient has a high probability of pulmonary embolism (see article on pulmonary embolism by Hunt and Bull elsewhere in this issue), the patient should be immediately started on low-molecular-weight heparin or unfractionated heparin, and a test for pulmonary embolism should be performed before a thoracentesis is attempted. The serum D-dimer level should be measured in patients with a low probability of pulmonary embolism. If the D-dimer level is normal, the diagnosis of pulmonary embolism is virtually ruled out. If the D-dimer level is increased, another test must be performed to confirm the diagnosis of pulmonary embolism.[49] The treatment of patients with pulmonary embolism and pleural effusion is the same as the treatment of patients with pulmonary emboli without pleural effusion. If the effusion increases in size with treatment, a diagnostic thoracentesis should be performed to rule out pleural infection or hemothorax.

PLEURAL EFFUSIONS CAUSED BY VIRAL DISEASES

It is estimated that viral infections are responsible for 100,000 pleural effusions annually in the United States (see **Table 1**). However, the diagnosis of a viral pleural effusion is rarely established because it depends on showing an increase in antibodies to the virus. The importance of viral pleural effusions is that they are self-limited. Accordingly, if a patient with an undiagnosed exudative effusion is improving, no additional diagnostic procedures are indicated.

PLEURAL EFFUSIONS CAUSED BY TUBERCULOSIS

In some parts of the world, tuberculous pleural effusions are the most common pleural effusions, but they are relatively uncommon in the United States (see **Table 1**). However, if a patient has tuberculous pleuritis, it is important to establish the diagnosis because if the patient is not treated, the effusion spontaneously resolves, but the patient has a high likelihood of subsequently developing pulmonary or extrapulmonary tuberculosis.[50]

The diagnosis of tuberculous pleuritis should be suspected in any patient with an undiagnosed exudative pleural effusion.[14] Patients with tuberculous pleuritis usually have a subacute illness characterized by cough, pleuritic chest pain, and fever. The pleural fluid with tuberculous pleuritis is an exudate that usually has predominantly small lymphocytes and often has a protein level more than 5 gm/dL. The diagnosis is established by showing a pleural fluid ADA level more than 40 IU/L in a lymphocytic pleural effusion.[14] In equivocal cases, needle biopsy or thoracoscopy may be necessary to establish the diagnosis. Cultures of pleural fluid are positive in less than 20% of patients with tuberculous pleuritis. The treatment of tuberculous pleuritis is the same as the treatment of pulmonary tuberculosis.

PLEURAL EFFUSIONS AFTER CABG

Almost all patients after CABG develop a pleural effusion, and approximately 10% develop a pleural effusion that occupies more than 25% of the hemithorax.[51] The primary symptom of patients with pleural effusions after CABG is dyspnea. Chest pain and fever are distinctly uncommon. The pleural effusions that occur after

CABG can be divided into those that occur within the first 30 days and those that occur after the first 30 days.[52] The pleural fluid in both instances is an exudate. The early effusions are frequently bloody and many contain more than 10% eosinophils. The late effusions are not bloody and contain mostly small lymphocytes.[53]

Patients who are dyspneic from a pleural effusion after CABG should undergo a therapeutic thoracentesis. Patients who are febrile or have pleuritic chest pain should also undergo a thoracentesis to rule out pleural infection. When a thoracentesis is performed in a patient with an effusion after CABG, studies should be performed to rule out CHF, chylothorax, and pleural infection. The possibility of pulmonary embolus should always be considered.[52] Most patients with a pleural effusion after CABG are cured with 1 to 3 therapeutic thoracenteses.[50] There is no evidence that the administration of diuretics or antiinflammatory agents are effective in the management of post-CABG effusion.[52]

PLEURAL EFFUSIONS CAUSED BY SYSTEMIC LUPUS ERYTHEMATOSUS

Pleural effusions occur in approximately 40% of patients with systemic lupus erythematosus.[1] The effusions are frequently bilateral but may be unilateral and change from 1 side to the other. Pericardial effusions are frequently present concomitantly with the pleural effusion. The pleural fluid is typically a serous exudate with normal pH and glucose levels and an LDH level less than 2 times the upper limit of normal.[54] The diagnosis of lupus pleuritis is established by using the diagnostic criteria published by the American Rheumatism Association. Patients with lupus pleuritis should be treated with oral prednisone, 80 mg every other day, with rapid tapering once the symptoms are controlled.

PLEURAL EFFUSIONS CAUSED BY RHEUMATOID DISEASE

Pleural effusions occur in approximately 4% of patients with rheumatoid pleuritis. Most rheumatoid pleural effusions occur in men and most patients have subcutaneous rheumatoid nodules. The effusion is usually small to moderate in size and only occasionally produces symptoms. The pleural fluid with rheumatoid pleuritis is distinctive, with a glucose level less than 30 mg/dL, an LDH level more than 2 times the upper limit of normal, and a pH level less than 7.20.[54] It is not clear that any medical therapy exerts a positive influence on the course of rheumatoid pleuritis.

PLEURAL EFFUSIONS CAUSED BY GASTROINTESTINAL DISEASE

Many different gastrointestinal diseases can have an associated pleural effusion, and it is beyond the scope of this article to discuss them all in detail. Patients with acute pancreatitis frequently have an associated pleural effusion, and at times chest symptoms dominate the clinical picture. The diagnosis is established by showing a high pleural fluid amylase level. Patients with pancreatic pseudocysts may have a large pleural effusion caused by a sinus tract from the pseudocyst into the mediastinum and then into the pleural space. Chest symptoms almost always dominate in this situation and the diagnosis is made by showing a high pleural fluid amylase level.[55]

Esophageal perforation is a diagnosis that should be considered in every critically ill patient with a pleural effusion because if the diagnosis is not made within several days, mortality approaches 100%. Most patients with an esophageal perforation have either a pleural effusion or a hydropneumothorax. The pleural fluid with esophageal perforation is distinctive, with a high amylase level (salivary type), a low pH level, a low glucose

level, and a high LDH level. At times food particles may be seen in the pleural fluid. The treatment is surgical repair of the perforation.

The diagnosis of intra-abdominal abscess should be considered in patients with pleural effusions containing predominantly neutrophils but without pulmonary infiltrates. The abscess can be subphrenic, intrahepatic, intrapancreatic, or intrasplenic. The diagnosis is made with abdominal CT scan and the treatment is drainage of the abscess.[1]

PLEURAL EFFUSIONS CAUSED BY DRUG REACTIONS

The possibility that an undiagnosed pleural effusion is caused by a drug reaction should be considered. The primary drugs responsible for pleural effusions include nitrofurantoin, dantrolene, ergot alkaloids, amiodarone, interleukin 2, procarbazine, methotrexate, and clozapine. The pleural effusions associated with the administration of drugs are frequently eosinophilic.

CHYLOTHORAX AND PSEUDOCHYLOTHORAX

When pleural fluid is found to be milky or opaque, the patient either has a high lipid pleural effusion or an empyema. If the fluid is centrifuged, the supernatant remains milky or opaque only if the patient has a high lipid pleural effusion. Chylothorax and pseudochylothorax are the 2 effusions with high lipid levels. A chylothorax occurs when the thoracic duct is disrupted and chyle accumulates in the pleural space. With chylothorax, the pleural fluid triglyceride levels usually exceed 110 mg/dL. The treatment of chylothorax is the implantation of a pleuroperitoneal shunt, thoracic duct ligation, or the percutaneous transabdominal thoracic duct blockage.[56]

The high lipid levels in a pseudochylothorax are caused by the accumulation of cholesterol or lecithin-globulin complexes in long-standing (>5 years) pleural effusions.[57] Most patients with pseudochylothorax have either rheumatoid pleuritis or have been treated in the past with an artificial pneumothorax for tuberculosis. If the patient is dyspneic from the pleural effusion and if the underlying lung is believed to be functional, a decortication should be considered.[57]

OTHER CAUSES OF PLEURAL EFFUSIONS

There are many other causes of pleural effusions (see **Box 1**), which are not discussed in this article because of space considerations. The reader is referred to Refs[1,58] for additional information.

REFERENCES

1. Light RW. Pleural diseases. 5h edition. Baltimore (MD): Lippincott Williams & Wilkins; 2007.
2. Light RW, MacGregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507–14.
3. Romero-Candeira S, Fernandez C, Martin C, et al. Influence of diuretics on the concentration of proteins and other components of pleural transudates in patients with heart failure. Am J Med 2001;110:681–6.
4. Romero-Candeira S, Hernandez L, Romero-Brufao S, et al. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions? Chest 2002;122:1524–9.

5. Porcel JM, Vives M, Cao G, et al. Measurement of pro-brain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions due to heart failure. Am J Med 2004;15(116):417–20.
6. Kolditz M, Halank M, Schiemanck S, et al. High diagnostic accuracy of NT-proBNP for cardiac origin of pleural effusions. Eur Respir J 2006;28:144–50.
7. Porcel JM, Martínez-Alonso M, Cao G, et al. Biomarkers of heart failure in pleural fluid. Chest 2009;136:671–7.
8. Light RW. Pleural effusion. N Engl J Med 2002;346:1971–7.
9. Kalomenidis I, Light RW. Eosinophilic pleural effusions. Curr Opin Pulm Med 2003;9:254–60.
10. Krenke R, Nasilowski J, Korczynski P, et al. Incidence and etiology of eosinophilic pleural effusion. Eur Respir J 2009;34:1111–7.
11. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest 2000;118:1158–71.
12. Cheng D-S, Rodriguez RM, Rogers J, et al. Comparison of pleural fluid pH values obtained using blood gas machine, pH meter, and pH indicator strip. Chest 1998; 114:1368–72.
13. Menzies SM, Rahman NM, Wrightson JM, et al. Blood culture bottle culture of pleural fluid in pleural infection. Thorax 2011;66(8):658–62.
14. Light RW. Update on tuberculous pleural effusion. Respirology 2010;15:451–8.
15. Maskell N, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet 2003;361:1326–30.
16. Prakash UR, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. Mayo Clin Proc 1985;60:158–64.
17. Chang S-C, Perng RP. The role of fiberoptic bronchoscopy in evaluating the causes of pleural effusions. Arch Intern Med 1989;149:855–7.
18. Diacon AH, Van de Wal BW, Wyser C, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J 2003;22:589–91.
19. Ferrer J, Roldan J, Teixidor J, et al. Predictors of pleural malignancy in patients with pleural effusion undergoing thoracoscopy. Chest 2005;127:1017–22.
20. Wiener-Kronish JP, Matthay MA, Callen PW, et al. Relationship of pleural effusions of pulmonary hemodynamics in patients with congestive heart failure. Am Rev Respir Dis 1985;132:1253–6.
21. Tang KJ, Robbins IM, Light RW. Incidence of pleural effusions in idiopathic and familial pulmonary arterial hypertension patients. Chest 2009;136:688–93.
22. Kataoka H, Takada S. The role of thoracic ultrasonography for evaluation of patients with decompensated chronic heart failure. J Am Coll Cardiol 2000;35:1638–46.
23. Alonso JC. Pleural effusion in liver disease. Semin Respir Crit Care Med 2010;31: 698–705.
24. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–7.
25. Milanez de Campos JR, Filho LOA, Werebe EC, et al. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. Chest 2000;118:137.
26. Mandell LA, Barltett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37:1405–33.
27. Rahman NM, Chapman SJ, Davies RJ. The approach to the patient with a parapneumonic effusion. Clin Chest Med 2006;27:253–66.

28. Davies CW, Gleeson FV, Davies RJ. BTS guidelines for the management of pleural infection. Thorax 2003;58(Suppl 2):II18–28.
29. Skouras V, Awdankiewicz A, Light RW. What size parapneumonic effusions should be sampled? Thorax 2010;65:91.
30. Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions. Am J Med 1980;69:507–11.
31. Rahman NM, Maskell NA, Davies CW, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest 2010;137:536–43.
32. Maskell NA, Davies CW, Nunn AJ, et al. U.K. controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med 2005;352:865–74.
33. Rahman NM, Maskell N, Davies CW, et al. Primary result of the 2nd multi-centre intrapleural sepsis (MIST2) trial; randomized trial of intrapleural tPA and DNAse in pleural infection. N Engl J Med 2011;365:518–26.
34. Landreneau RJ, Keenan RJ, Hazelrigg SR, et al. Thoracoscopy for empyema and hemothorax. Chest 1995;109:18–24.
35. Cassina PC, Hauser M, Hillejan L, et al. Video-assisted thoracoscopy in the treatment of pleural empyema: stage-based management and outcome. J Thorac Cardiovasc Surg 1999;117:234–8.
36. Lawrence DR, Ohri SK, Moxon RE, et al. Thoracoscopic debridement of empyema thoracis. Ann Thorac Surg 1997;64:1448–50.
37. Striffeler H, Gugger M, Im Hof V, et al. Video-assisted thoracoscopic surgery for fibrinopurulent pleural empyema in 67 patients. Ann Thorac Surg 1998;65: 319–23.
38. Cheng C-S, Rodriguez RM, Perkett EA, et al. Vascular endothelial growth factor in pleural fluid. Chest 1999;115:760–5.
39. Putnam JB Jr, Light RW, Rodriguez RM, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. Cancer 1999;86:1992–9.
40. Tremblay A, Robbins S, Berthiaume L, et al. Natural history of asymptomatic pleural effusions in lung cancer patients. J Bronchol 2007;14:98–100.
41. Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med 2010;26:70–6.
42. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest 2006;129:362–8.
43. Warren WH, Kim AW, Liptay MJ. Identification of clinical factors predicting PleurX catheter removal in patients treated for malignant pleural effusion. Eur J Cardiothorac Surg 2008;33:89–94.
44. Chee A, Tremblay A. The use of tunneled pleural catheters in the treatment of pleural effusions. Curr Opin Pulm Med 2011;17:237–41.
45. Lee YC, Baumann MH, Maskell NA, et al. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. Chest 2003;124:2229–38.
46. Dresler CM, Olak J, Herndon JE 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 2005;127:909–15.
47. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598–603.
48. Porcel JM, Madronero AB, Pardina M, et al. Analysis of pleural effusions in acute pulmonary embolism: radiological and pleural fluid data from 230 patients. Respirology 2007;12:234–9.

49. Light RW. Pleural effusion in pulmonary embolism. Semin Respir Crit Care Med 2010;31(6):716–22.
50. Patiala J. Initial tuberculous pleuritis in the Finnish Armed Forces in 1939–1945 with special reference to eventual post pleuritic tuberculosis. Acta Tuberc Scand 1954;36(Suppl):1–57.
51. Light RW, Rogers JT, Moyers JP, et al. Prevalence and clinical course of pleural effusions after coronary artery and cardiac surgery. Am J Respir Crit Care Med 2002;166:1563–6.
52. Light RW. Pleural effusions after coronary artery bypass graft surgery. Curr Opin Pulm Med 2002;8:308–11.
53. Sadikot RT, Rogers JT, Cheng DS, et al. Pleural fluid characteristics of patients with symptomatic pleural effusion post coronary artery bypass surgery. Arch Intern Med 2000;160:2665–8.
54. Halla JT, Schronhenloher RE, Volanakis JE. Immune complexes and other laboratory features of pleural effusions. Ann Intern Med 1980;92:748–52.
55. Ali T, Srinivasan N, Le V, et al. Pancreaticopleural fistula. Pancreas 2009;38: e26–31.
56. Itkin M, Kucharczuk JC, Kwak A, et al. Nonoperative thoracic duct embolization for traumatic thoracic duct leak: experience in 109 patients. J Thorac Cardiovasc Surg 2010;139:584–9.
57. Hillerdal G. Effusions from lymphatic disruptions. In: Light RW, Lee YC, editors. Textbook of pleural diseases. 2nd edition. London: Hodder Arnold; 2008. p. 389–96.
58. Light RW, Lee YC, editors. Textbook of pleural diseases. 2nd edition. London: Hodder Arnold; 2008.